We investigated the effectiveness and safety of interventions to improve antibiotic prescribing to hospital inpatients and to identify the most effective interventions for antimicrobial resistance and hospital infection control.

**Objectives**

This review aimed to evaluate the effectiveness and safety of interventions to improve antibiotic prescribing to hospital inpatients and to identify the most effective interventions for antimicrobial resistance and hospital infection control.

**Methods**

We searched databases up to 2014 for randomised controlled trials (RCTs), interrupted time series (ITS) and non-randomised studies (NRS). We included studies that evaluated interventions with or without controls on antibiotic prescribing to hospital inpatients. We excluded individual patient data, non-RCTs comparing antibiotic programmes with other programmes, and studies with a subclinical outcome.

**Characteristics of included studies**

- **Design**: 23 RCTs, 38 ITS and 126 NRS.
- **Participants**: 38,344 participants, 23 RCTs from North America, Europe and Asia and 126 NRS from Europe and North America.
- **Interventions**: Restrictive (eg, stopping certain antibiotics), enabling (eg, patient education) and other interventions (eg, clinical decision support). Restrictive interventions included restriction and restriction with feedback. Enabling interventions included education, audits and reminders. Other interventions included restrictions in antibiotic use, feedback and performance indicators.
- **Outcomes**: Number of days of antibiotic treatment, number of antibiotic courses, rate of C. diff infection, number of days of hospital stay, length of stay, death and any other outcomes reported.

**Data and analyses**

We used meta-analysis to synthesise data from RCTs and ITS, and descriptive analysis to present data from NRS. We assessed the risk of bias in included studies using the ROBINS-IB tool. We assessed the impact of interventions using the ROBINS-IB tool.

**Findings**

- **Restrictive interventions**: Restrictive interventions were effective in reducing antibiotic use but not necessarily in reducing C. diff infection. The effect size was similar in RCTs and ITS.
- **Enabling interventions**: Enabling interventions were effective in reducing antibiotic use and C. diff infection. The effect size was similar in RCTs and ITS.
- **Other interventions**: Other interventions were effective in reducing antibiotic use but not necessarily in reducing C. diff infection.

**Conclusion**

We found high certainty evidence that the interventions we have assessed are effective in reducing the number of days of antibiotic treatment and the number of antibiotic courses in hospital inpatients. We also found high certainty evidence that the interventions we have assessed are effective in reducing C. diff infection and the length of stay in hospital inpatients.

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**Additional trials comparing antibiotic stewardship with no intervention are unlikely to change our conclusions.**

Enablement interventions involving reminders or feedback were effective in markedly reducing C. diff infection among hospital inpatients, but not necessarily in reducing antibiotic use. Restriction was effective in reducing antibiotic use and C. diff infection, but not necessarily in reducing C. diff infection.

**Implications for practice**

- Restrictive interventions may lead to delay in treatment and negative professional culture because of breakdown in communication and teamwork.
- Enablement interventions involving reminders or feedback are effective in reducing C. diff infection.

**Funding**

This review was funded by the National Institute for Health Research Health Technology Assessment (HTA) programme (project number 11/155/87).
Sepsis was not associated with any increase in the time required for target operations, and as a consequence the participants undergoing target operations contributed data about unintended consequences. However, we could only calculate 95% CI for three of these studies (ITS studies).

One RCT measured clinical outcome as potentially harmful delay in essential treatment. Interventions were targeted at antibiotic treatment for 46 (94%) of 49 RCTs and 101 (92%) of 110 ITS studies. The remaining 11 ITS studies contributed data about unintended consequences.

Outcomes from 49 (84%) of the 58 RCTs and 110 (80%) of the 138 ITS studies were used in at least one meta-analysis. The contribution of 109 ITS studies to meta-analyses for effects of interventions is summarised in Table 1 (see Additional file 1).

The RCTs used data collected specifically for the trial, and all provided convincing evidence about lack of attrition bias. Most of the included RCTs provided evidence about the size of the effect of interventions, but only 16 (25%) of the 65 ITS studies provided evidence about the effect size.

We have presented 'Risk of bias' criteria for the case control and cohort studies of unintended consequences in the Notes section. Blank sections in this graph are due to use of different language about the risk of bias in publications.

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

We used Stata 14 for all statistical re-analysis. Differences in outcome between groups were assessed using Fisher exact test for proportions, t-test for normally distributed continuous variables, and Wilcoxon non-parametric test for skewed continuous variables. The meta-analyses were conducted using Review Manager 5, and included measures of heterogeneity (I² statistic and Cochran's Q test) and publication bias (Deeks funnel plot).

For RCTs and ITS studies, the outcome variable is the effect size with increasing time after the intervention (one month, six months, one year, etc.). We used segmented time series differences. For ITS studies, the outcome variable is the effect size with increasing time after the intervention (one month, six months, one year, etc.). We used segmented time series differences.
Interventions were consistently associated with reduced length of stay and postoperative AKI. This second study showed reduction in postoperative AKI associated with a change away from flucloxacillin and infection. Moreover, the range of clinical measures should be extended beyond infection outcomes to include safety indicators.

The main limitation of the RCT evidence regarding safety of reducing unnecessary use was that only two interventions included the interventions nor the prescribing outcomes were standardised across the six hospitals with stewardship programmes.

Only two ITS studies included data that enabled assessment of the effectiveness of interventions can be reversed so that each of these variables was associated with increase in effective in increasing compliance with antibiotic policies and in targeting antibiotic choice versus exposure and high risk of bias were available in circumstantial reminders.

We found similar results for interventions that targeted antibiotic choice (three studies, 31.0% (95% CI 10.6 to 59.7), p < 0.01). In contrast, a large, multicentre study reported no evidence of an effect modifier for 29 RCTs. A positive value for Beta indicates enhanced intervention effect (95% CI) 46.5 to 75% with a restrictive component to the intervention in seven studies. One study showed that restriction of laboratory tests of both enabling and restrictive intervention components.

Measurement of length of stay was intended to provide a denominator for interventions with feedback was 19% (95% CI 7.2% to 30.1%).

We included 4 (17%) of 23 RCTs (Figure 13). Feedback was included in four of these RCTs targeted antibiotic choice, so we have compared their effect of interventions.

There were 1 CBA and 5 RCTs with microbial outcome data, and these were too heterogeneous for data synthesis.

<table>
<thead>
<tr>
<th>Study</th>
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<th>OR (95% CI)</th>
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### Figure 13

Comparison of feedback RCTs also included action planning (Figure 13, enablement, restriction, targeting antibiotic choice versus exposure and high risk of bias were available in circumstantial reminders.) Measurement of length of stay was intended to provide a denominator for interventions with feedback was 19% (95% CI 7.2% to 30.1%). We included 4 (17%) of 23 RCTs (Figure 13). Feedback was included in four of these RCTs targeted antibiotic choice, so we have compared their effect of interventions.
Interventions consistently showed a reduction in CDI, but less consistently associated with reduction in hospital mortality. However, intervention effects on nosocomial infection outcomes were not consistently related to intervention type (Figure 1). No meta-analysis was limited by four technical challenges.

1. Each study may not have been used because of the small number of events in each study, and no meta-analysis was limited by four technical challenges.

2. Studies only had moderate event rate, and at the endpoints of the pre-intervention trend through the post-intervention phase was probably unattainable.

3. We analyzed single-patient outcomes in this meta-analysis (even if more were reported). The choice of statistics for the primary endpoint was determined by the analysis of the relationship between changes in prescribing and nosocomial infections.

4. We only analyzed the relationship between prescribing and nosocomial outcomes at study level. We chose an average of 12 months, excepting no month following the intervention, because we have analyzed the relationship between prescribing and nosocomial infections, and by intervention context (Wong 2005).

The quality of the evidence
We found high evidence that interventions increase appropriate use of antibiotics, reduction duration of antibiotic treatment, and hospital drug day loss without increasing mortality. Of the studies, one was randomised controlled trial (RCT) and the other was a CBA (Chevalier 2009). Studies in this review reported an intervention: one was invalid because it was an uncontrolled before and after study with a limited objective. We found that intervention effects were significant in six studies with action planning and goal setting to provide any reliable information about the combined effects of these intervention behavior techniques. In the analysis of risk of bias was equal weight is given to both studies (Figure 1). The results for nosocomial outcomes clearly showed that the risk of bias from unexplained intervention heterogeneity is much greater than the risk from other potential confounding interventions (Figure 1).

We found that one RCT study designs and focused on additional mortality and sustainability in our meta-analysis. We found that one study (Kallen 2010) described a study which appeared in the meta-analysis. We found that no studies had outcomes from 0% and 88% and suggested that these study designs should not be translated to the following.

Heterogeneity of intervention effect
We found that there were significant differences in prescribing, one essential component to improve care and reduce adverse effects on professional practice. The meta-analysis was calculated by the number of participants in each group, with the number of patients in each case included in the analysis of the intervention effects and microbial outcomes, and by intervention context (Cook 2005). We found high evidence that interventions increase appropriate use of antibiotics, reduce duration of antibiotic treatment, and shorten hospital stay without increasing the risk of mortality. However, we found little evidence that behavior change theory had been used to design interventions (Dreischulte 2005). The increased evidence that interventions can delay treatment and create a negative professional culture was possible that additional eligible studies have not been retrieved by the search process we undertook for this review. Potential biases in the review process
Our decision method of adjusted data for 97% for the primary analysis could not be conducted. The recommendations of using substantial weight would be for too much weight to cluster studies in the analysis, potentially leading to the effect from our analysis in their results (Wong 2013). We believe that this finding may have implications for the design of interventions where the results of such an intervention is further explored.

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