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Interventions to improve the prescribing of antibiotics by healthcare professionals in ambulatory care settings

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produces rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, and generate an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS:

Obaghe Edeghere – Main reviewer, wrote the protocol, searched for studies, undertook data extraction, data analysis, and wrote the first draft.

Jayne Wilson – Second reviewer, advised on the protocol, searched for studies, undertook data extraction, and data analysis, edited and revised the drafts.

Chris Hyde – Senior reviewer, advised on the protocol, undertook data extraction and analysis, edited and revised drafts.

The authors take responsibility for this work.

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None

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EXECUTIVE SUMMARY

Antimicrobial resistance (AMR) is a serious and growing public health problem and it is widely accepted that the major driver for the emergence and spread of antimicrobial resistance is the injudicious (particularly overuse and misuse) consumption of antimicrobial drugs in ambulatory care and other healthcare settings. This problem needs to be tackled by developing a clear and comprehensive strategy predicated on the implementation of a variety of interventions to improve the prescribing quality and behaviour of health professionals in various settings.

This review employs systematic review methodology in estimating the effectiveness of these interventions, given alone or in combination, in improving the quality of antibiotic prescribing by health professionals in ambulatory care settings. A second primary objective was to determine the cost-effectiveness of any of these interventions when implemented in an ambulatory care setting.

The following electronic databases were searched: MEDLINE, EMBASE, CINAHL, CENTRAL, and DARE for studies relating to antibiotic prescribing in ambulatory settings. Forty nine studies (38 RCTS/CRCTs; 9 CBAs and 2 ITS) were included in the review with publication dates spanning the period January 2000 to June 2008. The included studies were heterogeneous in their design, study setting, population, quality, definition and analysis of outcome measures. This meant we were unable to generate any summary estimates of effectiveness using meta-analytic techniques.

The results of the review are presented in a narrative format across four separate categories of interventions: multifaceted interventions; delayed antibiotic prescribing; ancillary testing; and single interventions such as education, reminders etc.

The multifaceted interventions defined as a combination of provider and patient education, plus one or more additional interventions such as reminders, academic detailing and audit and feedback was investigated by twenty one included studies. These studies demonstrated that multifaceted interventions produce small to moderate benefits in ambulatory settings but the ideal combination of interventions is uncertain, as is the key component of these multifaceted interventions. The durability of these multifaceted interventions is unknown as is their cost effectiveness.

Delayed antibiotic prescribing which is a patient focused intervention was investigated by nine included studies with findings ranging from moderate to large improvements in antibiotic prescribing in the intervention group compared with immediate prescribing. However, this impressive result should be viewed against the backdrop of the almost universal use of antibiotics in the control population. Nonetheless, delayed prescribing interventions appear quite promising and are likely to be even more effective if barriers to those patients need to navigate to obtain antibiotic prescriptions for self-limiting infections are increased. In the UK, this intervention has been recommended by the National Institute for Health and Clinical Excellence (NICE) as a viable approach in managing patients with common, largely self-limiting respiratory tract infections and is considered to be safe and acceptable to patients.

The use of ancillary testing is a provider focused intervention investigated by five studies included in this review. This intervention which is geared towards improving the diagnostic certainty and confidence of clinicians produced largely equivocal results which at best are small frequently non-significant improvements in prescribing behaviour. In the UK, this type of intervention is unlikely to have any pragmatic application due to limitations inherent in the structure and organisation of primary medical services in the country.

Single interventions such as education, audit and feedback, reminders, etc were investigated by fourteen included studies. The studies demonstrated very mixed results with any benefit shown likely to be small. These interventions do not appear to address the root causes of inappropriate prescribing and thus are unlikely to lead to large sustainable changes in prescribing and antibiotic resistance in the community.

The effectiveness of any of these interventions (singly or in combination) that aim to improve the prescribing behaviour of professionals in ambulatory care settings will vary depending on the type of intervention, and clinical setting, the targeted behaviour and disease condition. It is important to form a clear understanding of the multiple influences on prescribing behaviours and some insight and appreciation of other factors in operation in any health economy before deciding on and implementing any of the interventions investigated in this review.
Single interventions may be beneficial and probably cost effective in certain settings and context but they do not lead to large, sustained changes in prescribing behaviour and in some instances may be ineffective or possibly detrimental. The use of ancillary test to aid clinical decision making is also context specific and may not be a pragmatic option in some healthcare settings where the infrastructure for near-side testing is limited or absent. Delayed antibiotic prescribing strategies are promising in reducing the use of antibiotics in the management of some common, self-limiting infections in the community. Multifaceted interventions also appear to be effective in changing prescribing behaviour in a variety of clinical settings in diverse health care systems. Future research effort should focus on identifying the key components of complex multifaceted interventions, long term follow up studies to determine the durability of these interventions, and conducting high quality economic evaluation studies to improve our understanding of the cost effectiveness of these interventions.

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AIM OF THE REVIEW

The main aim of this work was to employ systematic review methodology in estimating the effectiveness of interventions, given alone or in combination, in improving the antibiotic prescribing by health professionals in ambulatory care settings.
The key prescribing behaviours examined include:

a) The decision to prescribe an antibiotic for a defined condition

b) The class of antibiotic prescribed (i.e. use of recommended antibiotics)

c) The dose and duration of antibiotic therapy

The secondary objective of this review was to estimate the effect of any of the interventions on patient outcomes related to antibiotic consumption, this includes:

a) Laboratory isolation or colonisation with antibiotic resistant organisms

b) Adverse events arising from the use of antibiotics

c) Adverse events arising from the non-use or reduced use of antibiotics

2. BACKGROUND

2.1 Description of underlying health problem

Antimicrobial resistance (AMR) is a serious and growing public health problem that requires concerted action using a range of interventions implemented in various settings. It is widely accepted that the major driver for the emergence and growing incidence and prevalence of antimicrobial resistance is the injudicious (particularly overuse and misuse) consumption of antimicrobial drugs in ambulatory care and other healthcare settings [1,2]. Antimicrobial agents are more commonly prescribed in ambulatory care settings with majority of these inappropriate prescriptions provided for common, largely self-limiting respiratory tract infections (RTI) such as acute otitis media (AOM); common cold, acute rhinosinusitis; and acute cough/acute bronchitis [3,4]

Globally, resistance to antimicrobial drugs has been identified in a number of medically important pathogens commonly encountered in the community. Antimicrobial resistance has been observed in *Streptococcus pneumoniae*, *Escherichia coli*, and *Neissera gonorrhoea* amongst others. Antimicrobial resistance has increased since the late 1980s and early 1990s, with ecological studies based on surveillance data showing substantial geographic differences in the occurrence and frequency of resistance to various classes of antibiotics in Europe [5,6]. In the United Kingdom (UK), surveillance of antimicrobial resistance undertaken by the Health Protection Agency (HPA) shows a mixed trend with observed rises and declines in the prevalence of drug resistance to important antibiotic classes over time. The global rise in antimicrobial resistance has been shown to be linked to rises

in morbidity, mortality, and costs arising from infection with resistant strains of common pathogens [7]. As the majority of antibiotic consumption in the UK is through prescriptions from general practitioners in primary care [8], this review focuses on identifying effective interventions to tackle the injudicious use of antimicrobials in ambulatory settings.

The European Antimicrobial Resistance Surveillance System (EARSS) and European Surveillance of Antimicrobial Consumption (EASC) monitor antibiotic resistance and consumption patterns at a national level to allow for comparison of trends between participating countries. Analyses of antimicrobial consumption in European countries found that from 2000 to 2004, antimicrobial use decreased (≥ 15%) in Bulgaria, Czech Republic, France and Germany and increased (≥15%) in Croatia, Denmark, Greece and Ireland [9]. Total antimicrobial use in outpatient settings was low in northern, moderate in central, and high in southern European countries. In 2004, antimicrobial consumption varied by a factor of 3.4 between the country with the highest rate (Greece: 33.4 defined daily doses per 1000 inhabitants daily (DID)) and the country with the lowest rate (The Netherlands: 9.7 DID) [10,11].This pattern was also observed in 2002 and 2003 although France had the highest consumption rate in 2002[12,13]. In 2004, the UK (15.2 DID) along with a number of northern European countries reported the lowest antimicrobial drug use in outpatient settings and this was found to correlate with a lower proportions of resistant strains [14,15]. At the population level, these direct correlations between geographic variation in the quantity of antimicrobials consumed and a corresponding variation in antimicrobial resistance, have been shown in a number of observational (ecological) studies, indicating that resistance may be explained in part by differential selection pressure[16-18]).

Other studies based on data from the same European surveillance systems have found large differences in the occurrence and magnitude of antimicrobial resistance reported in European countries (Ferech 2006; Van 2008). Like antibiotic consumption, resistance rates are lower in northern European countries; and approaching alarming levels in southern and central Europe [19,20]. Van et al examined the prevalence of penicillin and erythromycin-nonsusceptible *Streptococci. pneumoniae* (PNSP & ENSP) and floroquinolone-resistant *Escherichia. coli* resistance in European countries and found the highest resistance rates in Spain, Hungary and France and lowest rates in Sweden and The Netherlands [21]. From 2001 to 2005, resistance patterns remained relatively stable for PNSP but increased for the other two compound pathogen combinations [22]. In England and Wales, the trends in PNSP rose gradually in the 1990s, peaked at 6.7% in 2000, and declined afterwards with annual rates fluctuating between 2.3% and 4.0% [23]. Resistance to erythromycin was 9.7% in 2007, which is a continuation of a decline in resistance observed in 2004. These observed trends in PNSP and ENSP rates are comparable to that in northern European countries.
Bacteraemia due to *Escherichia.coli* (E.coli) infection in England, Wales and Northern Ireland increased in 2007 by 9% compared to 2006. This is set against the backdrop of the gradual increase in resistance of E.coli isolates to ampicillin/amoxicillin over the last 14 years, from 53% in 1994 to 61% in 2007. Resistance to third-generation cephalosporin's (e.g. cefotaxime & ceftazidime) has also increased markedly from lows in the 1990s to approximately 12% in

2007.Flouroquinolone resistance has also risen sharply from 1% in 1993 to 23% in 2006 and 2007, a finding that is comparable to most countries in Europe [24].

However, the relationship between antimicrobial consumption and resistance patterns are complex and these studies have not always demonstrated a direct linear correlation between the two variables. For example, Spain and the UK reported a significant decrease in penicillin resistance over a five-year period but this was not preceded by a decline in the consumption of penicillin in these countries [25]. Conversely, in the UK prescribing restrictions on the use of sulphonamides for *E.coli* infections introduced in 1991 lead to a significant reduction in prescription. However by 1999, this observed reduction in sulphonamide prescriptions contrasted sharply with a persistence in sulphonamide resistance in *E.coli* isolates [26,27]. In spite of this complex relationship, the body of literature shows compelling evidence of a link between exposure to antibiotics and increased risk of infection with resistant pathogens at a population level.

The cost of managing infections caused by antibiotic resistant pathogens is a growing problem. In the UK, analysis of the cost of treating patients diagnosed with resistant *E. coli* urinary tract infections (UTI) was found to be significant when compared to patients with fully sensitive *E.coli* infections. In general practice settings, patients presenting with an antibiotic resistant *E.coli* UTI incurred a mean cost that was £3.64 (95% CI £0.84-£6.24) higher than patients whose infections were fully sensitive to the six antibiotics assessed in the study [28].This increased cost incurred from managing antibiotic resistant *E.coli* was higher in patients diagnosed with trimethoprim resistant UTI (£11.21, 95% CI £7.27-£15.97).Although the frequency of occurrence of antibiotic resistant UTI described in this study may not be generalisable to the wider UK population, extrapolated national costs show that the total extra annual cost to general practices arising from treating patients with UTI that are resistant to at least one antibiotic would be in the order of £5.8 million (95% CI £1.5 million to £9.8 million) [29]. The overall (direct and indirect) cost of antimicrobial resistance particularly in ambulatory care settings is one area where more research is needed as shown by the dearth of economic evaluation studies. The costs arising from the misuse and overuse of antimicrobials and the subsequent emergence and spread of antimicrobial resistance do vary. Costs are incurred from increased morbidity and mortality following inadequate or failed treatment of patients; the cost of researching and developing new antibiotics to treat increasingly resistant pathogens; costs arising from disruption to the health service caused by outbreaks of multi-resistant bacteria (e.g. cost of isolation, cross-infection control and cancelled procedures); and finally a number of intangible costs arising from productivity losses, provision of informal care, etc [30,31]. Although these cost implications of antimicrobial resistance are not always apparent to clinicians when prescribing decisions are being made in the frontline settings, the key factors that drive inappropriate prescribing in ambulatory care settings are recognised by clinicians and are the main focus of most interventions that have been studied at the population level.

At the population level, a key risk factors associated with infection with antimicrobial resistant pathogens is the volume and rate of antimicrobial consumption. At the microbiological level, key factors driving the emergence of resistant strains of medically important pathogens are *de novo* mutations in genes of microorganisms; exchange of genetic material between organisms leading to a transfer of resistance

genes from one organism to the other; and selective pressure arising from the use of large volumes - often for inappropriate reasons – of antibiotics in health care, agricultural and aquacultures settings [32,33].

Studies undertaken in clinical settings have found that certain cultural, social, and health care factors can explain some of the inappropriate use of antimicrobials particularly in ambulatory settings [34]. A difference in diagnostic labelling, patient coping mechanisms, and health seeking behaviour may explain the variation in antibiotic consumption amongst European countries. In a study comparing general practitioners in Belgium and The Netherlands, countries with high and low antibiotic consumptions respectively, Dutch GPs labelled most episodes of upper respiratory tract infections as common cold or influenza while their Belgian colleagues labelled similar episodes as bronchitis thus triggering the use of an antibiotic (Deschepper et al).

Other explanations for the intra and inter-country variation in prescription of antimicrobials by physicians include inadequate physician knowledge, diagnostic uncertainty; physician experience (assessed by time since graduation); time pressure in primary care; practice characteristics, and patient expectations [35-37]. A number of studies have shown that GPs are more likely to prescribe an antibiotic inappropriately if they are unsure or not confident of the diagnosis, have little time during a consultation to provide patient education, work in a large practice with high patient volume, and have a desire to meet the patient's expectations [38-41]

2.2 Current service provision

Various countries have employed a variety of initiatives to prevent and slow the emergence and spread of resistant strains of pathogens. The cornerstone of these initiatives is the reduction of the pressure for resistance through improvements in the judicious use of antimicrobial drugs. These improvements are mainly being driven through the implementation of effective, evidence-based interventions aimed at improving the quality of prescribing of antimicrobial agents in clinical settings [42,43].In the UK, initiatives implemented in the 1990s were initially associated with an overall decline in prescribing from the late 1990s to 2000s, but since then, there has been a slow increase in antimicrobial prescribing [44-47].

Interventions that target one or more of those patient and physician characteristics mentioned earlier may contribute to a reduction in the injudicious use of antimicrobials by clinicians in ambulatory settings. Secondary studies of interventions to improve provider performance/compliance (i.e. reduction in prescribing) have either focused on antimicrobial prescribing or have assessed overall prescribing irrespective of drug class. These studies investigated the use of a variety of interventions in different health care settings, patient groups, and disease conditions. The range of interventions includes the use of printed, verbal and audio-visual educational material; audit and feedback of performance; financial and administrative restrictions/disincentives; use of scoring tools and clinical reminders amongst others.

2.3 Description of new intervention

The provision of educational material, clinical guidelines, educational seminars and academic detailing is mostly aimed at improving the knowledge and diagnostic confidence of health care professionals. A systematic review of printed educational material (PEM) found a beneficial effect on process outcomes like prescriptions of a particular drug rather than patient outcomes (measured blood pressure, etc) when used alone compared with no intervention [48] The review was unable to identify the ideal circumstances and context where PEM would be more effective or the specific characteristics that can make PEM more effective. This and another review were uncertain about the effectiveness of PEM compared to other interventions [48,49].

A second Cochrane review of educational outreach visits (academic detailing) found that this intervention when used alone or in combination with others had a small but relatively consistent effect on prescribing with a median-adjusted risk difference for compliance with prescribing guidance of 4.8% (IQR 3%-6.5%) [50]. Another review investigating the effectiveness of continuing education meetings and workshops for professionals showed a small but beneficial effect on professional practice when used alone or in combination with other interventions. The authors however noted that educational meetings alone are not likely to change complex behaviours [51].

The use of audit and feedback of practitioner performance against a benchmark can be effective in improving prescribing practice. The effects are generally small to moderate in magnitude but the absolute effects are likely to be larger when baseline adherence to recommended practice is low and the intensity of audit and feedback is high [52]. For dichotomous outcomes the median-adjusted risk difference of compliance with desired practice was 5% (IQR 3%-11%) while for continuous outcomes, the median-adjusted percentage change relative to control was 16% (IQR 5%-37%) [52].

These interventions described above are mainly targeted at providers. Interventions aimed at modifying the expectations and beliefs of patients and carers about the use and benefits of antibiotics for infections are mostly based on the providing passive and occasionally active education and a wait and see approach to prescribing (delayed antibiotic strategies). The educational interventions are delivered through mass campaigns on antibiotic use using a variety of formats and opportunistic sessions at GP practices [53]. The effectiveness of these patient-focused interventions has been the subject of a number of systematic reviews that addressed various aspects of our review question.

These systematic reviews have evaluated different provider and patient focused interventions with varying results [54-58]. Interventions evaluated in these reviews include antimicrobial prescribing strategies: no antibiotics, delayed antibiotics and immediate use antibiotic prescribing; interventions using clinician education alone; interventions using clinician education combined with audit and feedback; interventions using other quality improvement strategies (alone or in combination); the effect of pharmacists' led interventions on antibiotic use; and the effectiveness of anti-microbial stewardship.

The Cochrane review by Arnold and colleagues [59] investigated the effectiveness of provider (health professionals) directed interventions, alone or in combination, in

improving antibiotic prescription. The primary outcome was the rate of appropriate antibiotic prescribing. Secondary outcomes included measurements of the impact of interventions on reducing the incidence of antimicrobial resistant pathogens. A total of 39 studies were included in the review. The authors reported that the use of printed educational materials, and audit and feedback when undertaken in isolation, led to little or no improvements in appropriate prescribing. The interventions found to be successful were multifaceted interventions that combined physician, patient and public education in a variety of formats.

Overall, successful interventions from previous reviews appear to be those that target specific clinical diseases, specific antibiotics and specific prescribers. Active educational sessions appear to be effective while audit and feedback may have had a detrimental effect.

We present findings from a systematic review and cost effectiveness analysis aimed at identifying effective interventions to reduce the inappropriate use (overuse and misuse) of antibiotics in ambulatory settings through sustained improvements in the prescribing behaviour and attitudes of healthcare professionals in ambulatory care settings, with particular reference to the UK setting.

3 EFFECTIVENESS

3.1 Methods for reviewing effectiveness

3.1.1 Protocol development

This systematic review was undertaken in accordance with a pre-defined protocol based on guidance produced by the Cochrane Effective Practice and Organisation of Care Group (EPOC) (see Appendix 1 page 41). The protocol was developed and where necessary, modified by discussion between the review authors (OE, JW, CH). There were no major changes made to the protocol during the course of the review.

3.1.2 Search Strategy

The initial search was carried out in the following electronic databases: MEDLINE, EMBASE, CINAHL, CENTRAL, and DARE. The search date was restricted to the 7 year period between January 2000 and June 2008. No language restrictions were applied. Additional studies were identified from the bibliographies of retrieved articles. See Appendix 2 page 42 for search strategy.

3.1.3 Inclusion criteria

Population	• Healthcare consumers and health professionals of all ages and level of experience. • Settings – Ambulatory healthcare setting which is defined as one where the patient was first seen for the problem of interest. This includes healthcare settings where patients were not admitted to hospital at the time they were assessed (i.e. emergency department, outpatient clinics in hospitals and walk-in-clinics). • Country – Any country.
Intervention	• The interventions included in the review were professional interventions recommended by the Cochrane organisation 'Effective Practice and Organisation of Care' (EPOC) guidance and other interventions aimed at improving the quality of prescribing of antimicrobials by health professionals. The broad categories of interventions included one or more of the following: ▸ Distribution of educational materials ▸ Educational meetings ▸ Local consensus processes ▸ Educational outreach visits (academic detailing) ▸ Local opinion leaders ▸ Patient-mediated interventions ▸ Audit and feedback ▸ Reminders ▸ Marketing ▸ Mass media ▸ Financial interventions ▸ Delayed antibiotic strategies ▸ Ancillary testing
Control	• No intervention • Usual care • Other intervention
Outcomes	The primary outcome measure was the rate of appropriate antibiotic prescribing. This included the following: • The decision to prescribe an antibiotic, or not; or the rate of prescribing a recommended choice, dose or duration of use of antibiotics. Secondary outcome measures were: • The incidence of laboratory isolates of, colonisation with or infection due to, antibiotic resistant organisms and other adverse events associated with antibiotic use. • Incidence rate of adverse events arising from the decision to prescribe or not prescribe an antibiotic agent

Study Designs	• The following types of studies with an appropriate comparator group were included: ▸ All randomised and quasi-randomised controlled trials (including cluster RCTs) ▸ Controlled before and after studies (CBA) with at least 3 data points before and after the intervention. ▸ Interrupted time series studies (ITS)

3.1.4 Exclusion criteria

Population	• Specialist and other non ambulatory settings such as hospital populations were patients were admitted following assessment.
Control	• Hospital controls
Study Designs	• Studies with no comparator group e.g. cross sectional surveys

3.1.5 Study identification

Two review authors (OE) and (JW) independently assessed the identified papers for inclusion using the study title and, where available, the abstract. Any disagreements were resolved by a third reviewer (CH). Potentially relevant studies were examined in detail by obtaining full paper copies of the studies. Non English language publications were originally assessed for inclusion using the method described above, but resource constraints led to the exclusion of these studies. A list of excluded studies can be found in Appendix 3, page 44.

3.1.6 Data extraction strategy

Three reviewers (OE, JW, & CH) independently extracted data and assessed the study quality of the articles identified for inclusion in the review. Data was extracted using a standardised data extraction form derived from the EPOC group guidance that collected information on study design, population and settings, intervention, controls, type of targeted behaviour, statistical analysis, outcome measures, and results. The extraction form can be found in Appendix 4, page 46.

A random sample of the extracted data was checked for accuracy by CH, and any discrepancy was resolved through discussion between reviewers after referring to the original paper.

Data from the included articles were presented, depending on the study design, using the format outlined:

RCTs & Cluster RCTs	▪ Pre-intervention (baseline) & post-intervention means (median) or proportions of both study & control groups. ▪ Difference in absolute change from baseline along with 95% confidence intervals or P values, if available. ▪ Range of effect sizes across included studies. ▪ Relative risk (RR) or odds ratio's (OR) with 95% confidence intervals will be calculated for dichotomous variables.
CBA	▪ Pre-intervention (baseline) & post-intervention means (median) or proportions for both study & control groups. ▪ Percentage change (i.e. the percent improvement relative to the post intervention average of the control group).
ITS	▪ Number of data point's pre & post plus time interval between points. ▪ Pre & post intervention means. ▪ Absolute change in natural units. ▪ Percentage relative change (plus statistical significance).

3.1.7 Quality assessment strategy

Quality was assessed according to the Cochrane guidelines for assessing the risk of bias of included studies. This involved an assessment of the risk of selection bias, performance bias, attrition bias, and detection bias and whether the cluster design effect (where appropriate) was accounted for in the analysis (see Appendix 5, page 52 for a risk of bias summary).

3.1.8 Methods of analysis

Study characteristics and results were tabulated. The results of the individual studies were reported in natural units taking into account methodological quality and *a priori* subgroups. The potential impact of any incorrect analysis of the included studies was noted during the quality assessment phase, however, we did not re-analyse the data.

Unit of analysis issues

There was the potential for included studies to have unit of analysis issues. These could occur where the unit of allocation and analysis are different, for example, the unit of allocation is the general practice and the unit of analysis is the individual GP or in cluster randomised controlled trials where the authors had not taken into account cluster design effect (i.e. not reported the intercluster correlation co-efficient) in the analysis. In both cases these issues were taken into account during the quality assessment, but re-analysis was not done.

Dealing with missing data

In RCTs and cluster RCTs where intention-to-treat analyses have not been performed by the original authors of the studies and sufficient data was available to do so, intention-to-treat analyses were conducted before entry of data into the review

software in order to limit attrition bias. As a result of the considerable clinical heterogeneity of the included studies (i.e. differences in the type of intervention, intensity and duration) meta-analysis was deemed inappropriate, therefore a narrative review was undertaken.

The framework of the narrative review, was broadly similar to that utilised in the Cochrane review 9(Arnold & Straus, 2005) and are as follows:

Comparison 1: multifaceted interventions - defined as combinations of multiple interventions (two or more of the 13 interventions outlined in the inclusion criteria) to providers, patients or public compared to another intervention or control. If a single intervention was targeted at two or more groups (i.e. clinicians and patients, it was categorised as a single intervention even if different formats or content was employed.

Comparison 2: Delayed antibiotic prescribing – patient centred intervention employing a ‘wait and see’ strategy for the prescription and consumption of antibiotics.

Comparison 4: Ancillary test – intervention utilising laboratory test, clinical and other tools to guide the decision making process of clinicians during consultations.

Comparison 4: Single interventions – one intervention type applied to one or more target population using a variety of formats, media and content compared with another intervention or control.

3.2 Results

3.2.1 Search Results

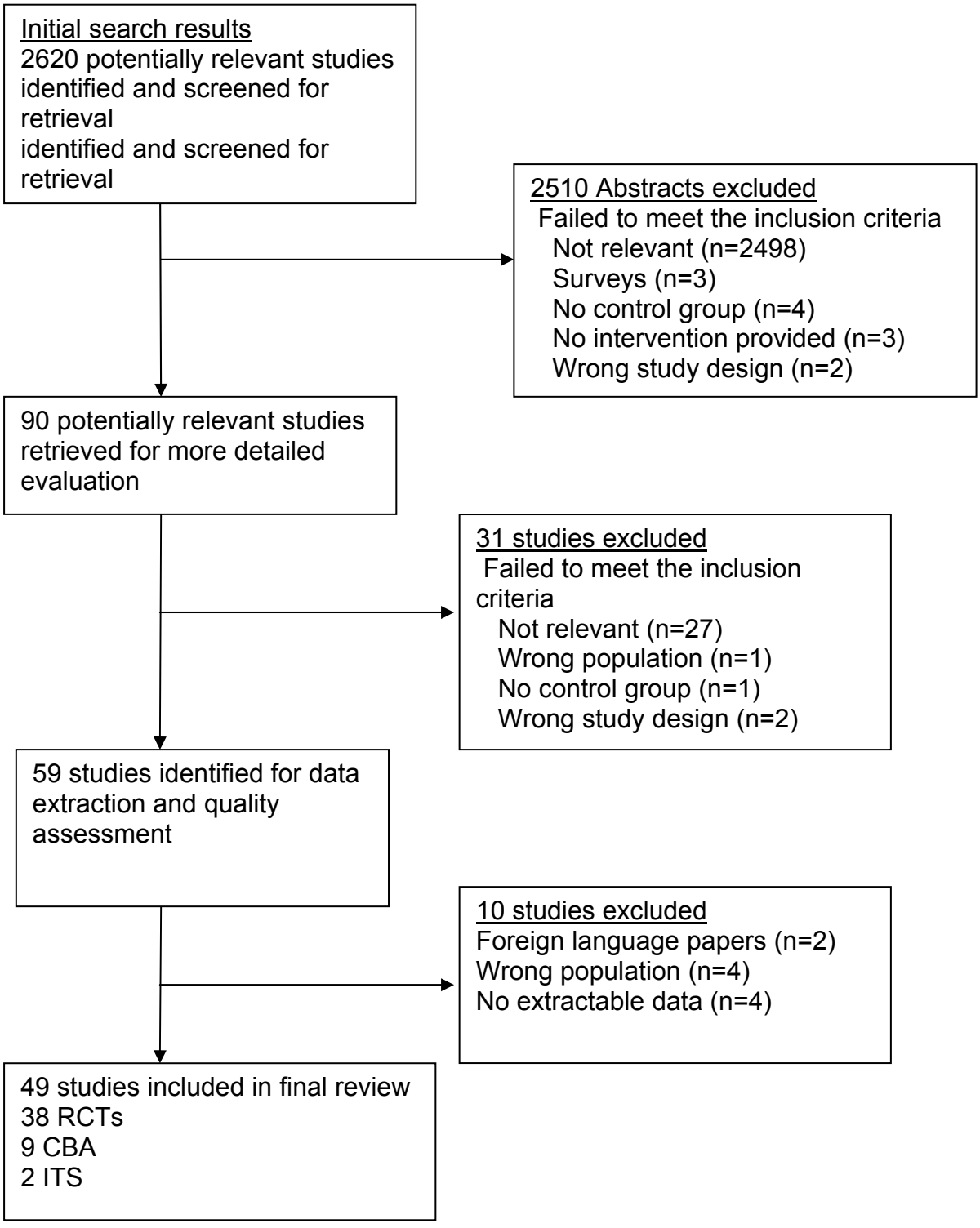

Figure 1 ***Flow diagram***

Forty nine studies met the clinical effectiveness inclusion criteria.

3.2.2 Description of studies

Two thousand six hundred and twenty references were retrieved from a search of the electronic databases from January 2000 through to June 2008 (see appendix 2 for search strategy). Two thousand and five hundred and ten studies were excluded prior to the full review on the basis of the title and abstract. These excluded studies were not relevant to the aims of the review for a variety of reasons including not being intervention studies, use of hospital based population, methodological reasons and being systematic reviews. Thirty one further studies were excluded after detailed review as they did not meet the methodological requirements outlined in the review protocol and a further ten studies were excluded for language and methodological reasons (see table of excluded studies, page).

A total of forty nine studies investigating a variety of interventions were reviewed, with several included studies investigating more than one intervention. The findings are presented in this review using broadly similar comparisons employed in the Cochrane review. The interventions employed by these studies were heterogeneous and targeted a variety of prescribing behaviours. Forty-nine studies were identified as eligible for this review and included thirty-eight randomised trials (14 C-RCTs and 24 RCTs); nine controlled before and after studies and two interrupted time series studies.

All thirty-eight randomised trials included in the review involved patients within ambulatory care settings and were spread across 17 countries. Nine were conducted in the USA (three focused on the provider and patient, three on providers only and three on patients only); six trials in the UK (one on provider only and five patient only), three trials each in Canada (all provider only) and The Netherlands (one provider and patient and two provider only) and two trials each in Australia, Denmark, Israel and Norway. Trials were also conducted in Bangladesh, Belgium, Finland, Germany, Iran, Japan, New Zealand, Switzerland and Sudan.
Sixteen trials utilised heterogeneous multifaceted interventions that consisted of various combinations of the following components: education (campaigns, guidelines, etc) of providers, patients and carers; audit and prescribing feedback; academic detailing; computerised decision support tools; computerised reminders; prescribing restrictions and financial penalties; and communication training. All of the multifaceted interventions employed by the studies included an educational intervention directed at either providers and service users or both. These educational interventions were delivered in a variety of settings and formats such as clinic based or community settings using paper, mass media, computerised, or verbal formats.

Nine trials utilised a delayed antibiotic prescribing strategy with six of these trials also providing educational material to the patients and parents as part of the intervention. Five trials employed an ancillary laboratory test (usually rapid, near side test) with or without a clinical scoring tool. Eight trials utilised single interventions like provider education (3 trials); patient education (1 trial); reminders (3 trials); and academic detailing (1 study).

Thirty-five trials reported on the primary outcome i.e. the number (or proportion) of consultation episodes resulting in an antibiotic prescription. Nine of the thirty eight trials reported on the number (proportion) of consultation episodes resulting in the use of recommended antibiotics; five studies reported on the proportion inappropriately prescribed antibiotics while four studies reported on secondary outcomes like occurrence of adverse events linked to the prescribing decisions of practitioners, cost of antibiotic use, and patient satisfaction.

The nine controlled before and after studies also targeted health professionals and/or patients in ambulatory settings within different healthcare systems. Seven of the nine studies were conducted in the USA (four provider and patient and three providers only), one study in Spain (provider only) and one in Germany (provider only). Three studies utilised a combination of provider and/or patient education plus audit and prescribing feedback, four utilised education only, one utilised education plus academic detailing and the final study utilised audit and feedback plus academic detailing. All nine studies reported on the number (or proportion) of consultation episodes resulting in an antibiotic prescription, two reported on the number (proportion) of consultation episodes resulting in the use of recommended antibiotics and two studies reported on the occurrence of antimicrobial resistant strains in treated patients.

The two interrupted time series study was conducted in the USA and Canada and targeted providers only. The Canadian study employed financial restrictions on reimbursements of prescription cost while the US study employed a combination of provider education, academic detailing plus audit and prescribing feedback. Both studies only reported on the number (or proportion) of consultation episodes resulting in an antibiotic prescription.

3.2.3 Risk of bias in included studies

The methodological characteristics of the reviewed studies are summarised in the characteristics of included studies table (see page). There were thirty eight randomised controlled trials (including cluster RCTs), 9 controlled before and after studies (CBA) and two interrupted time series (ITS) studies.

The overall quality of the included studies was variable, the lowest being the single intervention studies where inadequate blinding and poor randomisation techniques resulted in poor concealment of allocation. The delayed antibiotics studies were good at concealing treatment allocation, but poor at improving the completeness of follow up and undertaking appropriate analyses, therefore they were more likely to suffer from attrition bias. The studies that investigated ancillary tests were conversely poor at concealing treatment allocation, which may have introduced selection bias, but they performed better at reducing attrition bias. Studies in the multifaceted intervention group were also of variable quality, which probably reflects the substantial heterogeneity arising from the different study methods and interventions employed.

3.2.4 Effectiveness

Comparison 1: multifaceted interventions

This review identified twenty one studies that utilised multifaceted interventions that consisted of at least two different types of interventions. As mentioned, these multifaceted interventions were heterogeneous and employed an educational intervention directed at either providers and service users or both plus one or more of the following: audit and prescribing feedback; academic detailing; computerised decision support tools; computerised reminders; prescribing restrictions and financial penalties; and communication training.

These twenty one studies varied in terms of the study design used, the components of the multifaceted intervention, intervention format, target population, and outcomes reported. Fifteen studies (sixteen trials) utilised a RCT/C-RCT design; five studies used a controlled before and after design (CBA); and one study utilised an interrupted time series approach (ITS).

The sixteen randomised trials targeted health care professionals and/or patients in ambulatory care settings operating within different healthcare systems. Three studies conducted in the USA (Mainous 2000; Metlay 2007; Samore 2005) utilised the following interventions: patient education plus audit and feedback; provider education plus academic detailing plus audit and feedback; and provider and patient education plus reminders. Two Norwegian studies (Flottorp 2002; Lagerlov 2000) utilised provider education plus reminders; and education, local consensus plus audit and feedback respectively. Two Dutch studies (Martens 2006a; Welschen 2004) utilised provider education plus local consensus; and education, local consensus plus audit and feedback respectively. A UK based study (Seager 2006) utilised provider and patient education plus academic detailing); a study in Denmark (Sondegaard 2003) utilised provider education plus audit and feedback; an Australian study (Wilson 2003) utilised education plus local consensus plus audit and feedback; a Swiss study (Briel 2006) utilised education materials plus academic detailing ; a Belgian study (Coenen 2004) utilised provider and patient education plus academic detailing ; a Canadian study (Loeb 2005) utilised provider educational meetings and materials plus academic detailing; a Bangladeshi study (Azad Chowdury 2007) utilised provider educational material plus audit and feedback; a Sudanese study (Awad 2006) utilised provider academic detailing plus audit and feedback; and a German study utilised patient education plus academic detailing .

Fifteen of the trials reported on the primary outcome – number (or proportion) of consultation episodes resulting in an antibiotic prescription. Five of sixteen studies reported on the number (proportion) of consultation episodes resulting in the use of recommended antibiotics; three studies reported on the proportion inappropriately prescribed antibiotics while four studies reported on secondary outcomes like occurrence of adverse events linked to the prescribing decisions of practitioners, cost of antibiotic use, and patient satisfaction.

The five controlled before and after studies also targeted health professionals and/or patients in ambulatory settings within different healthcare systems. Three of the five studies were conducted in the USA (Belongia 2001; Gonzales 2004; Gonzales 2005) and utilised patient and provider educational meetings and materials plus academic detailing, and patient education plus audit and feedback for the other two studies. A Spanish study (Madridejos-Mora 2004) utilised academic detailing plus audit and

feedback, and a German study (Wensing 2004) utilised education plus local consensus plus audit and feedback.

All five studies reported on the number (or proportion) of consultation episodes resulting in an antibiotic prescription, two reported on the number (proportion) of consultation episodes resulting in the use of recommended antibiotics, two reported in the cost of antibiotic treatment and one study reported on the occurrence of antimicrobial resistant strains in treated patients.

The interrupted time series study was conducted in the USA (Doyne 2004) and utilised provider and patient focused education plus local consensus plus academic detailing plus audit feedback. The study only reported on the number (or proportion) of consultation episodes resulting in an antibiotic prescription.

The quality of the trials that used a multifaceted intervention was variable and probably reflects the heterogeneity of the study methodologies. These trials may be prone to some selection bias due to the poor quality of (or reporting of) treatment allocation although around 60% of these trails achieved a baseline balance between the groups. Blinding of participants and assessors within these trials was also poorly reported or did not occur thus raising the possibility of performance bias. However, the extent to which any performance bias affects the trial results and our interpretation is difficult to ascertain as most of the outcomes assessed were objectively determined. Trial completeness and the possibility of attrition bias were also variable in these trials.

The quality of the controlled before and after studies was good as most studies met all six quality parameters with the exception of blinding of assessment of primary outcomes. The interrupted tine series study was also well conducted and met almost all quality parameters with the exception of completeness of dataset which raises some possibility of attrition bias.

Primary outcome: Total antibiotic prescriptions

Fifteen RCTs/C-RCTs reported on overall antibiotic prescription/use in their study population following the intervention (table 1). Thirteen trials found a statistically significant reduction in total antibiotic prescription from baseline rates following a multifaceted intervention but two studies found no statistically significant reduction in antibiotic prescribing.

Mainous and colleagues found a 7.2% reduction in the overall proportion of antibiotics prescribed by practitioners. However, this trial was of poor quality as the authors did not report on key quality parameters or failed to undertake them and there was also some contamination of the control group. Significant reductions from baseline were also reported by Welschen et al who found a 12% reduction (95% CI -18.9,-4.0); Coenen et al found 6.5% reduction (OR = 0.56 95% CI 0.36, 0.87); Altiner et al found a 7.7% reduction (OR = 0.55 95% CI 0.38, 0.80); Metlay et al found a 10.5% reduction; Flottorp et al found a 3% reduction (p=0.032); and Azad Chowdury found a 15.5% reduction. These six trials were all of medium quality with some possibility of performance bias due a lack of or poor blinding of participants and assessors.

Wilson et al reported a significant reduction in the mean number of prescriptions from baseline (-1.13/100 episodes, p=0.026); Loeb found a reduction of -0.37/1000 resident days (95% CI -1.17, 0.44); Samore found a reduction of -6.2/100 person years; Awad found a reduction of -7.7 (95% CI -5.9, -9.5, P=<0.001); Seager et al found a 37% reduction (OR 0.63 95% CI 0.41, 0.95), and Lagerlov et al also found a significant reduction (p=<0.001). These six trials were of low to medium quality with poor reporting of quality parameters. This was particularly evident in the studies by Wilson et al, Lagerlov et al, and Samore et al where some degree of selection bias may have arisen due to poor treatment allocation processes.

Briel et al found a non-significant 14% reduction in overall antibiotic prescription following the intervention (OR 0.86 95% CI 0.40, 1.93). This study is a well conducted high quality study and had the highest quality score compared with the other trials.

Table 1 Multifaceted intervention versus other intervention or no intervention- RCTs/CRCTs

Study	Targeted Behaviour	Absolute change	Relative change	Note
Welschen 2004	Reducing antibiotic prescribing for respiratory tract symptoms	Absolute change (post): -14% Difference in absolute change from baseline: -12%	Relative percent change (post): -37.8%	
Azad Chowdury 2007	Reducing antibiotic prescribing for acute respiratory infections	Absolute change (post): -14.5% Difference in absolute change from baseline: -15.5%	Relative percent change (post): -17.8%	
Metlay 2007	Reducing antibiotic prescription for symptoms of acute respiratory infections in adults	Absolute change (post): -5.5% Difference in absolute change from baseline: -10.5%	Relative percent change (post): -11.6%	
Altiner 2007	Reducing antibiotic prescribing for acute cough	Absolute change (post): -28.1% Difference in absolute change from baseline: -9.8%	Relative percent change (post): -43.4%	
Coenen 2004	Reducing antibiotic prescribing for acute cough	Absolute change (post): -1.3% Difference in absolute change from baseline: -	Relative percent change (post): -4.5%	

		6.5%		
Flottorp 2002	Reduce antibiotic prescribing for sore throats in adults and urinary tract infections in women	Absolute change (post): -5.7% Difference in absolute change from baseline: -3%	Relative percent change (post): -11.5%	
Seager 2006	Reduce antibiotic prescribing for acute dental pain	Absolute change (post): -9% Difference in absolute change from baseline: -NA	Relative percent change (post): -28.1%	
Briel 2006	Reducing antibiotic prescribing for symptoms of acute respiratory infection	Absolute change (post): -2.2% Difference in absolute change from baseline: NA	Relative percent change (post): -14%	Multifaceted intervention compared against education only

All five CBA studies reported on overall antibiotic prescription in their study population following the intervention (table 2). Three studies (Wensing 2004; Madridejos-Mora 2004; Gonzales 2005 (adult arm)) found statistically significant reductions in total antibiotic prescription from baseline following a multifaceted intervention, two studies (Gonzales 2004; Gonzales 2005 (paediatric arm) found no statistically significant reduction in antibiotic prescribing and one study (Belongia 2001) found a non significant increase in antibiotic prescribing.

Wensing et al found a 2.8% (OR = 0.86 95% CI 0.82, 0.90) reduction in the overall proportion of antibiotics prescribed following the intervention; Gonzalez et al (Adult population) found a 5% reduction (P=0.002); while Madridejos-Mora et al found a significant reduction in the number of defined daily doses (DDD) of antibiotics per day (-2.0 DDD/day, P=0.026).These three studies were good quality studies with Gonzalez and Madridejos scoring high against all quality parameters while Wensing could not be assessed for the risk of performance and attrition bias due to poor reporting by the authors.

Gonzalez et al (2004) and Gonzalez 2005 (paediatric population) found non-significant reductions in overall antibiotic prescription of 5% (P=0.79) and 3% (P=0.18) respectively following the intervention. The latter is a well conducted high quality study and had the highest quality score of the group while the former, although of good quality, has some risk of performance and attrition bias. Belongia et al, a study of medium quality, found a non-significant increase (3.4%, P=0.66) in antibiotic prescription following the intervention.

Table 2 Multifaceted intervention versus other intervention or no intervention – CBA

Study	Targeted Behaviour	Absolute change	Relative change	Note
Wensing 2004	Reducing antibiotic prescribing	Absolute change (post): 1.7% Difference in absolute change from baseline: -2.8%	Relative percent change (post): -37.8%	
Gonzales 2005	Reducing antibiotic prescribing to adults with bronchitis and children with pharyngitis	*Adult population* Absolute change (post): -8% Difference in absolute change from baseline: -5% *Paediatric population* Absolute change (post): -9% Difference in absolute change from baseline: -3%	Relative percent change (post): -18.2% Relative percent change (post): -23.1%	
Madridejos-Mora 2004	Reducing overall antibiotic prescription Increasing the use of recommended drugs. Reducing cost of prescriptions	Absolute change (post): -2.7 Difference in absolute change from baseline: -2	Relative percent change (post): -16.5%	
Gonzales 2004	Reducing antibiotic prescriptions for acute respiratory infections in the elderly	Absolute change (post): -1% Difference in absolute change from baseline: -5%	Relative percent change (post): -2.4%	
Belongia 2001	Reducing antibiotic prescribing to children	Absolute change (post): 2% Difference in	Relative percent change (post): 3.2%	

		absolute change from baseline: 3.4%

The single ITS study (Doyne 2004) also reported on overall antibiotic prescription following the intervention and found an 18% reduction (OR 0.82 95% CI 0.71, 0.95) in overall antibiotic prescription. This is a good quality study with a low risk of bias.

Table 3 Multifaceted intervention versus other intervention or no intervention – ITS

Study	Targeted Behaviour	Absolute change	Relative change	Note
Doyne 2004	Reducing antibiotic prescribing to children	Absolute change (post): NA Difference in absolute change from baseline: NA	Relative percent change (post): NA	

Primary outcome: Use of recommended antibiotics

Five randomised trials reported on the overall prescription of recommended antibiotics in their study population following the intervention while three studies reported on inappropriate prescription of antibiotics. One study (Lagerlov 2000) reported a statistically significant increase in the use of recommended antibiotics following a multifaceted intervention; three studies (Coenen 2004; Briel 2006; Sondegaard 2003) found a non-significant increase, and one study (Samore 2005) found a statistically significant reduction in the use of recommended antibiotics. Of the studies reporting on the inappropriate use of antibiotics (Awad 2006; Seager 2006; Lagerlov 2000), all three found a statistically significant reduction following the intervention.

Lagerlov et al found a significant increase in the use of antibiotics for the duration recommended by guidelines. Coenen et al found a non-significant 13.7% increase (OR=1.90 95% CI 0.96, 3.75) in the use of recommended antibiotics following the intervention, Briel et al found a 3% increase (95% CI 0.30, 3.09) and Sondegaard et al found a 2% increase (95% CI -1, 5) both were also statistically non-significant. Samore et al found a statistically significant decrease of 4.5 prescriptions per 100 person years in the use of recommended antibiotics following the intervention.

Awad et al, Saeger et al, and Lagerlov et al, all found a significant reduction in inappropriate prescribing following the intervention. Awad et al found a reduction of -5.9 (95% CI -4.1, -7.7, P=<0.001) for second intervention group and -5.1 (95% CI -3.3, -6.9) for the third intervention group; Saeger found a 67% reduction (OR 0.33 95% CI 0.21, 0.54); and Lagerlov et al found a relative change of 9.6% (P = 0.0004)

Two CBA studies reported on the use of recommended antibiotics and also found a reduction following the intervention. Wensing et al found a non-significant 1% (OR = 0.99 95% CI 0.89, 1.11) reduction in the use of recommended antibiotics and Madridejos-Mora et al reported a significant reduction of 1.1 defined daily dose per day (P=0.035).

Comparison 2: Delayed Antibiotic Interventions

Nine studies utilised a wait and see approach to antibiotic prescription (delayed antibiotic prescription). The delayed prescribing intervention was used either alone or in combination with patient information leaflets (passive patient education). Six studies utilised a combination of delayed prescribing and passive patient education while the remaining three studies employed delayed prescribing alone. The delayed prescribing strategy used by these studies include advising the patient to collect a pre-filled script from the practice reception a few days after the consultation or issuing a script on the day that can be filled if symptoms do not improve in a few days. The length of time that participants had to wait before filling the prescriptions varied from 48 to 72 hours.

The studies were all randomised controlled trials conducted in ambulatory settings and targeting patients, parents, and carers. Five studies were conducted in the UK (two included passive patient education), two in USA (both included passive patient education), and one each in New Zealand and Israel (passive education). The quality of the delayed prescribing studies was good with almost all the trials judged as having a low risk of selection and performance bias. Trial completeness was variable across the trials and there is some risk of attrition bias in some trials particularly as only 40% of included trials analysed the data on an intention to treat basis. This is particularly true for Little et al (2005) where more than 10% of the study group had to be excluded from the analysis.

All nine trials reported on overall use of antibiotics following the intervention (table 4) and one trial reported on the proportion of patients experiencing adverse outcomes following the use of delayed prescribing. Eight trials (Little 2001, McFarlane 2002, Arroll 2002, Pshetizky 2003, Little 2005, Spiro 2006, McCormick 2005 and Everitt 2006) reported statistically significant reductions in the use of prescribed antibiotics in the delayed antibiotic arm compared to the immediate antibiotic arm. The relative risk for total reduction in antibiotic prescription was as follows: Arroll = 0.12 (95% CI 0.05, 0.29), Everitt = 0.54 (95% CI 0.45, 0.64), Little (2001) = 0.05 (95% CI 0.02, 0.08), Little (2005) = 0.01 (95% CI 0.00, 0.02), MacFarlane = 0.76 (95% CI = 0.59, 0.97), Pshetizky = 0.11 (95% CI 0.03, 0.33), Spiro = 0.43 (95% CI 0.34, 0.54), McCormick = 73% reduction. Dowell and colleagues found no difference in antibiotic prescription between intervention and control groups (relative reduction 55%, P = 0.45).

Table 4 Delayed prescribing intervention versus other intervention or no intervention – RCTs/CRCTs

Study	Targeted Behaviour	Absolute change	Relative change	Note
Little 2001	Reducing antibiotic use for acute otitis media in children	Absolute change (post): -74.5% Difference in absolute change from baseline: NA	Relative percent change (post): -75.6%	
Little 2005	Reducing antibiotic use	Absolute change (post): -76% Difference in absolute change from baseline: NA	Relative percent change (post): -79%	Passive education provided
MacFarlane 2002	Reducing antibiotic use for acute bronchitis	Absolute change (post): -15% Difference in absolute change from baseline: NA	Relative percent change (post): -24.2%	Passive education provided
Arroll 2002	Reducing antibiotic use for the common cold	Absolute change (post): -41% Difference in absolute change from baseline: NA	Relative percent change (post): -46%	
Pshetizky 2003	Reducing antibiotic use for acute otitis media in children	Absolute change (post): -26% Difference in absolute change from baseline: NA	Relative percent change (post): -41%	Passive education provided
Spiro 2006	Reducing antibiotic use for acute otitis media in children	Absolute change (post): -49%	Relative percent change (post): -56%	Passive education provided

		Difference in absolute change from baseline: NA		
McCormick 2005	Reducing antibiotic use for acute otitis media in children	Absolute change (post): -66% Difference in absolute change from baseline: -NA	Relative percent change (post): -66%	Passive education provided
Everitt 2006	Reducing antibiotic use for acute infective conjunctivitis in adults and children	Absolute change (post): -49% Difference in absolute change from baseline: NA	Relative percent change (post): -56%	Passive education provided
Dowell 2001	Reducing antibiotic use for uncomplicated respiratory tract infections	Absolute change (post): -55% Difference in absolute change from baseline: NA	Relative percent change (post): -55%	

Comparison 3: use of ancillary Testing

The five studies in this intervention category targeted health professionals only and used one or more ancillary test plus usual clinical assessment of patients. Two studies (Diederichsen 2000; Takemura 2005) used a C-reactive protein test (± WBC test) plus clinical assessment, one study (Poehling 2005) used a point of care rapid influenza test plus clinical assessment, another study (Spiro 2004) used tympanometry reports and clinical assessment while the fifth study (Worrall 2007) used a rapid antigen detection test and a clinical scoring tool. Two trials were conducted in USA and one each in Denmark, Japan, and Canada. All five trials reported on prescription/use of antibiotics following the intervention while one trial also reported on the proportion of patients experiencing adverse outcomes following the use of the intervention.

The trials in this category had variable quality scores. Overall, the trials either described treatment allocation poorly or undertook it in a way that could potentially introduce selection bias. The trials were better at blinding thus reducing the risk of performance bias and they were also better at reducing attrition bias as all five trials kept the proportion of participants lost to follow below 10%.

Two studies (Takemura 2005; Worrall 2007) found a statistically significant reduction in antibiotic prescription following the intervention while the remaining studies found non-significant reductions in prescriptions. This is interesting as these two studies scored lowest on quality assessment due to issues with the conduct and reporting of key quality parameters that may have introduced selection, performance and to some extent attrition biases. The likelihood of antibiotic prescription following the intervention in the included studies was as follows: Takemura = 0.24 (95% CI 0.15, 0.38); Worral = NA (Chi square = 16.7, P = <0.001); Diederichsen = 0.9 (95% CI 0.7, 1.2); Poehling = 0.89 (95% CI 0.44, 1.79); Spiro = 0.97 (95% CI 0.69, 1.36). Diederichsen and colleagues also found a non-significant 60% increase (95% CI 1.0, 2.6) in the occurrence of adverse events in the intervention group compared to controls.

Table 5 Ancillary test versus other intervention or no intervention – RCT

Study	Targeted Behaviour	Absolute change	Relative change	Note
Diederichsen 2000	Reducing antibiotic prescribing for respiratory tract infections	Absolute change (post): -3% Difference in absolute change from baseline: NA	Relative percent change (post): -6.5%	
Poehling 2005	Reducing antibiotic prescribing to children with respiratory illness	Absolute change (post): 3% Difference in absolute change from baseline: NA	Relative percent change (post): 10%	
Spiro 2004	Reducing antibiotic prescribing to children with acute otitis media	Absolute change (post): 2% Difference in absolute change from baseline: NA	Relative percent change (post): 7.5%	
Takemura 2005	Reducing antibiotic prescribing in patients with acute respiratory infections	Absolute change (post): -41% Difference in absolute change from baseline: NA	Relative percent change (post): -52%	
Worrall 2007	Reducing antibiotic prescribing for sore throat	Absolute change (post): -20% Difference in absolute change from baseline: NA	Relative percent change (post): -34.4%	

Comparison 4: Single Interventions - RCTs

The nine trials in this category utilised a variety of single component interventions to influence antibiotic prescribing in ambulatory settings. These single component interventions include educational campaigns, computerised decision support tools, academic detailing, continuing medical education, parental education, guideline development through consensus process, and computerised clinical reminders/prompts.

Provider education interventions were used in five trials, clinical decision tools in three trials, and the remaining trial utilised parental education. All trials targeted health care professionals and/or patients in ambulatory settings operating within different healthcare systems. Two trials were conducted in USA (one provider and

patient, one patient (parent) only), two trials in The Netherlands (providers only), one each in Israel (providers only), Australia (providers), Iran (providers), Canada (providers), and Finland (providers).

Seven of these trials reported on prescription/use of antibiotics following the intervention, four trials reported on the use of recommended antibiotics and two trials reported on inappropriate use of antibiotics.

Four of the five studies that utilised an educational intervention targeted at providers reported on prescription/use of antibiotics following the intervention by health care professionals with the remaining study reporting on the use of recommended antibiotics.

Overall, the quality of the trials in this category was variable and mainly low. These trials scored low on quality parameters assessing adequacy of treatment allocation, use of blinding, and completeness of follow up and appropriateness of analyses. The extent of poor reporting and/or conduct of these quality processes raise the possibility of a high risk of bias in most of these single intervention trials.

The four trials investigating provider education showed mixed results. One trial found a statistically significant reduction in antibiotic prescription in the intervention group compared with controls, two trials found non-significant reductions, and one found a non-significant increase. The magnitude of the total reduction in antibiotic prescription was as follows: Chazan = -1.2 DDD per day (95% CI 1.02, 1.07), Mohagheghhi = -4.1%, Sondergaard = -0.6 per 1000 patients (-2.8, 1.6), Illett = 1.03 (95% CI 0.95, 1.08). One trial (Ilett 2000) reported on the use of recommended antibiotics by practitioners and found a statistically significant reduction (P= 0.0001) in the use of recommended antibiotics in the intervention group compared with control.

These four trials were all of poor quality as they scored low or failed to report on a number of quality parameters to such an extent that it raises the potential of performance and attrition biases and selection bias.
Varonen and colleagues found an 83% (95% CI 0.98, 3.43) non-significant increase in the use of recommended antibiotics. This trial was of medium quality but poor reporting or conduct of treatment allocation and blinding could potentially introduce selection and performance biases.

The three studies utilising clinical scoring or decision support tools reported mixed results on the impact of this intervention on antibiotic prescription. One of these studies (McIssac 2002) found a non-significant 43% (0.57, 95% CI 0.27, 1.17) decrease in total antibiotic prescription and also a non-significant 24% (0.76, 95% CI 0.42, 1.40) reduction in inappropriate antibiotic prescription. McIssac et al was of medium quality with some potential for selection bias due to poor treatment allocation and differences in baseline characteristics of the groups.

Trials reporting on the use of recommended antibiotics found mixed results, Davis et al found a non-significant 15% (95%CI -1, 32) increase in use of recommended antibiotic (all conditions) and a statistically significant 15% (95% CI 2, 30) increase in patient with a diagnosis of otitis media. Martens and colleagues found a reduction in

the use of recommended antibiotics following the intervention. Both trials were good quality studies with the only methodological concern identified is the potential for performance bias arising from inadequate blinding of participants and assessors in both trials.

Taylor et al investigated the impact of parental education and found a non-significant reduction (P = 0.23) in total antibiotic prescription in the intervention group compared to control. Sub-group analysis of patients with otitis media also found similar results. This trial was judged to be of good quality with the main quality issue identified being the poor reporting of the use of blinding by the authors.

Single Interventions – CBA

The four studies in this category all targeted health professionals and/or patients in ambulatory settings within different healthcare systems using a variety of educational interventions. All the studies were conducted in the USA, three targeted providers and patients (Hennessy 2002; Perz 2002; Harris 2003) and the remaining study targeted providers only (Juzych 2005). The studies all reported on the number (or proportion) of consultation episodes resulting in an antibiotic prescription.
The magnitude of total reduction in antibiotic prescription was as follows: Perz = -11% (95% CI -14, -8, P=<0.001); Harris = -3% (p=<0.01); Juzych = -5.5% (p=<0.001); and Hennessey = -0.15 (NS).

These studies with the exception of Juzych et al were all judged to be of low quality with the main issues identified being the potential for selection and attrition bias in these studies.

Single Intervention - ITS

The single study (Marshall 2006) in this category targeted health care providers by imposing financial restrictions on reimbursements for use of certain classes of antibiotics. The study was conducted in Canada and reported on total antibiotic prescription.

This study like the other ITS study in this review was judged to be of good quality with a low risk of bias. The study found that compared to control, the intervention group had a non-significant 5.5% increase in antibiotic prescription.

4 DISCUSSION

4.1 Effectiveness review

As with the previous Cochrane review that addressed this question (Arnold & Straus 2005), the heterogeneous nature of the targeted behaviour, interventions explored, and differences in study settings (particularly health care systems) makes it hard to distil the results for individual studies into a single estimate of effect size or a single recommendation that will be broadly applicable to all possible scenarios. It is thus more appropriate to provide a narrative summary of the key findings in these included studies along with a statement on the implications for clinical practice and future research.

The multifaceted interventions employed a combination of provider and patient education plus one or more additional interventions such as reminders, academic detailing and audit and feedback. These interventions produced moderate to small changes in prescribing behaviour with the largest changes reported by studies of varying quality (low to medium) undertaken in three different countries (Azad Chowdury 2007; Welschen 2004; Seager 2006) while the smallest changes was found by the high quality Norwegian study (Flottorp 2002).

Similar to findings from previous reviews (Arnold & Straus 2005; Steinman 2006), this review also found that multifaceted interventions appear to be effective in changing prescribing behaviour but as with previous reviews, we are unable to disentangle the contribution of the individual components to the observed benefit nor recommend the best combinations of interventions to employ as any observed benefit in practice is likely to depend on the clinical setting and target population.

The last Cochrane review reported that when interventions are aimed at increasing the prescribing of first-line (usually narrow spectrum) antibiotics for specific infections, the effect on prescribing behaviour may be more substantial than when the interventions are focused on changing the inappropriate use of antibiotics (Arnold & Straus 2005). Four of the seven studies in our review that reported on changes in the use of recommended antibiotics demonstrated small to moderate improvements while three studies found reductions in the use of these recommended antibiotics following the intervention. Although these equivocal results may be explained by the varying quality and methodology of the studies, it is more plausible that they reflect the non-specific application of the interventions in these studies and the possibility that most of these studies were underpowered to measure this outcome. The only study (Lagerlov 2000) that demonstrated a statistically significant improvement in the use of recommended antibiotics was designed to measure this single outcome. Nonetheless, the role of multifaceted interventions in improving the use of recommended antibiotics is likely to be beneficial but this needs to be investigated further.

Nine studies investigated the use of a delayed antibiotic strategy to change the prescribing approach and use of antibiotics in the management of common, self-limiting community acquired infections. The rationale for such an intervention is that given the benign and self-limiting course of these infections, delaying treatment for a couple of days will allow for the natural resolution of the illness. Eight of the nine studies in this group found that when patients (or parents) were advised to delay collecting or filling a prescription, they were less likely to use antibiotics compared to

those offered an immediate prescription (Arroll 2002; Everitt 2006; Little 2001; Little 2005; McCormick 2005; MacFarlane 2002; Pshetizky 2003; Spiro 2006). The study by Dowell and colleagues (Dowell 2001) demonstrated a reduction in antibiotic use following the intervention but this was not statistically significant. Where these studies assessed the occurrence of adverse events arising from the delayed use or non-use of antibiotics, no significant difference in morbidity was demonstrated. It is important to note that the impressive effect estimates reported in these studies may be partly due to the nature of the control group, where almost all control participants used the prescribed antibiotics. Nonetheless, the findings are consistent with that of previous reviews (Spurling 2007; Arroll 2003; Lu 2008) where the authors concluded that the use of the delayed antibiotic strategy reduced the use of antibiotics without any significant increase in patient morbidity. This prescribing approach has now been recommended by the National Institute of Health and Clinical Excellence (NICE 2008) for managing common respiratory tract infections in children and adults. This patient focused intervention is believed to improve the understanding and acceptance by patients of the limited role of antibiotics in treating these self-limiting infections.

The use of provider focused interventions like ancillary testing was investigated by five studies, all of which demonstrated a downward trend in antibiotic prescribing although this was statistically significant in two studies only (Takemura 2005; Worrall 2007). These interventions which are usually laboratory based or nearside tests to detect changes in physiological parameters and/or presence of bacterial/viral antigens and antibodies are intended to improve the diagnostic certainty and confidence of clinicians during the clinical consultation. The expectation is that with increased diagnostic certainty, clinicians may be less likely to prescribe antibiotics and more confident in explaining the reasons to patients. Though this approach may be practical in North America and other regions where nearside test kits are widely used, in the UK, this intervention is unlikely to be practical or timely in a general practice setting where on-site laboratory facilities are unavailable and nearside test kits are not widely used.

Single interventions were investigated by fourteen of the included studies. Interventions employed by these studies include the use of printed educational materials, provider education, reminders, audit and feedback and academic detailing. The findings from these studies were very mixed leading to a largely equivocal picture of the effects of single interventions in changing prescribing behaviour.

The studies that investigated the benefits of passive provider education through the use of educational meetings, seminars and lectures demonstrated a limited benefit following this intervention. This is consistent with findings from previous reviews (Arnold 2005; Farmer 2008).

A similar picture was demonstrated by the studies utilising passive education of providers or patients through the use of educational materials in various formats. This small and frequently equivocal benefit of these passive education interventions probably reflects the inability of these interventions to provide the target population with the tools to change a behaviour that is longstanding, multifactorial and complex.

The use of financial restrictions and penalties did not result in a reduction in total antibiotic prescribing and expenditure as the observed reduction in prescribing the restricted antibiotics was offset by an increase in the use of other antibiotics (Marshall 2006).

Reminders to clinicians using computerised decision tools, pop up screens, tick boxes, stickers, etc are intended to provide timely and useful prompts to prescribers. A mixed picture was also demonstrated particularly in ambulatory settings where regular use is required to impact on prescribing rates (McIssac 2002). Three multifaceted studies (Awad 2006; Zad-Chowdury 2007; Mainous 2000) investigated the benefit of audit and prescribing feedback compared to no intervention in separate study arms. They all demonstrated small but similar reductions in antibiotic prescribing following the intervention and this benefit was more sizeable when audit and feedback was combined with other interventions. This is consistent with findings from a Cochrane review where it was suggested that the relative effectiveness of audit and feedback is likely to be greater when baseline adherence to recommended practice is low and when feedback is delivered more intensively (Jamtvedt 2006).

These single interventions are low cost and may result in some cost savings to insurers, but they do not appear to address the root causes of inappropriate prescribing and thus are unlikely to lead to large sustainable changes in prescribing and antibiotic resistance in the community (Arnold 2005; Forsetlund 2009, Lu 2008).

A handful of studies addressed outcomes like changes in antibiotic resistance rates following changes in prescribing patterns (Belongia 2001; Hennessy 2002; McCormick 2005; Perz 2002). These studies were unsuccessful in demonstrating any significant or sustained reduction in the occurrence of antibiotic resistant strains of pathogens over the study period. This is in part due to the limited duration of follow up as changes in resistance patterns may require several years of sustained reductions in inappropriate antibiotic use. It is also likely that the studies employed the wrong methodologically given that none of these studies used an ITS design which is considered a more efficient method for investigating this question.

The suggestion that a sustained reduction in antibiotic prescribing is a necessary precursor to any reduction in resistance patterns harkens to the problem of selection pressure and the possible role that these interventions may play in reducing selection pressure. The extent to which these interventions and the associated changes in prescribing behaviour can be maintained over time (i.e. beyond the active study period) was not addressed by most of the included studies. However, two studies that reported on the longevity of the interventions demonstrated a sustained effect from the intervention (Hennessy 2002, Altiner 2007). This is encouraging but the evidence is limited and incomplete.

5 CONCLUSIONS

5.1 Implications for practice

The effectiveness of interventions (singly or in combination) to improve the prescribing of antimicrobial agents in ambulatory settings varies depending on the

type and setting for the intervention, and the targeted behaviour and disease condition.
It is important to have a clear understanding of the multiple factors that influence prescribing behaviour and some insight into other relevant factors in operation in the health economy before implementing any intervention to improve the quality of prescribing.

Simple interventions may be beneficial and probably cost effective in certain settings and context but they do not lead to large, sustained changes in prescribing behaviour and in some instances may be ineffective or possibly detrimental.

The use of ancillary test to aid clinical decision making is also context specific and in the UK setting is unlikely to be of any practical benefit due to organisational constraints inherent in the UK health care system. They may still be useful as part of a suite of interventions targeted at prescribing for specific infections or in specific populations.

Delayed antibiotic prescribing strategies show some benefit in reducing the use of antibiotics used in managing certain common, self-limiting infections in the community. These include common respiratory tract infections like acute otitis media, acute tonsillitis, sore throat, acute pharyngitis, and acute cough. Increasing the barriers that patients need to navigate to get the prescription (i.e. picking up script days after the consultation) may improve the effectiveness of this intervention. In the UK, this intervention has been recommended by NICE and is considered to be safe and acceptable to patients.

Complex multifaceted interventions combining patient and provider education plus one or more interventions appear to be effective in changing prescribing behaviour in a variety of settings and health care systems. The ideal combination of interventions is uncertain as is the key component of these multifaceted interventions. The extent to which this and other interventions are durable and sustainable is also unknown as is their cost effectiveness.

5.2 Implications for research

The most recent Cochrane review (Arnold & Straus 2005) that addressed this question highlighted the need to investigate the benefits of multifaceted interventions and determine the cost effectiveness of this and other interventions. Since then, there have been a number of studies investigating the effectiveness of multifaceted interventions but few have provided any estimates of cost effectiveness and even fewer studies have attempted to determine the key components that provide the greatest benefit.

Good quality cost effectiveness studies are needed as existing estimates of cost effectiveness are mainly derived as secondary outcome measures by studies that are usually underpowered to provide accurate and reliable estimates.

New studies should be designed to determine the long term effect and durability of these interventions. Ideally, these studies should utilise an interrupted time series approach as this is the most statistically efficient method for addressing this question.

6 APPENDICES

Appendix 1

Protocol

Interventions to improve antimicrobial prescribing in primary care (an update)

Protocol information

Authors

Obaghe Edeghere1, Chris Hyde1, Jayne Wilson1, Babatunde Olowokure1, Jeremy Hawker1

1[Empty affiliation]

Citation example: Edeghere O, Hyde C, Wilson J, Olowokure B, Hawker J. Interventions to improve antimicrobial prescribing in primary care (an update) [Protocol]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Contact person

Obaghe Edeghere

Dates

Assessed as Up-to-date: 16 April 2008

Date of Search:

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Protocol First Published: Not specified

Review First Published: Not specified

Last Citation Issue: Not specified

What's new

Date / Event Description

History

Date / Event Description

Abstract

Background

Objectives

Search strategy

Selection criteria

Data collection and analysis

Results

Authors' conclusions

Plain language summary

[Plain language title]

[Summary text]

Background

The inappropriate use of antimicrobial agents is an important factor in the development and spread of antibiotic resistant micro-organisms and resistance to other antimicrobial drugs (Gosens 2005). Antimicrobial resistance can result in inefficient treatment of infections in patients and can lead to prolonged illness, disability, death and increased cost to the National Health Service (NHS).

The spread of antimicrobial resistance has been driven by the widespread use of antibiotics, either appropriately or inappropriately, and is costly in both human and financial terms. Furthermore, countries with higher community antibiotic prescribing have been shown to have higher antibiotic resistance rates in several pathogens (Goosens 2005). The 'SMAC' guidelines published by the DH in 1998 (SMAC 1998) made recommendations to limit inappropriate prescribing as a means of reducing the emergence of antimicrobial resistance and since then a range of guidance, national advisory bodies (including the HPA) and expert committees have emphasised reducing unnecessary prescribing in general practice. Action has included professional education about prudent prescribing and campaigns to educate the public that (e.g.) most respiratory tract infections (RTIs) do not need an antibiotic prescription (DH 1999). However, although some changes in behaviour have occurred, translating these recommendations into clinical practice has only had limited success so far (SMAC 1998).

It is therefore seen as a national and international priority to improve antibiotic usage, including promoting appropriate antimicrobial prescribing in primary care (primarily by GPs in the UK). Many bodies, including the Department of Health and the HPA have issued guidelines to help GPs reduce inappropriate prescribing. However, although some positive changes in GP prescribing behaviour have happened, a full scale adoption of appropriate prescribing has not occurred.

There are many reasons why the recommendations of expert groups may prove to be difficult to achieve in practice. These may include acceptance by the GP or patient that, for example the treatment (or giving no treatment) is safe, or practical considerations that inhibit wider adoption (eg GP concern that the patient will return, thus using another appointment). There have been many studies that have assessed the success or otherwise of various measures to attempt to influence what GPs actually prescribe in practice. These have studied different interventions and target groups and have varying results. They are also of varying quality, e.g. they have used varying study designs and analytical methods and this influences the strength of inference that can be drawn from their reported results. We propose to undertake a systematic review of the evidence in this field to identify and collect all potentially relevant studies, assess the quality of the study and then integrate the combined findings into evidence based recommendations on how to change GP prescribing in practice.

Why it is important to do this review

A systematic review in this field has previously been undertaken by the Cochrane collaboration (Arnold 2005). However, the information used in this review is now relatively old (the latest date used in the literature search is 2000), was not particularly focused on the United Kingdom (UK) situation (for example, our model of medical provision differs from many countries) and many gaps were identified in the evidence base. There is a review from a UK author, which did not use systematic review methodology and offers some contradictory conclusions to the Cochrane review, but again the latest evidence quoted was published in 2000 (McNulty 2001).

The Aggressive Research Intelligence Facility (ARIF) at the University of BIrmingham recently completed a report describing studies that have attempted to answer the question, which interventions improve antibiotic prescribing in primary care and ambulatory settings (ARIF 2008). The report identifies six reviews (including the cochrane review) that all focused on different aspects of interventions, populations, comparators and outcomes. The disparate nature of the reviews means that no clear, unequivocal recommendations can be made on effective interventions that can be used in primary care settings. The ARIF report concludes that given the inherent difficulties of undertaking systematic reviews of complex and varied interventions, future reviews should focus on areas that appear more promising and concentrate on newer, better designed studies while still retaining the format of previous reviews so as to ensure continuity of the reasearch base (ARIF 2008).

Objectives

This systematic review will estimate the effectiveness and cost of interventions (given alone or in combination) in improving antimicrobial prescribing by professionals with prescribing privileges in primary care and community settings.

The review will measure whether interventions to improve antimicrobial prescribing by healthcare providers in primary care and community settings can:

- Increase the rate of appropriate antimicrobial prescrbing. This includes, depending on the specific clinical condition, the decision tp prescribe an antimicrobial agent or not, the rate of prescribing a recommended choice, dose or duration of use of antimicrobials.
- Reduce the incidence of antimicrobial resistance in laboratory isolates derived from primary care and other community healthcare settings.
- Reduce the rate of adverse events arising from the decison to prescribe or not prescribe an antimicrobial agent.

Methods

Criteria for considering studies for this review

Types of studies

Note that although the Cochrane Effective Practice and Organisation of Care Group (EPOC) methodology has been empolyed in formulating this protocol, this is not a Cochrane review.

All patient and cluster Randomised Controlled Trials (P-RCT & C-RCT) and quasi-randomised controlled trials.We will also collect data on any relevant non-randomised controlled trails using a parallel group design. Controlled before and after studies (CBA) and interrupted time series studies (ITS) will be included with a

clear time point for the intervention and at least three (3) data points before and after the intervention.

Studies examining the prescribing of multiple drug classes will also be included provided specific and detailed prescribing data can be extracted.

Types of participants

Healthcare consumers, health professionals of all ages and level of experience (this may include physicians, nurses, pharmacist and other professionals) able to prescribe antimicrobials in primary care and community settings.

A primary care setting is consisdered one in which the patient is first seen and recieves first level care for the clinical problem of interest.

A community healthcare setting is considered one in which ambulatory care is provided without the need for admission to hospital (including the emergency department) at the time of clinical assessment. This will include all outpatient clinics, walk-in-clinics and out-of-hours clinics (government run or private).

Types of interventions

The review will include any intervention which aims to improve the quality of prescribing of antimicrobials by health professionals. Interventions must be focussed on changing professional behaviour and ultimately patient and process outcomes. Patient based interventions will be included if there is a clear program element that is aimed at changing professional behaviour.

Professional interventions to be included in this review are defined in the Effective Practice and Organisation of Care Group (EPOC) scope and are divided into categories which, are not considered to be mutually exclusive:

1. Distribution of educational materials: distribution of publishedor printed recommendations for clinical care, including clinical practice guidelines, audio-visual materials and electronic publications.The materials may have been delivered personally or through mass mailings.

2. Educational meetings: healthcare providers participating in conferences, lectures, workshops or traineeships.

3. Local consensus processes: inclusion of participating providers in discussion to ensure that they agree that the chosen clinical problem is important and the approach to managing the problem is appropriate.

4. Educational outreach visits: use of a trained person who meets with providers in their practice settings to give information with the intent of changing the providers' practices. The information given may have included feedback on the performance of the provider(s).

5. Local opinion leaders: use of providers nominated by their colleagues as 'educationally influential'. The investigators must have explicitly stated that their colleagues identied the opinion leaders.

6. Patient-mediated interventions: new clinical information (not previously available) collected directly from patients and given to the provider.

7. Audit and feedback: any summary of clinical performance of health care over a specied period of time. The summary may also have included recommendations

for clinical action. The information may have been obtained from medical records, computerised databases or observations from patients.

8. Reminders: patient or encounter-specific information provided verbally, on paper or on a computer screen, which is designed or intended to prompt a health professional to recall information.This would usually be encountered through their general education,in the medical records or through interactions with peers and so remind them to perform or avoid some action to aid individual patient care. Computer-aided decision support and drug dosage are included.

9. Marketing: use of personal interviewing, group discussion (focus groups) or a survey of targeted providers to identify barriers to change and subsequently lead to the design of an intervention that addresses identied barriers.

10. Mass media: (i) varied use of communication that reaches great numbers of people, including television, radio, newspapers, posters, leaets, and booklets, alone or in conjunction with other interventions; (ii) targeted at the population level.

11. Financial interventions: methods of physician remuneration, patient-oriented approaches such as user fees and formularies.

12. Miscellaneous: This category comprises of interventions such as the use of delayed antibiotic prescribing startegies and the use of pharmacist led interventions. We believe these interventions cannot be easily assigned to any of the existing categories in the EPOC framework.

Types of outcome measures

Primary outcomes

1. Rate of appropriate antimicrobial prescribing. This includes, depending on the specific condition, the decision to prescribe an antimicrobial , or not; or the rate of prescribing a recommended chioce, dose or duration of use of antibiotic.

Secondary outcomes

1. The incidence of colonisation with, or infection due to, antibiotic-resistant organisms

2. The incidence of adverse events associated with the use of antimicrobials

3. The incidence of adverse events associated with the reduced use or duration of treatment with antimicrobials or use of narrow-spectrum antimicrobial agents.

Search methods for identification of studies

See: Cochrane Effective Practice and Organsiation of Care (EPOC) Group methods used in reviews.

Electronic searches

The following electronic databases will be searched.

1. The Cochrane EPOC specialised register (and the database of studies awaiting assessment)

2. The Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effectiveness (DARE). (The Cochrane Library - current issue)

3. MEDLINE (2000-Date), EMBASE (2000-Date) and CINAHL (2000-Date). Note: see additional Table 01, 02, and 03 for MEDLINE, EMBASE, and CINAHL search terms.

4. Electronic seraches of specific internet sites that relate to Health Protection, Communicable Disease Control, Microbiology, Primary Care, Medicines Management and Translational research.

Searching other resources

The full reference list of all eligible papers will be handsearched to identify any additional papers. Reference lists of antimicrobial guidelines (National and Professional) and other relevant systematic review articles will be searched. Science Citation Index (SCI) will be used to forward search citations of key papers.

We will also contact, where possible, primary authors of eligible papers, national and international experts in the area, to enquire whether they are aware of other studies (including current and unpublished) in this area. There will be no language restrictions in our searches.

The search strategy for electronic databases and internet sites will be developed with the support of the West Midlands Health Technology Assessment Collaboration (WMHTAC) specialist team. The search strategy will combine the EPOC search strategy with MESH and free text term relating to interventions to improve antimicrobial prescribing or reducing the incidence of antimicrobial resistant infections.

Data collection and analysis

Selection of studies

Full text of all potentially eligible papers found after screening title and abstract (including papers which were in doubt after screening the title and abstract) will be assessed by two review authors (Obaghe Edeghere (OE)) and (Jayne Wilson (JW)) independently for inclusion using pre-determined criteria. Disagreements will be resolved by discussion between review authors, and involvement of a third reviewer (Chris Hyde (CH)) if a consensus agreement cannot be reached. If there is a dispute about eligibility, the paper will be taken to the whole review group for discusssion and a majority agreement.

Studies formally exculded at this stage will be noted, as will the reasons. One review author (OE) will also search reference lists of all included papers, and all identified review articles, for additional papers.

Data extraction and management

Once eligibility for the study has been determined, data wil be extracted onto pre-designed data forms independently by OE with JW assessing a random sample of the extracted data for accuracy. Disagreements will be resolved by discussion between review authors, and involvement of a third reviewer (Chris Hyde (CH)) if a consensus agreement cannot be reached.

Review authors will not be blinded as to the study authors or journal.

Assessment of risk of bias in included studies

Study quality and risk of bias assessment will be undertaken using the criteria outlined in the Cochrane Handbook of Systematic Reviews of Interventions - version 5.0 and as recommended in section 6.4 of the EPOC Data Collection Checklist.

Quality assessments will be performed by one review authors (OE). A random sample of the assesed studies will be checked by JW . Disagreements will be resolved by discussion between review authors, and involvement of a third reviewer (Chris Hyde (CH)) if a consensus agreement cannot be reached.

Each study will be assessed in terms of: selection bias (systematic difference between groups), performance bias (systematic difference in the care provided apart from the intervention being studied), attrition bias (systematic difference in withdrawals), detection bias (systematic difference in outcome assessment) and whether cluster design effect was accounted for in the analysis (cluster RCTs only). Studies will be rated as having low, moderate or high risk of bias, depending on the degree to which the bias have been minimised. Relevant information that will aid the quality assessment and not presented in the paper will be sought from the primary authors. A summary table showing the quality score of each study will be presented as part of the review.

Measures of treatment effect

The results of the individual studies will be reported in natural units takiing into account methodological quality and a priori subgroups. Metanalysis will be used to statistically combine study results where appropriate.

For RCTs and CCTs we will report (seperately for each study design):

1. Pre-intervention (baseline) and post-intervention means (median) or proportions for both study and control groups

2. Difference in absolute change from baseline along with 95% confidence interveals or P values, if available

3. Range of effect sizes across included studies

4. Relative risk or odds ratios (OR) with 95% confidence intervals will be calculated for dichotomous variables.

For CBA studies we will report (seperately for each study)

1. Pre-intervention (baseline) and post-intervention means (median) or proportions for both study and control groups

2. percentage change (i.e. the percent improvement relative to the post intervention average of the control group).

For ITS studies we will report (seperately for each study)

1. Number of data points pre and post and time interval between points

2. Pre and post intervention means

3. Absolute change in natural units

4. Percentage relative change (plus statistical significance)

Unit of analysis issues

Where identified, studies where the unit of allocation and analysis are different, for example, the unit of allocation is the general practice and the unit of analysis is the

indiviual GP, we will attempt to correct for this where possible by obtaining relevant missing information (estimates of intracluster correlation) from the authors. If sufficient data are present, we will recalculate results using the appropriate unit of analysis.

In cluster randomised controlled trials where the authors have not taken into account cluster design effect in the analysis, we will, if sufficient data is available, re-analyse the data by using a two sample t-test. Where the paper does not report sufficient data, we will undertake a sensitivity analysis by applying an intra-cluster correlation coefficient to test if the results are robust to different cluster scenarios.

To account for incorrect analysis of included ITS studies, we will reanalyse ITS comparisons. Time series regression will be used to reanalyse each comparison (where possible), the best fit pre-intervention and post-intervention lines will be estiimated using linear regression and autocorrelation, adjusted for using the Cochrane-Orcutt method where appropriate. First order autocorrelations will be tested statistically using the Durbin-Watson d statistic and higher order autocorrelations will be investigated using the autocorrelation and partial autocorrelation functions.

Dealing with missing data

In P-RCT and C-RCT papers where intention-to-treat analyses have not been performed by the original authors of the studies and sufficient data is available to do so, intention-to-treat analyses will be conducted before entry of data into the review software in order to limit attrition bias. If sufficient data is unavailable, a comparison of worst and best case scenarios will be attempted.

Assessment of heterogeneity

We anticipate some variation in the study findings due to various sources of heterogeneity such as differences in the type of intervention, intensity and duration of intervention, study design and methodological quality. Statistical heterogeneity across studies will be assessed using I2 statistics to describe the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins 2003). Trials in the meta-analysis will be considered to have low statistical heterogeneity if I2 is equal to or less than 25% and a fixed-effect model will be used. If I2 is greater than 25%, a random effects model will be used to incorporate heterogeneity amongst trials. Provided there is sufficient data available, we will explore and attempt to explain the source of the observed heterogeneity using meta-regression analysis (Thompson 2001).

If sufficient studies are not identified to allow for statistical analysis of heterogeneity, we will explore the heterogeneity visually by means of forest plots and box plots displaying medians, interquartile ranges (IQR) and ranges.

Data synthesis

If there is more than one study of a similar design with a specific intervention, we will perform a metanalysis using the Cochrane statistical software package Review Manager (RevMan 5). Where the same outcome measures are used (for example, rate of antibiotic prescribing), weighted mean difference (WMD) and 95% Confidence Intervals (CI) will be calculated for continious variables.Where outcome measures differ but still measure the same construct, the standardised mean difference (SMD) and 95% CI will be calculated.For dichotomous outcomes (for example, adverse

events), relative risks (RR) or odds ratios (OR) and 95% CI will be determined using a fixed effect model (where heterogeneity permits) or a random effects model. See assessment of heterogenity above.

If insufficient data are present to support the conduct of a metanalysis, we will report effect sizes and confidence intervals of the included studies using standard methods of presentation.

Subgroup analysis and investigation of heterogeneity

We plan to further assess heterogeneity by conducting a meta-regression using the following sub-group analysis.

- Type of intervention (category 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 & 12)
- Type of health professional (medical practitioner, nurses, pharmacist)
- Studies conducted in the UK health care setting/system (across all intervention categories)

If time and resources permit we will also investigate the influence of clinical credibilty of advice and variations in control group interventions on the measured effect sizes.

Sensitivity analysis

We will conduct a sensitivity analysis to assess robustness and consistency of the study results. We will conduct the sensitivity analyses based upon the study design (RCT vs. others) or risk of bias in the study (High, medium, low).

Results

Description of studies

Results of the search

Included studies

Excluded studies

Risk of bias in included studies

Allocation

Blinding

Incomplete outcome data

Selective reporting

Other potential sources of bias

Effects of interventions

Discussion

Summary of main results

Overall completeness and applicability of evidence

Quality of the evidence

Potential biases in the review process

Agreements and disagreements with other studies or reviews

Authors' conclusions

ARIF 2008

Wilson J. Interventions to improve prescribing practices of antibiotics in primary and ambulatory settings.. Aggressive Research Intelligence Facility, University of Birmingham. April 2008.

Arnold 2005

Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database of Systematic Reviews 2005, Issue 4.

DH 1999

Department of Health. Antibiotics: Don't wear me out. Department of Health 1999.

Goosens 2005

Goosens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. The Lancet 2005;365(9459):579-87.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

McNulty 2001

McNulty CA. Optimising antibiotic prescribing in primary care. International Hournal of Antimicrobial Agents 2001;18:329-33.

SMAC 1998

Standing Medical Advisory Committee. Sub-Group on antimicrobial resistance. The path of least resistance. Department of Health 1998.

Thompson 2001

Thompson SG. Why and how sources of heterogeneity should be investigated. In: Egger M, Davey Smith G, Altman DG, editor(s). Systematic Review in Health Care. Meta-analysis in context. Second edition. London: BMJ Publishing Group, 2001:157-75.

Other published versions of this review

Classification pending references

Data and analyses

Figures

Sources of support

Internal sources

- No sources of support provided

External sources

- No sources of support provided

Feedback

Appendices

Appendix 2

Search strategies

MEDLINE

Database: Ovid MEDLINE(R) 1950 to April Week 2 2008

1 antibiotic$.tw. (159999)
2 antimicrobial$.tw. (51990)
3 exp Anti-Infective Agents/ (986302)
4 1 or 2 or 3 (1049583)
5 (prescribe$ or prescribing or prescription$).tw. (73856)
6 Prescriptions, Drug/ (17433)
7 physicians practice patterns/ (25561)
8 5 or 6 or 7 (100496)
9 randomized controlled trial.pt. (254671)
10 controlled clinical trial.pt. (78053)
11 randomized.ab. (165274)
12 placebo.ab. (105589)
13 clinical trials as topic.sh. (138724)
14 randomly.ab. (120051)
15 trial.ti. (73511)
16 or/9-15 (591602)
17 humans.sh. (10343645)
18 16 and 17 (537939)
19 4 and 8 and 18 (1336)
20 limit 19 to yr="2000 - 2008" (795)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 18, 2008

1 antibiotic$.tw. (4919)
2 antimicrobial$.tw. (2517)
3 (prescribe$ or prescribing or prescription$).tw. (3964)
4 1 or 2 (6818)
5 3 and 4 (302)
6 limit 5 to yr="2000 - 2008" (279)

EMBASE

Database: EMBASE (Ovid) 1980 to 2008 Week 16

1 antibiotic$.tw. (126989)
2 antimicrobial$.tw. (48389)
3 exp Antiinfective Agent/ (1053606)
4 1 or 2 or 3 (1086366)
5 (prescribe$ or prescribing or prescription$).tw. (68987)
6 prescription/ (48797)
7 5 or 6 (91578)
8 4 and 7 (18221)
9 crossover procedure/ (20161)
10 double blind procedure/ (68905)
11 randomized controlled trial/ (156531)

12 single blind procedure/ (7481)
13 (random$ or factorial$ or crossover$ or cross over$).tw. (390863)
14 (placebo$ or assign$ or allocat$ or volunteer$).tw. (308536)
15 (doubl$ adj blind$).tw. (81645)
16 (singl$ adj blind$).tw. (7115)
17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (619971)
18 8 and 17 (1719)
19 limit 18 to yr="2000 - 2008" (1136)

CINAHL
CINAHL (EBSCOhost) 1977 – April 2008

S1 antibiotic? OR antimicrobial? (12767)
S2 DE “Prescriptions, Drug” (2132
S3 DE antibiotics (8971)
S4 prescribe? or prescription? (4785)
S5 S3 or S1 (12767)
S6 S4 or S2 (4785)
S7 S6 and S5 (345)
S8 S6 and S5 Limiters Publication year from: 2000 – 2008 (291)

Cochrane Library 2008 Issue 2 (all databases)
#1 antibiotic$54
#2 antimicrobial$7 #3 MeSH descriptor Anti-Infective Agents explode all trees38195 #4 (#1 OR #2 OR #3)38221 #5 (prescribe* or prescribing or prescription*)9375 #6 MeSH descriptor Prescriptions, Drug explode all trees536 #7 MeSH descriptor Physician's Practice Patterns explode all trees973 #8 (#5 OR #6 OR #7)10021 #9 (#4 AND #8)985 #10 (#9), from 2000 to 2008597

Appendix 3

Excluded studies

No	Study	Reason for exclusion
1	Zwar N, Henderson J, Britt H, McGeechan K, Yeo G. Influencing antibiotic prescribing by prescriber feedback and management guidelines: a 5-year follow-up. Family practice 2002; 19(1):12-17.	No data from original study
2	Touzet S, Refabert L, Letrilliart L, Ortolan B, Colin C. Impact of consensus development conference guidelines on primary care of bronchiolitis: are national guidelines being followed? Journal of Evaluation in Clinical Practice 2007; 13(4):651	No control population.
3	Sung L, Arroll J, Arroll B, Goodyear-Smith F, Kerse N, Norris P. Antibiotic use for upper respiratory tract infections before and after an education campaign as reported by general practitioners in New Zealand. New Zealand Medical Journal 2006; 119(1233).	Wrong study design
4	Smith GE, Smith S, Heatlie H, Bashford JNR, Hawker J, Ashcroft D et al. What has happened to antimicrobial usage in primary care in the United Kingdom since the SMAC report? Description of trends in antimicrobial usage using the General Practice Research Database. Journal of Public Health 2004; 26(4):359-364.	No control population
5	SmÃ¥brekke L, Berild D, GlÃ¦ver A, Myrbakk T, FuskevÃ¥g A, Ericson JU et al. Educational intervention for parents and healthcare providers leads to reduced antibiotic use in acute otitis media. Scandinavian journal of infectious diseases 2002; 34(9):657-659.	Wrong study setting
6	Siegel RM, Bien J, Lichtenstein P, Davis J, Khoury JC, Knight JE et al. A safety-net antibiotic prescription for otitis media: the effects of a PBRN study on patients and practitioners. Clinical Pediatrics 2006; 45(6):518-524.	Wrong study design
7	Rubin MA, Bateman K, Donnelly S, Stoddard GJ, Stevenson K, Gardner RM et al. Use of a personal digital assistant for managing antibiotic prescribing for outpatient respiratory tract infections in rural communities. Journal of the American Medical Informatics Association 2006; 13(6):627-634.	Wrong study design
8	Rosenberg P, McIsaac W, Macintosh D, Kroll M. Diagnosing streptococcal pharyngitis in the emergency department: Is a sore throat score approach better than rapid streptococcal antigen testing? CJEM Canadian Journal of Emergency Medical Care 2002; 4(3):178-184.	??
9	Raebel MA. Interventions to improve treatment of respiratory infections in ambulatory managed-care patients. Annals of Pharmacotherapy 2005; 39(4):699-705.	Wrong study design
10	Molstad S, Erntell M, Hanberger H, Melander E, Norman C,	No control

	Skoog G et al. Sustained reduction of antibiotic use and low bacterial resistance: 10-year follow-up of the Swedish Strama programme. The Lancet Infectious Diseases 2008; 8(2):125-132	population
11	Marchetti F, Ronfani L, Nibali SC, Tamburlini G. Delayed prescription may reduce the use of antibiotics for acute otitis media: a prospective observational study in primary care. Archives of pediatrics & adolescent medicine 20; 159(7):679	No control population
12	Gould IM, Mackenzie FM, Shepherd L. Use of the bacteriology laboratory to decrease general practitioners' antibiotic prescribing. The European journal of general practice 2007; 13(1):13	Wrong study design
14	Gilad J, Kopylov U, Admon G, Borer A, Schlaeffer F, Aviram EE. Auditing and benchmarking of azithromycin utilization in primary care military clinics. Military Medicine 2000; 172(10):1065	No control population
15	Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. Annals of Epidemiology 2000; 10(8):509-515	Wrong study design
16	Curry M, Sung L, Arroll B, Goodyear-Smith F, Kerse N, Norris P. Public views and use of antibiotics for the common cold before and after an education campaign in New Zealand. New Zealand Medical Journal May 2006 2006 ;(1233).	Wrong study design
17	Coley KC, Skledar SJ, Fine MJ, Yealy DM, Gleason PP, Ryan ML et al. Changing physician prescribing behavior: the community-acquired pneumonia intervention trial. American Journal of Health-System Pharmacy 2000; 57(16):1506-1510.	Wrong study setting and population
18	Bonner AB, Monroe KW, Talley LI, Klasner AE, Kimberlin DW. Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: Results of a randomized, prospective, controlled trial. Pediatrics 2003; 112(2 I): 363-367	Wrong study setting
19	Bjerrum L, Gahrn-Hansen B, Munck AP. C-reactive protein measurement in general practice may lead to lower antibiotic prescribing for sinusitis. British Journal of General Practice 2004; 54(506):659-662.	Wrong study design
20	Ashe D, Patrick PA, Stempel MM, Shi Q, Brand DA. Educational posters to reduce antibiotic use. Journal of Pediatric Health Care 2006; 20(3):192-197	Inadequate data points
21	Al-Khaldi YM, Al-Sharif AI, Al-Gelban KS, Al-Hamami QM, Al-Jaser AO. Impact of national protocol on management of acute respiratory infections in children. Saudi medical journal 2001; 22(9):780-783.	No control population
22	Lallana Alvarez MJ, Celaya Lecea MC, Za Pascual-Salcedo	Foreign

	M, Garjon PJ, Elfau MM, Labarta MC et al. Educational interview: Intervention to improve drug prescription in general practice. [Spanish]. Atencion Farmaceutica 2006; 8(5): 281-287.	language article
23	Weischen I, Kuyvenhoven M, Hoes A, Verheij T. Reduced antibiotic prescribing for respiratory tract symptoms after following a postgraduate program: A randomized, controlled study. [Dutch]. Huisarts en Wetenschap, 2005; 48(4):154-157.	Foreign language article
24	Bascelli LM, Losh DP. How does a "wait and see" approach to prescribing antibiotics for acute otitis media (AOM) compare with immediate antibiotic treatment? Journal of Family Practice 2001; 50(5):469.	
25	Bernstein SL, Whitaker D, Winograd J, Brennan JA. An electronic chart prompt to decrease proprietary antibiotic prescription to self-pay patients. Academic Emergency Medicine 20; 12(3):225-231.	No control population
26	Farquhar D. Reducing antibiotic use for acute bronchitis by giving patients written information. CMAJ Canadian Medical Association Journal 2002; 166(6):776.	No control population
27	Finkelstein JA, Davis RL, Dowell SF, Metlay JP, Soumerai SB, Rifas-Shiman SL et al. Reducing antibiotic use in children: a randomized trial in 12 practices. Pediatrics 2001; 108(1):1-7.	
28	Franz AR, Bauer K, Schalk A, Garland SM, Bowman ED, Rex K et al. Measurement of interleukin 8 in combination with C-reactive protein reduced unnecessary antibiotic therapy in newborn infants: a multicenter, randomized, controlled trial. Pediatrics 2004; 114(1):1-8.	Wrong study setting
29	Monette J, Miller MA, Monette M, Laurier C, Boivin JF, Sourial N et al. Effect of an educational intervention on optimizing antibiotic prescribing in long-term care facilities. Journal of the American Geriatrics Society 2007; 55(8):1231-1235.	Wrong study setting
30	Sheikh A. Delayed prescribing of antibiotics is an effective strategy in managing acute conjunctivitis. Journal of Pediatrics 2007; 150(1):114-115.	No control population
31	Siegel RM, Kiely M, Bien JP, Joseph EC, Davis JB, Mendel SG et al. Treatment of otitis media with observation and a safety-net antibiotic prescription. Pediatrics 20; 112(3):527-531.	
32	Solomon DH, Van HL, Glynn RJ, Baden L, Curtis K, Schrager H et al. Academic detailing to improve use of broad-spectrum antibiotics at an academic medical center. Archives of Internal Medicine 161(15) (pp 1897-1902), 2001 Date of Publication: 2001 2001; (15):1897-1902.	Wrong study setting
33	Straand J, Fetveit A, Rognstad S, Gjelstad S, Brekke M, Dalen I. A cluster-randomized educational intervention to reduce inappropriate prescription patterns for elderly patients in general practice - The Prescription Peer	

	Academic Detailing (Rx-PAD) study [NCT00281450]. BMC Health Services Research 6, 2006 Article Number: 72	
34	Van Hees BC, de RE, Wiltink EH, de Jongh BM, Tersmette M. Optimizing use of ciprofloxacin: a prospective intervention study. Journal of Antimicrobial Chemotherapy 2008; 61(1):210-213.	Wrong study population
35	Weber JT. Appropriate use of antimicrobial drugs: a better prescription is needed. JAMA: Journal of the American Medical Association 20; 294(18):2354-2356.	Wrong study population
36	Weissman J, Besser RE. Promoting appropriate antibiotic use for pediatric patients: a social ecological framework. Seminars in Pediatric Infectious Diseases 20; 15(1):41-51.	Wrong study design
37	Wilcock M, Hartley J, Gould D. Inappropriate use of oral terbinafine in family practice. Pharmacy World and Science 2003; 25(1):25-26.	Inadequate control

Appendix 4

Data extraction form

Data extraction – interventions to improve antimicrobial prescribing in ambulatory settings

Name of reviewer: Date:
Study reference ID:
Paper details

Paper title:	
First Author:	
Journal etc	
Publication year	
Authors contact address (if available)	
Full text article or only published as an abstract	
Does the trial meet all inclusion criteria	• Study design ☐ • The objective measurement of performance/provider behaviour or health/patient outcomes ☐ • Relevant and interpretable data presented or obtainable ☐
Number of trials included in this paper: (if more than one, complete separate extraction forms for each, and add letters A, B, C, etc to the paper name)	
Papers of other trials with which this may link: (if other papers report further results of this trial, incorporate them onto this form, and note what has been here)	
Funding:	
Country	
Ethical approval	
Reimbursement system	

Aim of Study

Study Design

	Yes	Describe
RCT design	☐	
Cluster RCT	☐	
Controlled CT	☐	
CBA	☐	
ITS	☐	
Other	☐	

Population/setting

[60]	Intervention [61]	Intervention [58]	Intervention [62]	Control [63]
Please give numbers and percentages	Group 1 [n=]	Group 2 [n=]	Group 3 [n=]	Group 4 [n=]
Type of participant (e.g. provider, patient, both)				
Location of care/intervention				
Clinical problem (please state whether defined, not defined or unclear)				
Age of participants (state if mean; median; range) GPs				
Gender of participants (GPs)				
Other characteristics of participants (profession, clinical specialty, level of training and time since graduation.				
Type of targeted behaviour (e.g. prescribing, patient education/advice)				
Academic status of setting				

Intervention

	Yes	Describe (see review protocol for guidance)
Provider oriented	☐	
Patient orientated	☐	
Both	☐	
Other	☐	
Evidence base of recommendation/intervention described?	☐	
Purpose of recommendation/intervention?	☐	
Was the format (medium) for the intervention described?	☐	
Recipient of intervention (e.g. individual, group, or unclear)	Individual and group	
Deliverer of intervention (e.g. state who or what delivered the intervention)	Research team	
Timing of intervention (state unclear if information is not available)		
1. Proximity to clinical decision-making. (assesses distance between intervention and expected response) E.g. low (audit & feedback), mid (clinical advice/education), and high (delayed prescribing)		
2. Frequency and number of intervention events		
3. Duration of intervention		
4. Duration of follow up		
5. Prospective identification by the investigators of barriers to change following the intervention?		

Control

	Yes	Describe
No intervention	☐	
Other interventions	☐	

Unit of allocation	
Unit of analysis	
Power calculation	
Was a ceiling effect identified? 1. Identified by investigator 2. Identified by reviewer 3. Unclear	
Consumer involvement	
Total length of trial	
Dates when trial commenced	
Dates when trial completed	
Data collected – daily, weekly, and monthly? (please also indicate total length of time during which outcomes were measured)	

Outcomes Sought

Primary outcomes	Yes	Definition given in paper
1. Rate of antimicrobial prescription	☐	
2. Rate of prescribing recommended antimicrobial	☐	
Secondary outcomes	Yes	Definition given in paper
3. Incidence of colonisation with, or infection due to, antibiotic-resistant organisms	☐	
4. Incidence of adverse events associates with the use of antimicrobial	☐	
5. Incidence of adverse events associated with the reduced use or duration of treatment with antimicrobial	☐	
Other (please specify)	☐	

Statistical analysis (for primary outcomes only)

Describe

Results

	Intervention	Control
1. Number of prescriptions provided		
2. Number of prescriptions provided in line with recommendations		
3. Number of participants colonised or infected with antibiotic resistant organisms		
4. Number of participants with an adverse event (please specify) associated with antimicrobial use		
5. Number of participants with an adverse event (please specify) associated with the reduced use of antimicrobial agents		
6. Other (please specify)	Please indicate reference ID only	

Event rate

	Intervention Rate of events (variance)	Control Rate of events (variance)	Difference
Overall Antimicrobial prescription			
Use of recommended antimicrobial			
Diagnoses of antibiotic resistant infection(s)			
Adverse events for use of antimicrobials (show subcategories if considered relevant)			
Adverse events arising from the reduced use of antimicrobial agents			

Analysis – seek crude data where possible i.e. number of events, number of student days lost.

Study Quality
RCT, C-RCT and CCT designs

	Yes	No	Unclear	Comments
SELECTION BIAS				
Treatment allocation				
Randomisation				
1. Was the trial described as randomised?	☐	☐	☐	
2. Was allocation truly random? Yes: random numbers, coin toss, shuffle etc. No: by pt number, dob, alternate allocation Unclear: method not stated or unclear	☐	☐	☐	
Concealment of allocation				
3. Was the treatment allocation concealed? Yes: central allocation at trials office or pharmacy, sequentially numbered or coded vials, other methods where the trialist allocating treatment could not be aware of the treatment. No: allocation was alternate, or based on information e.g. dob already known to the trialist Unclear: insufficient information given.	☐	☐	☐	
Similarity of groups	☐	☐	☐	
4. Were the pts characteristics at baseline similar in all groups?	☐	☐	☐	
PERFORMANCE BIAS				
Masking/blinding				
5. Was the trial described as double blind?	☐	☐	☐	
6. Was the treatment allocation masked from participants? (either stated explicitly or an identical placebo is used)	☐	☐	☐	
7. Was treatment allocation masked from investigators?	☐	☐	☐	
8. Was treatment allocation masked from outcome assessors?	☐	☐	☐	
ATTRITION BIAS				
Completeness of trial				
9. Were the number of withdrawals, dropouts and lost to follow up in each group stated? NB: yes if there have not been any drop outs or lost to follow up	☐	☐	☐	

10. Were the drop out rates similar in both groups?	☐	☐	☐	
11. Was an intention to treat analysis done?	☐	☐	☐	
12. If not ITT were there less than 10% of patients per study arm excluded?	☐	☐	☐	
OTHER				
13. Was the appropriate analysis undertaken on the data, particularly if cluster randomised? (e.g. were the results analysed by taking cluster design into account)	☐	☐	☐	
	High	Moderate	Low	Unsure
14. Risk of bias assessment	☐	☐	☐	☐

Interrupted Time Series (ITS) design

	Yes	No	Unclear	Comments
1. **Protection against secular trends** Yes: if the intervention occurred independently of other changes over time No: if reported that the intervention was not independent of other changes over time Unclear: if not specified or information unobtainable form authors	☐	☐	☐	
2. **Data was analysed appropriately** Yes: ARIMA model or time series regression models were used to analyse the data and serial correlation was adjusted/tested for No: if it is clear that neither of the conditions above were met Unclear: not specified in the paper	☐	☐	☐	
3. **Was the reason for the number of points pre and post intervention given?** Yes: rationale for the number of points stated OR sample size No: if it is clear that neither of the conditions above were met Unclear: not specified in the paper	☐	☐	☐	
4. **Shape of the intervention effect was specified.** Yes: rational explanation for the shape of the intervention effect provided by the authors No: if it is clear that the condition above was not met Unclear: not specified in the paper	☐	☐	☐	

DETECTION BIAS				
5. **Intervention unlikely to affect data collection** Yes: if reported that intervention itself was unlikely to affect data collection (e.g. sources and method of data collection was the same before and after the intervention) No: if the intervention itself was likely to affect data collection Unclear: if not reported	☐	☐	☐	
6. **Blind assessment of primary outcome(s)** Yes: authors state explicitly that primary outcome variables were assessed blindly OR the variables are objective (e.g. number of antibiotic resistant infections) No: outcomes were not assessed blindly Unclear: not specified in the paper	☐	☐	☐	
7. **Reliable primary outcome measure(s)** Yes: if outcome measure obtained from some automated system OR good agreement between raters (e.g. at least 90% agreement of kappa ≥ 0.8)	☐	☐	☐	
8. **Completeness of data set** Yes: if data set covers 80-100% of the total number of participants or episodes of care in the study No: if data set covers <80% of the total number of participants or episodes of care in the study Unclear: If not specified	☐	☐	☐	

Appendix 5

CHARACTERISTICS OF STUDIES
Characteristics of included studies

Altiner 2007

Methods	**RCT (CRCT)** unit of allocation: GPs unit of analysis: GPs power calculation: Done concealment of allocation: Unclear follow up of professionals: Incomplete blinded assessment of primary outcomes: No baseline measurement: Yes reliable primary outcome measure: Yes protection against contamination: Not applicable analysis appropriate: Yes	
Participants	104 primary care physicians in North Rhine, Germany treating patients with community acquired infections	
Interventions	1. Educational outreach visit (academic detailing) 2. Printed educational material for patients 3. No control intervention	
Outcomes	Professional practice: change in the rate of prescribing antibiotics Patient:	
Notes	The academic detailing intervention was led by GP peers.	
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment	Unclear	

Arroll 2002

Methods	**RCT** unit of allocation: Patient unit of analysis: Patient power calculation: Done concealment of allocation: Done follow up of patients: Done blinded assessment of primary outcomes: Unclear baseline measurement: Not applicable reliable primary outcome measure: Yes protection against contamination: Not applicable analysis appropriate: Yes
Participants	129 patients from a single practice of 15 physicians in New Zealand treated for a common cold
Interventions	1. Delayed treatment with antibiotics – patients instructed to fill their prescription after 3 days if no improvement is observed 2. Patient received immediate prescription of antibiotics from the clinician
Outcomes	Professional practice: None Patient: use of antibiotics by patients
Notes	

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	Yes	Good

Awad 2006

Methods	**RCT (CRCT)** unit of allocation: Health centres unit of analysis: GPs power calculation: Not clear concealment of allocation: Unclear follow up of professionals: Done blinded assessment of primary outcomes: Unclear baseline measurement: Yes reliable primary outcome measure: Yes protection against contamination: Yes analysis appropriate: Yes	
Participants	30 health centres in Khartoum state, Sudan treating patients of all ages with community acquired infections.	
Interventions	1. Audit and feedback 2. Audit and feedback + educational meeting 3. Audit and feedback + academic detailing 4. No control intervention	
Outcomes	Professional practice: change in the rate of prescribing antibiotics change in the rate of prescribing recommended antibiotics Patient:	
Notes	The academic detailing intervention was provided by clinical pharmacologist	
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment	Unclear	

Azad Chowdury 2007

Methods	**RCT** unit of allocation: Health centres unit of analysis: Health centres power calculation: No concealment of allocation: Unclear follow up of professionals: Not clear blinded assessment of primary outcomes: Unclear baseline measurement: Yes reliable primary outcome measure: Yes protection against contamination: Not applicable analysis appropriate: Yes	
Participants	24 health centres in Bangladesh. Aimed at physicians treating children <5 years old, presenting with acute upper respiratory tract infections.	
Interventions	1. Printed educational material (guidelines) + audit and feedback 2. Audit and feedback 3. No control intervention	
Outcomes	Professional practice: change in the rate of prescribing antibiotics Patient:	
Notes	The treatment guidelines were developed by the WHO for the management of ARI	
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment	Unclear	Moderate

Belongia 2001

Methods	**CBA** unit of allocation: community unit of analysis: GPs power calculation: not done baseline measurement: not done characteristics of studies using second site as control: not done blinded assessment of primary outcomes: unclear protection against contamination: done reliable primary outcome measure: done follow up of professionals: done follow up of patients: Not applicable analysis appropriate: no	
Participants	151 primary care physicians in different regions of Wisconsin, USA treating respiratory tract infections in children aged less than 48 months.	
Interventions	1. Multifaceted intervention that includes educational meetings and educational materials for professionals and educational materials and mass media campaign for patients 2. No control intervention	
Outcomes	Professional practice: change in the rate of prescribing antibiotics Patient: change in the proportion of penicillin resistant Streptococcus pneumoniae isolates in children	
Notes	Mass media campaign based on material from CDC guidelines.	
Risk of bias		
Item	**Authors Judgement**	**Description**

Briel 2006

Methods	**RCT (CRCT)** unit of allocation:GP unit of analysis: GP power calculation: Done concealment of allocation: Done follow up of professionals: Adequate blinded assessment of primary outcomes: Yes baseline measurement: Not done reliable primary outcome measure: Yes protection against contamination: Yes analysis appropriate: Yes	
Participants	Aimed at 45 physicians in primary care treating patients with upper respiratory tract infections.	
Interventions	1. Printed educational material (guidelines) 2. printed educational material (guidelines) + academic detailing 3. No control intervention	
Outcomes	Professional practice: change in the rate of prescribing antibiotics change in the rate of prescribing recommended antibiotics Patient: proportion of re-consultations within 14 days	
Notes	The full intervention utilised Prochaska and DiClemente model during the training programme	
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment	Yes	Good

Chazan 2007

Methods	**RCT** unit of allocation: Community unit of analysis: Patient power calculation: Unclear concealment of allocation: No follow up of professionals: No blinded assessment of primary outcomes: Not done baseline measurement: Done reliable primary outcome measure: Yes protection against contamination: Done analysis appropriate: No	
Participants	16 community outpatient clinics in northern district of Israel treating patients with community acquired infections.	
Interventions	1. Educational meeting – continuous basis 2. Educational meeting – seasonal basis	
Outcomes	Professional practice: change in the rate of prescribing antibiotics change in the rate of prescribing antibiotics inappropriately Patient:	
Notes	All participating clinics belonged to a single HMO	
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	No	Not used

Coenen 2004

Methods	**RCT (CRCT)** unit of allocation: GPs unit of analysis: Patients power calculation: Done concealment of allocation: Unclear follow up of professionals: Incomplete blinded assessment of primary outcomes: No baseline measurement: Yes reliable primary outcome measure: Yes protection against contamination: Not applicable analysis appropriate: Yes
Participants	85 primary care physicians in Belgium treating 1503 patients (all ages) with community acquired infections.
Interventions	1. Multifaceted intervention comprising an national campaign + printed educational material (guidelines) + reminders+ academic detailing 2. National campaign only
Outcomes	Professional practice: change in the rate of prescribing antibiotics change in the rate of prescribing recommended antibiotics Patient: proportion of re-consultations
Notes	The national campaign was run in the mass media to educate the public about the problems arising from antibiotic misuse.

Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment	Unclear	

Davis 2007

Methods	**RCT (CRCT)** unit of allocation: GPs and nurse practitioners unit of analysis: Patients power calculation: Done concealment of allocation: Done follow up of professionals: Done blinded assessment of primary outcomes: No baseline measurement: Done reliable primary outcome measure: Yes protection against contamination: Unclear analysis appropriate: Yes	
Participants	44 primary care doctors in Washington, USA providing primary medical care to patients of all ages.	
Interventions	1. Reminders (based on a computer aided decision support tool) 2. No control intervention	
Outcomes	Professional practice: change in the rate of prescribing recommended antibiotics for otitis media Proportion of patients treated with antibiotics for less than 10 days Patient:	
Notes	This study was conducted at two different clinic sites with separate controls identified at each site.	
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Yes	adequate

Diederichsen 2000

Methods	**RCT** unit of allocation: Patient unit of analysis: Patient power calculation: Not clear concealment of allocation: Yes follow up of professionals: Unclear blinded assessment of primary outcomes: No baseline measurement: No reliable primary outcome measure: Yes protection against contamination: No analysis appropriate: Yes
Participants	35 general practices in a single county in Denmark treating patients of all ages with respiratory tract infections.
Interventions	1. Decision tool based on ancillary tests (CRP testing) 2. No control intervention
Outcomes	Professional practice: change in the rate of prescribing recommended antibiotics for otitis media Patient: change in the proportion of patients who reported adverse events from the non-use of antibiotics
Notes	

Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Yes	Adequate

Dowell 2001

Methods	**RCT** unit of allocation: patient unit of analysis: patient power calculation: done concealment of allocation: done follow up of patients: done blinded assessment of primary outcomes: unclear baseline measurement: not applicable reliable primary outcome measure: Yes protection against contamination: not applicable analysis appropriate: yes
Participants	119 adults from 22 general practices in Scotland treated for uncomplicated cough
Interventions	1. Delayed treatment with antibiotics – patients instructed to return to the practice to collect a pre-filled prescription after 7 days if no improvement is observed 2. Patient received immediate prescription of antibiotics from the clinician
Outcomes	Professional practice: None Patient: collection of antibiotics by patients
Notes	

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	Done	Good

Doyne 2004

Methods	**ITS** unit of allocation: GP practices unit of analysis: Patients protection against secular trends: Yes sufficient data points to enable reliable statistical inference: formal test for trend: Yes protection against bias: Yes intervention unlikely to affect data collection: Yes blinded assessment of primary outcomes: Unclear completeness of data set: No reliable primary outcome measure: Yes analysis appropriate: Yes	
Participants	12 paediatric general practices in the greater Cincinnati area of USA treating children with community acquired infections	
Interventions	1. Local consensus process + educational material for professionals and patients + academic detailing + audit and feedback 2. Educational materials + audit and feedback	
Outcomes	Professional practice: change in the proportion of antibiotics prescribed Patient:	
Notes	Educational material was based on evidence-based information provided by the CDC	
Risk of bias		
Item	**Authors Judgement**	**Description**

Everitt 2006

Methods	**RCT** unit of allocation: patient unit of analysis: patient power calculation: Done concealment of allocation: Done follow up of patients: done blinded assessment of primary outcomes: Unclear baseline measurement: Not applicable reliable primary outcome measure: Yes protection against contamination: Not applicable analysis appropriate: Yes
Participants	307 children and adults from 30 general practices (38 GPs and practice nurses) in Wiltshire, England treated for acute conjunctivitis
Interventions	1. Delayed treatment with antibiotics ± patient educational material ± clinical decision tool using ancillary testing – patients instructed to 2. Patients did not get any antibiotic prescription ± patient educational material ± clinical decision tool using ancillary testing 3. Patient received immediate prescription of antibiotics from the clinician ± patient educational material ± clinical decision tool using ancillary testing
Outcomes	Professional practice: None Patient: use of antibiotics by patients
Notes	

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	Yes	Adequate

Flottorp 2002

Methods	**RCT (CRCT)** unit of allocation: GPs unit of analysis: GPs power calculation: Done concealment of allocation: Unclear follow up of professionals: Incomplete blinded assessment of primary outcomes: No baseline measurement: Yes reliable primary outcome measure: Yes protection against contamination: Not done analysis appropriate: Yes
Participants	16939 consultations for sore throat in patients aged over 3 years and 9887 consultations for UTI in women aged 16-55 years from 142 practices in Norway.
Interventions	1. Multifaceted intervention comprising educational material (sore throat guidelines) + educational material for patients + reminders 2. Educational material (UTI guidelines) + educational material for patients + reminders
Outcomes	Professional practice: change in the rate of prescribing antibiotics for sore throat Patient:
Notes	Recommendations for sore throat was that most patients did not need antibiotics and the recommendations for UTI was that non-pregnant women aged 16-55 years with typical symptoms can be given antibiotics.

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	Unclear	Inadequate

Gonzales 2004

Methods	**CBA** unit of allocation: GP practices unit of analysis: Patients power calculation: Yes baseline measurement: Yes characteristics of studies using second site as control: Yes blinded assessment of primary outcomes: Unclear protection against contamination: Yes reliable primary outcome measure: Yes follow up of professionals: Unclear follow up of patients: analysis appropriate: Yes
Participants	55 ambulatory office practices in Denver, USA managing adults with acute respiratory infections
Interventions	1. Multifaceted intervention comprising prescribing audit and feedback for professionals + educational material for patients 2. prescribing audit and feedback only
Outcomes	Professional practice: change in the rate of prescribing antibiotics for ARIs Patient:
Notes	Patients were registered with a Medicare managed care programme

Risk of bias		
Item	**Authors Judgement**	**Description**
Blinding?	Unclear	

Gonzales 2005

Methods	**CBA** unit of allocation: GP unit of analysis: Patients power calculation: Yes baseline measurement: Yes characteristics of studies using second site as control: Yes blinded assessment of primary outcomes: Yes protection against contamination: Yes reliable primary outcome measure: Yes follow up of professionals: Yes follow up of patients: Not applicable analysis appropriate: Yes
Participants	Ambulatory practices affiliated to four managed care organisations in Denver, USA treating children and adults with ARI
Interventions	1. Multifaceted intervention that comprised evidence based educational material for patients + audit and feedback (prescribing data) for professionals 2. Distant and local controls received audit and feedback
Outcomes	Professional practice: change in the rate of prescribing antibiotics for ARI in children and adults Patient:
Notes	

Risk of bias

Item	Authors Judgement	Description

Harris 2003

Methods	**CBA** unit of allocation: Patient unit of analysis: Patient power calculation: No baseline measurement: Yes characteristics of studies using second site as control: No blinded assessment of primary outcomes: Unclear protection against contamination: No reliable primary outcome measure: Yes follow up of professionals: Not applicable follow up of patients: Yes analysis appropriate: No	
Participants	Patients treated for ARI in a single Walk in Centre in Colorado, USA	
Interventions	1. Educational meetings and materials for both professionals and patients using a variety of formats 2. No control intervention	
Outcomes	Professional practice: change in the rate of prescribing antibiotics Patient: Proportion of antibiotic treated sinusitis visits with an illness duration of > 7 days	
Notes	Educational meetings based on evidence based CDC guidelines	
Risk of bias		
Item	**Authors Judgement**	**Description**

Hennessy 2002

Methods	**CBA** unit of allocation: Communities unit of analysis: Patients power calculation: Unclear baseline measurement: Yes characteristics of studies using second site as control: No blinded assessment of primary outcomes: Unclear protection against contamination: Yes reliable primary outcome measure: Yes follow up of professionals: Unclear follow up of patients: Unclear analysis appropriate: Yes
Participants	Patients receiving ambulatory care in 13 remote villages in 3 regions in Alaska, USA
Interventions	1. Educational meetings and materials for professionals and patients in a variety of settings 2. No control intervention
Outcomes	Professional practice: change in the rate of prescribing antibiotics Patient: proportion of positive nasopharyngeal swab cultures
Notes	Healthcare in these regions is free at the point of use.

Risk of bias		
Item	**Authors Judgement**	**Description**
Blinding?	Unclear	

Ilett 2000

Methods	**CBA** unit of allocation: GP unit of analysis: GP power calculation: No baseline measurement: Yes (for demographics), no (for number of prescriptions) characteristics of studies using second site as control: Unclear blinded assessment of primary outcomes: Unclear protection against contamination: No reliable primary outcome measure: Unclear follow up of professionals: Yes follow up of patients: Not applicable analysis appropriate: No	
Participants	112 GPs in Australia, being treated for: urinary tract infections, bacterial tonsillitis, otitis media, acute bacterial bronchitis, mild pneumonia	
Interventions	1. Academic detailing only 2. No control intervention	
Outcomes	Professional practice: change in the rate of prescribing antibiotics change in the proportion of recommended antibiotics used Patient:	
Notes	Educational meetings based on evidence based CDC guidelines	
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Unclear	Poor

Juzych 2005

Methods	**CBA** unit of allocation: GP practices unit of analysis: GPs power calculation: No baseline measurement: Yes characteristics of studies using second site as control: Yes blinded assessment of primary outcomes: Unclear protection against contamination: Yes reliable primary outcome measure: Yes follow up of professionals: Yes follow up of patients: Yes analysis appropriate: Yes	
Participants	30 primary care physicians in Toronto, Canada treating patients with community acquired infections	
Interventions	1. Educational meeting + educational material for professionals and patients 2. No control intervention	
Outcomes	Professional practice: change in the rate of prescribing antibiotics Patient: Proportion of patients re-consulting following the non-use of antibiotics	
Notes	Educational meetings based on evidence based guidelines	
Risk of bias		
Item	**Authors Judgement**	**Description**
Blinding?	Unclear	Not used

Lagerlov 2000

Methods	**RCT** unit of allocation: GP practices unit of analysis: GP practices and individual GPs power calculation: No concealment of allocation: Unclear follow up of professionals: Incomplete blinded assessment of primary outcomes: Unclear baseline measurement: Not done reliable primary outcome measure: Yes protection against contamination: No analysis appropriate: Yes
Participants	Aimed at GPs in Norway. 6 practices in each group (consisting of 4 to 8 GPs). Intervention patients had upper respiratory tract infections whilst the control group focused on patients with asthma.
Interventions	1. Multifaceted intervention comprising local consensus process + educational meetings and materials (management of UTI) +audit and feedback 2. Educational material (management of asthma)
Outcomes	Professional practice: change in the proportion of antibiotics prescribed for the recommended duration change in the proportion of antibiotics prescribed inappropriately Patient:
Notes	

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	Unclear	poor

Little 2001

Methods	**RCT** unit of allocation: patient unit of analysis: patient power calculation: done concealment of allocation: done follow up of patients: done blinded assessment of primary outcomes: Yes baseline measurement: not applicable reliable primary outcome measure: done protection against contamination: not applicable analysis appropriate: yes	
Participants	315 patients from 93 general practices in three health authorities in South West England treating children aged 6 months to 10 years with otitis media	
Interventions	1. Delayed treatment with antibiotics – patients instructed to return to the practice to collect a pre-filled prescription after 72 hours if no improvement is observed 2. Patient received immediate prescription of antibiotics from the clinician	
Outcomes	Professional practice: None Patient: collection of antibiotics by patients proportion of patients experiencing adverse events from use of antibiotics proportion of patients with missed school days	
Notes		
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Clear	Good

Little 2005

Methods	**RCT** unit of allocation: patient unit of analysis: patient power calculation: done concealment of allocation: done follow up of patients: done blinded assessment of primary outcomes: Yes baseline measurement: not applicable reliable primary outcome measure: done protection against contamination: not applicable analysis appropriate: yes	
Participants	UK study aimed at patients. Patients presented with acute lower respiratory tract infection and were given a leaflet or no leaflet regarding the usefulness of antibiotic treatment. They were also randomised to +/- delayed antibiotics. Total number of patients = 807.	
Interventions	1. Delayed treatment with antibiotics ± patient educational material – patients instructed to return to the practice to collect the prescription if no improvement is observed after 72 hours 2. Patient received no antibiotic prescription ± patient educational material 3. Patient received immediate prescription of antibiotics from the clinician ± patient educational material	
Outcomes	Professional practice: None Patient: collection of antibiotics by patients	
Notes		
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Clear	good

Loeb 2005

Methods	**RCT (CRCT)** unit of allocation: Nursing home unit of analysis: Nursing home power calculation: Done concealment of allocation: Done follow up of professionals: Complete blinded assessment of primary outcomes: Unclear baseline measurement: Not done reliable primary outcome measure: Unclear protection against contamination: Yes analysis appropriate: Yes
Participants	4217 residents from 24 nursing homes in Ontario, Canada and Idaho, USA treated fro urinary tract infections
Interventions	1. Multifaceted intervention comprising educational meetings and materials + outreach visits + reminders 2. No control intervention
Outcomes	Professional practice: change in the rate of antibiotic prescription change in the rate of antibiotic prescription for UTI Patient: change in the proportion of adverse events (hospital admissions) following the intervention
Notes	

Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	clear	Good

MacFarlane 2002

Methods	**RCT** unit of allocation: patient unit of analysis: patient power calculation: done concealment of allocation: done follow up of patients: done blinded assessment of primary outcomes: Done baseline measurement: not applicable reliable primary outcome measure: done protection against contamination: not applicable analysis appropriate: yes	
Participants	259 adults from 3 general practices in Nottingham, England treated for acute bronchitis	
Interventions	1. Delayed treatment with antibiotics + educational material for patients – patients instructed to take the antibiotics if no improvement is observed (time limit not specified) 2. Patient received immediate prescription of antibiotics from the clinician	
Outcomes	Professional practice: None Patient: collection of antibiotics by patients Proportion of patients re-consulting within 1 month	
Notes		
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Yes	Good

Madridejos-Mora 2004

Methods	**CBA** unit of allocation: Health clinics unit of analysis: Physicians (GPs) power calculation: Unclear baseline measurement: Yes characteristics of studies using second site as control: Yes blinded assessment of primary outcomes: Unclear protection against contamination: Yes reliable primary outcome measure: Yes follow up of professionals: Yes follow up of patients: analysis appropriate: Yes
Participants	282 family physicians in six health districts in Spain treating patients of all ages with community acquired infections
Interventions	1. Audit and feedback + academic detailing 2. No control intervention
Outcomes	Professional practice: change in the rate of prescribing antibiotics Patient:
Notes	

Risk of bias		
Item	**Authors Judgement**	**Description**
Blinding?	Unclear	Not used

Mainous 2000

Methods	**RCT (CRCT)** unit of allocation: GPs unit of analysis: Patients power calculation: Not clear concealment of allocation: Not clear follow up of professionals: Not clear blinded assessment of primary outcomes: Unclear baseline measurement: Yes reliable primary outcome measure: Yes protection against contamination: Not applicable analysis appropriate: No
Participants	216 physicians in Kentucky, USA treating patients less than 18 years with upper respiratory tract infections.
Interventions	1. Audit and feedback 2. Educational material (patients) 3. Audit and feedback + educational materials 4. No control intervention
Outcomes	Professional practice: change in the rate of antibiotic prescription Patient:
Notes	

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	unclear	poor

Marshall 2006

Methods	**ITS** unit of allocation: Region unit of analysis: patient protection against secular trends: Yes sufficient data points to enable reliable statistical inference: Yes formal test for trend: Yes protection against bias: Yes intervention unlikely to affect data collection: Yes blinded assessment of primary outcomes: Unclear completeness of data set: Yes reliable primary outcome measure: Yes analysis appropriate: Yes
Participants	All patients with pharmacy filled prescriptions provided by a government funded drug insurance programme in Ontario, Canada.
Interventions	1. Financial restrictions 2. No control intervention
Outcomes	Professional practice: change in the proportion of antibiotics prescribed Patient:
Notes	Financial restrictions applied to the use of three floroquinolone antibiotics

Risk of bias		
Item	**Authors Judgement**	**Description**

Martens 2006a

Methods	**RCT** unit of allocation: GP practice unit of analysis: GP individual power calculation: Yes concealment of allocation: unclear follow up of professionals: Yes blinded assessment of primary outcomes: unclear baseline measurement: Yes reliable primary outcome measure: Yes protection against contamination: No analysis appropriate: Unclear	
Participants	107 GPs from the Netherlands targeting prescribing behaviour – not disease specific	
Interventions	1. Local consensus + educational material (guidelines) 2. No control intervention	
Outcomes	Professional practice: change in the rate of antibiotic prescription Patient:	
Notes		
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	unclear	poor

Martens 2006b

Methods	**RCT** unit of allocation: GP practice unit of analysis: GP (individual) power calculation: Yes concealment of allocation: Unclear follow up of professionals: adequate blinded assessment of primary outcomes: Unclear baseline measurement: Not done reliable primary outcome measure: Yes protection against contamination: Not applicable analysis appropriate: No
Participants	53 GP practices (circa 12 GPs per group), study based in the Netherlands targeting prescribing behaviour – not disease specific
Interventions	1. Reminders (computer aided decision tool for antibiotic use) 2. Reminders (targeting cholesterol lowering drugs)
Outcomes	Professional practice: change in the rate of antibiotic prescription Change in the proportion prescribed recommended antibiotics Patient:
Notes	

Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	unclear	poor

McCormick 2005

Methods	**RCT** unit of allocation: patient unit of analysis: patient power calculation: done concealment of allocation: done follow up of patients: done blinded assessment of primary outcomes: Done baseline measurement: not applicable reliable primary outcome measure: done protection against contamination: not applicable analysis appropriate: yes
Participants	223 children aged 6 months to 12 years in a single health setting in Texas, USA treated for non severe acute otitis media
Interventions	1. Delayed treatment with antibiotics + education of patients – patients instructed to fill the prescription if no improvement is observed (time limit not specified) 2. Patient received immediate prescription of antibiotics from the clinician
Outcomes	Professional practice: financial cost of antibiotic use Patient: use of antibiotics by patients Patient satisfaction with consultation Proportion with antibiotic resistant streptococcus pneumoniae isolates
Notes	Use of antibiotics by participants was not the primary outcome of this study

Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Clear	Good

McIssac 2002

Methods	**RCT** unit of allocation: GP unit of analysis: Patient power calculation: Yes concealment of allocation: Unclear follow up of professionals: Incomplete blinded assessment of primary outcomes: Unclear baseline measurement: Not done reliable primary outcome measure: Yes protection against contamination: Unclear analysis appropriate: Yes
Participants	GPs (number not specified) treating people with sore throat in Canada.
Interventions	1. Reminders – clinical scoring tool 2. No control intervention
Outcomes	Professional practice: change in the rate of antibiotic prescription Change in the proportion prescribed antibiotics inappropriately Patient:
Notes	

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	unclear	poor

Metlay 2007

Methods	**RCT** unit of allocation: Hospital Emergency Departments unit of analysis: Patients power calculation: Yes concealment of allocation: Unclear follow up of professionals: Yes blinded assessment of primary outcomes: Unclear baseline measurement: Yes reliable primary outcome measure: Yes protection against contamination: Yes analysis appropriate: Yes
Participants	Based in USA, patients with viral infections targeted, with interventions aimed at both patients and physicians.
Interventions	1. Educational material for patients and GPs + academic detailing + audit and feedback 2. No control intervention
Outcomes	Professional practice: change in the rate of antibiotic prescription Change in the proportion prescribed antibiotics inappropriately Patient:
Notes	

Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	unclear	poor

Mohagheghi MA 2005

Methods	**RCT** unit of allocation: GP unit of analysis: GP power calculation: Unclear concealment of allocation: Yes follow up of professionals: Yes blinded assessment of primary outcomes: Unclear baseline measurement: Unclear reliable primary outcome measure: Yes protection against contamination: No analysis appropriate: No
Participants	80 GPs based in primary care in Iran, no specific diseases specified.
Interventions	1. Intervention consisted of a structured short course planned for 25 hours of presentations, case discussion, questions, and answers, panel discussion and evaluation. 2. No intervention control
Outcomes	Professional practice: change in the rate of antibiotic prescription Patient:
Notes	

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	Yes	Moderate

Perz 2002

Methods	**CBA** unit of allocation: Communities unit of analysis: patients power calculation: Unclear baseline measurement: No characteristics of studies using second site as control: Yes blinded assessment of primary outcomes: Unclear protection against contamination: Yes reliable primary outcome measure: Yes follow up of professionals: Unclear follow up of patients: Unclear analysis appropriate:
Participants	Children aged less than 15 years enrolled in the Tennessee Medicaid Managed Care Programme and residing in any of four counties in Tennessee, USA
Interventions	1. Educational meetings and materials for providers and patients 2. No control intervention
Outcomes	Professional practice: change in the rate of prescribing antibiotics Patient: proportion of children < 15 years with resistant isolates of *Streptococcus pneumoniae*
Notes	Educational sessions and materials based on evidence-based information from the CDC

Risk of bias		
Item	**Authors Judgement**	**Description**
Blinding?	Unclear	Not used

Poehling 2005

Methods	**RCT** unit of allocation: Patients unit of analysis: Patients power calculation: Done concealment of allocation: Unclear follow up of professionals: Unclear blinded assessment of primary outcomes: Yes baseline measurement: Not applicable reliable primary outcome measure: Yes protection against contamination: Not applicable analysis appropriate:
Participants	Children aged less than 5 years seen for care for fever or acute respiratory complaints in a single county in Tennessee, USA
Interventions	1. Reminder – using an ancillary test 2. No control intervention
Outcomes	Professional practice: change in the rate of antibiotic prescription Patient:
Notes	Study was conducted in two separate clinic settings with separate control groups identified.

Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	unclear	poor

Psheitizky 2003

Methods	**RCT** unit of allocation: patient unit of analysis: patient power calculation: Not clear concealment of allocation: done follow up of patients: done blinded assessment of primary outcomes: Done baseline measurement: not applicable reliable primary outcome measure: done protection against contamination: not applicable analysis appropriate: yes
Participants	81 children from two primary care clinics in Israel treated for acute otitis media
Interventions	1. Delayed treatment with antibiotics + education of patients – patients instructed to fill prescription after 24-48 hours if no improvement is observed 2. Patient received immediate prescription of antibiotics from the clinician
Outcomes	Professional practice: None Patient: use of antibiotics by patients
Notes	

Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Clear	Good

Samore 2005

Methods	**RCT (CRCT)** unit of allocation: Community unit of analysis: Community power calculation: Not done concealment of allocation: Unclear follow up of professionals: Incomplete blinded assessment of primary outcomes: Not done baseline measurement: Yes reliable primary outcome measure: done protection against contamination: not applicable analysis appropriate: Yes	
Participants	334 primary care clinicians in 18 rural communities in Utah and Idaho, USA treating patients with acute respiratory infections.	
Interventions	1. Reminders (paper and PD) 2. A based decision tools) + educational meetings + patient education + mass media messages 3. Mass media messages + patient education 4. No control intervention	
Outcomes	Professional practice: rate of prescribing antibiotics rate of prescribing recommended antibiotics Patient: use of antibiotics by patients	
Notes		
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	unclear	Poor

Seager 2006

Methods	**RCT** unit of allocation: General dental practitioners unit of analysis: general dental practitioners power calculation: done concealment of allocation: Unclear follow up of professionals: incomplete blinded assessment of primary outcomes: unclear baseline measurement: not done reliable primary outcome measure: done protection against contamination: Not done analysis appropriate: yes
Participants	70 GDPs from 4 health authorities in Wales, UK providing general dental care to people of all ages.
Interventions	1. Educational materials (patients and professionals) + academic detailing 2. Educational materials (guidelines) 3. No control intervention
Outcomes	Professional practice: rate of prescribing antibiotics proportion of antibiotics prescribed inappropriately Patient: Patient satisfaction
Notes	The guidelines were developed through a consensus process involving several clinical stakeholders

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	unclear	Poor

Sondergaard 2003

Methods	**RCT** unit of allocation: unit of analysis: power calculation: concealment of allocation: Unclear follow up of professionals: Incomplete blinded assessment of primary outcomes: unclear baseline measurement: Yes reliable primary outcome measure: protection against contamination: not applicable analysis appropriate: No	
Participants	GP practices in Denmark targeting respiratory tract infections. Total of 299 GPs from 181 practices randomised.	
Interventions	1. Education (provider) + audit and feedback 2. Education	
Outcomes	Professional practice: rate of prescribing antibiotics Patient:	
Notes		
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	unclear	Poor

Spiro 2004

Methods	**RCT** unit of allocation: patient unit of analysis: patient power calculation: done concealment of allocation: Yes follow up of professionals: done blinded assessment of primary outcomes: Yes baseline measurement: not applicable reliable primary outcome measure: Yes protection against contamination: not applicable analysis appropriate: yes	
Participants	698 children aged 6 to 35 months investigated for Acute Otitis Media in a paediatric unit in Alabama, USA.	
Interventions	1. Reminders – decision aid using tympanometry 2. No control intervention	
Outcomes	Professional practice: rate of prescribing antibiotics Patient:	
Notes		
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Yes	Adequate

Spiro 2006

Methods	**RCT** unit of allocation: patient unit of analysis: patient power calculation: done concealment of allocation: done follow up of patients: done blinded assessment of primary outcomes: done baseline measurement: not applicable reliable primary outcome measure: done protection against contamination: not applicable analysis appropriate: yes	
Participants	283 children aged 6 months to 12 years in an emergency outpatient setting in Connecticut, USA and treated for acute otitis media	
Interventions	1. Delayed treatment with antibiotics – patients instructed to fill prescription after 48 hours if no improvement is observed 2. Patient received immediate prescription of antibiotics from the clinician	
Outcomes	Professional practice: None Patient: use of antibiotics by patients Proportion of patients experiencing adverse events from the use of antibiotics Proportion of patients with unscheduled re-consultations after 14 days	
Notes	The delayed prescription was designed to expire 3 days after the date of issue if not filled	
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Clear	Good

Takemura 2005

Methods	**RCT** unit of allocation: patient unit of analysis: patient power calculation: Not clear concealment of allocation: Not done follow up of professionals: Unclear blinded assessment of primary outcomes: unclear baseline measurement: not applicable reliable primary outcome measure: done protection against contamination: not applicable analysis appropriate: yes
Participants	305 patients (all ages) with acute febrile illness seen by 11 physicians in a regional health centre in Japan
Interventions	1. Reminders – decision aid using ancillary test (CRP + WBC) 2. No control intervention
Outcomes	Professional practice: rate of prescribing antibiotics Patient:
Notes	

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	unclear	Poor

Taylor 2005

Methods	**RCT** unit of allocation: Parent unit of analysis: Child power calculation: No concealment of allocation: Unclear follow up of professionals: adequate blinded assessment of primary outcomes: unclear baseline measurement: Not done reliable primary outcome measure: Yes protection against contamination: not applicable analysis appropriate: yes	
Participants	Intervention aimed at educating the parents of children about antibiotic prescribing with the control who received education regarding injury prevention. All the children had upper respiratory tract infections, specifically acute otitis media and sinusitis (n=499)	
Interventions	1. Educational materials - parents (antibiotic use) 2. Educational materials (injury prevention)	
Outcomes	Professional practice: rate of prescribing antibiotics rate of prescribing antibiotics for otitis media Patient: number of visits where an antibiotic was prescribed.	
Notes		
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	unclear	Poor

Varonen 2007

Methods	**RCT** unit of allocation: Health centre unit of analysis: Health centre power calculation: Not clear concealment of allocation: Unclear follow up of professionals: done blinded assessment of primary outcomes: No baseline measurement: Yes reliable primary outcome measure: Yes protection against contamination: Yes analysis appropriate: yes	
Participants	Primary care physicians in 30 Health centres in rural and urban settings in Finland providing care to a population of 819777 people	
Interventions	1. Educational meetings using problem based learning 2. Educational meeting using academic detailing 3. No control intervention	
Outcomes	Professional practice: rate of prescribing antibiotics for sore throats Patient:	
Notes	Intervention based on a nationwide initiative (MIKSTRA programme)	
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	Unclear	Poor
Blinding?	No	Not used

Welschen 2004

Methods	**RCT** unit of allocation: GPs unit of analysis: GPs power calculation: Done concealment of allocation: Unclear follow up of professionals: blinded assessment of primary outcomes: unclear baseline measurement: Done reliable primary outcome measure: done protection against contamination: not applicable analysis appropriate: yes
Participants	100 primary care physicians with collaborating pharmacist in the Utrecht region, Netherlands
Interventions	1. Local consensus + educational meetings + educational materials (professionals and patients) + audit and feedback 2. No control intervention
Outcomes	Professional practice: rate of prescribing antibiotics Patient:
Notes	

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	unclear	Poor

Wensing 2004

Methods	**CBA** unit of allocation: Physicians unit of analysis: patients power calculation: Unclear baseline measurement: Yes characteristics of studies using second site as control: Yes blinded assessment of primary outcomes: Unclear protection against contamination: No reliable primary outcome measure: Yes follow up of professionals: Unclear follow up of patients: analysis appropriate: Yes	
Participants	177 primary care doctors from a single region in Germany treating patients of all ages with community acquired infections.	
Interventions	1. Local consensus + educational materials (professionals and patients) + audit and feedback 2. Educational materials (guidelines)	
Outcomes	Professional practice: change in the rate of prescribing antibiotics Change in the proportion of recommended antibiotics prescribed Patient:	
Notes	Patients recruited to this study were all registered with a private insurance group	
Risk of bias		
Item	**Authors Judgement**	**Description**
Blinding?	Unclear	Not used

Wilson 2003

Methods	**RCT** unit of allocation: GPs unit of analysis: GPs power calculation: Not clear concealment of allocation: Unclear follow up of professionals: Incomplete blinded assessment of primary outcomes: unclear baseline measurement: Done reliable primary outcome measure: done protection against contamination: not applicable analysis appropriate: yes	
Participants	54 GPs from Canberra, Australia treating children with ARI	
Interventions	1. Local consensus + educational meetings + educational materials (professionals and patients) + audit and feedback 2. No control intervention	
Outcomes	Professional practice: rate of prescribing antibiotics Patient:	
Notes		
Risk of bias		
Item	**Authors Judgement**	**Description**
Allocation concealment?	unclear	Poor

Worrall 2007

Methods	**RCT (CRCT)** unit of allocation: GPs unit of analysis: patient power calculation: done concealment of allocation: Unclear follow up of professionals: incomplete blinded assessment of primary outcomes: unclear baseline measurement: not done reliable primary outcome measure: unclear protection against contamination: not done analysis appropriate: No
Participants	40 GPs in eastern Newfoundland, Canada treating patients of all ages with sore throat
Interventions	1. Reminders – decision aid using ancillary test & scoring tool 2. No control intervention
Outcomes	Professional practice: rate of prescribing antibiotics for sore throats Patient:
Notes	The ancillary test was a rapid antigen detection test for group A streptococci and the scoring tool was a sore throat decision rule.

Risk of bias

Item	Authors Judgement	Description
Allocation concealment?	Unclear	Poor

Appendix 6

Clinical Effectiveness tables

Table 1 Effectiveness results randomised controlled studies (RCT and CRCT)

Multifaceted Interventions					
Study ID	**Population (s)**	**Results (Primary Outcomes)**		**Results (Secondary Outcomes)**	
Altiner A (2007) CRCT - Germany	General practitioners Persons with ARI	% of consultation episodes prescribed antibiotics: ACB 0.3% vs. 10.1%; DACB at 12 months = -9.8% (OR = 0.32 (0.26,0.38)) OR_{adj} = 0.55 ((0.38, 0.80) P= 0.002)			
Awad AI (2006) CRCT - Sudan	Community health centre Persons with ARI, diarrhoea and malaria	Mean number of consultation episodes prescribed AB (Int [2] & Int [3]): ACB -7.4 & -6.9; DACB -7.7 (-5.9 to -9.5, P = <0.001) & -7.2 (-5.4 to -8.9, P = <0.001)	Mean number of consultation episodes prescribed AB inappropriately (Int [2] & Int [3]): ACB -6.5 & -5.7; DACB -5.9 (-4.1 to -7.7, P = <0.001) & -5.1 (-3.3 to -6.9, P = <0.001)		
Azad Chowdury AK (2007) RCT - Bangladesh	Community health centre	% of consultation episodes prescribed antibiotics: DACB -15.5%			
Briel M (2006) CRCT - Switzerland	General practitioners	% of consultation episodes prescribed antibiotics: OR = 0.84 (0.52, 1.35) OR_{Adj} 0.86 (0.40 to 1.93)	% of consultation episodes prescribed recommended antibiotics: OR = 0.81 (0.44, 1.48) OR_{Adj} 1.03 (0.30 to 3.09)	% of re-consultation within 14 days: OR_{Adj} 0.97 (0.78 to 1.21)	
Coenen S	General	% of	% of	Reconsultati	Cost of

(2004) CRCT - Belgium	practitioners Persons aged 18-65 years diagnosed with an acute cough	consultation episodes prescribed antibiotics: ACB -15.6% vs. -9.1%; DACB -- 6.5% OR = 0.94 (0.67, 1.31) OR_{adj} = 0.56 (95% CI = 0.36 to 0.87))	consultation episodes prescribed recommended antibiotics: ACB 13.6% vs. -0.1%; DACB - 13.7% OR = 1.00 (0.54, 1.86) OR_{adj} = 1.90 (95% CI = 0.96 to 3.75))	on rate: ACB -4% vs. 2%; DACB -6% (NS)	prescribed antibiotics:
Flottorp S (2002) CRCT - Norway	General practices Patients aged 3 years and over with a diagnosis of sore throat	The % of sore throat episodes prescribed antibiotics: ACB (-4.3% vs. -1.3%); DACB -3.0% (P= 0.032) OR = 0.79 (0.73, 0.87)			
Lagerlov P (2000) RCT - Norway	General Practitioners	% of consultation episodes prescribed antibiotics for recommended duration: RPCP 13.1% P = <0.0001	% of consultation episodes prescribed antibiotics inappropriately: RPCP - 9.6% P = 0.0004		
Loeb M (2005) CRCT - Canada	Nurses and General Practitioners Nursing home residents	Overall AB prescription per 1000 resident days: DACB -0.41 wt. mean diff = -0.37 (95%CI = -1.17 to 0.44)	AB prescription for UTI per 1000 resident days: DACB - 0.42 wt. mean diff = -0.017 (95%CI = -0.056 to 0.02)	Overall admission to hospital (all cause) per 1000 resident days: DACB -0.17 (95%CI = -0.14 to 0.48)	
Mainous AG (2000)	Physicians in private or hospital based	The % of ARI episodes prescribed antibiotics: ACB 15.3% vs. 22.5%; DACB - 7.2%			

CRCT - USA	practice providing ambulatory care. Patients under 18 years of age diagnosed with an ARI	P=<0.05			
Metlay JP (2007) CRCT - USA)	General practitioners Patients with URTI and ARI in ED settings	% of consultation episodes prescribed AB: DACB = -10.5% OR 1.27 (1.04, 1.55)		Reconsultation rate:	Admission to hospital within 14 days of consultation:
Samore MH (2005) RCT - USA	Communities All persons with ARI	Overall AB prescribing rate per 100 person years: ACB -8.8 vs. -2.6; DACB -6.2 (Sig.)	Prescription of recommended AB per 100 person years: ACB -4.1 vs. 0.4; DACB -4.5 (Sig.)		
Seager JM (2006) CRCT - UK	General Dental practitioners Persons with dental pain	% of consultation episodes prescribed AB: OR = 0.63 (0.41 to 0.95)	% of consultation episodes prescribed AB inappropriately: OR = 0.33 (0.21 to 0.54)		
Sondegaard J (2003) RCT - Denmark	General Practitioners	No of consultation episodes with antibiotics prescribed: DACB -0.6 (-2.8 to 1.6)	% of consultation episodes where recommended AB was used: DACB: 2% (-1% to 5%)		
Welschen I (2004)	General practice peer review groups	% of consultation episodes prescribed	Mean number of AB per 1000 patients:		

RCT – The Netherlands	All persons diagnosed with URTI	antibiotics: ACB -4% vs. 8%; DACB -12% (95% CI = -18.9 to -4.0)	ACB -9.7 vs. 1.9; DACB -12 (95% CI = -23.2 to -0.03)		
Wilson EJ (2003) RCT - Australia	General practitioners Children with a diagnosis of ARI	The mean number of AB prescribed per 100 ARI episodes (2 years post intervention): ACB -0.78 vs. 0.35; DACB -1.13 P= 0.026			

Table 2 Effectiveness results randomised controlled studies (RCT and CRCT)

Delayed Antibiotic Prescribing					
Study ID	**Population (s)**	**Results (Primary Outcomes)**		**Results (Secondary Outcomes)**	
Arroll B (2002) RCT – New Zealand	Person presenting with symptoms of a common cold	% of consultation episodes that used the prescribed antibiotics: OR 0.12 (0.05 to 0.29) Chi Square = 28.21 (P= <0.0001)*			
Dowell J (2001) RCT – UK	Persons aged 16 years and over with acute cough	% of consultation episodes that used the prescribed antibiotics: Chi Square = 0.563, P= 0.45*			
Everitt HA (2006) RCT - UK	Persons diagnosed with Acute infective conjunctivitis	% of consultation episodes that used the prescribed antibiotics: OR 0.01 (0.0015 to 0.08)* RR 0.54 (0.45 to 0.64)*		Mean symptom score and mean duration of moderate symptoms:	
Little P (2001) CCT/RCT – UK	General practitioners Children aged 6 months to 10 years with AOM	% of consultation episodes that used the prescribed antibiotics: OR 0.05 (0.02, 0.08) Chi Square = 162.6 (P= <0.0001)*		% of patients developing diarrhoea and rash:	Incidence of adverse events associated with the non use of AB: DACB Chi square = 10.3, P= <0.01
Little P (2005) RCT - UK	General Practitioners Persons aged 3 years and above with ARI	% of consultation episodes that used the prescribed antibiotics: RPCP = -79% OR 0.01 (0.00 to 0.02; P= <0.0001)			
McCormack DP (2005) RCT - USA	Children 6 months to 12 years with non severe AOM	% of consultation episodes that used the prescribed antibiotics:	% of patients diagnosed with AB resistant S pneumoniae strains:	Cost of Antibiotic prescription:	

		OR = 0.00 (0.00, 0.04)			
MacFarlane J (2002) RCT - UK	General practitioners Adults with acute bronchitis	% of consultation episodes that used the prescribed antibiotics: OR = 0.59 (0.34, 1.01) RR 0.76 (0.59 to 0.97, P= 0.04) Chi Square = 5.43 (p= 0.01)		Reconsultation within 4 weeks of initial consultation: Chi Square = 0.377 (P= 0.54)	
Pshetizky Y (2003) ID No: 179 RCT - Israel	Children aged 6 months to 36 months with AOM	% of consultation episodes that used the prescribed antibiotics: OR 0.11 (0.04 to 0.33)* Chi Square = 17.67 (P= <0.0001)*			
Spiro DM (2006) ID No: 83 RCT - USA	Children 6 months to 12 years with non severe AOM	% of consultation episodes that used the prescribed antibiotics: OR 0.09 (0.05 to 0.17)* RR 0.43 (0.34 to 0.540)*		Reconsultation within 11-14 days of initial consultation:	% of patients developing diarrhoea/vomiting at 11-14 days after intervention:

Table 3 Effectiveness results randomised controlled studies (RCT and CRCT)

Ancillary Testing				
Study ID	**Population (s)**	**Results (Primary Outcomes)**		**Results (Secondary Outcomes)**
Diederichsen HZ (2000) RCT - Denmark	General practitioners Persons with ARI	% of consultation episodes that used the prescribed antibiotics: OR 0.9 (0.7 to 1.2)* Chi Square = 0.736 (P= 0.391)*		Incidence of adverse events associated with the non use of AB: OR 1.6 (1.0 to 2.6)* Chi Square = 3.81 (P= 0.05)*
Poehling KA (2005) RCT - USA	Children under 5 years with ARI	% of consultation episodes that used the prescribed antibiotics (ED): OR 1.1 (0.69 to 1.76)* Chi Square = 0.33 (P= 0.57)*	% of consultation episodes that used the prescribed antibiotics (Clinic): OR 0.89 (0.44 to 1.79)* Chi Square = 0.10 (P= 0.75)*	
Spiro DM (2004) RCT - USA	Children aged 6 to 35 months with AOM	% of consultation episodes that used the prescribed antibiotics: OR 0.976 (0.69 to 1.36)* P= 0.62 Chi Square = 0.33 (P= 0.565)*		
Takemura Y (2005) RCT - Japan	Persons with ARI	% of consultation episodes that used the prescribed antibiotics OR 0.24 (0.15 to 0.38)* Chi Square = 36.4 (P= <0.0001)*		
Worrall G (2007) CRCT - Canada	General Practitioners Persons with Sore throat	% of consultation episodes prescribed antibiotics: Chi Square = 16.705 (P= <0.001)		

Table 4 Effectiveness results randomised controlled studies (RCT and CRCT)

Single Interventions				
Study ID	**Population (s)**	**Results (Primary Outcomes)**		**Results (Secondary Outcomes)**
Chazan B (2007) RCT - Israel	Community clinics	% of consultation episodes that used the prescribed antibiotics: DACB: -1.2 (P= <0.0001; 95% CI = 1.02 to 1.07)	(% of consultation episodes where inappropriate AB (Broad spectrum) was used: DACB: -1.2 (P= <0.0001; 95% CI = 1.02 to 1.19)	
Davis RL (2007) CRCT - USA	Health care practitioners Persons with AOM	% of consultation episodes where recommended AB was used (trial 1) DACB: 3% ($Diff_{Adj}$ = 15%, 2% to 30%)	% of consultation episodes where recommended AB was used (trial 2) DACB: 22% ($Diff_{Adj}$ = 24%, 8% to 40%)	
Ilett KF (2000) RCT - Australia	General practitioners	Change in total (median) number of antibiotics prescribed: DACB = -908 (-6.5) Chi-Square = 1.85 (P = 0.177)	Change in total (median) number of recommended antibiotics prescribed: DACB = 24 (-2.5) Chi-Square = 17.18 (P = 0.0001)	Overall cost of antibiotics prescribed (3 months):
Mohagheghi MA (2005) RCT - Iran	General practitioners	% of consultation episodes that an antibiotic was prescribed: DACB: -4% NS (unable to calculate CI – no count data)		
Taylor JA (2005) RCT - USA	Parents of unwell (URTI) children (aged < 24 months)	Mean number of consultation episodes with antibiotics prescribed: P= 0.23	Mean number of AOM consultation episodes with antibiotics prescribed DACB: -1.2 P= 0.23	
Martens JD (2006) CRCT – The Netherlands	General practitioners	Mean antibiotic prescription per GP per 1000 listed patients:		
Martens JD	General	Number of	% of consultation	

(2006) CRCT – The Netherlands	practitioners	consultation episodes with antibiotics prescribed per GP per 1000 listed patients:	episodes that used the recommended antibiotics: RPCP = -28.9%	
McIssac WJ (2002) RCT - Canada	General practitioners	% of consultation episodes with antibiotics prescribed: RPCP = 0.7% OR_{adj} 0.57 (0.27, 1.17; P = 0.96)	% of consult0ation episodes prescribed unnecessary antibiotics: RPCP = 27% OR_{adj} 0.76 (0.42, 1.40; P = 0.17)	
Varonen H (2007) CRCT - Finland	Health centres Persons with acute maxillary sinusitis	% of consultation episodes where recommended AB was used (AD) OR = 1.83 (0.98 to 3.43) P= 0.716	% of consultation episodes where recommended AB was used (PBL) OR = 1.18 (0.67 to 2.08) P= 0.716	

Table 5 Effectiveness results controlled before and after studies (CBA)

Multifaceted Interventions				
Study ID	**Population**	**Results (Primary Outcomes)**		**Results (Secondary Outcomes)**
Belongia EA (2001) USA	Children with a diagnosis of streptococcus pneumonia	% of consultation episodes that used the prescribed antibiotics:	% of children with carriage of Penicillin non-susceptible pneumoniae (PNP):	
Gonzales R (2004) USA	Primary care doctors Persons with ARI	% of consultation episodes that used the prescribed antibiotics: DACB: -5.0% P = 0.16; P_{adj} = 0.79		
Gonzales R (2005) USA	Primary care doctors Persons with ARI	% of consultation episodes that used the prescribed antibiotics (Adults): DACB: -5.0% P = <0.002	% of consultation episodes that used the prescribed antibiotics (children): DACB-3.0% P = 0.18	
Madridejos-Mora R (2004) Spain	Primary care doctors	Consultation episodes that used the prescribed antibiotics: DACB: -2.0 DDD per day P = 0.026	Consultation episodes where recommended AB was used DACB: -1.1 DDD per day P = 0.035	Total expenditure on AB per GP and Mean cost per prescription:
Wensing M (2004) Germany	Primary care doctors	% of consultation episodes that used the prescribed antibiotics: DACB: -2.8% OR = 0.86 (0.82 to 0.90)	% of consultation episodes where recommended AB was used DACB: -0.1% OR = 0.99 (0.89 to 1.11)	Cost of antibiotic prescription:

Table 6 Effectiveness results controlled before and after studies (CBA)

Education			
Study ID	Population	Results (Primary Outcomes)	Results (Secondary Outcomes)
Harris RH (2003) USA	General practitioners Adults with ARI	% of consultation episodes that used the prescribed antibiotics: DACB: 3% P = <0.01	% of AB treated sinusitis with an illness duration of ≥ 7 days:
Hennessy TW (2002) USA	Communities	% of consultation episodes that used the prescribed antibiotics: DACB: -0.15	% of positive nasopharyngeal swab cultures: ACB = 2% (NS)
Juzych NS (2005) USA	General practitioners	% of consultation episodes that used the prescribed antibiotics: DACB: -5.5% (P = <0.001)	Reconsultation following initial visit:
Perz JF (2002) USA	Communities	% of consultation episodes that used the prescribed antibiotics: DACB: -11% (95% CI -14 to -8, P = <0.001)	% of children under 15 years with AB resistant isolates of invasive S. pneumoniae:

Table 7 Effectiveness results Interrupted Time Series studies (ITS)

Education and Financial Restrictions			
Study ID	Population	Results (Primary Outcomes)	Results (Secondary Outcomes)
Doyne EO (2004) USA	General practices Young children	% of consultation episodes that used the prescribed antibiotics: DACB: 0.82 (95% CI 0.71 to 0.95)	
Marshall D (2006) Canada	Region	% of consultation episodes that used the prescribed antibiotics: DACB: -5.5% (95% CI NS)	

Appendix 7

Results data using EPOC format

1. RCT & C-RCT – Multifaceted Interventions

Altiner A (2007)

% of consultation episodes prescribed AB	Peer led communication training (academic detailing) plus passive patient education (information leaflets and posters) – 6 weeks	Control (No intervention)	Peer led communication training (academic detailing) plus passive patient education (information leaflets and posters) – 12 months	Control (No intervention)
Pre	36.4%	54.7%	36.4%	54.7%
Post (6 weeks and 12 months)	29.4%	59.4%	36.7%	64.8%
Absolute change from baseline	-7.0%	4.7%	0.3%	10.1%
Absolute change (post)	-30.0%	-	-28.1%	-
Relative % change (post)	-50.5%	-	-43.4%	-
Difference in absolute change from baseline (95% CI)	-11.7% OR = 0.28 (0.24, 0.34) OR_{Adj} = 0.38 (0.26,0.56; P = 0.001)		-9.8% OR = 0.32 (0.26, 0.38) OR_{Adj} = 0.55 (0.38,0.80 ; P= 0.002)	

Awad AI (2006)

Mean number of consultation episodes prescribed AB	**Audit and feedback alone**	**Audit and feedback plus interpersonal educational meeting (academic detailing)**	**Audit and feedback plus educational seminar**	**Control (No intervention)**
Pre	13.4	14.0	14.2	14.3
Post (3 months)	10.8	6.6	7.3	14.6
Absolute change from baseline	-2.6	-7.4	-6.9	0.3
Absolute change (post)	-3.8	-8.0	-7.3	
Relative % change (post)	-26.0%	-54.8%	-50%	
Difference in absolute change from baseline (95% CI)	-2.9 (1.1 to 4.6), P = 0.004	-7.7 (-5.9 to -9.5, P = <0.001)	-7.2 (-5.4 to -8.9, P = <0.001)	
Mean number of consultation episodes prescribed AB inappropriately	**Audit and feedback alone**	**Audit and feedback plus interpersonal educational meeting (academic detailing)**	**Audit and feedback plus educational seminar**	**Control (No intervention)**
Pre	6.5	7.4	7.3	7.5
Post (3 months)	3.9	0.9	1.6	6.9
Absolute change from baseline	-2.6	-6.5	-5.7	-0.6
Absolute change (post)	-3.0	-6	-5.3	
Relative % change (post)	-43.5%	-87%	-76.8%	
Difference in absolute change from baseline (95% CI)	-2.0 (0.1 to 3.7), P =0.040	-5.9 (-4.1 to -7.7, P = <0.001)	-5.1 (-3.3 to -6.9, P = <0.001)	

Briel M (2006)

% of consultation episodes prescribed AB	**Clinical Guidelines plus communication training (N = 259)**	**Guidelines only N = 293 †**	**Control (No intervention) N = 285‡ Not randomised**
Pre	-	-	-
Post (4 months)	13.5% (35)	15.7% (46)	21.4% (61)
Absolute change from baseline	-	-	-
Absolute change (post)	-7.9% & -2.2%	-5.7%	
Relative % change (post)	-37% & -14%	-26.6%	
Difference in absolute change from baseline (95% CI)	OR 0.57 (0.36 to 0.90)‡ OR 0.83 (0.52 to 1.35); OR_{Adj} 0.86 (0.40 to 1.93)†	OR 0.68 (0.44 to 1.04)‡	
% of consultation episodes prescribed recommended AB	**Clinical Guidelines plus communication training (N = 259)**	**Guidelines only N = 293 †**	**Control (No intervention) N = 285‡ Not randomised**
Pre	-	-	-
Post (4 months)	53.8% (21)	53.1% (26)	41.1% (30)
Absolute change from baseline	-	-	-
Absolute change (post)	12.7% & 0.7%	12.0%	
Relative % change (post)	31% & 1.3%	29%	
Difference in absolute change from baseline (95% CI)	OR 0.75 (0.42 to 1.35)‡ OR 0.94 (0.5 to 1.7); OR_{Adj} 1.03 (0.30 to 3.09)†		
% of re-consultations within 14 days	**Clinical Guidelines plus communication training (N = 259)**	**Guidelines only N = 293 †**	**Control (No intervention) N = 285‡ Not randomised**
Pre	-	-	-
Post (4 months)	44.7% (113)	49.3% (143)	41.9% (39)
Absolute change from baseline	-	-	-
Absolute change (post)	-4.6%		

Relative % change (post)	-9.3%		
Difference in absolute change from baseline (95% CI)	OR 0.73 (0.52 to 1.01); OR_{Adj} 0.97 (0.78 to 1.21)†		

Coenen S (2004)

% of consultation episodes prescribed AB	**Public educational campaign; guidelines, academic detailing and postal reminders for providers**	**Control (Public educational campaign)**
Pre	43.0%	37.8%
Post (14 months)	27.4%	28.7%
Absolute change from baseline	-15.6%	-9.1%
Absolute change (post)	-1.3%	-
Relative % change (post)	-4.5%	-
Difference in absolute change from baseline	-6.5% (OR_{adj} = 0.56 (95% CI = 0.36 to 0.87))	
% of consultation episodes prescribed recommended AB	**Public educational campaign; guidelines, academic detailing and postal reminders for providers**	**Control (Public educational campaign)**
Pre	40.1%	37.5%
Post (14 months)	53.8%	37.4%
Absolute change from baseline	13.6%	-0.1%
Absolute change (post)	16.4%	-
Relative % change (post)	36.6%	-
Difference in absolute change from baseline	13.7% (OR_{adj} = 1.90 (95% CI = 0.96 to 3.75))	
% of patients re-consulting	**Public educational campaign; guidelines, academic detailing and postal reminders for providers**	**Control (Public educational campaign)**
Pre	23%	20%
Post (14 months)	19%	22%
Absolute change from baseline	-4%	2%
Absolute change (post)	-3%	-
Relative % change (post)	-13.6%	-
Difference in absolute change from baseline	-6% (NS)	

Flottorp S (2002)

% of consultation episodes prescribed AB	Evidence based guidelines for diagnosis and management of **sore throat** and educational material for patients and providers; CDST plus reminders & increases in charges for telephone consultation	Evidence based guidelines for diagnosis and management of **UTI** and educational material for patients and providers; CDST plus reminders & increases in charges for telephone consultation
Pre	48.1%	50.8%
Post (4 months)	43.8%	49.5%
Absolute change from baseline	-4.3%	-1.3%
Absolute change (post)	-5.7%	-
Relative % change (post)	-11.5%	-
Difference in absolute change from baseline	-3.0% (p= 0.032)	

Lagerlov P (2000)

% of consultation episodes prescribed antibiotics for recommended duration (mean % (SD) per GP)	**Educational sessions and plenary discussion (guideline on UTI diagnosis and management) plus audit and feedback**	**Control – Educational sessions and plenary discussion (guideline on Asthma diagnosis and management) plus audit and feedback**
Pre	12% (16%)	12% (18%)
Post (12 months)		
Absolute change from baseline		
Absolute change (post)		
Relative % change (post)	13.1%	
Difference in absolute change from baseline (95% CI)	(P = <0.0001)	
% of consultation episodes prescribed AB inappropriately (mean % (SD) per GP)	**Educational sessions and plenary discussion (guideline on UTI diagnosis and management) plus audit and feedback**	**Control – Educational sessions and plenary discussion (guideline on Asthma diagnosis and management) plus audit and feedback**
Pre	67% (24%)	64% (26%)
Post (12 months)		
Absolute change from baseline		
Absolute change (post)		
Relative % change (post)	-9.6%	
Difference in absolute change from baseline (95% CI)	(P = 0.0004)	

Loeb M (2005)

Overall AB Prescription rate per 1000 residents days	**Educational sessions and materials plus reminders based on clinical guidelines**	**Control (No intervention)**
Pre	-	-
Post (12 months)	3.52	3.93
Absolute change from baseline	-	-
Absolute change (post)	-	-
Relative % change (post)	-	-
Difference in absolute change from baseline	-0.41 (wt. mean diff = -0.37 (95%CI = -1.17 to 0.44)	
AB prescription rate for UTI per 1000 residents days	**Educational sessions and materials plus reminders based on clinical guidelines**	**Control (No intervention)**
Pre	-	-
Post (12 months)	1.17	1.59
Absolute change from baseline	-	-
Absolute change (post)	-	-
Relative % change (post)	-	-
Difference in absolute change from baseline	-0.42 (wt. mean diff = -0.017 (95%CI = -0.056 to 0.02)	
Hospital admission rate (all causes) per 1000 residents days	**Educational sessions and materials plus reminders based on clinical guidelines**	**Control (No intervention)**
Pre	-	-
Post (12 months)	0.98	0.81
Absolute change from baseline	-	-
Absolute change (post)	-	-
Relative % change (post)	-	-
Difference in absolute change from baseline	-0.17 (95%CI = -1.14 to 0.48)	

Mainous AG (2000)

% of consultation episodes prescribed AB	Patient education only	Performance feedback only	Provider performance Feedback & Patient education	Control (No intervention)
Pre	31.9%	28.4%	34.4%	31.0%
Post (5 months)	44.5%	43.6%	49.7%	53.5%
Absolute change from baseline	12.6%	15.2%	15.3%	22.5%
Absolute change (post)	-9%	-9.9%	-3.8%	-
Relative % change (post)	-16.8%	-18.5%	-7.1%	-
Difference in absolute change from baseline	-9.9%	-7.3%	-7.2% (<0.05)	

Metlay JP (2007)

% of consultation episodes prescribed AB	Provider and patient education, academic detailing and audit/feedback	Control (No intervention)
Pre (Adjusted)	52%	47%
Post (12 months) - adjusted	42%	47.5%
Absolute change from baseline	-10%	0.5%
Absolute change (post)	-5.5%	
Relative % change (post)	-11.6%	
Difference in absolute change from baseline (95% CI)	-10.5%	

Samore MH (2005)

AB prescribing rate per 100 person-years	**Provider and community education plus clinical decision support tool**	**Community education only**	**Control (No intervention)**
Pre	84.1	84.3	72.3
Post (24 months)	75.3	85.2	74.9
Absolute change from baseline	-8.8	0.9	2.6
Absolute change (post)	0.4	10.3	-
Relative % change (post)	0.53%	13.7%	-
Difference in absolute change from baseline	-11.4 (Sig.)	-1.7	
Prescription of recommended AB per 100 person-years	**Provider and community education plus clinical decision support tool**	**Community education only**	**Control (No intervention)**
Pre	16.0	15.2	15.8
Post (24 months)	11.9	15.5	16.2
Absolute change from baseline	-4.1	0.3	0.4
Absolute change (post)	-4.3	-0.7	
Relative % change (post)	-26.5%	-4.3%	
Difference in absolute change from baseline	-4.5 (Sig.)	-0.1	

Seager JM (2006)

% of consultation episodes prescribed AB	**Educational materials and guidelines for providers plus academic detailing (N=556)**	**Provider Education only (N=451)**	**Control (No intervention) N=490**
Pre	-	-	-
Post	23%	29%	32%
Absolute change from baseline	-	-	-
Absolute change (post)	-9%	-3%	
Relative % change (post)	-28.1%	-9.4%	
Difference in absolute change from baseline	OR = 0.63 (0.41 to 0.95)	OR = 0.83 (0.55 to 1.21)	
% of consultation episodes prescribed AB inappropriately	**Educational materials and guidelines for providers plus academic detailing (N=29)**	**Provider Education only (N=32)**	**Control (No intervention) N=32**
Pre	-	-	-
Post	7%	15%	18%
Absolute change from baseline	-	-	-
Absolute change (post)	-11%	-3%	
Relative % change (post)	-61.1%	-16.6%	
Difference in absolute change from baseline	OR = 0.33 (0.21 to 0.54)	OR = 0.82 (0.53 to 1.29)	

Sondegaard J (2003)

No of consultation episodes that AB was prescribed	**Guideline and prescribing feedback No of prescriptions per 1000 patients (IQR)**	**Control (Guideline only)**
Pre	23.5 (16.7;30.9)	22.3 (17.1;26.8)
Post (12 months)	34.6 (23.4;44.8)	34.0 (24.2;40.8)
Absolute change from baseline	11.1	11.7
Absolute change (post)	0.6	
Relative % change (post)	1.8%	
Difference in absolute change from baseline (95% CI)	-0.6 (-2.8 to 1.6)	
% of consultation episodes that recommended (narrow spectrum) AB was prescribed	**Guideline and prescribing feedback No of prescriptions per 1000 patients (IQR)**	**Control (Guideline only)**
Pre	52% (44;62)	52% (43;62)
Post (12 months)	45% (39;53)	43% (34;54)
Absolute change from baseline	-7%	-9%
Absolute change (post)	2%	
Relative % change (post)	4.6%	
Difference in absolute change from baseline (95% CI)	2% (-1 to 5)	

Welschen I (2004)

% of consultation episodes prescribed AB	Consensus guidelines, provider education, prescribing feedback and patient education	Control (No intervention)
Pre	27%	29%
Post (12 months)	23%	37%
Absolute change from baseline	-4%	8%
Absolute change (post)	-14%	-
Relative % change (post)	-37.8%	-
Difference in absolute change from baseline	-12% (95% CI = -18.9 to -4.0)	
Mean no of prescribed AB per 1000 patients	Consensus guidelines, provider education, prescribing feedback and patient education	Control (No intervention)
Pre	76.4	85.4
Post (12 months)	66.7	87.4
Absolute change from baseline	-9.7	1.9
Absolute change (post)	-20.7	-
Relative % change (post)	-23.7%	-
Difference in absolute change from baseline	-12 (95% CI = -23.2 to -0.03)	

Wilson EJ (2003)

Mean number of AB prescription per 100 consultation episodes	Consensus guidelines, provider education, prescribing feedback and patient education	Control - Consensus guidelines, provider and patient education
Pre	7.52	7.16
Post (24 months)	6.74	7.51
Absolute change from baseline	-0.78	0.35
Absolute change (post)	-0.77	-
Relative % change (post)	-10.2%	-
Difference in absolute change from baseline	-1.13 (P= 0.026)	

Zad Chowdury (2007)

(% of consultation episodes prescribed AB)	Clinical guidelines plus audit	Audit only	Control (No intervention)
Pre	90.3%	85.7%	89.3%
Post (unclear)	66.6%	70.7%	81.1%
Absolute change from baseline	-23.7%	-15.7%	-8.2%
Absolute change (post)	-14.5	-10.4%	-
Relative % change (post)	-17.8%	-12.8%	-
Difference in absolute change from baseline	-15.5%	-7.5%	

2. RCT & C-RCT – Delayed Antibiotic Prescribing

Arroll B (2002)

% of consultation episodes who used the prescribed AB	Delayed AB	Control (immediate AB)
Pre		
Post (10 days)	48%	89%
Absolute change from baseline		
Absolute change (post)	-41%	
Relative % change (post)	-46%	
Difference in absolute change from baseline (95% CI)	OR 0.12 (0.05 to 0.29) Chi Square = 28.21 (P= <0.0001)	

Dowell J (2001)

% of consultation episodes who used the prescribed AB	Delayed AB	Control (immediate AB)
Pre		
Post (14 days)	45%	100%
Absolute change from baseline		
Absolute change (post)	-55%	
Relative % change (post)	-55%	
Difference in absolute change from baseline (95% CI)	Chi square = 0.563, P= 0.45*	

Everitt HA (2006)

% of consultation episodes who used the prescribed AB	**Delayed AB ± leaflet**	**Control (Immediate AB ± leaflet)**
Pre		
Post (14 days)	53%	99%
Absolute change from baseline		
Absolute change (post)	-49%	
Relative % change (post)	-56%	
Difference in absolute change from baseline (95% CI)	OR 0.01 (0.0015 to 0.08)* RR 0.54 (0.45 to 0.64)*	

Little P (2001; 2006)

% of consultation episodes who used the prescribed AB	**Delayed AB**	**Control (immediate AB)**
Pre		
Post (11 days)	24%	98.5%
Absolute change from baseline	-	-
Absolute change (post)	-74.5	
Relative % change (post)	-75.6%	
Difference in absolute change from baseline (95% CI)	Chi Square = 162.6 (P= <0.0001)*	
% of AOM cases who did not feel better	**Delayed AB**	**Control (immediate AB)**
Pre	-	-
Post (12 months)	30%	14%
Absolute change from baseline	-	-
Absolute change (post)	16%	-
Relative % change (post)	114.3%	-
Difference in absolute change from baseline (95% CI)	Chi square = 10.3, P= <0.01	

Little P (2005)

% of consultation episodes who used the prescribed AB	Delayed AB ± leaflet	Control (Immediate AB ± leaflet)
Pre		
Post (days)	39 (20%)	185 (96%)
Absolute change from baseline		
Absolute change (post)	-76%	
Relative % change (post)	-79%	
Difference in absolute change from baseline (95% CI)	OR 0.011 (0.005 to 0.023) Chi Square = 230.6 (P= <0.0001)	

McCormick DP (2005)

% of consultation episodes who used the prescribed AB	Delayed AB plus parent education	Control (Immediate AB)
Pre		
Post (30 days)	34%	100%
Absolute change from baseline		
Absolute change (post)	-66%	
Relative % change (post)	-66%	
Difference in absolute change from baseline (95% CI)		

MacFarlane J (2002)

% of consultation episodes who used the prescribed AB	Delayed AB plus verbal advice plus leaflet	Control (Delayed AB plus verbal advice)
Pre		
Post (14-30 days)	47%	62%
Absolute change from baseline		
Absolute change (post)	-15%	
Relative % change (post)	-24.2%	
Difference in absolute change from baseline (95% CI)	RR 0.76 (0.59 to 0.97, P= 0.04) Chi Square = 5.43 (p= 0.01)	

Pshetizky Y (2003)

% of consultation episodes who used the prescribed AB	**Delayed AB plus parent education**	**Control (delayed AB)**
Pre		
Post (10 days)	37%	63%
Absolute change from baseline		
Absolute change (post)	-26%	
Relative % change (post)	-41%	
Difference in absolute change from baseline (95% CI)	OR 0.1 (0.03 to 0.33)* Chi Square = 17.67 (P= <0.0001)*	

Spiro DM (2006)

% of consultation episodes who used the prescribed AB	**Delayed AB plus parent education**	**Control (Immediate AB)**
Pre		
Post (40 days)	38%	87%
Absolute change from baseline		
Absolute change (post)	-49%	
Relative % change (post)	-56%	
Difference in absolute change from baseline (95% CI)	OR 0.09 (0.05 to 0.16)* RR 0.43 (0.34 to 0.540)*	

3. RCT & C-RCT – Ancillary Testing

Diederichsen HZ (2000)

% of consultation episodes who used the prescribed AB	**CRP testing plus clinical assessment**	**Control (clinical assessment)**
Pre		
Post (40 days)	43%	46%
Absolute change from baseline		
Absolute change (post)	-3%	
Relative % change (post)	-6.5%	
Difference in absolute change from baseline (95% CI)	OR 0.9 (0.7 to 1.2)* Chi Square = 0.736 (P= 0.391)*	
% of consultation episodes who reported increased or unchanged morbidity (AB not used)	**CRP testing plus clinical assessment**	**Control (clinical assessment)**
Pre		
Post (40 days)	12%	8%
Absolute change from baseline		
Absolute change (post)	-49%	
Relative % change (post)	-56%	
Difference in absolute change from baseline (95% CI)	OR 1.6 (1.0 to 2.6)* Chi Square = 3.81 (P= 0.05)*	

Poehling KA (2005)

% of consultation episodes who used the prescribed AB – emergency department	**Rapid influenza test plus clinical assessment**	**Control (clinical assessment)**
Pre		
Post (6 months)	32%	29%
Absolute change from baseline		
Absolute change (post)	3%	
Relative % change (post)	10%	
Difference in absolute change from baseline (95% CI)	OR 1.1 (0.69 to 1.76)* Chi Square = 0.33 (P= 0.57)*	
% of consultation	**Rapid influenza test**	**Control (clinical**

episodes who used the prescribed AB - Clinic	**plus clinical assessment**	**assessment)**
Pre		
Post (6 months)	26%	29%
Absolute change from baseline		
Absolute change (post)	-3%	
Relative % change (post)	-10%	
Difference in absolute change from baseline (95% CI)	OR 0.89 (0.44 to 1.79)* Chi Square = 0.10 (P= 0.75)*	

Spiro DM (2004)

% of consultation episodes who used the prescribed AB	**Tympanometry plus clinical assessment**	**Control (clinical assessment)**
Pre		
Post (15 months)	28.8%	26.8%
Absolute change from baseline		
Absolute change (post)	2%	
Relative % change (post)	7.5%	
Difference in absolute change from baseline (95% CI)	OR 0.976 (0.69 to 1.36)* P= 0.62 Chi Square = 0.33 (P= 0.565)*	

Takemura Y (2005)

% of consultation episodes who used the prescribed AB	**CRP plus WBC counts plus clinical assessment**	**Control (clinical assessment)**
Pre		
Post (15 months)	37%	78%
Absolute change from baseline		
Absolute change (post)	-41%	
Relative % change (post)	-52%	
Difference in absolute change from baseline (95% CI)	OR 0.24 (0.15 to 0.38)* Chi Square = 36.4 (P= <0.0001)*	

Worrall G (2007)

% of consultation (sore throat) episodes prescribed AB	**Clinical decision support tool plus ancillary testing**	
Pre	-	-
Post (3 months)	38.2%	58.2%
Absolute change from baseline	-	-
Absolute change (post)	-20%	-
Relative % change (post)	-34.4%	-
Difference in absolute change from baseline (95% CI)	Chi Square = 16.705 (P= <0.001)	

4. RCT & C-RCT – Single interventions

Chazan B (2007)

% of consultation episodes who used the prescribed AB	**Continuous educational campaign (DDD per 1000 patients/day)**	**Control - Seasonal educational campaign (DDD per 1000 patients/day)**
Pre	28.7	27.8
Post (30 months) Median	22.9	23.2
Absolute change from baseline	-5.8	-4.6
Absolute change (post)	-0.3	
Relative % change (post)	-1.3%	
Difference in absolute change from baseline (95% CI)	-1.2 (P= <0.0001; 95% CI = 1.02 to 1.07)	
% of consultation episodes where inappropriate AB was used	**Continuous educational campaign (DDD per 1000 patients/day)**	**Control - Seasonal educational campaign (DDD per 1000 patients/day)**
Pre	8.5	7.4
Post (30 months) Median	7.0	7.1
Absolute change from baseline	-1.5	-0.3
Absolute change (post)	-0.1	
Relative % change (post)	-17%	
Difference in absolute change from baseline (95% CI)	-1.2 (P= <0.0001; 95% CI = 1.02 to 1.19)	

Davis RL (2007) – Otitis Media only

% of consultation episodes where recommended AB was used	**Computerised clinical decision support system**	**Control 1 (No intervention)**
Pre	28%	32%
Post (50 months) Median	8%	9%
Absolute change from baseline (median)	-20%	-23%
Absolute change (post)	-1.0%	
Relative % change (post)	-11.1%	
Difference in absolute change from baseline (95% CI)	3% (AdjDiff = 15%, 2% to 30%)	
% of consultation episodes where recommended AB was used	**(Computerised clinical decision support system)**	**Control 2 (No intervention)**
Pre	55%	55%
Post (18 months) Median	50%	28%
Absolute change from baseline (median)	-5%	-27%
Absolute change (post)	22%	
Relative % change (post)	78.6%	
Difference in absolute change from baseline (95% CI)	22% (AdjDiff = 24%, 8% to 40%)	

Davis RL (2007) -all conditions combined*

% of consultation episodes where recommended AB was used	**Computerised clinical decision support system**	**Control 1 (No intervention)**
Pre	28%	32%
Post (50 months) Median	43%	35%
Absolute change from baseline (median)	15%	3%
Absolute change (post)	8%	
Relative % change (post)	23%	
Difference in absolute change from baseline (95% CI)	12% (AdjDiff = 15%, -1% to 32%)	
% of consultation episodes where recommended AB was used	**(Computerised clinical decision support system)**	**Control 2 (No intervention)**
Pre	72%	56%
Post (15 months) Median	58%	37%
Absolute change from baseline (median)	-14%	-19%
Absolute change (post)	21%	
Relative % change (post)	57%	
Difference in absolute change from baseline (95% CI)	5% (AdjDiff = 26%, -41% to 94%)	

* including constipation and urticaria

Ilett KF (2000)

% of consultation episodes prescribed AB	**Academic detailing using clinical pharmacist (Median per GP)**	**Control (No intervention)**
Pre	5182 (67.5)	6666 (83.5)
Post (7 months)	7262 (98.5)	9654 (121)
Absolute change from baseline	2080 (31)	2988 (37.5)
Absolute change (post)	-2392 (-22.5)	
Relative % change (post)	-24.7% (-18.6%)	
Difference in absolute change from baseline (95% CI)	-908 (-6.5) Chi-Square = 1.85 (P = 0.177) ?? OR = 1.03 (0.95 to 1.08)	
% of consultation episodes prescribed recommended AB	**Academic detailing using clinical pharmacist (Median per GP)**	**Control (No intervention)**
Pre	308 (5.5)	721 (5.5)
Post (7 months)	604 (7.5)	993 (10)
Absolute change from baseline	296 (2)	272 (4.5)
Absolute change (post)	-389 (-2.5)	
Relative % change (post)	-39.2% (-25%)	
Difference in absolute change from baseline (95% CI)	24 (-2.5) Chi-Square = 17.18 (P = 0.0001)	

Mohagheghhi MA (2005)

Mean % of consultation episodes that an AB was prescribed	**Provider Continuing Medical Education(Short course)**	**Control (No intervention)**
Pre	66.8% (±11.5)	71.4% (±15.4)
Post (6 months)	66.1% (±14.5)	74.8% (±15.4)
Absolute change from baseline	-0.7%	3.4%
Absolute change (post)	-8.7%	
Relative % change (post)	-11.6%	
Difference in absolute change from baseline (95% CI)	-4.1%	

Taylor JA (2005)

Mean number of consultation episodes prescribed AB	**Parental education – antibiotic leaflet**	**Control (injury prevention leaflet)**
Pre	-	-
Post (12 months)	2.2 (±2.6)	2.5 (±2.9)
Absolute change from baseline		
Absolute change (post)	-0.3	
Relative % change (post)	-12%	
Difference in absolute change from baseline (95% CI)	NS (P= 0.23)	
Mean number of Otitis Media consultation episodes prescribed AB	**Parental education – antibiotic leaflet**	**Control (injury prevention leaflet)**
Pre	1.1 (±1.9)	1.1 (±2.1)
Post (12 months)	1.7 (±2.1)	2.9 (±2.4)
Absolute change from baseline	0.6	1.8
Absolute change (post)	-1.2	
Relative % change (post)	-41.4%	
Difference in absolute change from baseline (95% CI)	-1.2 (P= 0.23)	

Martens JD (2006)

% of consultation episodes prescribed AB	Development of clinical guidelines through consensus process.	Guidelines issued by post (no role in developing the guidelines)
Pre		
Post (36 months)		
Absolute change from baseline		
Absolute change (post)		
Relative % change (post)		
Difference in absolute change from baseline (95% CI)		

Martens 2006

% of consultation episodes prescribed recommended AB	Computerised reminder system for AB use AB per 1000 patients per GP	Control (Computerised reminder for statin use) AB per 1000 patients per GP
Pre		
Post (12 months)	28.2	39.7
Absolute change from baseline		
Absolute change (post)	-11.5	
Relative % change (post)	-28.9%	
Difference in absolute change from baseline (95% CI)		
% of consultation episodes prescribed AB	Computerised reminder system for AB use AB per 1000 patients per GP	Control (Computerised reminder for statin use) AB per 1000 patients per GP
Pre		
Post (12 months)		
Absolute change from baseline		
Absolute change (post)		
Relative % change (post)		
Difference in absolute change from baseline (95% CI)		

McIssac WJ (2002)

% of consultation episodes prescribed AB	**Clinical scoring prompts plus stickers for Provider**	**Control (No clinical score prompts)**
Pre		
Post (months)	85 (28.1%)	88 (27.9%)
Absolute change from baseline		
Absolute change (post)	0.2%	
Relative % change (post)	0.7%	
Difference in absolute change from baseline (95% CI)	AdjOR 0.57 (0.27 to 1.17; P = 0.96)	
% of consultation episodes prescribed unnecessary AB	**Clinical scoring prompts plus stickers for Provider**	**Control (No clinical score prompts)**
Pre		
Post (months)	61 (20.4%)	48 (16.1%)
Absolute change from baseline		
Absolute change (post)	4.3%	
Relative % change (post)	27%	
Difference in absolute change from baseline (95% CI)	AdjOR 0.76 (0.42 to 1.40; P = 0.17)	

Varonen H (2007)

% of consultation episodes where recommended AB was used	**Guideline implementation: Academic detailing**	**Guideline implementation: Problem based learning**	**Control (No intervention)**
Pre	36%	35%	35%
Post (24 months) Median	39.3%	48.2%	54.3%
Absolute change from baseline (median)	3.3%	13.2%	19.3%
Absolute change (post)	-15%	-6.1%	
Relative % change (post)	-27.6%	-11.2%	
Difference in absolute change from baseline (95% CI)	P= 0.716 C/W External controls (2002) OR = 1.83 (0.98 to 3.43)	P= 0.716 C/W External controls (2002) OR = 1.18 (0.67 to 2.08)	

5. Controlled before and after studies – Multifaceted and single interventions

Belongia EA (2001)

% of consultation episodes who used the prescribed AB	**Patient and provider education plus academic detailing sessions**	**Control (No intervention)**
Pre	57.6%	60%
Post (months)	59.5%	61.5%
Absolute change from baseline	1.9%	-1.5%
Absolute change (post)	2%	
Relative % change (post)	3.2%	
Difference in absolute change from baseline (95% CI)	3.4% (P = 0.66)	
% of consultation episodes with penicillin resistant streptococcus	**Patient and provider education plus academic detailing sessions**	**Control (No intervention)**
Pre	12.8%	24.7%
Post (months)	12.0%	18.6%
Absolute change from baseline	-0.8%	-6.1%
Absolute change (post)	-6.6%	
Relative % change (post)	-35.5%	
Difference in absolute change from baseline (95% CI)	5.3% (NS)	

Gonzales R (2004)

% of consultation episodes who used the prescribed AB	**Provider and patient education, audit and feedback**	**Control (provider intervention only)**
Pre	45%	51%
Post (4 months)	40%	41%
Absolute change from baseline	5%	10%
Absolute change (post)	-1%	
Relative % change (post)	-2.4%	
Difference in absolute change from baseline (95% CI)	-5.0% (P = 0.16; Adj P = 0.79)	

Gonzales R (2005) - Paediatric population

% of consultation episodes who used the prescribed AB	Provider and patient education, audit and feedback	Control (provider intervention only)	Control (No intervention)
Pre	34%	39%	38%
Post (6-12 months) Median	30%	37%	39%
Absolute change from baseline (median)	-4%	-2%	-1%
Absolute change (post)	-9%	-2%	
Relative % change (post)	-23.1%	-5%	
Difference in absolute change from baseline (95% CI)	-3.0% (P = 0.18)		

Gonzales R (2005) -Adult population

% of consultation episodes who used the prescribed AB	Provider and patient education, audit and feedback	Control (provider intervention only)	Control (No intervention)
Pre	60%	55%	51%
Post (6-12 months) Median	36%	45%	44%
Absolute change from baseline (median)	-24%	-10%	-7%
Absolute change (post)	-8%	1%	
Relative % change (post)	-18.2%	2.3%	
Difference in absolute change from baseline (95% CI)	-5.0% (P = <0.002)		

Harris RH (2003)

% of consultation episodes who used the prescribed AB	Provider and patient education	Control (provider education only)
Pre	46%	46%
Post (4 months)	34%	31%
Absolute change from baseline	-12%	-15%
Absolute change (post)	3%	
Relative % change (post)	9.6%	
Difference in absolute change from baseline (95% CI)	3% (P = <0.01 *)	

Hennessy 2002

Number of consultation episodes who used the prescribed AB	**Provider and patient education**	**Control (No intervention)**
Pre (mean)	0.39	0.25
Post (6 months) (mean)	0.26	0.27
Absolute change from baseline	-0.13	0.02
Absolute change (post)	-0.01	
Relative % change (post)	-3.7%	
Difference in absolute change from baseline (95% CI)	-0.15	
(% of positive nasopharyngeal swab cultures)	**MF (provider and patient education, audit and feedback)**	**Control (No intervention)**
Pre	33%	-
Post (24 months)	31%	
Absolute change from baseline	2%	
Absolute change (post)	-	
Relative % change (post)	-	
Difference in absolute change from baseline (95% CI)	NS	

Madridejos-Mora R (2004)

Consultation episodes who used the prescribed AB	**Audit and feedback plus academic detailing sessions (DDD per day)**	**Control (No intervention)**
Pre	15.7	16.4
Post (3 months) Median	13.7	16.4
Absolute change from baseline (median)	-2	0
Absolute change (post)	-2.7	
Relative % change (post)	-16.5%	
Difference in absolute change from baseline (95% CI)	-2.0 (P = 0.026)	
Consultation episodes where recommended AB was used	**Audit and feedback plus academic detailing sessions (DDD per day)**	**Control (No intervention)**
Pre	78.7	76.6
Post (3 months) Median	79.4	78.4
Absolute change from baseline (median)	0.7	1.8
Absolute change (post)	1.0	
Relative % change (post)	1.3%	
Difference in absolute change from baseline (95% CI)	-1.1 (P = 0.035)	

Perz JF (2002)

% of consultation episodes who used the prescribed AB	**Provider and patient education (AB prescription per 100 person years)**	**Control (No intervention)**
Pre	163	147
Post (24 months)	144	139
Absolute change from baseline	-19%	-8%
Absolute change (post)	5	
Relative % change (post)	3.6%	
Difference in absolute change from baseline (95% CI)	-11% (95% CI -14 to -8, P = <0.001)	

Wensing M (2004)

% of consultation episodes who used the prescribed AB	**Audit and feedback plus academic detailing sessions**	**Control (No intervention)**
Pre	81.3%	76.8%
Post (3 months) Median	79.5%	77.8%
Absolute change from baseline (median)	-1.8%	1%
Absolute change (post)	1.7%	
Relative % change (post)	-2.2%	
Difference in absolute change from baseline (95% CI)	-2.8% OR = 0.86 (0.82 to 0.90)	
% of consultation episodes where recommended AB was used	**Audit and feedback plus academic detailing sessions**	**Control (No intervention)**
Pre	46.3%	43.6%
Post (3 months) Median	47.2%	44.6%
Absolute change from baseline (median)	0.9%	1%
Absolute change (post)	2.6%	
Relative % change (post)	5.8%	
Difference in absolute change from baseline (95% CI)	-0.1% OR = 0.99 (0.89 to 1.11)	

Juzych NS (2005)

(% of consultation episodes who used the prescribed AB)	**Provider education**	**Control (no intervention)**
Pre	49.9%	45%
Post (5 months)	37.6%	42.8%
Absolute change from baseline	-7.7%	-2.2%
Absolute change (post)	-5.2%	
Relative % change (post)	-12.1%	
Difference in absolute change from baseline (95% CI)	-5.5% (P = <0.001)	

6. Interrupted Time Series studies – Multifaceted interventions

Doyne EO (2004)

% of consultation episodes who used the prescribed AB	**Patient and provider education plus feedback plus academic detailing sessions**	**Control (Guidelines and feedback only)**
Pre	-	-
Post (12 months)	-	-
Absolute change from baseline (mean)	-	-
Absolute change (post)		
Relative % change (post)		
Difference in absolute change from baseline (95% CI)	0.82 (0.71 to 0.95)	0.86 (0.77 to 0.95)

Marshall D (2006)

% of consultation episodes who used the prescribed AB	**Financial restrictions on reimbursement**	**Control (No intervention)**
Pre	-	-
Post (36 - 48 months)	-	-
Absolute change from baseline (mean)	-	-
Absolute change (post)		
Relative % change (post)		
Difference in absolute change from baseline (95% CI)	5.5% (NS)	

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