Dear Sarah, Andy and Newton

Please find attached the second draft of the Antibiotic review. I have not added in the references as it creates an unwieldy and very long document. (We may wish not to do this if it’s not necessary as it takes a long time to format them correctly).

A few things to note:

1.      Yellow highlighted text refer to things I still need to fix, such as placing the correct link/number into the appendix, so ignore those

2.      The main issues for discussion with this review are:

a.      How to handle the ROB tables for the observational studies and what this will mean for the REVMAN tables and flexibility?

b.      How to report - in the results text - on the observational study findings presented in tables and where these fit best?

c.      Where to place the Meta-regression figures?

Note that - as for the Vaccine review - I had to completely renumber all the plots to fit our template so the links are to the plot numbers in my version, not in the original review (NB for Sarah to note this). I copied them from REVMAN so the quality is probably better than from the Pdf.

Andy, as always, please cast your eye on my ‘Messages’ sections which I created.

Newton, please confirm if you will do the EP tables and remember we need the absolute values for the Vaccine review to complete it.

Nandi

**LAYER 1 A starts here**

CR Review formatting

Interventions to improve antibiotic prescribing practices for hospital inpatients. (Review)

rewritten to fit prototype format

November 27 2018

A review will have the following sections/pages:

Summary

Full text

Appendices

Related content

Messages for media

Article information

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# **Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)**

Cochrane Systematic Review – Intervention

Published date: 9 February 2017| Date of last search: January 2015 (see what’s changed)

Authors: Davey P | Marwick CA | Scott CL | Charani E | McNeil K | Brown E | Gould IM | Ramsay CR | Michie S |

View author’s declarations of interest

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

SUMMARY

# Background

Antibiotic resistance is a major public health problem. Infections caused by multidrug-resistant bacteria are associated with prolonged hospital stay and death compared with infections caused by susceptible bacteria. Bacterial resistance often occurs because antibiotics are used when they are not needed. Appropriate antibiotic use in hospitals should ensure effective treatment of patients with infection and reduce unnecessary prescriptions. **This updated review aimed to assess the impact of interventions to improve antibiotic prescribing to hospital inpatients.** See more detail about interventions to improve prescribing practices for hospital patients.

# More detail about interventions to improve antibiotic prescribing practices

## What are interventions to improve prescribing practices?

There are several types of interventions to help physicians prescribe antibiotics properly. Examples include audit of records and feedback of findings to physicians, education and training, regular verbal or written reminders, and structural changes to enhance effective prescribing. Such interventions may either restrict practice by using rules to limit incorrect prescribing, or enable better practice by increasing capability or opportunity.

## 

## Who can use interventions to improve prescribing practices?

Physicians who work in hospitals may receive interventions to improve prescribing practices. Hospital authorities and ministries of health may select specific interventions to improve prescribing practices for implementation in hospital settings.

## 

## What other options are there?

Adequate training of medical students and trainee doctors and regular continuiung professional development may enhance prescribing practices. Inspection of health facilities and report back is another option to improve prescribing practice.

See systematic reviews of other options.

## 

## How do people experience the intervention?

Physicians who receive the interventions may welcome or resist the intervention, depending on the nature of the intervention and their own personal circumstances. For instance, many physicians may welcome the opportunity to receive feedback on their prescribing practice in order to improve it, but others may feel threatened and concerned that their practice will be found to be at fault. Some physicians may not wish to attend training or document additional prescription details if it increases their busy workload.

## 

## Is there anything else someone should know before using the intervention?

The effect of interventions, such as training or audit and feedback, may be time-limited and physicians may be required to receive future interventions in order to maintain the beneficial effect. In addition, antimicrobial resistance is likely to change over time in response to newer antibiotics, with the result that the content of interventions may require updating and delivery will require repeating.

# What this review is based on

Cochrane Reviews are based on systematic and robust selection of relevant studies. We included 221 studies, of which 58 were clinical trials, in this review. See what studies we searched for and what we found.

1st link to standard description of what a Cochrane Review is.

2nd link leads to the text below, which is a narrative summary of the table in the Full text called “What review authors searched for and found”:

## What studies we searched for

We searched for studies up until January 2015. We searched for randomised trials or non-randomised comparative studies (non-randomised trials, controlled before-after studies and interrupted time series studies) comparing delivery of an intervention to improve antibiotic prescribing practices to no intervention in a hospital setting. We also searched for non-comparative studies (case control, cohort, and qualitative studies) to identify unintended consequences.

## What we found

We included 221 studies: 58 randomised trials, 152 non-randomised comparative studies and 11 non-comparative studies.

# Main findings

→ **Interventions to improve antibiotic prescribing practices compared to no intervention:** Interventions to improve antibiotic prescribing practices increased the number of hospital patients receiving the appropriate treatment for their condition according to prescribing policy (high-certainty evidence). Interventions probably reduce the length of hospital stay (moderate-certainty evidence). Both restriction and enabling techniques were successful in achieving the effectiveness of the intervention (high-certainty evidence).

→ **Adverse effects and unintended consequences:** Compared to no intervention, interventions to improve antibiotic prescribing practices probably make no difference in number of hospital deaths (moderate-certainty evidence). Restrictive interventions may increase the risk of delay in treatment (low-certainty evidence) and lead to a negative professional culture (low-certainty evidence).

Standard sentences: See current Plain language summary guidance: http://www.cochrane.no/sites/cochrane.no/files/public/uploads/how\_to\_write\_a\_cochrane\_pls\_27th\_march\_2017.pdf

## Summary of findings 1

## **Summary of Findings should be numbered when there is more than one. Number 1 should be the one that appears in the summary. This will have consequences for the order of the comparisons listed in the full text.**

iSoF generator: See isof.epistemonikos.org.

Create a log-in and let me add you to our organization.

Standard sentences: See current Plain language summary guidance: http://www.cochrane.no/sites/cochrane.no/files/public/uploads/how\_to\_write\_a\_cochrane\_pls\_27th\_march\_2017.pdf

# Authors’ conclusions

Interventions were successful in safely reducing unnecessary antibiotic use in hospitals. More research is required on unintended consequences of restrictive interventions.

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

## Related content

* More information for patients and the public, health professionals and policy makers
* Cochrane Reviews of other options for improving antibiotic prescribing practices

(Links leads to texts in ‘Related content’ section – see end of document, after Appendix 3)

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

## Messages for media

(Link leads to ‘Messages for media’ section, created for the most part by people other than authors.)

**LAYER 1 A ends here**

**LAYER 1 B starts here**

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Cochrane Systematic Review – Intervention

Published date: 9 February 2017| Date of last search: January 2015 (see what’s changed)

Authors: Davey P | Marwick CA | Scott CL | Charani E | McNeil K | Brown E | Gould IM | Ramsay CR | Michie S |

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# Objectives

This review aimed to estimate the effectiveness and safety of interventions to improve antibiotic prescribing to hospital inpatients and to investigate the effects of two intervention functions: restriction and enablement.

# Main Findings

→ **Interventions to improve antibiotic prescribing practices compared to no intervention:** Interventions to improve antibiotic prescribing practices increased the number of hospital patients receiving the appropriate treatment for their condition according to prescribing policy (high-certainty evidence). Interventions probably reduce the length of hospital stay (moderate-certainty evidence). Both restriction and enabling techniques were successful in achieving the effectiveness of the intervention (high-certainty evidence).

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# Background

Antibiotic resistance is a major public health problem. Infections caused by multidrug-resistant bacteria are associated with prolonged hospital stay and death compared with infections caused by susceptible bacteria. Bacterial resistance often occurs because antibiotics are used when they are not needed. Appropriate antibiotic use in hospitals should ensure effective treatment of patients with infection and reduce unnecessary prescriptions. **This updated review aimed to assess the impact of interventions to improve antibiotic prescribing to hospital inpatients.** See more detail about interventions to improve prescribing practices for hospital patients.

# More detail about interventions to improve antibiotic prescribing practices

## What are interventions to improve prescribing practices?

There are several types of interventions to help physicians prescribe antibiotics properly. Examples include audit of records and feedback of findings to physicians, education and training, regular verbal or written reminders, and structural changes to enhance effective prescribing. Such interventions may either restrict practice by using rules to limit incorrect prescribing, or enable better practice by increasing capability or opportunity.

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Adequate training of medical students and trainee doctors and regular continuiung professional development may enhance prescribing practices. Inspection of health facilities and report back is another option to improve prescribing practice.

See systematic reviews of other options.

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## How do people experience the intervention?

Physicians who receive the interventions may welcome or resist the intervention, depending on the nature of the intervention and their own personal circumstances. For instance, many physicians may welcome the opportunity to receive feedback on their prescribing practice in order to improve it, but others may feel threatened and concerned that their practice will be found to be at fault. Some physicians may not wish to attend training or document additional prescription details if it increases their busy workload.

## 

## Is there anything else someone should know before using the intervention?

The effect of interventions, such as training or audit and feedback, may be time-limited and physicians may be required to receive future interventions in order to maintain the beneficial effect. In addition, antimicrobial resistance is likely to change over time in response to newer antibiotics, with the result that the content of interventions may require updating and delivery will require repeating.

# What this review is based on

Cochrane Reviews are based on systematic and robust selection of relevant studies. We included 221 studies, of which 58 were clinical trials, in this review. See what studies we searched for and what we found.

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## What we found

We included 221 studies: 58 randomised trials, 152 non-randomised comparative studies and 11 non-comparative studies.

# Authors’ conclusions

Interventions were successful in safely reducing unnecessary antibiotic use in hospitals. More research is required on unintended consequences of restrictive interventions.

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

## Related content

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## Messages for media

(Link leads to ‘Messages for media’ section, created for the most part by people other than authors.)

**LAYER 1 B ends here**

## \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

FULL TEXT

References in the text will be linked to reference lists in the final published version, but I have not bothered to recreate these links in the prototype sketches.

# Background

## Description of the condition

Antibiotic resistance is a major public health problem. In comparison with infections caused by susceptible bacteria, those caused by multidrug-resistant bacteria are associated with higher incidences of mortality and prolonged hospital stay (de Kraker 2011). *Clostridium difficile* infection (CDI) is another manifestation of the collateral damage caused by antimicrobial prescribing (Davey 2010). Such infections are also associated with increased costs resulting from the need to use more expensive antibiotics, prolonged hospital stay (the principal contributor), and expenses related to

screening and surveillance, eradication regimens, and consumables (the gloves, gowns, and aprons used to prevent cross-infection) (de Kraker 2011).

The UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018 recognises the importance of reducing inappropriate antibiotic prescribing (Department of Health 2013), the implication being that antibiotic resistance is largely a consequence of the selective pressures of antibiotic usage, and that reducing these pressures by the judicious administration of antibiotics will facilitate a return of susceptible bacteria or, at least, will prevent or slow the pace of the emergence of resistant strains. At the same time, sepsis is a major cause of avoidable mortality in hospitals, with an estimated 100,000 cases per year in the UK alone (NCEPOD 2015).

## Description of the intervention

Antibiotic stewardship has two aims: first, to ensure effective treatment of patients with infection, and second, to minimise collateral damage from antimicrobial use (Davey

2010). The UK Department of Health’s Guidance on Antimicrobial Stewardship emphasises the need for urgent treatment of serious infections in addition to minimising unnecessary use of antibiotics (Department of Health 2013).

Interventions which improve the practice of antibiotic prescribing by physicians can be classified by their intervention function (Michie 2011):

1. Education – increasing knowledge or understanding
2. Persuasion – using communication to induce positive or negative feelings or to stimulate action
3. Restriction - using rules to reduce the opportunity to engage in the target behaviour (or increase the target behaviour by reducing the opportunity to engage in competing behaviours)
4. Environmental restructuring – changing the physical context
5. Enablement – increasing means or reducing barriers to increase capability or opportunity

## Why it is important to do this review

This review is an update of Davey 2005 and Davey 2013. As antimicrobial resistance continues to increase with grave consequences in hospital settings, it is essential to delineate current evidence-based interventions to ensure physicians prescribe antibiotics effectively and safely.

# Objectives

1. To assess the effectiveness and safety of interventions to improve antibiotic prescribing to hospital inpatients; and
2. To investigate the effects of two intervention functions: restriction and enablement.

# Methods

## Criteria for considering studies for this review

### Types of studies

We included randomised controlled trials (RCTs) and non-randomised comparative studies (non-randomised trials, controlled before-after (CBA) studies and interrupted time series (ITS) studies). We used Cochrane Effective Practice and Organisation of Care (EPOC) Group eligibility guidance for CBAs and NRTs (EPOC 2016).

For the assessment of unintended consequences, we included three additional non-comparative study designs (case control, cohort, and qualitative studies) to identify additional evidence about long-term effects and harms of interventions in order to enhance the directness of evidence from RCTs (Schünemann 2013).

### Types of participants

Healthcare professionals who prescribe antibiotics to hospital inpatients receiving acute care (including elective inpatient surgery).

We excluded interventions targeted at residents in nursing homes or other long-term healthcare settings.

### Types of interventions

We included interventions relevant to improving antibiotic prescribing as outlined in the EPOC taxonomy (EPOC 2015).

1. Audit and feedback defined as any summary of clinical performance of health care over a specified period of time
2. Education through meetings or distribution of educational materials
3. Educational outreach through academic detailing or review of individual patients with recommendation for change
4. Reminders provided verbally, on paper, in the workplace environment (e.g. posters or messages printed on equipment) or on computer
5. Structural: the influence on antibiotic prescribing of changing from paper to computerised records and of the introduction of new technology for rapid microbiology testing or measurement of inflammatory markers.

We included the following restrictive interventions:

1. Selective reporting of laboratory susceptibilities
2. Formulary restriction
3. Requiring prior authorisation (expert approval) for therapeutic substitution
4. Automatic stop orders

The following were classified as enabling interventions:

1. Audit and feedback
2. Educational outreach through review of individual patients with recommendation for change
3. Circumstantial reminders that were targeted at doctors who were managing specific patients

We classified reminders in the form of posters or pocket cards summarising antibiotic

policies as environmental restructuring but not as enabling.

Terms used to describe interventions are described in more detail in APPENDIX the Data extraction and management section. TABLE 1??

### Types of outcome measures

(isof.epistemonikos.org).

The primary outcomes of the review were:

1. The effect of interventions on antibiotic prescribing measured as either compliance with antibiotic guidelines or policies
2. The duration of antibiotic treatment
3. Decision to treat
4. Total duration of treatment

We included studies without reliable or adequate information addressing the primary outcome measure, but we did not use these studies in data synthesis.

Secondary outcomes were:

1. Mortality
2. Length of stay
3. Other clinical outcomes (e.g. surgical site infection or acute kidney injury)
4. Microbial outcomes (*Clostridium Difficile* infection, colonisation or infection with antimicrobial-resistant bacteria)
5. Unintended-consequences measures (e.g. a delay in start of antibiotic treatment, a change in threshold for diagnosis of hospital-acquired infection to justify existing prescribing practice).

Note that clinical outcomes could be indicators of improved clinical outcomes

associated with interventions to increase effective antibiotic treatment, or unintended consequences (e.g. to provide evidence about the safety of interventions to reduce unnecessary antibiotic treatment).

## Methods for identifying studies

See: Additional details: Methods for identifying studies

## Methods for collecting and analysing data

See: Additional details: Methods for collecting and analysing data

# Results

## Results of the search

Our searches resulted in 221 studies, of which 211 evaluated the intended effect of interventions and 11 evaluated the unintended consequences of interventions. Below, Table 1 presents more detail about what we searched for and found. Figure 1 illustrates our inclusion and exclusion process in a study flow diagram. Then, in a series of tables and figures, we present the characteristics of included, excluded, and ongoing studies, as well as our judgements about risk of bias. (See Additional Details for a list of all results tables and figures.)

‘Figure 1’ link is the flow chart of included and excluded studies in Additional Details.

**Table 1: What review authors searched for and found**

|  |  |  |
| --- | --- | --- |
|  | **What the review authors searched for** | **What the review authors found** |
| ***Study designs*** | Randomised trials or non-randomised comparative studies (non-randomised trials, controlled before-after studies and interrupted time series studies).    Non-comparative studies (case control, cohort, and qualitative studies) to identify unintended consequences. | 211 studies evaluated the intended effect of interventions:   * interrupted time series studies (138) * randomised controlled trials (58) * controlled before-after studies (6) * non-randomised trials (8)   11 studies evaluated unintended consequences:   * cohort (8) * case control (1) * qualitative study (1) |
| ***Interventions*** | Any intervention to improve antibiotic prescribing practices compared to no intervention in a hospital setting.  Interventions include:   1. Audit and feedback 2. Education 3. Educational outreach 4. Reminders 5. Structural   Interventions were classified as enablement or restriction. | Delivery of interventions was by:   * Multidisciplinary team (112 (51%)) * Specialist infectious disease or mircobiologist physicians (54 (24%)) * Department physician (35 (16%) * Pharmacist (20 (9%) |
| ***Participants*** | Healthcare professionals who prescribe antibiotics to hospital inpatients receiving acute care. | 23,394 healthcare professionals participated in 29 randomised controlled trials of effectiveness |
| ***Settings*** | Hospital setting in any country. | Region (number of studies)   * North America (96) * Europe (87, includes Israel) * Asia (19) * South America (8) * Australia (8) * East Asia (3) |
| ***Outcomes*** | *Primary outcomes*   * Compliance with antibiotic guidelines or policy * Duration of antibiotic treatment * Decision to treat * Total duration of treatment   *Secondary outcomes*   * Mortality * Length of stay * Other clinical outcomes (e.g. surgical site infection or kidney injury) * Microbial outcomes * Unintended consequences (e.g. a delay in start of antibiotics) | *Primary outcomes (Number of trials)*   * Compliance with antibiotic guidelines or policy (29) * Duration of antibiotic treatment (14) * Decision to treat ( * Total duration of treatment (   *Secondary outcomes (Number of studies)*   * Mortality (28 RCTs, 4 ITS) * Length of stay (15 RCTs) * Other clinical outcomes (e.g. surgical site infection or kidney injury) (3 ITS) * Microbial outcomes (5 RCTs, 1 CBA, 26 ITS) * Unintended consequences (e.g. a delay in start of antibiotics) (1 RCT, 4 cohort, 1 case control, 1 qualitative) |

**Figure 1.** Study flow diagram of searches conducted for this update: How the authors selected the studies to be included in the review

**Table 2.** Characteristics of included studies: Details of the studies that the authors agreed to include in this review, according to the methods described for collecting and analysing data

**Table 3.** Characteristics of excluded studies: Details of the studies that the authors agreed to not include in this review

**Table 4.** Characteristics of ongoing studies

**Table 5.** Risk of bias of included studies: Details about the authors’ judgments about the risk of bias in the included studies

**Figure 2.** Risk of bias summary

## Effects of interventions

Effects according to outcome:

Key characteristics of included studies 1

Summary of findings 1

### Compliance with antibiotic prescribing guidelines or policy

Interventions to improve antibiotic prescribing practices increased the proportion of hospital patients receiving the appropriate treatment for their condition according to prescribing policy by 15% (95% CI 14% to 16%) (high-certainty evidence). See Analysis 1.1 (link to Analysis 1.1). We obtained similar results in sensitivity analyses for unit of analysis errors (Analysis 1.2) (link to Analysis 1.2) and risk of bias (Analysis 1.3) (link to Analysis 1.3).

*Meta-regression and Subgroup analysis*

We explored heterogeneity by conducting a meta-regression of 29 trials. Enablement, restriction, targeting antibiotic choice versus exposure (decision to treat or duration of all antibiotic treatment), and high risk of bias were significantly associated with greater intervention effect in univariate analysis, and all remained significant in multivariate analysis. See Figures XX

We also compared the effects of four trials of enabling interventions which targeted antibiotic choice combined with feedback, with seven trials of enabling interventions also targeting antibiotic choice but without feedback. The mean risk difference for interventions with feedback was 19% (95% CI 16% to 22%) (Figure 8) compared with 13% (95% CI 9% to 17%) (Figure 9) for interventions with no feedback.

### Duration of all antibiotic treatment

Interventions reduced the duration of all antibiotic treatment by 1.95 fewer days (95% CI 2.22 to 1.67) (high-certainty evidence). See Analysis 2.1 (link to Analysis 2.1). We obtained similar results in sensitivity analyses for unit of analysis errors (Analysis 2.1) (link to Analysis 2.1) or risk of bias (Analysis 2.3) (link to Analysis 2.3).

### Consumption of targeted antibiotic only

In four RCTs the prescribing outcome was the consumption of targeted antibiotics measured in different units (cost, days, or defined daily dose), so results were expressed as standardised mean reduction of 0.25 (95% CI -0.37 to -0.13). See Analysis 3.1 (link to Analysis 3.1). This result was not evaluated for certainty.

### Adverse effects: Mortality

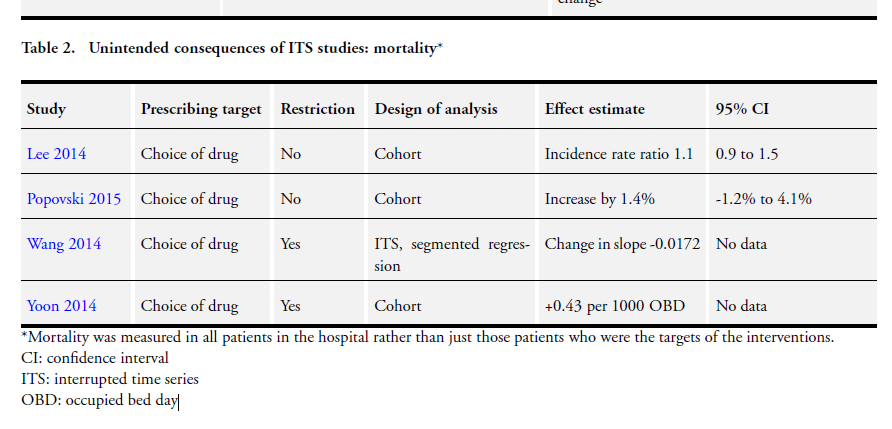
1. *Evidence from RCTs*

Interventions probably did not increase mortality (Risk Difference: -0.00; 95% CI -0.01 to 0.00) or 1 to 0 fewer deaths per 100 participants (moderate-certainty evidence). See Analysis 4.1 (link to Analysis 4.1). We obtained similar results in sensitivity analyses for unit of analysis errors (Analysis 4.2) (link to Analysis 4.2) and risk of bias (Analysis 4.3) (link to Analysis 4.3). We found no difference in results for interventions that targeted antibiotic exposure (decision to treat or duration of all antibiotic treatment) (Analysis 4.4) (link to Analysis 4.4) versus the choice of antibiotic (Analysis 4.5) (link to Analysis 4.5).

1. *Evidence from Observational Studies*

FROM THE AUTHORS’ TEXT:

Clinical outcome data were measured as mortality in four ITS studies (Table 2). However,we could only calculate 95%CI for three of these studies (Lee 2014; Popovski 2015; Skaer 1993), and the outcome data came from all participants in the hospital rather than just the participants who were the targets of the interventions.



### Adverse effects: Length of hospital stay

1. *Evidence from RCTs*

Interventions probably reduced mean length of hospital stay by 1.1 fewer days (95% CI -1.54 to -0.70) (moderate certainty evidence). See Analysis 5.1 (link to Analysis 5.1). We obtained similar results in sensitivity analysis for unit of analysis errors (Analysis 5.2) (link to Analysis 5.2) and risk of bias (Analysis.5.3) (link to Analysis 5.3). We found no difference in results for interventions that targeted antibiotic exposure (decision to treat or duration of all antibiotic treatment) (Analysis 5.4) (link to Analysis 5.4) versus the choice of antibiotic (Analysis 5.5) (link to Analysis 5.5).

1. *Evidence from Observational studies*

Interventions may not make a difference to the length of stay as indicated by results from a single cohort study (Mean difference = -0.1 days; 95% CI -0.49 to 0.29). The result was not evaluated for certainty.

### Adverse effects: Delay in treatment

*Evidence from RCTs and observational studies*

Interventions that restrict antibiotic choice by requiring prior approval may increase/cause a delay in treatment (low-certainty evidence). The data was from two cohort studies and a single randomised controlled trial. The Trial Monitoring Committee stopped the trial early when four participants were found to have potentially harmful delays in treatment. (link to tables - ? where shall we put these? in appendices?)

### Adverse effects: Negative professional culture

1. *Evidence from RCTs:*

No trials evaluated this adverse effect.

1. *Evidence from observational studies*

Interventions that restrict antibiotic choice by requiring prior approval may increase negative professional culture through breakdown in trust and communication (low-certainty evidence). The data was from two cohort studies, a case control study and a qualitative study. (link to tables - ? where shall we put these? in appendices?)

### Adverse effects – others: AT THIS POINT THE SINGLE STUDY ADVERSE EFFECTS WOULD FOLLOW BRIEFLY IN TEXT

### Antimicrobial outcomes

We have not attempted to synthesise microbial outcome data because of the small number of studies, the heterogeneity of intervention targets and prescribing outcomes, and the wide confidence intervals for estimated relative effect.

We have focused on the 20 interrupted time series studies of planned interventions and separated the results by microbial outcome type. Interventions were associated with consistent reduction in *Clostridium Difficile* infection (median -48.6%, interquartile range -80.7%to -19.2%) but inconsistent effect on resistant gram-negative bacteria (median -12.9%, interquartile range -35.3% to 25.2%) and resistant gram-positive bacteria (median -19.3%, interquartile range -50.1% to 23.1%). There were too few studies with too much variance in microbial outcomes to reliably assess the relationship between change in antibiotic use and each of the microbial outcomes.

# Discussion

## Key findings and certainty of the evidence

The RCTs provide high-certainty evidence that interventions are effective in increasing compliance with antibiotic policies and in reducing duration of antibiotic treatment safely, without an increase in mortality. Furthermore, interventions were associated with a reduction in length of stay. The mechanism is not clear, and further investigation is required. However, reducing length of stay is a key organisational objective for most hospitals, so this evidence should be used to prioritise antimicrobial stewardship in hospitals.

Analysis of effect modifiers in RCTs and interrupted time series studies consistently supported the theory that involving enablement increases intervention effect, including those with restrictive components. However, feedback was only used in a minority of enablement interventions, and very few included goal setting or action planning.

## Applicability of evidence

**Table 2:** *Applicability of evidence*

|  |  |
| --- | --- |
| Findings | *Interpretation* |
| The RCTs show that interventions increase compliance with policies or guidelines by 15%. | *This is a clinically important effect size and the consistency of findings across studies indicates it is likely to be replicable* |
| 70% of ITS studies reported on  hospital-wide interventions (compared with only 31% of RCTs) supporting the effectiveness of the interventions. | *It is likely that the results can be reproduced in routine practice and are generalizable.* |
| Health professionals’ adherence to prescribing recommendations increased by 15% but from a background rate of 43% to 58%. Three studies achieved 90% compliance with guidelines by making this an explicit goal for the intervention and using action planning to revise interventions until the goal was achieved. | *58% compliance is probably still far too low. Interventions should ideally include explicit goal-setting and action planning to ensure compliance.* |

## Agreements and disagreements with other studies or reviews

**Table 3:** *Agreements and disagreements with other studies or reviews*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Author / Year | Review or study type | Compliance reported? | Safety  reported? | Study type or study types included | No. of  included studies | Summary of main conclusions |
| Ivers 2012 | Review | Effect of audit and feedback of any interventions on professional practice | Unclear | RCTs | 140 | Interventions were more effective if they also included goal setting and action planning. |
| Charani 2011 | Review | Yes | Unclear | Not stated | Not stated | Behavioural  determinants and social norms were not given due consideration in the design and evaluation of interventions to change antibiotic prescribing. |
| Avery 2012;  Dreischulte 2016; Lester 2010 | Single studies (design not reported) | Not applicable | Not applicable |  |  | Removal of financial incentives is associated with reversal of intervention effects in primary care. |
| (Schuts 2016 | Review | Unclear | Yes | 39 | Case control and cohort | Guideline-adherent empirical therapy was associated with a reduction for mortality (odds ratio 0.65, 95% CI 0.54-0.80 |
| Feazel 2014) | Review | CDI |  | Not reported | 16 interrupted time series and uncontrolled before-after studies | Antibiotic stewardship programmes were associated with  a consistent, significant protective effect on *Clostridium difficile* infection (pooled risk ratio = 0.48, 95% CI 0.38 to 0.62). |

# Authors’ conclusions

## Implications for practice

The high-certainty evidence of the effectiveness of antibiotic prescribing interventions from this review should inform implementation decisions regarding antimicrobial stewardship interventions in hospitals.

In randomised controlled trials and interrupted time series studies, enablement consistently increased the effectiveness of interventions, including restrictive interventions.

Feedback was used in only a minority of enablement interventions, and very few included goal setting or action planning. Antimicrobial management teams might consider using evidence about effective feedback from other clinical settings.

Training in the design and reporting of behaviour change interventions should be a priority for antimicrobial management teams.

## Implications for research

**Table 6:** *Implications for research*

|  |  |
| --- | --- |
| **Trialists** | Given the high certainty of evidence for our primary outcome, we believe that additional trials comparing antibiotic stewardship with no intervention are unlikely to change our conclusions or build on our understanding of the current evidence. No new trials are required. |
| **Systematic  reviewers** | Future syntheses should focus on the relationship between prescribing and microbial outcomes of studies done in multi-centre settings. |
| **Other researchers** | Future research should focus on measuring clinical outcomes and assessing other measures of patient safety and different stewardship interventions and explore the barriers and facilitators to implementation.  There should be greater use of qualitative methods for investigation of consequences of interventions, for example in process evaluation alongside clinical trials. Anticipated, undesirable consequences should be regarded as trade-offs which may need to be accepted in exchange for a greater good so future research should examine how decisions are made about the acceptability of trade-offs. The purpose, design, and use of balancing measures in quality and safety improvement has been identified as a priority for research on methods in improvement science.  We propose three key questions:  1. What behaviour change approaches can be recommended now to optimise hospital stewardship programmes?  2. How can hospital stewardship programmes be designed to maximise implementation across countries?  3. What is the research agenda to optimise efficient implementation of antibiotic stewardship programmes worldwide?  There is an urgent need for co-ordinated, multicentre research studies to build future syntheses of the relationship between prescribing and microbial outcomes.  Further research is required to understand the mechanism for reduced length of stay and interventions that target choice of antibiotic or duration of antibiotic treatment. |

# References

Jump to: Included studies | Excluded studies | Ongoing studies | Other references | Other published versions of this review

## Included studies

## Ongoing studies

## Other references

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

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# Methods details

## a. Methods for identifying studies

*Electronic searches*

We searched the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) for related systematic reviews and the following databases for primary studies without language, publication year, or publication

status restrictions in January 2015.

* Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 1) in the Cochrane Library (searched 22 January 2015)
* MEDLINE (1946 to 19 January 2015) (OvidSP)
* Embase (1947 to 22 January 2015) (OvidSP)

The MEDLINE search strategy was developed by the Cochrane EPOC Group Information Specialist in consultation with the review authors and translated for use in other databases employing appropriate syntax and vocabulary. Results were limited by

two methodological filters: the Cochrane Highly Sensitive Search Strategy (sensitivity- and precision-maximising version, 2008 revision) to identify randomised trials (Higgins 2011), and a Cochrane EPOC Group study design filter to identify NRS.

See Appendix 2 for the search strategies used to identify trials.

* + 1. *Searching other resources*

We searched for additional studies using the bibliographies of included articles, personal files, and by contacting experts in the field regarding any unpublished work.

# Methods for collecting and analysing data

## Selection of studies

Two review authors (EB and PD) independently reviewed citations and abstracts retrieved in the search to identify all reports that included original data about interventions to change antibiotic prescribing. If either review author had doubts about eligibility, then both review authors reviewed the full papers. The review authors were not blinded to study author or location.We resolved disagreements by discussion and consensus.

We excluded studies that had no relevant and interpretable data presented or obtainable. We defined ’relevant data’ as an intervention that included a change in antibiotic treatment for hospital inpatients and where at least one of the study’s reported outcomes was directly attributable to change in antibiotic treatment.We defined ’interpretable data’ as follows: CBA, NRT, or RCT designs had to include sufficient data to estimate effect size as change in at least one relevant outcome after the intervention. Interrupted time series studies had to include a clearly defined intervention point. We did not exclude studies due to high risk of bias.

## Data extraction and management

Working in pairs, five review authors (PD, CM, CS, EC, KM) independently performed data abstraction using data extraction sheets including information on: study design, type of intervention (intervention components and functions), presence of controls,

type of targeted behaviour, participants, setting, methods (unit of allocation, unit of analysis, study power, methodological risk of bias, consumer involvement), outcomes, and results.

*Explanation of terms used to describe interventions*

* Restriction   
  We defined restriction as ’using rules to reduce the opportunity to engage in the target behaviour (or increase the target behaviour by reducing the opportunity to engage in competing behaviours)’.
* Enablement

We defined enablement as ’increasing means/reducing barriers to increase capability or opportunity’.

* Goal setting

We documented the specific prescribing behaviour that was targeted by the intervention (e.g. switch participants from parenteral to oral antibiotics) and how this was incorporated into an aim for the intervention. Was the aim simply a directional change of the target behaviour (e.g. increase or decrease behaviour?), or did the intervention include a specific threshold to be reached (e.g. target behaviour performed more than 95% of the time) or the duration within which the target had to be achieved (e.g. more than 95% reliability within six months)? If the study reported a power calculation, we did not accept this as evidence of a specific threshold unless it was clearly communicated to the professionals who were the targets of the intervention. For example, a power calculation showing that the study could detect a 10% improvement in the targeted behaviour would have to be accompanied by some explicit statement about the intervention aim being at least 10% improvement.

* Feedback

We classified interventions as including feedback only if they provided a “summary of clinical performance of healthcare over a specified period of time” (EPOC2015).We found that some studies did not meet this definition, even though they described their intervention as including feedback in the title (e.g. Elligsen 2012 and Newland 2012) or in the methods (e.g. Palmay 2014). The intervention in these studies was educational outreach by review and recommended change, so the feedback was limited to the individual participants who were reviewed with no feedback about the treatment of other participants over time. In contrast, Buising 2008a is an example of an intervention in which “a formal feedback was provided to units regarding their compliance with the approval system over time” in addition to review and recommend change for individual participants. For studies thatmet our definition of feedback, we recorded frequency, format (verbal, written, or both) and whether it was delivered by a colleague, supervisor, or somebody external to the clinical team.

* Action planning

We documented whether there was a reward for meeting a target, which could bematerial or social reward (either fromself or others) and the use of action plans if the targetwas notmet.Our definition of an action plan was: prompt, detailed planning of performance of the behaviour, which had to include at least one of context, frequency, duration, or intensity. If there was evidence of action planning, we recorded to whom the action plan was tailored (e.g. individual participant or group) and whether participants were involved in developing the action plan.

Note that each intervention component may have more than one intervention function. We have presented definitions of intervention functions and their

relationship to intervention components in Table 1.

## Assessment of risk of bias in included studies

We applied the 2013 EPOC ’Risk of bias’ criteria to all papers in the review, including articles in the 2003 review (EPOC 2013). We scored each study for risk of bias as ’low’ if all criteria were scored as ’low’, ’medium’ if one or two criteria were scored as ’unclear’ or ’high’, and ’high’ if more than two criteria were scored as ’unclear’ or ’high’.

We applied three additional criteria to studies with microbial outcomes, based on the ORION statement: Guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection (Orion Statement; Stone 2007).

1. Case definition: score as ’low’ if there is a clear definition either of infection or of colonisation and there were no major changes in laboratory diagnostic methods during the study period.
2. Planned intervention: score as ’low’ if the intervention was planned to reduce endemic rates of colonisation or infection and was not implemented in response to an outbreak. Regression to the mean following an outbreak is an important risk of bias for estimates of the effect of interventions in ITS studies of infection (Davey-Smith 2001; Stone 2007).
3. Other infection control measures: score as ’low’ if infection control practices (hand hygiene, gowning, or other personal protection) and isolation or cohorting policies are described and there were no changes coincident with the intervention to change antibiotic prescribing.

We have presented microbial ’Risk of bias’ results in the Notes section of the Characteristics of included studies. We have not included them in the ’Risk of bias’ tables unless there might also be a risk to prescribing outcomes (e.g. appointment of additional infection control practitioners who might have influenced prescribing).

We assessed risk of bias in case control or cohort studies of unintended consequences with ROBINS-I: a tool for assessing Risk of Bias in Non-randomised Studies of Interventions (Sterne 2016). We have reported these ’Risk of bias’ assessments in the Notes section of the Characteristics of included studies.

## Measures of treatment effect

We assessed the impact of interventions on clinical outcome for studies that provided reliable data about mortality, length of hospital stay, or other clinical outcomes such as acute kidney injury.

We did not include clinical outcomes for studies that estimated the impact of their intervention based on modelling (Barlow 2007). We analysed dichotomous data (such as increase in desired practice and mortality) as risk differences and analysed continuous data (such as length of hospital stay) as mean differences.

We critically examined the methods of analysis of ITS data. The preferred method is a statistical comparison of time trends before and after the intervention. If the original paper did not include an analysis of this type, we extracted the data presented in tables or graphs in the original paper and used them to perform new analyses where possible.We used segmented time series regression analysis to estimate the effect of the intervention whilst taking account of time trend and autocorrelation among the observations.

We obtained estimates for regression coefficients corresponding to two standardised effect sizes for each study: a change in level and a change in trend before and after the intervention. A change in level was defined as the difference between the observed level at the first intervention time point and that predicted by the preintervention time trend. A change in trend was defined as the difference between post- and pre-intervention slopes (Ramsay 2003).

We evaluated the direct effect of the intervention using results reported one month after the start of the intervention. We also reported the level effects at six months, and yearly thereafter when possible. We standardised the results of some ITS studies so that they were on the same scale (per cent change in outcome), thereby facilitating comparisons of different interventions. To do this, we used the change in level and change in slope to estimate the effect size with increasing time after the intervention (one month, six months, one year, etc.) as the per cent change in level at each time point. We did not extrapolate beyond the end of data collection after the intervention.We anticipated that the eligible studies would exhibit significant heterogeneity, due to variations in target clinical behaviours, patient and provider populations, methodological features, characteristics of the interventions, and the contexts in which the interventions were delivered. To address the source of variation in results due to the use of enabling or restrictive interventions, we undertook a random-effects meta-regression analysis on study-level summary effect size at each time point.

We assessed the impact of interventions on microbial outcomes if the study provided reliable data about colonisation or infection with *Clostridium difficile* or with antibiotic-resistant bacteria. We did not include microbial outcomes for studies that estimated the future impact of their intervention based on modelling (Paul 2006), or that used clinical definitions of infection that did not distinguish between resistant and sensitive bacteria (Micek 2004; Singh 2000).

## Unit of analysis issues

*Cluster trials*

If an RCT did not take into account the effect of clustering in the analysis, we stated this in the ’Risk of bias’ assessment. We incorporated consideration of unit of analysis issues as part of the sensitivity analyses.

We estimated intracluster correlation (ICC) for each outcome. The ICCs used reflect that process measures usually have higher ICC than outcome measures and were obtained from the database of ICCs held by the Health Services Research Unit, University of Aberdeen (Health Services Research Unit 2016).

* Prescribing 0.2
* Mortality 0.01
* Length of stay 0.2

Average cluster size (m) = (total number of participants (intervention + control)) (total number of clusters). Inflation factor = 1 + (m-1) x ICC. For dichotomous outcomes, we divided events and participants by the inflation factor for intervention and control groups. For continuous outcomes, wemultiplied intervention and control standard deviation by the inflation factor.

## Dealing with missing data

We have not attempted to account for missing data in the metaanalysis of RCTs or meta-regression of ITS studies. For ITS studies, we only analysed effects at a specified time point when data were available, we have not carried forward regression lines beyond the last observation or used regression lines to estimate missing data.

## Assessment of heterogeneity

We quantified heterogeneity among studies using the I2 statistic and Cochran’s Q test (Cochran 1954). The I2 statistic quantifies the percentage of the total variation across studies that is due to heterogeneity rather than chance (Higgins 2003); smaller percentages suggest less observed heterogeneity.

## Data synthesis

We have analysed the results for RCTs, CBAs,NRT, and ITS studies separately. For the RCT data, we employed a standard metaanalysis approach using ReviewManager 5 for binary (e.g. compliance with guidelines) and continuous (e.g. duration of treatment)

outcomes. We analysed the data with a fixed-effect model (Review Manager 5). We used Stata 14 for all statistical re-analyses and meta-regressions (Stata 2015), and ReviewManager 5 for all data synthesis (Review Manager 5).

## Subgroup analysis and investigation of heterogeneity

We used meta-regression to investigate potential effect modifiers. Inmeta-regression, the outcome variable is the effect estimate (e.g. a mean difference or a risk difference). The explanatory variables are characteristics of studies that might influence the size of intervention effect (Higgins 2011).

We prespecified four subgroups as explanatory variables for the meta-regression (Davey 2014):

1. Iinterventions that included enablement versus those that did not;
2. Interventions that included restriction versus those that did not;
3. Enabling interventions that included feedback versus those that did not;
4. Feedback interventions that included goal setting or action planning versus those that did not.

Definitions of these terms can be found in Data extraction and management and Table 1.

We expected restriction, enablement, feedback goal setting and action planning to be associated with increased effectiveness of interventions (Ivers 2012).

We included the following three additional variables in the metaregression because they might influence the size of intervention effect and explain heterogeneity.

1. Target: choice of antibiotic regimen versus time to first antibiotic dose or exposure to antibiotics, effects possibly greater for interventions targeting choice.
2. Setting: single unit versus multiple wards, effects possibly greater in single unit.
3. Intent: increase effective versus decrease excessive, effects possibly greater with increase effective.

The meta-regression was performed using standard weighted (by standard error of estimate) linear regression (Higgins 2011).

## Sensitivity analysis

We conducted sensitivity analyses by re-analysing data to investigate the effect of two risks of bias.

1. Lack of adjustment for the effect of clustering in cluster RCTs. We repeated all analyses that included cluster RCTs with adjusted numbers of events and total participants for dichotomous variables and adjusted standard deviation for continuous variables (Analysis 1.2; Analysis 1.5; Analysis 2.2; Analysis 2.5).
2. Overall high risk of bias. We analysed all studies at medium and low risk of bias separately in sensitivity analyses (Analysis 1.3; Analysis 1.6; Analysis 2.3; Analysis 2.6).

## Summary of findings table

We summarised the findings of themain intervention comparison for the most important outcomes in Summary of findings for the main comparison (Link to SOF). Two review authors independently assessed the certainty of the evidence for each key outcome (high, moderate, low, and very low) using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) (Guyatt 2011). We assessed the following outcomes:

Compliance with desired practice

Duration of antibiotic treatment

Mortality

Length of hospital stay

Delay in treatment

Negative professional culture

We also assessed the evidence from the meta-regression in terms of the extent to which we believed it helped explain variation of effect.We included the following effect modifiers in our analysis.

1. Enablement (Yes/No)

2. Restriction (Yes/No)

3. Addition of feedback to enablement (Yes/No)

4. Addition of enablement to restriction (Yes/No)

We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions,* (Higgins 2011), and the EPOC worksheets (EPOC 2013a). Disagreements on certainty ratings were resolved by discussion, and justification for decisions to down- or upgrade the ratings are provided in footnotes in the table and comments made to aid readers’ understanding of the review where necessary.

We used plain language statements to report these findings in the review. Further details about each of the five GRADE criteria are in Appendix 2.

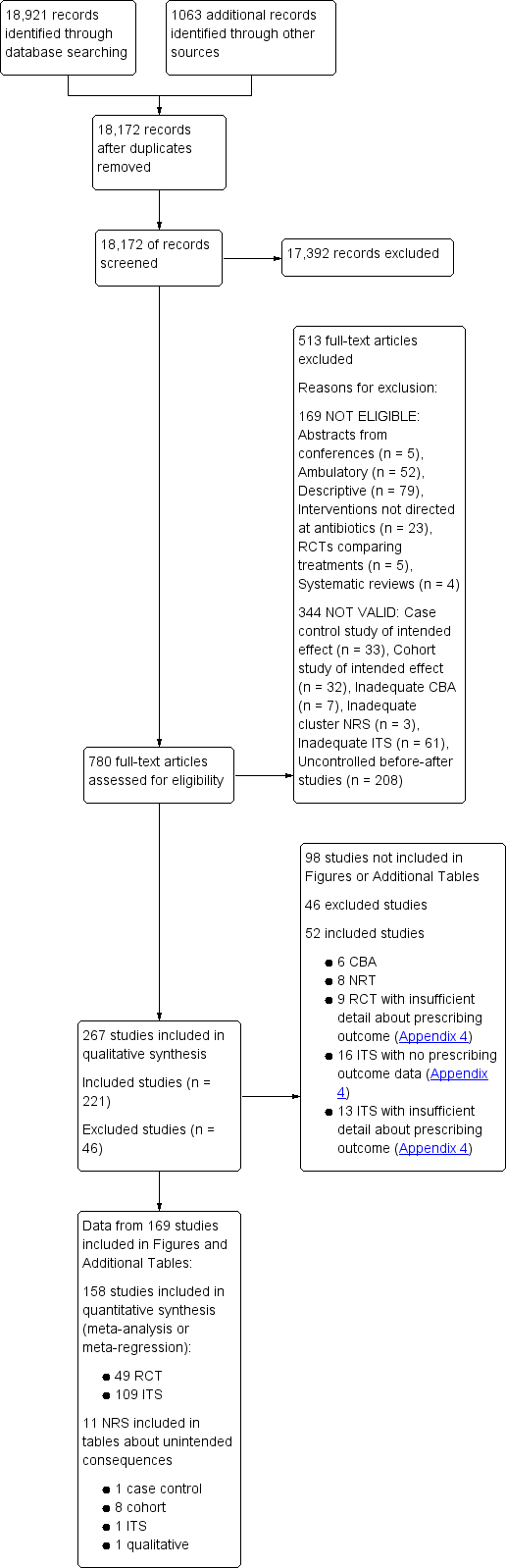
Evidence from randomised studies started at high certainty and was downgraded according to the five considerations described above. Evidence from non-randomised studies started at low certainty and was assessed against the same five criteria.We only considered upgrading for non-randomised evidence in the presence of a large treatment effect, dose response, or where plausible confounding would have reduced the observed effect.

# Study Characteristics

**Table 1:** *What review authors searched for and found*

Same as above in Full text

**Figure 1.** *Study flow diagram of searches conducted for this update*



**Table 2.** *Characteristics of included studies*

**Key features of the included studies**

We included 221 studies (58 randomised controlled trials and 163 non-randomised studies). Of these, 211 used the following designs to evaluate the intended effect of interventions: 138 interrupted time series studies, 58 randomised controlled trials (14 cluster), 6 controlled-before after studies and 8 non-randomised trials. A further 11 studies were designed to identify unintended consequences of interventions and used the following designs: 8 cohort, 1 case control, and 1 qualitative (semi-structured interviews), and 1 interrupted time series.

Most studies were from North America (96) or Europe (87). The remaining studies were from Asia (19), South America (8), Australia (8), and the East Asia (3).

A total of 178 (79%) studies were conducted in one hospital, 9 studies in 2 hospitals, 18 studies in 3 to 9 hospitals, and 16 studies in 10 or more hospitals.

Of the 221 interventions, 112 (51%) were designed and delivered by a multidisciplinary team, 54 (24%) by specialist physicians (infectious diseases or microbiology), 35 (16%) by department physicians (e.g. emergency department or critical care), and 20 (9%) by pharmacists.

Five studies received some funding from manufacturers of drugs or laboratory tests. The remaining 216 studies were funded by government agencies or the participating hospitals.

Sort tables by: comparison | study design

***Randomized controlled trials***

| **Study /setting** | **Participants** | | | **Interventions and comparisons** | **Outcomes** |
| --- | --- | --- | --- | --- | --- |
| **Inclusion  criteria** | **Exclusion  criteria** | **Enrolled** |
| **Annane 2013**  RCT  Hospital (multiple 8)  France | Providers: all physicians in participating intensive care units  Participants: all patients in the intensive care units with sepsis. |  | Total N: 62  Over a 3-year period, 62/1250 screened patients were eligible for the study, of whom 31 were randomised to each arm | Intervention: Structural - rapid testing of PCT with decision support algorithm delivered by departmental physician. Intervention Functions: enablement, environmental restructuring  Comparison: Usual care | * Exposure: % receiving antibiotics at day 5 * Cinical:   + Mortality   + Length of ICU stay   + Length of hospital stay * Microbial: colonisation with MRSA (nasal swab) and GNRB (rectal swabs) |
| **Bailey 1997**  RCT  Hospital (multiple 2)  USA | Providers: All physicians at 2 teaching hospitals, excluding Intensive Care Units  Participants:  patients receiving Intravenous antibiotics for at least 3 days, but excluded if in Intensive Care Unit or with uncontrolled infection or close to discharge | Not reported | Total N: 102 inpatients  51 randomised into intervention and 51 control | Intervention: Pharmacist-delivered educational outreach by review and recommend change.  Intervention Functions: education, enablement, persuasion  Comparison: Usual care | * Prescribing: reduce vancomycin prescribing and increase appropriate use of vancomycin * Valid fInancial savings |
| **Bouadma 2010**  RCT  Hospital (multiple 5)  France | Providers: All physicians in the Intensive Care Units  Participants:  All patients in the Intensive Care Unit requring antibiotic treament | Not reported | Total N: 630 inpatients  311 randomised into intervention and 319 control | Intervention: Departmental physician (Anaesthesiology and Intensive Care)-delivered reminders - circumstantial; structural - procalcitonin testing with decision support by treatment algorithm  Intervention Functions: enablement, environmental restructuring  Comparison: Usual care | * Exposure: days of antibiotic exposure per 1000 patient days * Clinical:   + Mortality (28 and 60 day)   + Length of Intensive Care Unit stay   + Length of hospital stay |
| Rest of the RCTs would follow here… | | | | | |
|  |  |  |  |  |  |

***Observational studies***

| **Study /setting** | **Participants** | | | **Interventions and comparisons** | **Outcomes** |
| --- | --- | --- | --- | --- | --- |
| **Inclusion  criteria** | **Exclusion  criteria** | **Enrolled** |
| **Abramowitz 1982**  Interrupted Time Series  Hospital (single)  USA | Providers: All physicians in a single hospital  Participants: All adult patients in the hospital receiving treatment with target antibiotics | Nil reported |  | Intervention: Pharmacist-delivered educational meetings with dissemination of materials; audit and feedback; educational outreach by review and recommend change. Intervention Functions: education; enablement; persuasion  Comparison: Usual care measured at 9 months pre-intervention | * Choice: decrease in use of cefoxitin and cefamandole * Total cost of 6 target antibiotics |
| **Adachi 1997**  Interrupted Time Series  Hospital (single)  USA | Providers: All physicians in a single hospital  Participants: All adult patients in the hospital requiring antibiotic treatment | Nil reported |  | Intervention: Pharmacist-delivered dissemination of educational materials; educational outreach by review and recommend change; reminders (physical - newsletter). Intervention Functions: education; enablement; environmental restructuring; persuasion  Comparison: Usual care | * Choice: reduce vancomycin prescribing and increase appropriate use of vancomycin * Valid financial savings |
| At this point there would be further ITS studies, but I selected to test out for qualitative, cohort and case control so these are the next consecutive references with different designs | | | | | |
| **Baysari 2013**  Qualitative study  Hospital (single)  Australia | Providers: 36 physicians  Participants: patients receiving antibiotic treatment that the hospital policy designated as requiring approval | Nil reported | 36 physicians | Intervention: AMT-delivered audit and feedback; restriction by prior approval. Intervention Functions: enablement; persuasion; restriction  Comparison: Nil as qualitative study | * Unintended consequences: problems with antibiotic policy and approval process identified through semi-structured interviews with prescribers who had received feedback letters |
| **Calfee 2003**  Case control study  Hospital (single)  USA | Providers: all physicians In adult medical and surgical units  Participants: all patients in the units regarding use of targeted antibiotics (3rd-generation cephalosporins, piperacillin/tazobactam, aztreonam, carbapenems, parenteral clindamycin, oral and parenteral vancomycin, parenteral fluoroquinolones and macrolides, and fluconazole) | Nil reported |  | Intervention: AMT-delivered restrictions by review and make change, automatic stop order for prescriptions not meeting policy indications. Intervention functions: restriction.  Comparison: Case control study | * Unintended consequences: proportion of nosocomial infections reported soley on the basis of a treating physican's diagnosis during the endemic and epidemic periods |
| **Connor 2007**  Cohort  Hospital (single)  USA | Providers: all physicians prescribing vancomycin  Participants: 120 patients with vancomycin prescription approved for only 72 hours | Nil reported | 120 patients | Intervention: AMT-delivered reminders (circumstantial and physical) stickers in medical records on day 3 warning of impending stop order; restrictive: stop order if approval not obtained. Intervention Functions: enablement, environmental restructuring, restriction  Comparison: Participants with and without stickers | * Unintended consequences: interruption of vancomycin treatment |
| **CBA** |  |  |  |  |  |

**Table 3.** *Characteristics of excluded studies (ordered by study ID)*

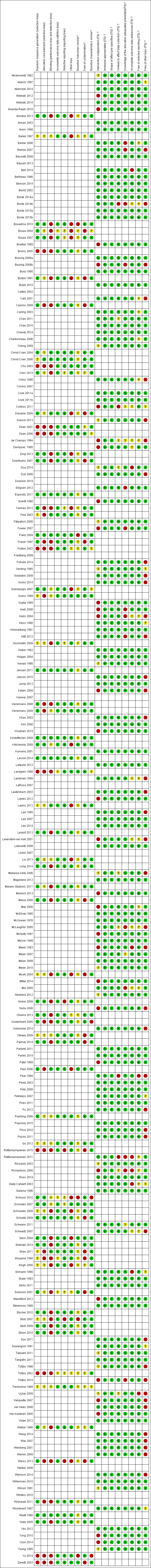
|  |  |
| --- | --- |
| **Study** | **Reason for exclusion** |
| **Ahronheim 2000** | RCT with no relevant data. Antibiotics were only part of a complex care plan for 6% of participants in the intervention group, and the outcome data do not include information about the effect of the intervention on antibiotic prescribing. |
| **Bruno-Murtha 2005** | ITS of antibiotic cycling with no interpretable data because there are no pre-cycling data. Only provides data for 4 phases of cycling. |
| **Burke 1997** | ITS with no interpretable data. 2 different interventions (education, then restriction via order form) with 3 points before the education intervention and 3 after, but the restriction intervention started after the 4th point. |
| **Cook 2006** | ITS with no interpretable data because no clearly defined point in time at which the intervention started. |
| **Crist 1987** | NRT with no interpretable data. Unacceptable allocation bias ("the allocation of a patient to a particular group was determined by the attending physician"). |
| **Cunningham 2008** | ITS with no relevant data. The only valid outcome data are about compliance with a guideline about generic documentation of prescription rather than any specific antibiotic prescribing outcome. The data about time to first antibiotic dose are UBA. |
| **Dellinger 2005** | ITS with no interpretable data because no clearly defined point in time at which the intervention started. Only 4 data points for antibiotic use, and the intervention included multiple components in addition to antibiotic use, so even if an intervention effect could be calculated reliably it could not be attributed to change in antibiotic prescribing. |
| **ETC** | **ETC** |

**Table 4.** *Characteristics of ongoing studies*

| **Study /setting**  **(RCT)** | **Participants** | | | **Interventions and comparisons** | **Outcomes** |
| --- | --- | --- | --- | --- | --- |
| **Inclusion  criteria** | **Exclusion  criteria** | **Enrolled** |

# Risk of Bias

**Figure 2.** *Risk of bias summary*

**

**Table 5.** *Risk of bias table*

**Abramowitz 1982**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Intervention independent (ITS)? | Unclear risk | Not stated. |
| Analysed appropriately (ITS)? | Low risk | Re-analysed. Not done in original paper (comparison of means, uncontrolled before-after). |
| Shape of effect pre-specified (ITS)? | Low risk | Done, intended effect was decrease in primary outcome and point of analysis was point of intervention |
| Unlikely to affect data collection (ITS)? | Low risk | Done, data were from routine systems and unlikely to change over study period |
| Knowledge of the allocation adequately prevented (ITS)? | Low risk | Done, data were from routine systems and unlikely to change over study period |
| Incomplete outcome data addressed (ITS)? | Low risk | Done, data were from routine systems and unlikely to change over study period |
| Free of selected reporting (ITS)? | Low risk | Done, data were from routine pharmacy systems database |
| Free of other bias (ITS)? | Low risk | Price of target antibiotics constant over the study period. |

**Adachi 1997**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Intervention independent (ITS)? | Low risk | > 1 year data pre- and post-intervention |
| Analysed appropriately (ITS)? | Low risk | Re-analysed. Not done in original paper (comparison of means, uncontrolled before-after). |
| Shape of effect pre-specified (ITS)? | Low risk | Done, intended effect was decrease in primary outcome and point of analysis was point of intervention |
| Unlikely to affect data collection (ITS)? | Low risk | Done, data were from routine systems and unlikely to change over study period |
| Knowledge of the allocation adequately prevented (ITS)? | Low risk | Done, data were from routine systems and unlikely to change over study period |
| Incomplete outcome data addressed (ITS)? | Low risk | Done, data were from routine systems and unlikely to change over study period |
| Free of selected reporting (ITS)? | Low risk | Done, data were from routine systems and unlikely to change over study period |
| Free of other bias (ITS)? | Low risk | Not clear, no information about changes In price of vancomycin over the study period |

**Annane 2013**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | Low risk | Computer generated |
| Allocation concealment  (selection bias) | Low risk | Central allocation |
| Blinding (performance bias and detection bias) | High risk | PCT levels not reported on control participants |
| Incomplete outcome data (attrition bias) | Low risk | No participants lost to follow-up |
| Selective reporting (reporting bias) | Low risk | No participants lost to follow-up |
| Other bias | High risk | Trial stopped prematurely because of low recruitment |
| Baseline outcomes similar? | Unclear risk | No data |
| Free of contamination | Low risk | PCT levels not reported on control participants |
| Baseline characteristics similar | Low risk | Table 1 |

**Bailey 1997**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | Unclear risk | "Physicians of patients considered candidates for intervention were randomised to be either contacted by the clinical pharmacist ... or to be observed" |
| Allocation concealment  (selection bias) | Unclear risk | Not stated |
| Blinding (performance bias and detection bias) | Unclear risk | Not stated |
| Incomplete outcome data (attrition bias) | Low risk | No problems found |
| Selective reporting (reporting bias) | Low risk | No problems found |
| Other bias | High risk | No power calculation. Prices of antibiotics unlikely to change over 6-month study period. |
| Baseline outcomes similar? | Unclear risk | Not stated |
| Free of contamination | Unclear risk | Not stated |
| Baseline characteristics similar | Low risk | See Table 1 in study |

**Baysari 2013**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) |  |  |
| Allocation concealment  (selection bias) |  |  |
| Blinding (performance bias and detection bias) |  |  |
| Incomplete outcome data (attrition bias) |  |  |
| Selective reporting (reporting bias) |  |  |
| Other bias |  |  |
| Baseline outcomes similar? |  |  |
| Free of contamination |  |  |
| Baseline characteristics similar |  |  |

**Bouadma 2010**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) | Low risk | Computer-generated randomisation sequence |
| Allocation concealment  (selection bias) | Low risk | Assignment concealed before allocation |
| Blinding (performance bias and detection bias) | High risk | Assignment not concealed post allocation |
| Incomplete outcome data (attrition bias) | Low risk | Outcome data reported on 98% of participants in control and intervention groups |
| Selective reporting (reporting bias) | Low risk | Outcome data reported fully on all included participants |
| Other bias | High risk | Patients assigned to the trial were > 50% of all patients receiving antibiotics (630/1315) |
| Baseline outcomes similar? | High risk | No data |
| Free of contamination | Low risk | PCT only reported on intervention participants |
| Baseline characteristics similar | Low risk | ITS |

**Calfee 2003**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) |  |  |
| Allocation concealment  (selection bias) |  |  |
| Blinding (performance bias and detection bias) |  |  |
| Incomplete outcome data (attrition bias) |  |  |
| Selective reporting (reporting bias) |  |  |
| Other bias |  |  |
| Baseline outcomes similar? |  |  |
| Free of contamination |  |  |
| Baseline characteristics similar |  |  |

**Connor 2007**

|  |  |  |
| --- | --- | --- |
| **Bias** | **Author’s judgement** | **Support for judgment** |
| Random sequence generation  (selection bias) |  |  |
| Allocation concealment  (selection bias) |  |  |
| Blinding (performance bias and detection bias) |  |  |
| Incomplete outcome data (attrition bias) |  |  |
| Selective reporting (reporting bias) |  |  |
| Other bias |  |  |
| Baseline outcomes similar? |  |  |
| Free of contamination |  |  |
| Baseline characteristics similar |  |  |

# Evidence tables

* 1. **Summary of findings 1**

Interactive table: isof.epistemonikos.org

Or see:

Isof.epistemonikos.org

For examples

**Table 6.** GRADE evidence profile

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient or population:** Providers and patients  **Intervention:**  **Comparison:** | | | | | | | | | | | | | | |
| **Quality assessment** | | | | | | | | Illustrative comparative risks\* (95% CI) | | | | |  | |
| Number of participants (studies) | | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other  considerations | Assumed  risk1 | Corresponding risk | | Relative effect | Absolute effect | Certainty of the evidence  (GRADE) | Importance |
| Control | Vaccine | |
|  | | | | | | | | | | | | | | |
|  | | RCT | Not serious2 | Not serious | Serious3 | Not serious | None |  |  | |  |  | ⊕⊕⊕⊝  Moderate | CRITICAL |
| **Influenza-like illness** | | | | | | | | | | | | | | |
| 25,795 (16 RCTs) | | RCT | Not serious2 | Serious4 | Not serious | Not Serious | None | 1442/9223 | 1646/16572 | | RR 0.84 (0.75 to 0.95) |  | ⊕⊕⊕⊝  Moderate | CRITICAL |
| **Hospitalisation** | | | | | | | | | | | | | | |
| 11,924 (3 RCTs) | | RCT | Serious5 | Not serious | Not serious | Serious6 | None | 1331/9084 | 272/2840 | | RR 0.96 (0.85 to 1.08) |  | ⊕⊕⊝⊝  Low | CRITICAL |
| **Time off work** | | | | | | | | | | | | | | |
| 3726  (4 RCTs) | | RCT | Serious7 | Serious8 | Not serious | Not serious | None | 1865 | 1861 | | MD -0.04 (-0.14 to 0.06) |  | ⊕⊕⊝⊝  Low | CRITICAL |
| **Fever** | | | | | | | | | | | | | | |
| 23,850  (13 RCTs) | | RCT | Not serious | Not serious | Not serious | Not serious | None | 166/11295 | 357/12555 | RR 1.55 (1.26 to 1.91) | |  | ⊕⊕⊕⊕  High | CRITICAL |
| **Nausea or Vomiting** | | | | | | | | | | | | | | |
| 6,315  (4 RCTs) | | RCT | Serious7 | Not serious | Not serious | Serious6 | None | 166/11295 | 357/12555 | RR 1.80 (0.65 to 5.04) | |  | ⊕⊕⊝⊝  Low | CRITICAL |
|  | **CI:** Confidence interval; **RR:** Risk ratio; **RCT:** randomized controlled trial. | | | | | | | | | | | | | |
|  | \*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). | | | | | | | | | | | | | |
|  | GRADE Working Group grades of evidence:  **High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different\* is low.  **Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different\* is moderate.  **Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different\* is high.  **Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially   different\*\* is very high.  \*\* Substantially different = a large enough difference that it might affect a decision | | | | | | | | | | | | | |
|  | 1 Control group risk calculated as the sum of events over total sample size from the control groups. For the outcome of influenza-like illness, control group risk was stratified as low, moderate (or median), and high due to variation in risk groups across the studies. For the remaining outcomes, the control group risk was taken as aggregate.  2Sensitivity analysis by excluding studies with two or more domains at unclear risk of bias did not meaningfully alter the direction, size, or precision of effect. We are confident that bias is unlikely to exaggerate the intervention effect because the absolute reduction in influenza and relative reduction in the risk of influenza-like illness are small with vaccination.  3Downgraded one level due to serious indirectness. Uncertainty over definition, surveillance and testing of influenza in older trials.  4Downgraded one level for serious inconsistency. There is discordance between the direction and size of effects across the studies. Different definitions of influenza-like illness across the studies could explain why there is variation in the event rates across the control arms.  5Downgraded one level due to serious risk of bias. Meta-analysis heavily influenced by a large study with high risk of bias across several domains.  6Downgraded one level due to serious imprecision. Confidence interval includes meaningful reduction and increase in effect.  7Downgraded one level due to serious risk of bias. Effect is influenced by studies judged to be at unclear risk of bias.  8Downgraded one level due to serious inconsistency. Direction and magnitude of effect differed across the studies (I2 = 82%). Wide confidence interval reflects the range of study effect sizes. | | | | | | | | | | | | | |

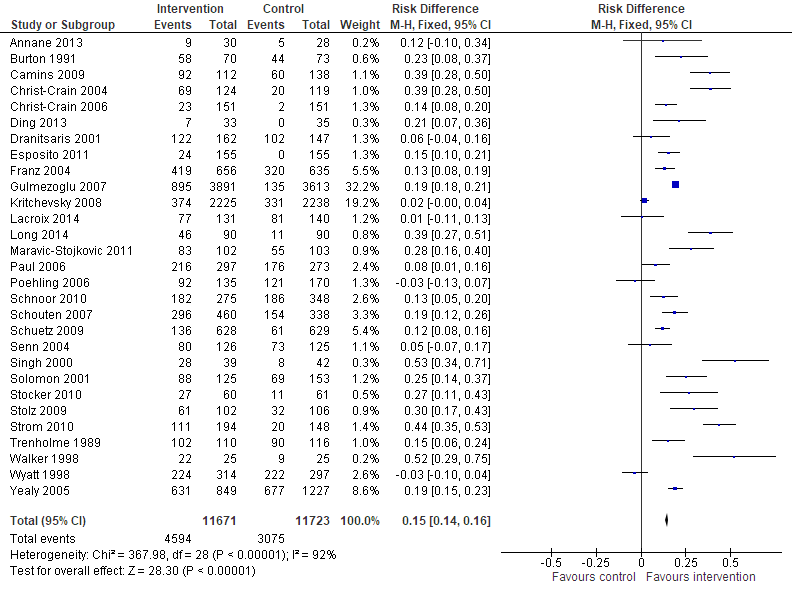
# Analyses with forest plots

* 1. *Overview of analyses*

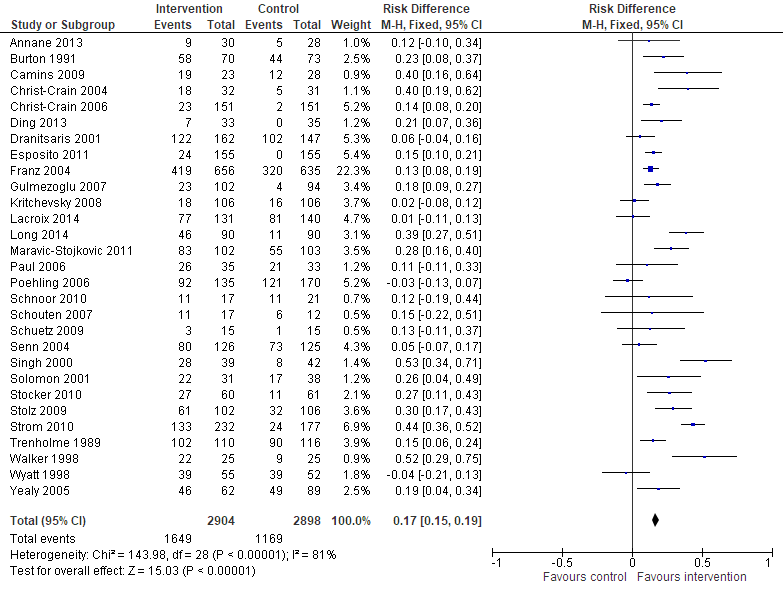
**Comparison:** Interventions to improve antibiotic prescribing practice versus no intervention

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Analysis** | **Outcome or subgroup** | **Studies** | **Participants** | **Statistical method** | **Effect estimate** |
| Analysis 1 | 1.1 Increase in desired practice - all RCTs | 29 | 23394 | Risk Difference (M-H, Fixed, 95% CI) | 0.15 [0.14, 0.16] |
|  | 1.2 Increase in desired practice - all RCTs with results of cluster RCTs adjusted by inflation factor | 29 | 5802 | Risk Difference (M-H, Fixed, 95% CI) | 0.17 [0.15, 0.19] |
|  | 1.3 Increase in desired practice - all RCTs with results of low or medium risk of bias studies only | 15 | 13086 | Risk Difference (M-H, Fixed, 95% CI) | 0.11 [0.10, 0.12] |
| Analysis 2 | 2.1 Duration of antibiotic treatment - all RCTs | 14 | 3318 | Mean Difference (IV, Fixed, 95% CI) | -1.95 [-2.22, -1.67] |
|  | 2.2 Duration of antibiotic treatment - all RCTs with results of cluster RCTs adjusted by inflation factor | 14 | 3318 | Mean Difference (IV, Fixed, 95% CI) | -1.95 [-2.23, -1.67] |
|  | 2.3 Duration of antibiotic treatment - with results of low or medium risk of bias studies only | 3 | 755 | Mean Difference (IV, Fixed, 95% CI) | -3.06 [-3.76, -2.37] |
| Analysis 3 | 3.1 Consumption of targeted antibiotic only, standardised mean reduction (original outcome cost, days or DDD) | 4 | 1053 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.25 [-0.37, -0.13] |
| Analysis 4 | 4.1 Adverse effect: Mortality - all RCTs | 28 | 15827 | Risk Difference (M-H, Fixed, 95% CI) | -0.00 [-0.01, 0.00] |
|  | 4.2 Adverse effect: Mortality - all RCTs with results of cluster RCTs adjusted by inflation factor | 28 | 8332 | Risk Difference (M-H, Fixed, 95% CI) | -0.01 [-0.02, 0.01] |
|  | 4.3 Adverse effect: Mortality - with results of low or medium risk of bias studies only | 8 | 6249 | Risk Difference (M-H, Fixed, 95% CI) | -0.00 [-0.02, 0.01] |
|  | 4.4 Adverse effect: Mortality - interventions targeting antibiotic exposure | 18 | 9173 | Risk Difference (M-H, Fixed, 95% CI) | -0.00 [-0.01, 0.01] |
|  | 4.5 Adverse effect: Mortality - interventions targeting antibiotic choice | 11 | 7658 | Risk Difference (M-H, Fixed, 95% CI) | -0.00 [-0.02, 0.01] |
| Analysis 5 | 5.1 Adverse effect: Duration of hospital stay - all RCTs | 15 | 3834 | Mean Difference (IV, Fixed, 95% CI) | -1.12 [-1.54, -0.70] |
|  | 5.2 Adverse effect: Duration of hospital stay - all RCTs with results of cluster RCTs adjusted by inflation factor | 15 | 3834 | Mean Difference (IV, Fixed, 95% CI) | -1.22 [-1.68, -0.76] |
|  | 5.3 Adverse effect: Duration of hospital stay - with results of low or medium risk of bias studies only | 6 | 1731 | Mean Difference (IV, Fixed, 95% CI) | -0.85 [-1.38, -0.32] |
|  | 5.4 Adverse effect: Duration of hospital stay - interventions targeting antibiotic exposure | 8 | 1558 | Mean Difference (IV, Fixed, 95% CI) | -0.87 [-1.42, -0.33] |
|  | 5.5 Adverse effect: Duration of hospital stay - interventions targeting antibiotic choice | 7 | 2276 | Mean Difference (IV, Fixed, 95% CI) | -1.50 [-2.16, -0.83] |

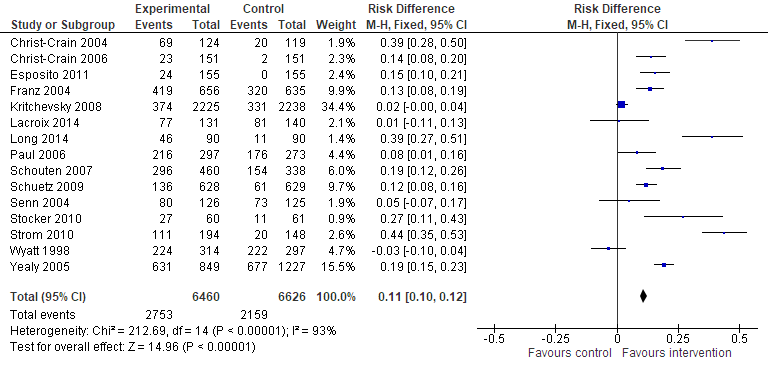
**b. Analysis 1.1. Interventions to improve antibiotic prescribing practice versus no intervention: Increase in desired practice**



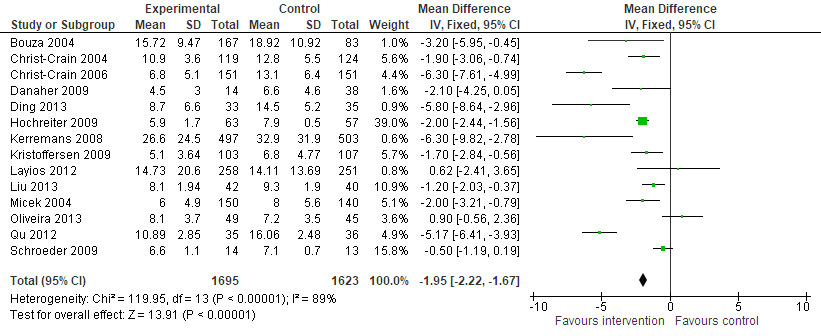
**Analysis 1.2. Interventions to improve antibiotic prescribing practice versus no intervention: Increase in desired practice (with results of cluster trials adjusted by inflation factor)**

****

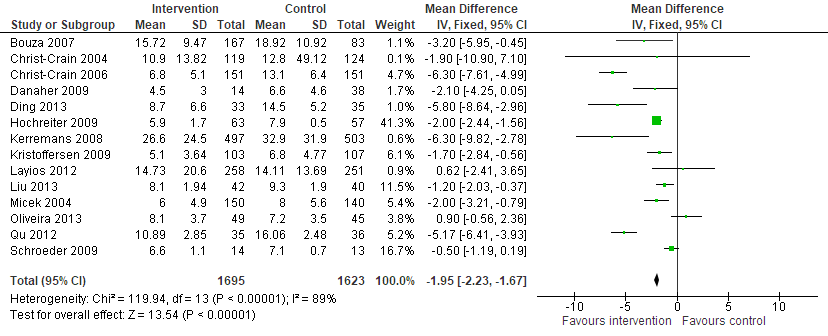
**Analysis 1.3. Interventions to improve antibiotic prescribing practice versus no intervention: Increase in desired practice (low or medium risk of bias studies only)**

****

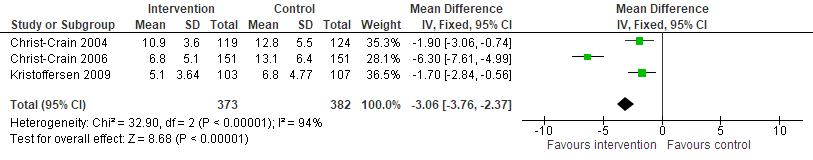
**Analysis 2.1. Interventions to improve antibiotic prescribing practice versus no intervention: Duration of all antibiotic treatment in days**

****

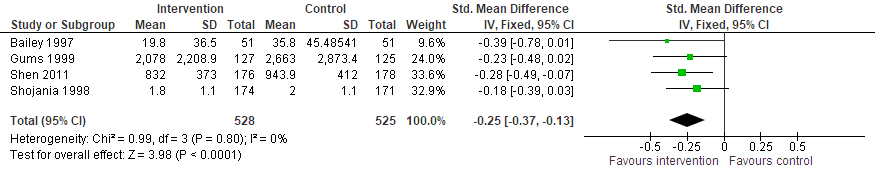
**Analysis 2.2 Interventions to improve antibiotic prescribing practice versus no intervention: Duration of all antibiotic treatment in days with results of cluster RCTs adjusted by inflation factor**

****

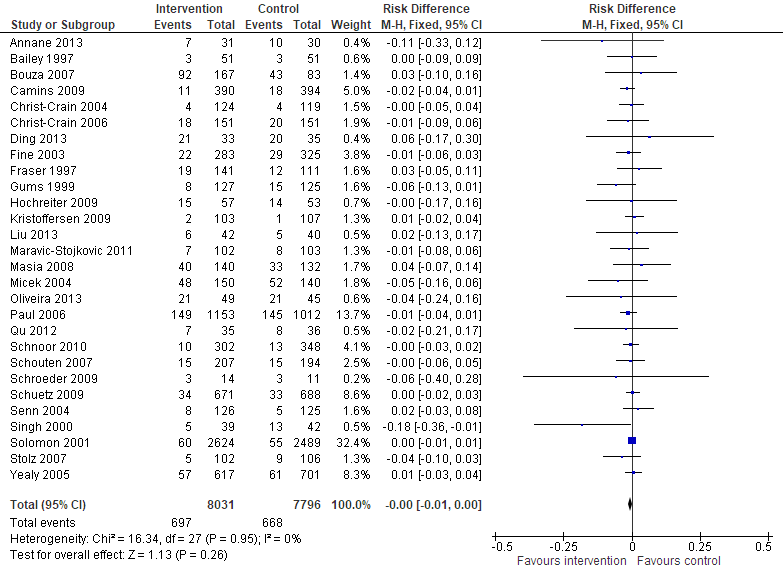
**Analysis 2.3 Interventions to improve antibiotic prescribing practice versus no intervention: Duration of all antibiotic treatment in days with low or medium risk of bias studies only**

****

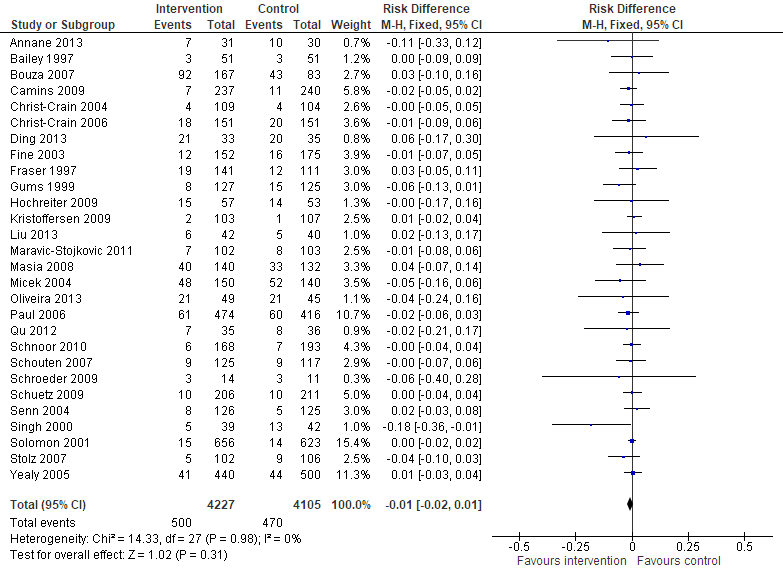
**Analysis 3.1 Interventions to improve antibiotic prescribing practice versus no intervention: Consumption of targeted antibiotic only, standardised mean reduction (original outcome cost, days or DDD)**

****

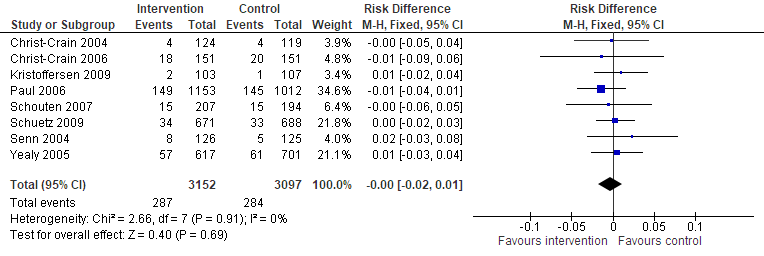
**Analysis 4.1. Interventions to improve antibiotic prescribing practice versus no intervention: Adverse effects Mortality**

****

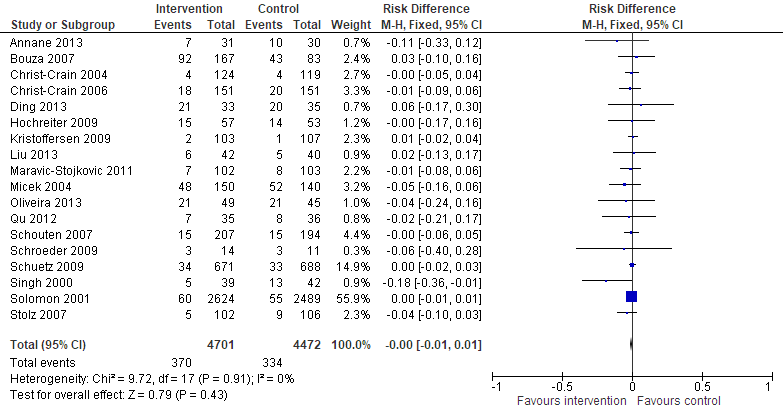
**Analysis 4.2 Interventions to improve antibiotic prescribing practice versus no intervention: Adverse effect Mortality with results of RCTs adjusted by inflation factor**

****

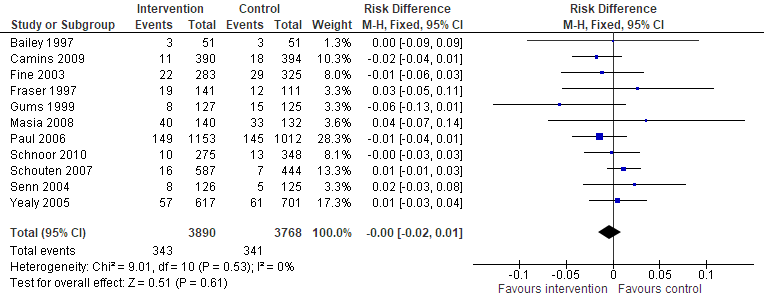
**Analysis 4.3 Interventions to improve antibiotic prescribing practice versus no intervention: Adverse effect Mortality with low or medium risk of bias studies only**

****

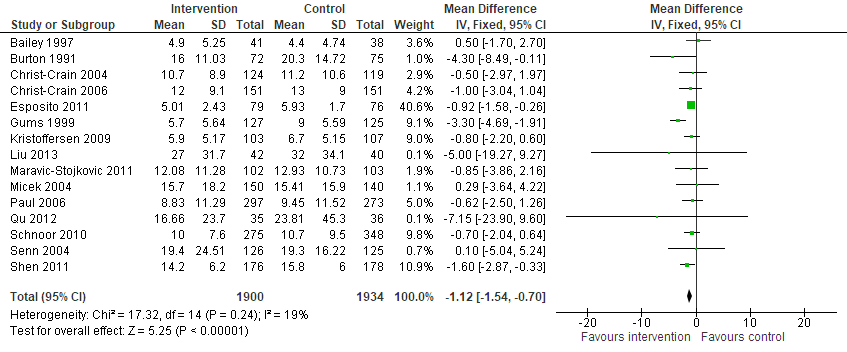
**Analysis 4.4 Interventions to improve antibiotic prescribing practice targeting antibiotic exposure versus no intervention: Adverse effect Mortality**

****

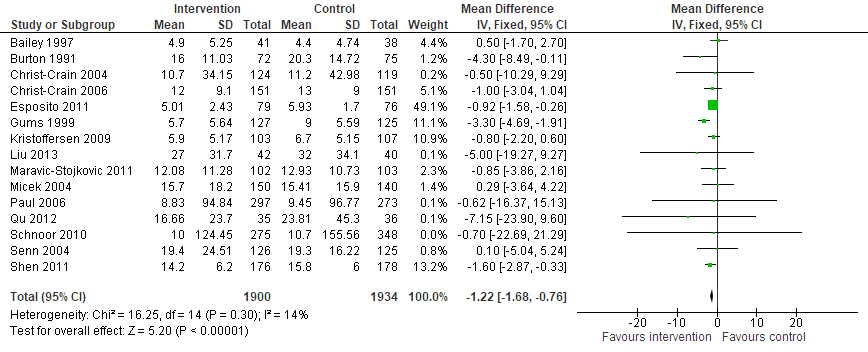
**Analysis 4.5 Interventions to improve antibiotic prescribing practice targeting antibiotic choice versus no intervention: Adverse effect Mortality with low or medium risk of bias studies only**

****

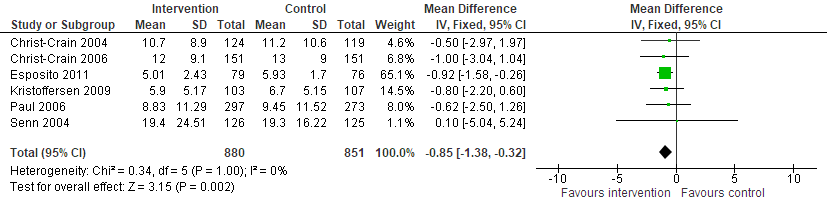
**Analysis 5.1 Interventions to improve antibiotic prescribing practice targeting antibiotic choice versus no intervention: Adverse effect Duration of hospital stay**

****

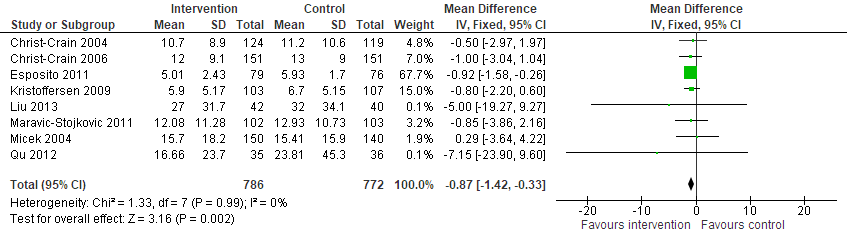
**Analysis 5.2 Interventions to improve antibiotic prescribing practice targeting antibiotic choice versus no intervention: Adverse effect Duration of hospital stay with results of cluster RCTs adjusted by inflation factor**

****

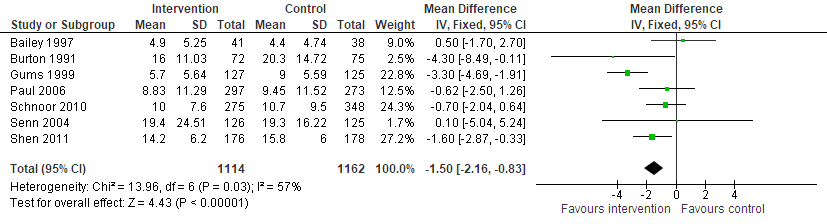
**Analysis 5.3 Interventions to improve antibiotic prescribing practice targeting antibiotic choice versus no intervention: Adverse effect Duration of hospital stay with results of low and medium risk of bias studies only**

****

**Analysis 5.4 Interventions to improve antibiotic prescribing practice targeting antibiotic exposure versus no intervention: Adverse effect Duration of hospital stay**

****

**Analysis 5.5 Interventions to improve antibiotic prescribing practice targeting antibiotic choice versus no intervention: Adverse effect Duration of hospital stay**

****

Appendices

## **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

Additional sections

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Ian M Gould

Craig R Ramsay

Susan Michie

## **Authors’ contributions**

Peter Davey (Clinical Pharmacologist) wrote the protocol; assisted with the literature search; reviewed all intervention studies for risk of bias using Cochrane Effective Practice and Organisation of Care (EPOC) Group methodology; contributed to re‐analysis of data from interrupted time series (ITS) studies and meta‐regression of ITS studies and randomised controlled trials (RCTs); wrote the first draft of the review and was responsible for final decisions about included studies; contributed to EPOC check sheets, data extraction, and GRADE assessment of certainty of evidence.  
  
Charis Marwick (Infectious Diseases Physician) re‐analysed all of the ITS studies and performed meta‐regression of ITS studies and RCTs with an analysis plan written by Craig Ramsay (Statistician); was a member of the review writing group; and contributed to EPOC check sheets, data extraction, and GRADE assessment of certainty of evidence.

Claire Scott (Psychologist) managed the review; set up the database; was a member of the review writing group; and contributed to EPOC check sheets, data extraction, and GRADE assessment of certainty of evidence.

Esmita Charani (Pharmacist) and Kirsty McNeil (Medical Student) were members of the review writing group and contributed to EPOC check sheets, data extraction, and GRADE assessment of certainty of evidence.

Erwin Brown (Medical Microbiologist) initiated the review in 2000 and for this update handsearched bibliographies of individual papers for additional references; screened titles and abstracts; and reviewed all papers to identify those that reported the results of an intervention to change antibiotic prescribing.

Ian Gould (Medical Microbiologist) reviewed papers for microbial risk of bias and was a member of the review writing group.

Craig Ramsay (Statistician) wrote the analysis plan for re‐analysis of ITS studies and meta‐regression of ITS studies and RCTs.

Susan Michie (Psychologist) advised on the design of data extraction for behaviour change techniques and the analysis of intervention functions; was a member of the review writing group; and contributed to GRADE assessment of certainty of evidence.

# Declarations

## **Authors’ declarations of interest**

Peter Davey is an author of four of the included studies. Charis Marwick is an author of two of the included studies. Ian Gould is an author of one of the included studies. Craig Ramsay is an author of one of the included studies. Other review authors completed data extractions for these studies. The institutions of the following authors received funding from the Chief Scientist Office that helped to support the conduct of this review: Peter Davey, Charis Marwick, Esmita Charani.

Peter Davey, none other than as indicated above.

Charis Marwick, none other than as indicated above.

Claire Scott, none other than as indicated above.

Esmita Charani, none other than as indicated above.

Kirsty McNeil, none other than as indicated above.

Susan Michie, none other than as indicated above.

Erwin Brown, none other than as indicated above.

Ian Gould, none other than as indicated above.

Craig Ramsay, none other than as indicated above.

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Lynda Fenelon, Roger Finch, Giles Hartman, Alison Holmes, Eric Taylor, Phil Wiffen, and Mark Wilcox were authors on the previous versions of this review.

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We are grateful to Weihua Meng, Celine Pulcini, and Virginia Hernandez‐Santiago for help with translation of papers from Chinese, French, and Spanish.

We are grateful to Jemma Hudson (Statistician), Paul Miller (Information Specialist), Kay Wang (External Referee), Atle Fretheim (Internal Editor), Sasha Shepperd (Contact Editor), and Julia Worswick (Managing Editor) for their comments and contributions to the review.

We are grateful to the Chief Scientist Office for a major grant that funded Claire Scott full time for 18 months (CSO CZH\_4\_861) and to the British Society for Antimicrobial Chemotherapy for their significant financial support for the costs of meetings, literature searches, obtaining full texts of papers, and construction of a web‐based system for double data entry. We are grateful to Keith Milburn for creating and managing the online database.

The authors (EC) would also like to acknowledge the National Institute of Health Research Imperial Biomedical Research Centre and the National Institute for Health Research, Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infection and Antimicrobial Resistance at Imperial College London in partnership with Public Health England (PHE) and the NIHR Imperial Patient Safety Translational Research Centre.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding and a Cochrane programme grant to the EPOC Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.

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### Internal support

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* Imperial College, London, England, UK.
* University of Dundee, Dundee, Scotland, UK.
* University of Aberdeen, UK.
* UK Cochrane Centre, UK.
* University College London, UK.

### External support

* British Society for Antimicrobial Chemotherapy, UK.
* Chief Scientist Office for Scotland, UK.
* Major grant CZH4861

# History

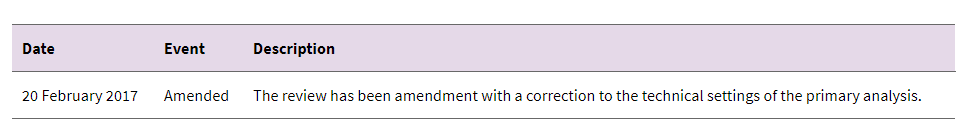
## **Version history**

Protocol first published: Issue 1, 2002  
Review first published: Issue 3, 2005

## **Search history**

## **What’s changed**

Last assessed as up‐to‐date: 19 January 2015.



## **Difference between protocol and review**

The protocol was completely revised for this update of the review. The most notable changes to the original protocol used for the first version of the review are as follows.

1. We amended the main outcome of interest to reflect desired change in practice. This fits better with the overall objective of the review relating to appropriate prescription in order to provide evidence of better targeting of antibiotic prescribing.
2. We changed the measure of effect from risk ratios to risk differences to better convey the intervention effect in absolute terms.
3. We adjusted for the effect of clustering in sensitivity analyses, as we had not considered this aspect of trial design in the previous version of the review.

# Messages for Media

Increasing resistance to antibiotics is an emerging threat to global health. This can be partly attributed to incorrect prescribing of antibiotics in the hospital setting. Several methods to influence doctors to improve their prescribing practices have been tested in clinical trials. Methods include providing up-to-date and regular education and training on current hospital antibiotic guidelines to staff, as well as auditing doctors’ records and feeding this back to the doctors, amongst others.

In this review, we analysed 221 studies from around the world. We combined the findings of 29 trials to test the methods to increase better prescribing practices in hospitals. We found that providing interventions to doctors compared to no intervention, increased the number of patients receiving the correct antibiotic by 15% and probably reduced the length of hospital stay by just over 1 day. The risk of death was similar whether doctors received the intervention or not. There was an indication from one trial and from six studies which did not compare groups that interventions which restrict doctors’ selection of antibiotic may lead to delays in treatment and create a negative professional culture.

Overall, our findings indicate that management of antibiotic prescribing practices successfully and safely reduces the unnecessary use of antibiotics in hospitals.

# Information for decision-makers

# For patients and the public - additional information

## What are interventions to improve prescribing practices?

There are several types of interventions to help physicians prescribe antibiotics properly. Examples include audit of records and feedback of findings to physicians, education and training, regular verbal or written reminders, and structural changes to enhance effective prescribing. Such interventions may either restrict practice by using rules to limit incorrect prescribing, or enable better practice by increasing capability or opportunity.

## 

## Who can use interventions to improve prescribing practices?

Physicians who work in hospitals may receive interventions to improve prescribing practices. Hospital authorities and ministries of health may select specific interventions to improve prescribing practices for implementation in hospital settings.

## 

## What other options are there?

Adequate training of medical students and trainee doctors and regular continuiung professional development may enhance prescribing practices. Inspection of health facilities and report back is another option to improve prescribing practice.

See systematic reviews of other options.

## 

## How do people experience the intervention?

Physicians who receive the interventions may welcome or resist the intervention, depending on the nature of the intervention and their own personal circumstances. For instance, many physicians may welcome the opportunity to receive feedback on their prescribing practice in order to improve it, but others may feel threatened and concerned that their practice will be found to be at fault. Some physicians may not wish to attend training or document additional prescription details if it increases their busy workload.

## 

# For clinical decisions

## **Indications and contraindications**

Interventions to improve antibiotic prescribing practices are indicated to increase the appropriate use of antibiotics by doctors in hospital settings. This may be required to address incorrect practices or to ensure that appropriate practice continues and remains current.

There are no specific contraindications to implementing interventions to improve prescribing practice, but clinicians should be aware of potential unintended consequences of the use of restrictive interventions as these may delay treatment and impair professional culture.

## **Delivery**

Interventions to improve prescribing practices can be delivered as:

1. Audit of records and feedback of findings to physicians
2. Education and training
3. Regular verbal or written reminders
4. Structural changes to enhance effective prescribing.

Interventions may either restrict practice by using rules to limit incorrect prescribing, or enable better practice by increasing capability or opportunity.

## **Cautions**

Clinicians should be aware of potential unintended consequences of the use of restrictive interventions as these may delay treatment and impair professional culture.

## **Counselling patients**

Patients need to be informed that their healthcare providers should prescribe antibiotics appropriately according to current hospital guidelines and policy. Patients may wish to ask if their prescribing doctor is aware of current antibiotic guidelines and whether he or she has received an intervention to ensure that they prescribe appropriate antibiotics for the condition.

# For policy decisions

Reducing antimicrobial resistance and hospital-associated infection is a public health priority. Our review shows that antimicrobial stewardship interventions can safely reduce unnecessary antibiotic use in hospitals, despite the fact that the majority of interventions did not use the most effective behaviour change techniques.

Consequently, effective dissemination of the review results could have considerable health service and policy impact through greater use of interventions that enhance enablement.

## **Policy options**

Policy options include decisions about the nature and scale of interventions to improve antibiotic prescribing practices. These should be based on local prevalence of disease and indicated antibiotic(s) and may include consideration of the level of background antimicrobial resistance present.

## **Equity considerations**

Antimicrobial resistance has global implications with over-use of antibiotics in well-resourced settings not only limiting future use in these settings, but also potentially limiting the utility of antibiotics for managing disease in less-resourced regions of the world. Ensuring that antibiotics are used appropriately throughout the world can thus contribute to improving equity.

The effects of antimicrobial resistance may be life-threatening, especially in vulnerable groups such as the older person, babies, and the immune-compromised. Delivery of interventions to improve prescribing practices may be targeted at doctors who care primarily for these groups.

## **Economic considerations**

Provision of effective antimicrobial stewardship will require ongoing investment to ensure interventions are current and available. Such provision may prove cost-effective by reducing the use of expensive antibiotics when these are not indicated and reducing the length of hospital stay in the short-term. In the long-term, ensuring that available antibiotics remain effective into the future will lead to cost benefits as patients continue to receive effective therapy.

## **Monitoring and evaluation**

Regular evaluation of interventions to improve prescribing practices following implementation will ensure that content remain current and delivery follows evidence-based behavioural techniques.

# Other options

## **Cochrane Reviews of other options to improve antibiotic prescribing in hospital settings**

Computerized advice on drug dosage to improve prescribing practice

Florence Gillaizeau, Ellis Chan, Ludovic Trinquart, Isabelle Colombet, RT Walton, Myriam Rège‐Walther, Bernard Burnand, Pierre Durieux | 12 November 2013

## **Related systematic reviews**

[Interventions to improve antibiotic prescribing practices in ambulatory care](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003539.pub2/full?highlightAbstract=antibiotic%7Cwithdrawn%7Cantibiot%7Cprescribing%7Cprescrib).

Sandra R Arnold, Sharon E Straus | 19 October 2005

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

Jack W O'Sullivan, Robert T Harvey, Paul P Glasziou, Amanda McCullough **|**25 November 2016

Clinician‐targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews

Sarah KG Tonkin‐Crine, Pui San Tan, Oliver van Hecke, Kay Wang, Nia W Roberts, Amanda McCullough, Malene Plejdrup Hansen, Christopher C Butler, Chris B Del Mar | 7 **September 2017**

# Related topics