Effectiveness and safety of electronically-delivered prescribing feedback and decision support on antibiotic utilisation for respiratory illness in primary care. REDUCE cluster-randomised controlled trial

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Effectiveness and safety of electronically-delivered prescribing feedback and decision support on antibiotic utilisation for respiratory illness in primary care.

REDUCE cluster-randomised controlled trial

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ABSTRACT

Objectives: To evaluate the effectiveness and safety at population-scale of electronically-delivered prescribing feedback and decision support interventions at reducing antibiotic (AB) prescribing for self-limiting respiratory infections (RTI).

Design: Open-label, two-arm, cluster randomised controlled trial

Setting: UK general practices in the Clinical Practice Research Datalink

Participants: 79 general practices (582,675 patient years) randomised (1:1) to antimicrobial stewardship (AMS) intervention or usual care.

Interventions: The AMS intervention comprised a brief training webinar, automated monthly feedback reports of AB prescribing, and electronic decision support tools to inform appropriate AB prescribing over 12 months.

Main outcome measures: The primary outcome was the rate of AB prescriptions for RTI from electronic health records. Bacterial infections were evaluated as safety outcomes. Analysis was by Poisson regression with general practice as a random effect, adjusting for covariates. Pre-specified sub-group analyses by age-group are reported.

Results: There were 41 AMS trial arm practices (323,155 patient-years) and 38 usual care trial arm practices (259,520 patient-years). The adjusted AB prescribing rate ratio (RR) was 0.88 (95% CI, 0.78 to 0.99, P=0.040) with AB prescribing rates of 98.7 per 1,000 patient-years for AMS (31,907 AB prescriptions) and 107.6 per 1,000 for usual care (27,923 AB prescriptions). AB prescribing was reduced in adults aged 15-84 years (RR 0.84, 95%CI 0.75 to 0.95), with one antibiotic prescription per year avoided for every 62 (40 to 200) patients. There was no evidence of effect for children less than 15 years (RR 0.96, 0.82 to 1.12) or adults aged 85 years and older (RR 0.97, 0.79 to 1.18). Bacterial infections were not increased (RR 0.92, 0.74 to 1.13).

Conclusions: Electronically-delivered interventions, integrated into practice workflow, may safely reduce AB prescribing for RTI in adults but may not alter prescribing to children or people 85 years and older.

Trial registration: ISRCTN95232781

[296 words]

Key words: antibiotics; primary care; respiratory tract infections; pneumonia; peritonsillar abscess; mastoiditis; implementation science, audit, decision support

What is already known on this topic

Widespread unnecessary prescribing of antibiotics is contributing to the emergence of antimicrobial drug resistance.

A systematic review of antimicrobial stewardship interventions found low- to moderate-strength evidence that single interventions including patient and public education, point-of-care testing, audit and feedback and electronic decision support might be associated with reduced antibiotic utilisation, but previous interventions have been resource-intensive and have not been implemented at scale.

The relevance of previous trials to clinical practice is also unclear because of limited reporting of adverse clinical outcomes and lack of detail concerning possible effect modifiers, including patient characteristics.

What this study adds

This large study included more than 0.5 million patients from 79 general practices from throughout the UK, using used 'real-world' data from electronic health records (EHRs) to evaluate effectiveness and safety outcomes. The multi-component intervention comprised a training webinar, monthly feedback of antibiotic prescribing data from EHRs, and electronic decision support tools.

The results showed that use of this multi-faceted intervention was associated with reduced antibiotic prescribing. Patient age was identified as an effect modifier; the intervention reduced antibiotic prescribing for adults but not children or people aged 85 years or older. There was no evidence that the incidence of bacterial infections was increased.

Multi-faceted interventions, drawing on electronic health records data, may be safely scaled-up to promote effective antimicrobial stewardship in primary care. The needs of very young or old patients require further consideration.

INTRODUCTION

Over-utilisation of antibiotics in medical practice is contributing to the emergence of antimicrobial drug resistance (AMR). The US Centers for Disease Control estimated that each year in the U.S. at least 2 million people acquire antibiotic resistant infections and at least 23,000 people die as a direct result.[1] General practice and ambulatory care account for nearly three-quarters of all antibiotic (AB) prescribing, with respiratory tract infections (RTIs) representing the largest single group of indications for antibiotic treatment, including cough, acute bronchitis, common colds, otitis media, sinusitis and sore throat.[2] Antibiotic treatment generally has little if any effect on the severity or duration of RTI symptoms, is commonly associated with side-effects,[3,4] and encourages patients to re-consult in future episodes.[5] Current treatment recommendations suggest that a no antibiotic prescribing strategy should be agreed on with most patients presenting with self-limiting RTIs.[6] While there is limited evidence available to date, a lower AB prescribing strategy does not appear to compromise patient safety in terms of bacterial infections.[7,8]

A systematic review, updated to 2018, found that educational activities aimed at clinicians or patients, electronic decision support systems, and audit of antibiotic prescribing with feedback of results might be used to reduce unnecessary antibiotic prescribing.[9,10] However, the review concluded that it was unclear how useful these interventions might be in usual clinical practice because of a lack of information about possible adverse events, including possible increases in bacterial infections.[10] Previous studies also lacked information about effect modification by patient characteristics, such as age, gender and comorbidity, that might influence intervention effectiveness.[10] The review suggested that a strategy of combining interventions might hold promise and recommended that trials of multi-faceted interventions, including two or more interventions found to be effective individually, should be undertaken.[10] While some recent trials have used electronic media to deliver

interventions,[11,12] previous interventions have often been resource-intensive[13] and have not yet shown potential to be translated on a wide and sustainable scale into routine healthcare. The present research focused on low-cost interventions that can be readily integrated into routine practice workflow and scaled-up through remote delivery using electronic media to a large sample of unselected practices. The research developed a multi-component intervention that included a brief training webinar for prescribers, followed by monthly feedback reports of AB prescribing at RTI consultations and decision support tools to inform appropriate AB prescribing. The primary objective was to evaluate whether this multi-component intervention was effective and safe, when delivered electronically into general practices over 12 months, at reducing prescribing of antibiotics when patients consult with RTIs.

METHODS

Study design and participants

The study was an open-label, two-arm, parallel-group randomised trial with general practices as the unit of allocation. The target population for this trial was the general population registered with general practices in the United Kingdom, including England, Scotland, Wales, and Northern Ireland. The trial was conducted using the anonymised electronic health records of general practices contributing to the UK Clinical Practice Research Datalink (CPRD). The CPRD is one of the world's largest databases of primary care electronic health records, it includes monthly-updated data from general practices throughout the UK. CPRD data have been extensively evaluated and employed for epidemiological[14] and interventional research.[15] General practices contributing to CPRD were invited to participate in the study from September 2015. General practices were included in the trial if they were actively contributing data to CPRD and consented to participation in the trial. Data for all registered patients from trial practices in CPRD were included; there were no exclusion criteria.

The protocol was approved by the NHS London-Dulwich research ethics committee and by the CPRD Independent Scientific Advisory Committee (ISAC 14_130). Trial oversight was provided by Independent Trial Steering (TSC) and Data Monitoring Committees (DMC). Each participating general practice gave written informed consent for participation. General practices were randomised between 11th November 2015 and 9th August 2016 and final follow-up was on 9th August 2017. The trial was stopped when the last general practices completed 12 months of follow-up. The study protocol has been reported previously,[16] the updated protocol including amendments to the sample size calculation and statistical analysis plan has been published online.

Randomisation and masking

Cluster randomisation was employed because intervention was delivered at general practice-level. CPRD staff (JS and KS) were responsible for recruiting practices to the trial and communicating allocations but had no access to the allocation procedure. Allocation to antimicrobial stewardship and usual care trial arms was performed at King's College London (MG, TP) by minimisation using the MINIM program,[17] stratifying for region and pre-trial antibiotic prescribing quartile. 'Region' comprised Scotland, Wales and Northern Ireland and, in England, North (including North East, North West and Yorkshire and Humber), Midlands (including East and West Midlands), South and East (including East of England, South Central and South East Coast), South West and London. As only two practices were recruited in the Midlands, this region was combined with North for analysis. As general practices consented to participation over an extended recruitment period, they were allocated in six waves, which were combined for analysis into three periods including: Period 1, practices randomised in November 2015; Period 2, January and February 2016; and Period 3, June to August 2016 respectively. One practice allocated to the intervention trial arm withdrew from CPRD before the intervention started and was excluded from further analysis

because no data were available. There was no blinding of health professionals to trial arm allocation.

Interventions

An intervention development study was conducted and is described in detail elsewhere.[16,18] Development of the antimicrobial stewardship (AMS) intervention drew on social cognitive theory[19] and self-determination theory,[20] experience from development of a previous intervention,[15,21,22] and qualitative interviews with 31 prescribers to refine prototype versions of interventions. The intervention comprised three elements that were delivered remotely into practices using electronic media. A six-minute pre-recorded webinar introduced and provided brief training in use of the trial interventions. Prescribing reports were prepared through analysis of CPRD electronic health records, which are updated monthly. These were sent to each practice by email, to present monthly-updated feedback of data for counts of respiratory consultations and antibiotic prescriptions for that practice, in comparison with the preceding 12 months. Decision support tools were deployed remotely into existing practice software to provide patient information sheets and advice on the positive indications for antibiotic prescription during consultations for RTI. Patient information sheets were provided for common colds and upper respiratory infections, sore throat, otitis media, sinusitis, and cough and bronchitis. Separate sheets for children were provided for otitis media and cough and bronchitis. Recommendations for positive indications for antibiotic prescription followed NICE guidance.[6] Intervention materials were accessible to all prescribers in AMS trial arm practices. General practices identified a 'champion' for the study who ensured that all prescribers were aware of the trial interventions. Practices were encouraged to discuss the webinar and antibiotic prescribing feedback reports at practice meetings. The antimicrobial stewardship intervention is summarised in Supplementary Table 1; a more extensive description of the intervention is published elsewhere.[18] There were no modifications during

the course of the study. General practices randomised to usual care received no study interventions.

Outcomes

Outcomes for both antimicrobial stewardship and usual care trials arms were evaluated using anonymised individual-patient electronic health records from CPRD. Consultations for self-limiting RTIs were identified from medical codes for cough and bronchitis, otitis media, rhinosinusitis, sore throat and common colds. Medical codes were drawn from the Read code classification, which was in use in the UK at this time, including symptoms and medical diagnoses. Lower respiratory tract infections including 'chest infections', exacerbations of chronic bronchitis and pneumonia were not included because they are subject to different treatment recommendations. Antibiotic prescriptions were identified from product codes for antibiotics included in the *British National Formulary* section 5.1. We determined whether antibiotics were prescribed on the same date as the RTI consultation. Repeat consultations for any RTI during the same episode were excluded using a 14-day time window. The primary outcome measure was the rate of AB prescribing for RTI per 1,000 patient-years over the 12-month intervention period. Secondary outcome measures were the proportion of RTI consultations with antibiotics prescribed; the consultation rate for RTI per 1,000 patient years; AB prescribing for sub-groups of RTI; and total antibiotic prescribing for all indications. Safety outcomes were identified by the DMC as new occurrences of a wide range of bacterial infections including pneumonia, peritonsillar abscess, mastoiditis, intracranial abscess, empyema, scarlet fever, pyelonephritis, septic arthritis, osteomyelitis, meningitis, toxic shock syndrome and septicaemia, and Lemierre's syndrome. Interim analyses of safety outcomes were presented to the DMC in October 2016 and April 2017. The comorbidity status of patients consulting with RTI was classified as present or absent based on 'seasonal flu at-risk' status including diagnoses of significant heart, lung, renal, liver or neuromuscular disease,

as well as cystic fibrosis, diabetes, and immunosuppression or immunosuppressive treatment.[23]

Statistical Analysis

The primary outcome for the trial was the rate of antibiotic prescriptions for RTI per 1,000 registered patients. The sample size calculation was informed by data from our previous eCRT trial[15] in CPRD. The distribution of general practice-specific AB prescribing rates had a mean 111.9 (SD 39.8) AB prescriptions per 1,000 registered patients, with a correlation coefficient of 0.82 between AB prescribing in the baseline and intervention periods. We initially aimed to recruit 120 CPRD general practices but this target was not achieved because of declining numbers of general practices contributing to CPRD. In an updated sample size calculation, we estimated that a total of 80 practices would give 80% power (with alpha 0.05) to detect an absolute reduction in AB prescribing rate of 15 per 1,000 registered patient years, compared with 12 per 1,000 if 120 practices had been recruited.

Individual-level patient data for primary, secondary and safety outcomes were analysed according to the intention-to-treat principle. The original protocol[16] proposed a general practice-level analysis but this was amended in the statistical analysis plan, approved by the CPRD-ISAC, because attrition of practices during the trial and increased focus on safety outcomes[7] required consideration of individual patient-level covariates and temporal effects in an individual-level analysis.

The trial dataset comprised full electronic health records data for all patients who consulted with RTI on one or more occasions during the trial baseline and intervention periods, together with denominator data for all patients registered at trial practices. For each registered patient, we evaluated the person-time at risk during the 12-month intervention

period of the trial. A random effects Poisson model was fitted using the 'hglm' package in the R program,[24] with a random intercept for general practice and the log of person years as offset. The dependent variable was a count of antibiotic prescriptions. Covariates were trial arm, gender, age-group, comorbidity status, region, study quarter and baseline AB prescribing rate. The period of randomisation was included, as well as the interaction of period with the baseline AB prescribing rate. The baseline AB prescribing rate was included as an age-standardised rate for each practice, using the European standard population for reference. For practices that withdrew during the intervention period, baseline time was included pro-rata. Forest plots were constructed. A sensitivity analysis was conducted for the primary outcome by fitting an over-dispersed Poisson model using the 'dhglm' package in the R program.[24]

Safety outcomes were ascertained from CPRD clinical and referral files. The latter includes coded data for hospital referrals and discharge letters but linked Hospital Episode Statistics data were not available for all practices and were not analysed. Safety outcomes were analysed adjusting for age-group, gender and comorbidity. A random effect for general practice was included for the most common outcome of pneumonia, and for the composite, but this was omitted for the remaining outcomes.

Interaction terms were tested and pre-specified sub-group analyses were conducted. The statistical analysis plan included pre-specified sub-group analyses by age-group, gender, comorbidity, region, type of infection and baseline antibiotic prescribing quartile. Age-group was categorised: from 0 to 14 years, then ten-year bands, until 85 and over. The sub-group effect was assessed statistically on this basis and the effect was summarised more simply in those 0 to 14 years classed as children, those 15-84, and those 85 and over.

A process evaluation[21,25] was conducted including analysis of data on utilisation of decision support tools, which was collected directly into the proprietary software used to deliver the tools. We estimated for each general practice the proportion (%) of RTI consultations at which decision support tools (DST) were viewed and evaluated a linear trend for the primary outcome across quartiles of DST utilisation adjusting for the same covariates.

Patient and Public Involvement

The trial procedure and proposed intervention were presented to a primary care patient participation group and feedback and views were obtained on all aspects of the intervention including the way in which messages would appear on GP screens, and information which would be presented to patients.

RESULTS

We recruited 80 general practices to the trial, of which one withdrew from CPRD before the start of intervention and the remaining 79 were included in the intention-to-treat analysis (Figure 1). The trial included general practices from throughout the UK (Table 1) and the registered population included patients of all ages. Family practices at antimicrobial stewardship trial arm practices had slightly higher numbers of registered patients, but the range of practice sizes was similar across trial arms. In the baseline period, RTI consultation and AB prescribing rates showed wide variation among practices. (Table 1)

Primary outcome

Figure 2 presents the results for analysis of the primary outcome. The adjusted rate ratio for AB prescribing for RTI was 0.88 (95%CI, 0.78 to 0.99). There were 31,907 AB prescriptions for RTI during 323,155 patient-years at 41 antimicrobial stewardship trial arm practices and 27,923 AB prescriptions during 259,520 person-years at 38 usual care trial arm practices.

There were 98.7 AB prescriptions per 1,000 patient-years in the antimicrobial stewardship trial arm and 107.6 per 1,000 in the usual care trial arm. Adjustment for covariates was pre-planned, prior to analysis, in order to improve the precision of estimated intervention effects. For comparison, the unadjusted rate ratio would have been 0.89 (0.68 to 1.16). Adjusting for covariates reduced the standard error of the coefficient and this was largely accounted for by adjustment for practices' baseline antibiotic prescribing for RTI. In a sensitivity analysis, an over-dispersed Poisson model gave an adjusted rate ratio of 0.86 (95%CI, 0.75 to 0.97), which confirmed conclusions.

Secondary outcomes

There was insufficient evidence for difference between trial arms for consultation rate for self-limiting respiratory infections (RR, 0.94, 0.86 to 1.03), the proportion of consultations with antibiotics prescribed (where RTI consultations rather than person-time represented the denominator) (RR, 0.96, 0.89 to 1.03), and antibiotic prescribing for all indications (RR, 0.93, 0.83 to 1.04) (Supplementary Table 2).[16] During the intervention period there were 185,924 antibiotic prescriptions in the intervention trial arm and 150,539 in the control trial arm (Supplementary Table 2).

Safety outcomes

Figure 3 presents numbers of bacterial infections by trial arm together with a Forest plot of rate ratios. There was no evidence to suggest that bacterial infections were more frequent in the antimicrobial stewardship trial arm (RR, 0.92, 0.74 to 1.13). There were slightly more scarlet fever events in the usual care trial arm, and slightly more empyema events in the antimicrobial stewardship trial arm, but these were likely to be chance findings. There was one case of Lemierre's syndrome in the usual care trial arm. There was no evidence that the adjusted rate ratio varied by age-group (chi-square=1.228, df=8, P=0.996); the adjusted rate

ratio for children was 0.82 (0.44 to 1.51) and for adults aged 85 and older, 0.99 (0.59 to 1.70).

Sub-group analyses

Sub-group analyses by individual patient characteristics are shown in Figure 2. AB prescribing was strongly associated with age. A Wald test of the trial arm by age-group interaction gave chi-square=65.5, df=8, P<0.001. Results of a pre-specified sub-group analysis by age are shown in Figure 2. There was no evidence of an effect of intervention in children aged under 15 years (RR 0.96, 95%CI 0.82 to 1.12) or in people aged 85 years or older (RR 0.97, 0.79 to 1.18). In the control trial arm, children accounted for 23% of AB prescriptions, while people aged 85 years and older accounted for 2%. At intermediate ages, AB prescribing was lower in the antimicrobial stewardship trial arm. We summarised effect modification by age by comparing effect measures in children, adults aged 15 to 84 years and people aged 85 years and older (Supplementary Table 3). The intervention was associated with lower AB prescribing for RTI in adults aged 15-84 years (RR 0.84, 0.75 to 0.95). Based on the AB prescribing rate for adults aged 15-84 years in the usual care trial arm of 100.2 per 1,000, the absolute risk reduction was 16.0 (5.0 to 25.1) AB prescriptions per 1,000 patient years. This is equivalent to the saving of one antibiotic prescription per year for every 62 (95%CI, 40 to 200) registered patients aged 15 to 84 years. There was no evidence that the effect of intervention might differ by gender (chi-square=1.264, df=1, P=0.261) or comorbidity (chi-square=2.424, df=1, P=0.120). Analysis by sub-group of practice-level covariates (region and baseline antibiotic prescribing quartile) showed no consistent pattern of association (Supplementary Table 4). There was no evidence of association of intervention with AB prescribing for any sub-group of RTI separately (Supplementary Table 5).

Process Evaluation

We evaluated the primary outcome measure in relation to the level of utilisation of decision support tools (DST) at antimicrobial stewardship trial arm practices. In the lowest quartile of utilisation, DST were viewed at fewer than 1% of RTI consultations but up to 28% in the highest utilisation quartile (Table 2). There was evidence of a linear trend in the primary outcome across quartiles of DST utilisation (RR 0.97, 0.93 to 1.00 per quartile). This association appeared to be stronger for adults, with no evidence of association for children or people aged 85 or older (Table 2).

DISCUSSION

In a nationwide sample of general practices, a low-cost remotely-delivered intervention using electronic health records data to provide antibiotic prescribing feedback reporting, together with computer-delivered decision support tools was effective at reducing antibiotic prescribing for self-limiting RTIs to adults. The reduction in AB utilisation was greater at practices that used the trial intervention decision support tools more frequently. There was no evidence that the intervention was effective at reducing antibiotic prescribing to children or people aged 85 years or older. The trial decision support tools specifically addressed common diagnostic concerns in children, including otitis media and cough and bronchitis but prescribing to the youngest and oldest age groups may be more difficult to modify because safety concerns may be more salient at these ages.[26] Conversely, unnecessary prescribing may be more frequent, and possibly more readily modified, at intermediate ages.[27]

The trial was designed with the AB prescribing rate as primary outcome because AB prescribing can influence subsequent consultation patterns for respiratory illness. Patients are more likely to consult for RTI if they have been prescribed antibiotics recently.[5] The effect of AMS interventions on AB prescribing may be partly mediated by changes in RTI consultation patterns. Consequently, measures such as the proportion of RTI consultations

with AB prescribed may under-estimate intervention effects. This study did not find sufficient evidence that the proportion of RTI consultations with antibiotics prescribed, or the rate of RTI consultations, were reduced by the AMS intervention but both measures tended to be slightly lower in the AMS trial arm.

The study did not find evidence that the intervention might influence the total utilisation of antibiotics at these practices. Antibiotic prescriptions coded to respiratory indications represented a minority of prescriptions, consistent with another recent study.[28] Dolk et al.[28] drew attention to the appreciable proportion of antibiotic prescriptions that are associated with non-specific medical codes or with no code recorded. Future studies should therefore address a wider range of prescribing indications, as well as issues of coding quality. We also note that only 25% of eligible general practices agreed to participate in the trial, and if this level of uptake were to be replicated in any future intervention roll-out, then any possible population benefits would be proportionately smaller.[29] The trial intervention did not address selection of different antimicrobial drugs, though nationally there has been a substantial reduction in prescribing of broad-spectrum antibiotics in recent years.[30]

Analysis of electronic health records data for bacterial infections as safety outcomes revealed no difference between trial arms. We caution that the study was not designed to provide conclusive evidence concerning the safety of reducing antibiotic prescribing. The study had limited power to evaluate less frequent safety outcomes or vulnerable sub-groups. The results of the trial suggest that further research is necessary and future interventions might stratify feedback and advice by age.

Previous studies of audit and feedback interventions across a range of indications show that these often have only small effects,[31] though some studies report larger effects.[32] Roshanov

et al.[31] found that feedback interventions that provide advice to patients as well as physicians are associated with greater chance of success. This was exemplified in the REDUCE trial decision support tools, which offered patient information leaflets that could be viewed online or printed, as well as offering advice to physicians on the recognised indications for giving an antibiotic prescription. Gjelstad et al.[33] reported a comparable effect from face-to-face delivery of feedback and guideline recommendations in a study from Norway. A recent trial reported on the outcome of quarterly feedback on antibiotic prescribing over two years among 2,900 Swiss physicians.[34] Over the first and second years of the trial, there was no difference in antibiotic prescribing to all patients but there was evidence of reduced antibiotic prescribing to adults aged 19 to 65 years that was not consistently observed over time. The feedback employed by Hemkens and colleagues[34] was less immediate, being provided quarterly rather than monthly. Additionally, Switzerland already has low antibiotic prescribing rates.[35] Hallsworth et al.[36] reported reduction in antibiotic utilisation following social norm feedback in a study focused on high prescribing general practices. A study of dental practices in Scotland found that feedback of past antibiotic prescription data was associated with a 5.7% relative reduction in AB prescribing over 12 months.[37] Audit and feedback has also been employed successfully to reduce other forms of high-risk prescribing in primary care.[38] However, purposely designed interventions might be more effective for prescribing to children.[39]

Limitations of study

The trial was conducted in the context of national efforts to reduce unnecessary antibiotic prescribing in primary care that might have impacted on both trial arms with possible under-estimation of intervention effects. Trial general practices represented all parts of the UK but CPRD general practices in Scotland, Wales and Northern Ireland were almost twice as likely to agree to participate in the trial as practices in England, though the reasons for this are unclear. It is possible that general practices that agreed to take part might be more motivated

to reduce AB prescribing and mere participation in a trial might also influence prescribing behaviour. The number of practices included was smaller than originally intended and several practices were unable to continue with the trial because they transferred to a different practice information system. Additionally, there was very wide variation in antibiotic prescribing between different general practices. This is consistent with data that we and others have reported previously for this outcome.[2,40] Consequently, the primary measure of effect was estimated imprecisely and neither a smaller effect nor a larger effect can be excluded. Based on sub-group analysis, we caution that the intervention appeared to be effective in adults but may not have effect on prescribing to children or adults aged 85 and older. We acknowledge that evaluation of multiple sub-group analyses might lead to false positive interpretations. However, our interpretation was guided by interaction tests, which provided strong evidence that the intervention effect varied by age-group but not by gender or comorbidity. We do not present P values within sub-groups. We found from analysis of data captured by the intervention delivery software that utilisation of decision support tools was associated with effect size, which adds evidence of a causal association. Decision support tools were used at a minority of consultations but it is possible that learning from the tools might be applied in consultations in which they were not viewed. All prescribers also received antibiotic prescribing reports but we were not able to determine whether all prescribers read these each month. We acknowledge that there is likely to have been variation among prescribers within practices but we did not have consistent data for the prescriber level and no information concerning prescriber characteristics. We analysed data for antibiotic prescriptions issued by trial general practices. Patients may have received antibiotic prescriptions at consultations with walk-in centres and out-of-hours or emergency services and these alternative patterns of antibiotic utilisation might differ between trial arms. Additional data sources will be needed to evaluate this possibility. Altered diagnostic code selection might have occurred in order to justify antibiotic prescriptions,[41] we included both symptoms and diagnosis codes in order to limit this. Safety outcomes were ascertained from medical codes in primary care records and we were not aware of whether any confirmatory

tests might have been performed. There was necessarily no blinding of general practice staff to the intervention.

In this cluster randomised controlled trial, an antimicrobial stewardship intervention that was delivered remotely into practices and integrated into routine care delivery was associated with a 12% reduction in antibiotic prescriptions for RTI overall, with no evidence of increased bacterial infections. We caution that the intervention might not be effective at reducing AB utilisation for children or people aged 85 or older. Intervention using data from electronic health records may be used to promote antimicrobial stewardship in primary care and might be readily scaled-up but the needs of very young or old patients require further consideration.

[4,307 words]

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Data sharing: The data analysed in this study were obtained from Clinical Practice Research Datalink (https://www.cprd.com) under licence, which does not permit further distribution or sharing. Further material is provided in our *Health Technology Assessment* report (reference 18).

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Conflict of Interest: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Trial Steering Committee: Jackie Cassell (Chair), Susan Hopkins (Public Health England), Tim Chadborn (Public Health England), Nanik Pursani (Lay member)

Data Monitoring Committee: Christine A'Court (Chair), Helen Strongman (CPRD/MHRA), Derek Cook (St George's, University of London), Jason Oke (University of Oxford).

Contributorship: MG, trial design, conduct, analysis; TP, trial design, statistical analysis plan and statistical advice; JC intervention delivery, trial analysis; DJ, LM, LY design of the interventions and evaluation; JS, KS, MW, recruitment and coordination of trial; RF, AH, PL, MM, MA, design of the study, intervention development and interpretation of results. All authors contributed to and approved the final manuscript. MG is guarantor.

Transparency: The lead author (MG) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Table 1: Characteristics of trial general practices and patient populations at baseline. Figures are frequencies (percent of column total).

		Antimicrobial Stewardship Trial Arm	Usual Care Trial Arm
Family Practice Characteristics		**41**	**38**
Region	London	4 (9.8)	3 (7.9)
	Midlands and North England	4 (9.8)	4 (10.5)
	Northern Ireland	4 (9.8)	5 (13.2)
	Scotland	10 (24.4)	9 (23.7)
	South and East England	8 (19.5)	6 (15.8)
	South West England	3 (7.3)	4 (10.5)
	Wales	8 (19.5)	7 (18.4)
Period of randomisation	Nov 2015	7 (17.1)	11 (28.9)
	Jan-Feb 2016	18 (43.9)	13 (34.2)
	June-Aug 2016	16 (39.0)	14 (36.8)
Practice list size, median [range]		8,936 (1,086 to 18,425)	6,777 (2,530 to 18,557)
Total registered patients		348,158	278,467
Age Group (Years)	Under 15	55,577 (16.0)	47,509 (17.1)
	15-24	40,544 (11.6)	30,610 (11.0)
	25-34	45,545 (13.1)	37,444 (13.4)
	35-44	46,288 (13.3)	38,766 (13.9)
	45-54	52,447 (15.1)	41,507 (14.9)
	55-64	42,275 (12.1)	33,769 (12.1)
	65-74	35,746 (10.3)	26,760 (9.6)
	75-84	20,919 (6.0)	15,264 (5.5)
	Over 85	8,817 (2.5)	6,838 (2.5)
Gender	Male	173,383 (49.8)	138,588 (49.8)
	Female	174,775 (50.2)	139,879 (50.2)
Co-morbidity	No	288,594 (82.9)	238,106 (85.5)
	Yes	59,564 (17.1)	40,361 (14.5)
AB prescribing rate, median [range], per 1,000[a]		108 (4 to 244)	114 (20 to 266)
RTI consultation rate, median [range], per 1,000[a]		261 (11 to 454)	261 (76 to 526)
Proportion of RTI consultations with AB prescribed, median [range], %[a]		43 (12 to 64)	43 (24 to 78)

[a]figures were age-standardised using the European standard population for reference

Table 2: Association of AB prescribing rate for RTI with utilisation of decision support tools (DST).

Quartile of DST utilisation	RTI consultations with DST viewed (%)	All AB/ Person-years	Children 0:14 years AB/ Person-years	Adults 15:84 years AB/ Person-years	Adults 85+ years AB/ Person-years
Control Trial Arm	-	27,923 / 259,519.7	6,432 / 46,019.6	20,811 / 207,611.4	680 / 5,888.7
Lowest quartile	0 to 0.6	7,190 / 85,805.1	1,932 / 15,699.9	5,089 / 68,220.1	169 / 1,885.1
Second quartile	0.6 to 2.9	7,765 / 74,868.3	1,706 / 12,009.4	5,837 / 60,825.5	222 / 2,033.4
Third quartile	2.9 to 6.1	10,647 / 91,986.9	2,339 / 15,233.4	7,957 / 74,735.5	351 / 2,018.0
Highest quartile	6.1 to 27.6	6,305 / 70,495.1	1,520 / 10,883.6	4,668 / 58,060.1	117 / 1551.3
Test for linear trend	RR (95% CI)[a,b]	0.97 (0.93 to 1.00)	0.98 (0.94 to 1.03)	0.96 (0.93 to 0.99)	0.99 (0.94 to 1.05)
	P value	0.043			

AB, antibiotic prescribing for RTI; DST, decision support tools; RTI, self-limiting respiratory tract infections
[a]adjusted for random effect of general practice and fixed effects of gender, age-group, comorbidity, region, quarter in study, practice-specific baseline rate and interaction with period
[b] RR represents the reduction in AB utilisation per quartile increase in decision support tools.

Legend for Figure 1: Flow chart showing trial general practices and registered populations.

Legend for Figure 2: Effect of intervention on primary outcome of antibiotic prescribing rate for self-limiting respiratory tract infection.

Footnote to Figure 2: Estimates were adjusted for random effect of general practice and covariates including gender, age-group, comorbidity, region, quarter in study, practice-specific baseline rate and interaction with period of randomisation. AB, antibiotic prescribing for RTI; AMS, antimicrobial stewardship intervention; RR, rate ratio.

Legend for Figure 3: Forest plot showing rate ratios (95% confidence interval) of safety outcomes in the antimicrobial stewardship trial arm compared to usual care trial arm as reference. Figures are frequencies except where indicated.

Footnote to Figure 3: Estimates were from a Poisson model adjusted for age-group, gender and comorbidity. Analyses for pneumonia and combined outcome were adjusted for random effect of general practice. One case of Lemierre's syndrome in the usual care trial arm is not shown. AMS, antimicrobial stewardship intervention; RR, rate ratio.

Figure 1

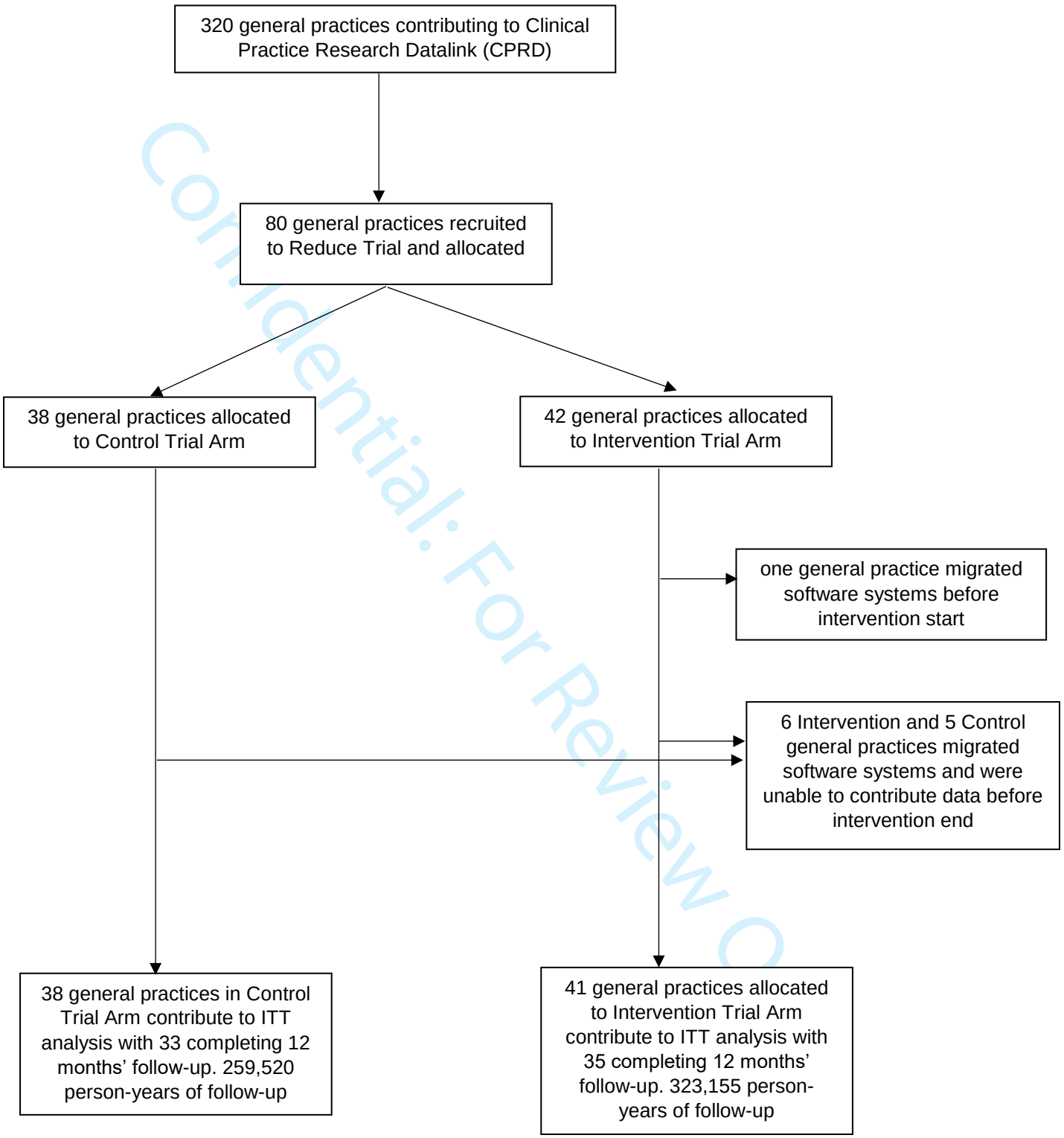


Figure 2

Covariate	AB prescribing rate per 1,000 AMS	Usual Care	RR (95%CI)	P Value
Total				
	98.7	107.6	0.88 (0.78 to 0.99)	0.040
Age−group (years)				
<15	139.3	139.8	0.96 (0.82 to 1.12)	
15−24	83.6	94.3	0.92 (0.81 to 1.04)	
25−34	78.2	86.4	0.90 (0.79 to 1.02)	
35−44	78.6	83.4	0.90 (0.79 to 1.03)	
45−54	79.9	86.0	0.84 (0.73 to 0.96)	
55−64	99.6	112.8	0.79 (0.69 to 0.91)	
65−74	113.8	132.8	0.80 (0.70 to 0.91)	
75−84	121.7	146.1	0.79 (0.69 to 0.91)	
85+	114.7	115.5	0.97 (0.79 to 1.18)	
Gender				
Male	80.0	87.7	0.90 (0.80 to 1.01)	
Female	117.3	127.3	0.87 (0.77 to 0.98)	
Comorbidity				
Absent	60.9	72.5	0.86 (0.74 to 1.00)	
Present	287.0	314.7	0.88 (0.79 to 0.99)	

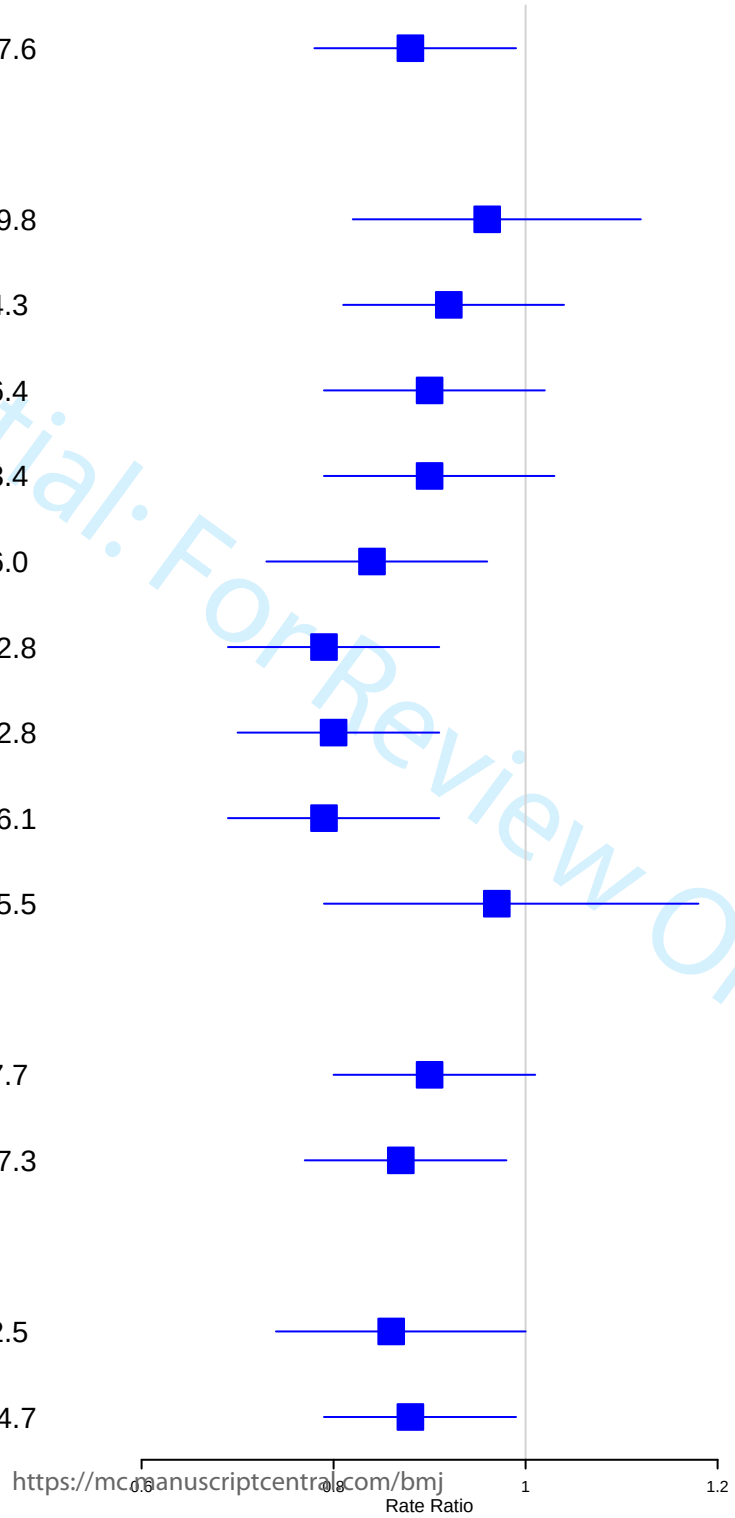
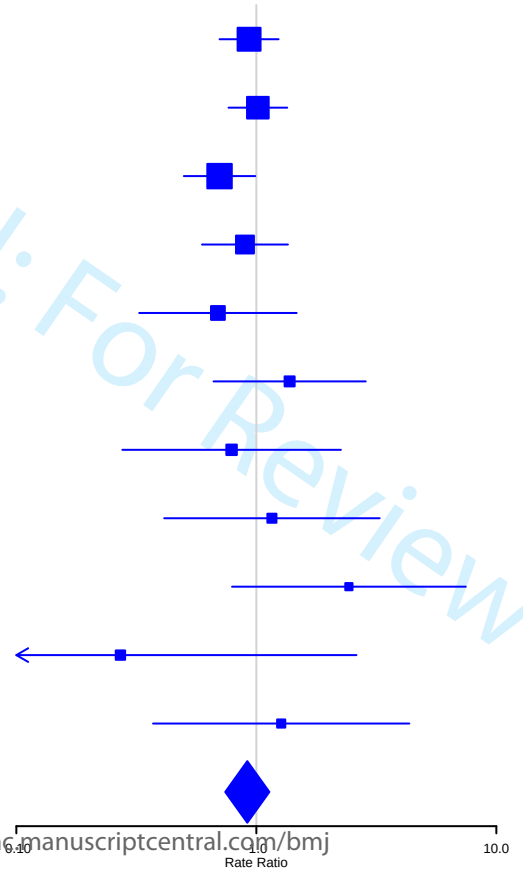


Figure 3

Condition	AMS	Usual Care	RR (95%CI)
Person Years	323,155	259,520	
Pneumonia	367	299	0.93 (0.70 to 1.24)
Pyelonephritis	115	84	1.01 (0.77 to 1.34)
Scarlet Fever	60	72	0.70 (0.50 to 0.99)
Peritonsillar Abscess	49	42	0.90 (0.59 to 1.35)
Septic Arthritis	13	14	0.69 (0.32 to 1.47)
Osteomyelitis	21	11	1.38 (0.66 to 2.86)
Mastoiditis	7	7	0.79 (0.28 to 2.25)
Meningitis	9	6	1.16 (0.41 to 3.27)
Empyema	13	4	2.43 (0.79 to 7.46)
Intracranial Abscess	1	3	0.27 (0.03 to 2.61)
Septicaemia	7	4	1.27 (0.37 to 4.34)
All	**662**	**546**	**0.92 (0.74 to 1.13)**



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The Editor

British Medical Journal

12th September 2018

Dear Dr Godlee

Effectiveness and safety of electronically-delivered prescribing feedback and decision support on antibiotic utilization for respiratory illness in primary care. REDUCE cluster-randomized controlled trial

We would be grateful if you will consider our trial report for possible publication in the *British Medical Journal.*

The study is of methodological interest: we conducted an efficient trial using electronic health records, including 79 general practices from throughout the UK with more than 500,000 individual participants. The substantive results of the trial show that a low-cost intervention, informed by electronic health records data and integrated into practice information systems, may be associated with reduced antibiotic prescribing for respiratory infection, with no evidence of safety hazards in terms of increased bacterial infections. An important qualification is the finding that prescribing for very young or old patients is less amenable to change and this requires evaluation in future research.

The paper is about 4,300 words in length, with two Tables and three Figures. We have aimed to address all relevant issues that may be of concern to reviewers and readers. However, we would be prepared to edit the paper for length if this is required.

We have previously included the present data in our final report to the research funders, the UK National Institute for Health Research. This report is expected to be published in the NIHR Journals Library *Health Technology Assessment* series. Please let us know if you require further information about this publication.

The paper itself is not being considered by any other journal and none of the authors has any conflict of interest concerning this work.

Thank you for considering our paper.

With best wishes

Yours sincerely

Martin Gulliford MA FRCP FFPH

Professor of Public Health