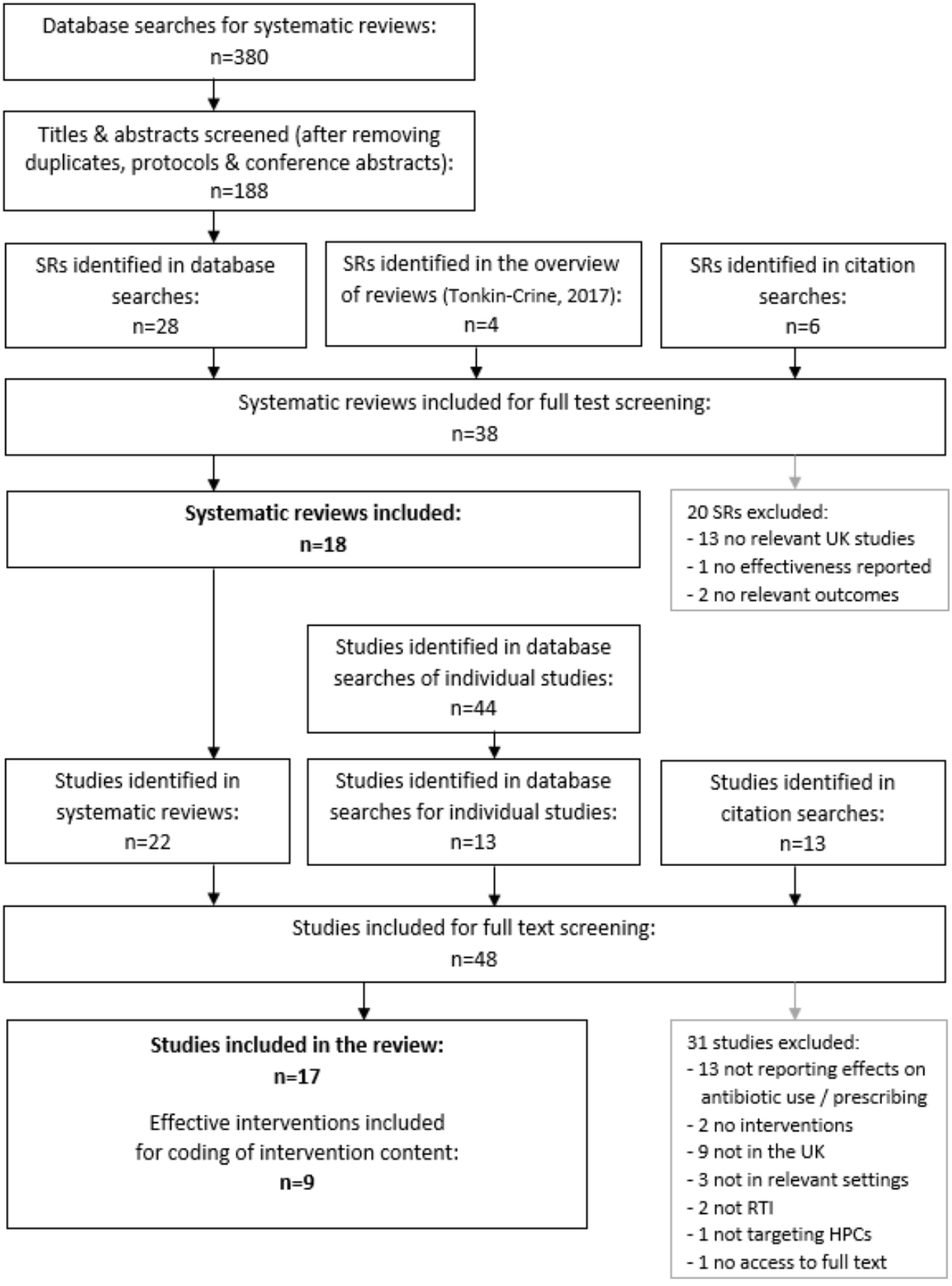
Exploring the implementation of interventions to reduce antibiotic use (ENACT study)

Appendices E, F and G

Contents

Appendix E: Flow chart of selection process of research studies of interventions



This flowchart describes the stages of identifying and selecting systematic reviews and primary studies of AMS interventions which were targeted at HCPs to reduce antibiotic prescribing or use. There were 4 stages to the selection process, identification, screening, eligibility and included articles. These stages were repeated for systematic review and primary studies identification and screening respectively.

Systematic reviews

Stage 1: Identification

Records were identified through database searching (380 records). A further 4 systematic reviews were identified from within an overview of reviews (20), and 6 were identified through citation searches

Stage 2: Screening

The 380 records identified through database searching in Stage 1 were then subjected to a title and abstract screening. A total of 192 records were excluded at this stage, after removing duplicates, protocols and conference abstracts. This left a total of 188 records to be reviewed. A total of 28 systematic reviews were identified from the database searches, therefore providing a total of 38 systematic reviews which were included for full test screening.

Stage 3: Eligibility

The 38 systematic review records retained at the end of the preliminary screening were subjected to a full-text eligibility assessment. A total of 20 reviews were excluded at this stage, for the following reasons; 13 were excluded because they didn't include any relevant UK studies, 1 due to no effectiveness reported, and 2 had no relevant outcomes. This left a total of 18 systematic reviews to be carried forward to Stage 4.

Stage 4: Included

No further exclusions were made at this stage, leaving 18 systematic reviews included within the review.

Individual studies

Stage 1: Identification

Records were identified through database searching (44 records). A further 22 records were identified within the included systematic reviews included within the review, and 13 were identified through citation searches.

Stage 2: Screening

The 44 records identified through database searching in Stage 1 were then subjected to a title and abstract screening. A total of 31 records were excluded at this stage, leaving a total of 13 records to be reviewed. A total of 48 individual studies were carried forward to stage 3.

Stage 3: Eligibility

The 48 records retained at the end of the preliminary screening were subjected to a full-text eligibility assessment. A total of 31 articles were excluded at this stage, for the following reasons; 13 did not report effects on antibiotic use of prescribing, 2 did not include interventions, 9 were not UK based articles, 3 were not in relevant settings, 2 not RTI, 1 did not target HCPs and 1 had no access to full text. This left a total of 17 studies to be carried forward to stage 4.

Stage 4: Included

No further exclusions were made at this stage, leaving 17 individual studies included within the review. A total of 9 effective interventions within the records were included for coding of intervention content.

Appendix F: Characteristics of included systematic reviews and of research studies of AMS interventions

Table F1. Characteristics of included systematic reviews of research studies of AMS interventions

Abbreviations used in this table
CI = confidence interval
CPR = clinical prediction rule
CRP = C-Reactive Protein
MA = meta analysis
POCT = point-of-care test(ing)
RAD = rapid antigen detection (test)
RCT = randomised controlled trial
RTI = respiratory tract infection
SR = systematic review

First author, year, title; Review type	Review objective	Dates and databases searched	Study selection criteria	Outcomes	Number of included studies	Key results (on effectiveness of interventions targeted at HCPs)
Kochling 2018 Reduction of antibiotic prescriptions for acute respiratory tract infections in primary care: a systematic review SR	To summarise the evidence on the effectiveness of interventions in primary care aiming to reduce antibiotic prescriptions in patients greater than or equal to 13 years for acute RTI.	January 2005 to July 2016 MEDLINE, Cochrane Library	(Cluster-) RCTs of interventions aiming to reduce antibiotic prescriptions for RTIs for patients greater than or equal to 13 years in primary care settings. Excluded pilot studies, non-randomised trials, public campaigns.	Antibiotics prescription rate, # antibiotics prescribed for RTIs; also: reconsultation rates, days to recovery, class of antibiotics prescribed, antibiotics prescribing rate for specific RTIs, usage of diagnostic devices.	17 trials (2 in the UK)	Most effective interventions: communication skills training, point-of-care testing (POCT) (including CRP and RAD testing) and clinical decision support systems, alone or in combination. Pre-intervention antibiotics prescribing rates varied between 13.5% and 80% and observed reductions ranged from 1.5 to 23.3%. Studies with post-intervention rates lower than 20% had no significant effects.
McDonagh 2018 Interventions to reduce inappropriate prescribing of antibiotics for acute respiratory tract infections: summary and update of a systematic review SR	To summarize and update a previous SR (conducted for the Agency for Healthcare Research and Quality, 2016) of interventions to reduce inappropriate use of antibiotics for acute RTIs.	To January 2018 MEDLINE, Cochrane Library	RCTs and comparative observational studies of single or multifaceted intervention compared with usual care and that reported antibiotic prescribing outcomes.	Antibiotics prescribing, appropriate vs inappropriate prescribing as defined per study, measures of adverse consequences (return visits, hospitalization, duration of symptoms, patient satisfaction).	95 studies of 26 interventions (14 in the UK)	Moderate-strength evidence of improved or reduced antibiotics prescribing and low-strength evidence of no adverse consequences: combined clinician and patient education (7.3% reduction in antibiotics prescribing, no change in complications or satisfaction); procalcitonin POCT for adults with lower RTIs in emergency department or out-patient setting (12 to 72% reduction, no increased adverse consequences);

First author, year, title; Review type	Review objective	Dates and databases searched	Study selection criteria	Outcomes	Number of included studies	Key results (on effectiveness of interventions targeted at HCPs)
						electronic decision support systems (9.2% reduction in antibiotics prescribing, 13 to 24% improvement in appropriate antibiotics prescribing, but only with more frequent use of the system). Evidence of reducing antibiotics prescribing with mixed impact on adverse consequences: Clinicians' communication training (9 to 26% reductions in antibiotics prescribing, conflicting evidence on symptom improvement); delayed prescribing (34 to 76% reduction in antibiotics use compared to immediate prescriptions, without affecting return visits of the duration of symptoms, but with decreased patient satisfaction); CRP POCT (13 to 33% reduction in antibiotics prescribing, but increased return visits within 4 weeks); multifaceted interventions combining communication training and CRP POCT (large reduction in antibiotics prescribing, but with small increase in hospitalizations at 1 month and duration of symptoms). Low to moderate-strength evidence of reducing antibiotics prescribing with no or insufficient evidence of adverse consequences: rapid strep testing for sore throat, rapid viral testing, clinician education combined with audit and feedback, nurse telephone care combined with audit and feedback, rapid white blood cell count testing combined with delayed prescribing, clinician communication training combined with electronic decision support and audit and feedback, clinician education alone

First author, year, title; Review type	Review objective	Dates and databases searched	Study selection criteria	Outcomes	Number of included studies	Key results (on effectiveness of interventions targeted at HCPs)
						and combined clinician and patient education, audit and feedback, CRP measurement, and academic detailing.
Spurling 2017 Delayed antibiotic prescriptions for respiratory infections SR + MA (Cochrane) (Update of Cochrane reviews from 2007, updated in 2010 and 2013)	To evaluate the effects of a delayed prescription of antibiotics on clinical outcomes, antibiotic use, antibiotic resistance, and patient satisfaction in RTIs.	To May 2017 Cochrane, MEDLINE, Embase, CINAHL, Web of Science, WHO International Clinical Trials Registry, ClinicalTrials.gov	RCTs involving participants of all ages defined as having a RTI, where delayed antibiotics were compared to immediate antibiotics or no antibiotics.	Clinical outcomes (symptom duration and severity), antibiotics use, antibiotic resistance, patient satisfaction.	11 studies (6 in primary care) (3 in the UK)	For many clinical outcomes, there were no differences between prescribing strategies. Symptoms for acute otitis media and sore throat were modestly improved by immediate antibiotics compared with delayed antibiotics. There were no differences in complication rates. Delaying prescribing did not result in significantly different levels of patient satisfaction compared with immediate provision of antibiotics (86% versus 91%) (moderate quality evidence). However, delay was favoured over no antibiotics (87% versus 82%). Delayed antibiotics achieved lower rates of antibiotic use compared to immediate antibiotics (31% versus 93%) (moderate quality evidence). The strategy of no antibiotics further reduced antibiotic use compared to delaying prescription for antibiotics (14% versus 28%).
Tonkin-Crine 2017 Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews Overview of SRs (Cochrane)	To systematically review the existing evidence from systematic reviews on the effects of interventions aimed at influencing clinician antibiotic prescribing behaviour for acute RTIs in primary care.	To June 2016 (update search in May 2017 to reviews awaiting classification) Cochrane, MEDLINE, Embase, CINAHL, Database of Abstracts of Reviews of Effects (DARE), PsycINFO, Science Citation Index	Systematic reviews of RCTs evaluating the effect of any clinician-focussed intervention on antibiotics prescribing in primary care for acute RTIs.	Change in antibiotics prescribing for RTIs; also: percentage of patients with acute RTI given immediate or delayed antibiotics, percentage of patients with antibiotic-resistant bacteria, adverse events, symptom duration or severity, health-related quality of life, patient satisfaction, any measure of management failure (for	8 systematic reviews	Evidence that CRP POCT, shared decision making, and procalcitonin-guided management reduce antibiotic prescribing for patients with acute RTIs in primary care. These interventions may therefore reduce overall antibiotic consumption and consequently antibiotic resistance. There do not appear to be negative effects of these interventions on the outcomes of patient satisfaction and reconsultation, although there was limited measurement of these outcomes in the trials.

First author, year, title; Review type	Review objective	Dates and databases searched	Study selection criteria	Outcomes	Number of included studies	Key results (on effectiveness of interventions targeted at HCPs)
				example, reconsultation, hospital or emergency department attendance), healthcare resource costs.		
O'Sullivan 2016 Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care SR (Cochrane)	To assess if written information for patients (or parents of child patients) reduces the use of antibiotics for acute upper RTIs in primary care.	To Jul 2016 CENTRAL, MEDLINE, Embase, CINAHL, LILACS, Web of Science, Clinical trials.gov, WHO trials registry	RCTs involving patients (or parents of child patients) with acute upper RTIs that compared written patient information (delivered immediately before or during prescribing) with no information; studies needed to measure primary outcome (antibiotics use) to be included.	Antibiotics use; also: reconsultation rates, resolution of symptoms, patient knowledge about antibiotics for acute upper RTIs, patient satisfaction, complications or adverse effects.	2 studies	Moderate quality evidence from one study showed that clinicians providing written information to parents of children with acute upper RTIs in primary care significantly reduced the number of antibiotics used by patients without any impact on reconsultation rates or parent satisfaction with consultation (compared to usual care). Low quality evidence from 2 studies showed that written information also reduced antibiotics prescriptions given by clinicians (compared to usual care). No study measured resolution of symptoms, patient knowledge about antibiotics for acute upper RTIs, or complications. Low quality evidence showed that written information plus prescribing feedback significantly increased the number of antibiotics prescribed by clinicians, compared to prescribing feedback alone.
Wallace 2016 Impact analysis studies of clinical prediction rules relevant to primary care: a systematic review SR	To narratively review and critically appraise clinical prediction rules (CPRs) impact analysis studies relevant to primary care.	1980 to 2009, updated to the end of 2013 PubMed, JAMA Rational Clinical Examination series, Handbook of CPRs, personal resources	Studies (RCT, controlled before-after, interrupted time series) that implemented the CPR compared to usual care in primary care.	Physician behaviour (for example, ordering of diagnostic tests, process of care, number of inpatient days), and/or patient outcomes (for example, duration of symptoms)	18 studies of 14 CPRs 5 for respiratory infections (1 in the UK)	Of 5 respiratory studies, 2 were effective in reducing antibiotic prescribing for sore throat following CPR implementation. Only one reported significantly reduced antibiotic prescription rates in the intervention group (age-adjusted relative risk 0.74, 95% CIs 0.60 to 0.92) versus usual care. The other study found that use of the CPR alone or CPR in combination with a RAD test improved patient-reported symptom severity and duration, and reduced antibiotic use by 29% (adjusted risk ratio 0.71, 95% CI

First author, year, title; Review type	Review objective	Dates and databases searched	Study selection criteria	Outcomes	Number of included studies	Key results (on effectiveness of interventions targeted at HCPs)
						0.50 to 0.95).31 [31 - is the study by Little 2013]
Cooke 2015 Narrative review of primary care point-of-care testing (POCT) and antibacterial use in respiratory tract infection (RTI) SR	To consider whether POCTs improve antibacterial prescribing, whether they are acceptable to patients and clinicians, and their cost-effectiveness for the NHS.	1995 to 2015 EMBASE, Excerpta Medica, Journals@ Ovid, PubMed, MEDLINE, Highwire Press, nature.com, Science Direct, Springer Link, Wiley Interscience Journals, NHS Evidence, Cochrane	Any studies or papers on CRP or procalcitonin POCT	Any	10 pivotal studies (listed in table 1) (1 in the UK)	Many studies demonstrated that the use of CRP tests in patients presenting with RTI symptoms reduces antibiotic prescribing by 23.3 to 36.2%. Procalcitonin is not currently available as a POCT, but has shown value for patients with RTI admitted to hospital. GPs and patients report a good acceptability for a CRP POCT and economic evaluations show cost-effectiveness of CRP POCT over existing RTI management in primary care. POCTs increase diagnostic precision for GPs in the better management of patients with RTI.
Coxeter 2015 Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care SR + MA (Cochrane)	To assess whether interventions that aim to facilitate shared decision making increase or reduce antibiotic prescribing for acute RTIs in primary care.	To December 2014 CENTRAL, MEDLINE, EMBASE, Web of Science, trial registries at the National Institutes of Health and WHO	(Cluster-) RCTs evaluating the effectiveness of interventions that promote shared decision making (as the focus or a component of the intervention) about antibiotics prescribing for acute RTIs in primary care.	Antibiotics prescribing; also: clinically important endpoints (for example, re-consultations, hospital admissions, mortality) and process measures (for example, patient satisfaction)	9 studies (10 articles) (3 in the UK)	Moderate quality evidence that interventions that aim to facilitate shared decision making reduce antibiotics use for acute RTIs in primary care (immediately after or within 6 weeks of the consultation), compared with usual care (47 to 29%, risk ratio 0.61, 95% CI 0.55 to 0.68). Reduction in antibiotics prescribing occurred without an increase in patient-initiated re-consultations (risk ratio 0.87, 95% CI 0.74 to 1.03, moderate quality evidence) or a decrease in patient satisfaction with the consultation (odds ratio 0.86, 95% CI 0.57 to 1.30, low quality evidence). There were insufficient data to assess the effects of the intervention on sustained reduction in antibiotics prescribing, adverse clinical outcomes (for example, hospital admission, incidence of pneumonia and mortality),

First author, year, title; Review type	Review objective	Dates and databases searched	Study selection criteria	Outcomes	Number of included studies	Key results (on effectiveness of interventions targeted at HCPs)
						or measures of patient and caregiver involvement in shared decision making (for example, satisfaction with the consultation, regret or conflict with the decision made, treatment compliance following the decision).
de Bont 2015 Patient information leaflets to reduce antibiotic use and reconsultation rates in general practice: a systematic review SR	To systematically review effectiveness of information leaflets used for informing patients about common infections during consultations in general practice.	To April 2014 MEDLINE, EMBASE	RCTs and non-randomised intervention trials in which the effect of a written information tool was studied during general practice consultations in developed countries. Leaflets had to be given to patients in person by GPs or nurses. Excluded leaflets aimed at prevention, multifaceted studies in which no leaflet specific effect could be extracted, studies concerning decision aids, and studies on patient empowerment tools.	Antibiotics use, reconsultation rates	8 studies (5 in RTIs) (3 in the UK)	One high quality study showed significant reductions of antibiotics prescriptions in children with RTIs in leaflet group. Another study in adults with lower RTIs showed non-significant reduction in antibiotics prescriptions. Four studies focused showed significant reductions of patient leaflets on antibiotics use: one of leaflets alone and 3 studies used leaflets together with delayed prescriptions. Effects on reconsultation varied widely. One large study showed lower reconsultation rates (RR 0.70 (0.53 to 0.91), 2 studies showed no effect, and one study showed increased reconsultation rates (RR 1.53 (1.03 to 2.27)).
Pinder 2015 Antibiotic prescribing and behaviour change in healthcare settings: literature review and behavioural analysis SR	To identify: i) prescribing behaviours and contexts contributing to antibiotic resistance; and ii) areas amenable to behavioural intervention based in previously published evidence.	1946 to 18 November 2013 Medline	Any studies published in English and describing behaviours contributing to AMR or interventions targeting behaviours contributing to AMR.	Any.	54 articles (30 in primary care)	Varying evidence of the effectiveness of: education and training; guideline implementation and real-time decision-support; audit and feedback; and back-up prescribing. GPs are recommended not to issue antibiotics for colds, runny noses or other self-limiting infections. Where some clinical doubt remains, a number of approaches have been tried to maximise antibiotic stewardship: issuing back-up-prescriptions, explaining prescribing decisions more fully, and highlighting the implications of taking antibiotics to patients. The literature

First author, year, title; Review type	Review objective	Dates and databases searched	Study selection criteria	Outcomes	Number of included studies	Key results (on effectiveness of interventions targeted at HCPs)
						indicates that potential for behavioural interventions to include: addressing GPs concern about the consequences of not prescribing, improving their belief in the consequences of overprescribing, and enhancing their perceived capability regarding the impact of their personal behaviour on antibiotic resistance.
Aabenhus 2014 Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care SR + MA (Cochrane)	To assess the benefits and harms of point-of-care biomarker tests of infection to guide antibiotic treatment in patients presenting with symptoms of acute RTI in primary care.	To January 2014 CENTRAL, MEDLINE, EMBASE, CINAHL, Web of Science, LILACS	(Cluster-) RCTs in primary care patients with acute RTIs that compared use of POC biomarkers with standard care.	Number of patients given antibiotics prescription at the consultation and follow-up; patients with substantial improvement at day 7; total mortality at 8 days follow-up; secondary: re-consultations, hospital admissions at 28 days follow-up; duration of RTI; number of satisfied patients; number of patients with substantial improvement at 28 days.	6 studies (2 in the UK)	The only point-of-care biomarker of infection currently available to primary care identified in this review was CRP. 6 trials evaluated CRP POCT. The available information was from trials with a low to moderate risk of bias. CRP POCT showed reduced use of antibiotics (631 out of 1,685) versus standard care (785 out of 1,599). There was no difference between using CRP POCT and standard care in clinical recovery (defined as at least substantial improvement at day 7 and 28 or need for re-consultations at day 28). One study showed an increase in hospitalisations in the CRP POCT group, but this was based on few events and may be a chance finding.
Vodicka 2013 Reducing antibiotic prescribing for children with respiratory tract infections in primary care: a systematic review SR	To assess the effectiveness of primary care based interventions to reduce antibiotic prescribing for children with RTIs.	To June 2012 MEDLINE, Embase, CINAHL, PsycINFO, Cochrane	(Cluster-) RCTs and non-randomised studies testing educational and/or behavioural interventions to change antibiotic prescribing for children (under 18 years) with RTIs in primary care.	Change in proportion of antibiotics prescriptions issued, change in appropriate antibiotics prescriptions.	17 studies of 19 interventions (1 in the UK)	Interventions that combined parent education with clinician behaviour change decreased antibiotics prescribing rates by 6 to 21%; structuring the parent–clinician interaction during the consultation may further increase the effectiveness of these interventions. Automatic computerised prescribing prompts increased prescribing appropriateness, while passive information, in the form of waiting room educational materials, yielded no benefit.

First author, year, title; Review type	Review objective	Dates and databases searched	Study selection criteria	Outcomes	Number of included studies	Key results (on effectiveness of interventions targeted at HCPs)
Andrews 2012 Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis SR + MA	To assess the effectiveness of interventions directed towards parents or caregivers which were designed to influence consulting and antibiotic use for RTIs in children in primary care.	To November 2011 MEDLINE/ PubMed, EMBASE, CINAH, PsycINFO, Cochrane Library	(Cluster-) RCTs, non-randomised controlled, or pre or post studies of educational or behavioural interventions directed at caregivers to influence consulting or antibiotics use for acute RTIs in children (<18 years) in developed countries.	1) Parental knowledge related to consultations or parental consultation rate; 2) Parental knowledge or attitudes related to antibiotics use, 3) Antibiotics use. Secondary: adverse effects, health outcomes, costs of interventions.	23 studies of 20 interventions (2 in the UK)	Materials designed to engage children in addition to parents were effective in modifying parental knowledge and behaviour, resulting in reductions in consulting rates ranging from 13 to 40%. Providing parents with delayed prescriptions significantly decreased reported antibiotic use (Risk Ratio 0.46 (0.40, 0.54). A delayed or no prescribing approach did not diminish parental satisfaction.
van der Velden 2012 Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections SR	To assess the effectiveness of physician-targeted interventions aiming to improve antibiotic prescribing for respiratory tract infections (RTIs) in primary care, and to identify intervention features mostly contributing to intervention success.	1990 to July 2009 MEDLINE, EMBASE, Cochrane Library	Interventions primarily targeted at physicians in primary care aiming to improve antibiotics prescribing for RTIs, in high-income country, presenting a standardised outcome of first choice prescription, published in English.	First choice prescription measured in defined daily dosage, prescriptions or rates	58 studies of 87 interventions (1 in the UK)	60% of interventions significantly improved antibiotic prescribing; interventions aiming to decrease overall antibiotic prescription were more frequently effective than interventions aiming to increase first choice prescription. On average, antibiotic prescription was reduced by 11.6%, and first choice prescription increased by 9.6%. Multiple interventions containing at least ‘educational material for the physician’ were most often effective. No significant added value was found for interventions containing patient directed elements. Communication skills training and POCT sorted the largest intervention effects.
Boonacher 2010 Interventions in health care professionals to improve treatment in children with upper respiratory tract infections SR	To analyse which strategies are used to promote evidence based management of children with upper RTIs in; to assess the effectiveness of these interventions, and when more are effective – which works best; to analyse the costs	To February 2009 Pubmed, Embase, CENTRAL	RCT, non-randomised controlled trials, controlled before after studies that used implementation methods to change HCPs' behavior regarding the treatment of children with upper RTIs, and that investigated the	Effectiveness of strategies (proportion of participants with outcome present in the intervention group minus proportion of participants with outcome in the control group; if data not available - outcome data as presented in the article)	10 studies	Most strategies were aimed at changing antibiotic prescribing behaviour in children with acute otitis media. All strategies used (that is, computer interventions, educational sessions with or without education materials, collaborative development of guidelines and a training video in combination with a risk factor checklist) were effective in changing health care professionals

First author, year, title; Review type	Review objective	Dates and databases searched	Study selection criteria	Outcomes	Number of included studies	Key results (on effectiveness of interventions targeted at HCPs)
	associated with these interventions.		effectiveness of these strategies.			practice regarding children with upper RTIs. Multifaceted and computer strategies work best. Computer interventions reduced antibiotic prescribing by 4% and 34% and increased guideline compliance by 41%. Educational sessions combined with education materials reduced inappropriate antibiotic prescription by 2% and 17% and increased knowledge of compliance enhancing strategies by 28% and 29%. Collaborative guideline development combined with educational materials reduced inappropriate antibiotic prescription by 24% and 40%. Finally, by a combination of a training video and a risk factor checklist appropriate referrals by the GP to the otolaryngologist increased by 37%. Due to lack of data, no conclusion on cost-effectiveness can be drawn.
Ranji 2008 Interventions to reduce unnecessary antibiotic prescribing: a systematic review and quantitative analysis SR	To assess the effectiveness of quality improvement (QI) strategies to reduce antibiotic prescribing for acute outpatient illnesses for which antibiotics are often inappropriately prescribed.	1966 to March 2007 Cochrane Collaboration Effective Practice and Organization of Care (EPOC) database	(Cluster-) RCTs, controlled before after (non-randomised studies with a control group) and interrupted time series studies that evaluated an intervention aimed to reduce unnecessary prescribing of antibiotics for acute nonbacterial illness in the outpatient setting, and reported data on antibiotics prescribing or antibiotics use before and after the intervention.	Proportion of patient visits at which antibiotics was prescribed	43 studies (of 55 trials; 38 studies in acute RTIs (4 in the UK)	Among the 30 trials eligible for quantitative analysis, the median reduction in the proportion of subjects receiving antibiotics was 9.7% interquartile range (IQR), 6.6 to 13.7% over 6 months median follow-up. No single QI strategy or combination of strategies was clearly superior. However, active clinician education strategies trended toward greater effectiveness than passive strategies (P 0.096). Compared with studies targeting specific conditions or patient populations, broad-based interventions extrapolated to larger community-level impacts on total antibiotic use, with savings of 17 to 117 prescriptions per 1,000 person-years.

First author, year, title; Review type	Review objective	Dates and databases searched	Study selection criteria	Outcomes	Number of included studies	Key results (on effectiveness of interventions targeted at HCPs)
Arnold 2005 Interventions to improve antibiotic prescribing practices in ambulatory care SR (Cochrane)	To assess the effectiveness of professional interventions in improving the selection, dose and treatment duration of antibiotics prescribed in the outpatient setting; to evaluate the impact of these interventions on reducing the incidence of antimicrobial resistant pathogens.	1980 to May 2000 Cochrane Effective Practice and Organisation of Care Group (EPOC), Scientific Citation Index	RCTs or quasi-RCTs, before after studies and interrupted time series studies of healthcare consumers or HCPs who provide primary care in the outpatient setting; any professional intervention, or a patient-based intervention.	Rate of appropriate antibiotics prescriptions; secondary: incidence of colonisation with or infection due to antibiotics-resistant organisms and other adverse events associated with antibiotics use; incidence of adverse events associated with reduced use or duration of treatment with antibiotics or use of narrow-spectrum antibiotics	39 studies (4 in the UK)	Printed educational materials or audit and feedback alone resulted in no or only small changes in prescribing. Interactive educational meetings appeared to be more effective than didactic lectures. Educational outreach visits and physician reminders produced mixed results. Patient-based interventions, particularly the use of delayed prescriptions for infections for which antibiotics were not immediately indicated effectively reduced antibiotic use by patients and did not result in excess morbidity. Multi-faceted interventions combining physician, patient and public education in a variety of venues and formats were the most successful in reducing antibiotic prescribing for inappropriate indications. Only one of 4 studies demonstrated a sustained reduction in the incidence of antibiotic-resistant bacteria.
Arroll 2003 Do delayed prescriptions reduce antibiotic use in respiratory tract infections? A systematic review SR	To systematically review controlled trials of delayed prescriptions to establish their capacity to reduce antibiotic intake.	1996 to April 2003 Medline, Embase, Cochrane Controlled Trials Register	RCTs in which a delayed prescriptions were compared to immediate antibiotics prescriptions for patients with upper RTIs in general practice.	Use of, or filling of, the prescription, and any reported side effects	5 studies; 2 UK	Four randomised controlled trials and one before–after controlled trial contributed to the review. The relative risk in the randomised trials for lower antibiotic usage when a delayed prescription was given ranged from 0.54 for the common cold to 0.25 for otitis media.

Table F2. Characteristics of included research studies of AMS interventions

Abbreviations used in this table
CI = confidence interval
CPR = clinical prediction rule
CRP = C-Reactive Protein
MA = meta analysis
POCT = point-of-care test(ing)
RAD = rapid antigen detection (test)
RCT = randomised controlled trial
RTI = respiratory tract infection
SR = systematic review

First author, year, title (study name)	Study design	Setting and participants	Interventions and comparators	Outcomes measured	Key results (on effectiveness of interventions on antibiotics prescription or use) (The initials SSE and green shading indicate statistically significant effects)
McNulty 2018 Effects of primary care antimicrobial stewardship outreach on antibiotic use by general practice staff: pragmatic randomized controlled trial of the TARGET antibiotics workshop	McNulty-Zelen RCT (a form of cluster-RCT where practices were not aware that they were taking part in a trial)	General practice: 152 practices	1) TARGET workshop (1 hour workshop facilitated by existing NHS healthcare staff with promotion of the TARGET website resources) 2) Control (no workshop offered)	Antibiotics dispensed per 1,000 practice patients; workshop uptake; dispending of antibiotics typically prescribed for RTIs, UTIs and broad-spectrum antibiotics	SSE Antibiotics dispensing was 2.7% lower in intervention practices (95% CI to 5.5% to 1%, P = 0.06) compared with controls. Dispensing in intervention practices was 4.4% lower for amoxicillin or ampicillin (95% CI 0.6% to 8%, P=0.02); 5.6% lower for trimethoprim (95% CI 0.7% to 10.2%, P=0.03); and a non-significant 7.1% higher for nitrofurantoin (95% CI 0.03 to 15%, P=0.06).
Ward 2018 Point-of-care C-reactive protein testing to optimise antibiotic use in a primary care urgent care centre setting	Service evaluation	Urgent care centre or walk-in service: prescribers	CRP POCT (Alere Afinion) (no comparator group)	Use of CRP POCT; type of antibiotics prescription (immediate, delayed or no prescription)	Pre-test decision (that is, the decision that would have been made if no test was available): 72 out of 141 (51.1%) patients would have been given an immediate antibiotic prescription, 6 (4.2%) would have been given a delayed prescription and 63 (44.1%) would not have received an antibiotic. Decision after doing CRP tests: 32 (22.7%) patients received an immediate antibiotic, 22 (15.6%) received a delayed prescription and 87 (61.7%) received no antibiotic.
Blair 2017 Feasibility cluster randomised controlled trial of a within-	Cluster RCT (feasibility study)	General practice:	1) Within-consultation complex intervention (interactive web-based tool, including recording	Feasibility and acceptability; use of intervention; RTI-related antibiotics	The overall antibiotic prescribing rates for children's RTIs were 25% (19.9% immediate

First author, year, title (study name)	Study design	Setting and participants	Interventions and comparators	Outcomes measured	Key results (on effectiveness of interventions on antibiotics prescription or use) (The initials SSE and green shading indicate statistically significant effects)
consultation intervention to reduce antibiotic prescribing for children presenting to primary care with acute respiratory tract infection and cough (CHICO)		32 practices, 501 children (3 months – 11 years) with acute cough and RTI	symptoms and signs elicitation and recording of carers' concerns, guidelines on antibiotics associated with risk strata, personalised printout for carers) 2) Control (Usual care)	prescriptions; re-consultations; RTI-related hospitalisations	and 5.1% delayed) in intervention group and 15.8% (p=0.018) in control group. (In the Discussion, the authors suggest that this result might be due to a post-randomisation differential recruitment (with intervention arm having more children with more severe baseline characteristics) that might have biased the estimated intervention effect.)
Hallsworth 2016 Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial	RCT	General practice: 1581 practices with antibiotics prescribing rates in the top 20% of the NHS Local Area	1) Prescribing feedback (a letter from England's Chief Medical Officer stating that the practice was at a higher rate of antibiotics prescribing than 80% of practices in its area plus a patient leaflet) 2) patient-focused information (promoting reduced use of antibiotics) 3) Control (no intervention)	Antibiotics items dispensed per 1000 weighted population, controlling for past prescribing	SSE 1) Feedback intervention: difference of 4.27 (3.3%; incidence rate ratio 0.967 [95% CI 0.957 to 0·977]; p less than 0.0001), representing an estimated 73 406 fewer antibiotic items dispensed. 2) Patient-focused intervention: incidence rate ratio for difference between groups 1.01, 95% CI 1.00 to 1.02; p=0.105.
Thornley 2016 A feasibility service evaluation of screening and treatment of group A streptococcal pharyngitis in community pharmacies	Service evaluation	Community pharmacy: 35 pharmacies, 367 patients	Sore throat test-and-treat service (assessing patient's condition using the Centor score and patients meeting 3 or all 4 Centor criteria were offered a throat swab test) (no comparator group)	Uptake of the throat swab testing; antibiotics provision by the pharmacist	Following screening by pharmacy staff, 149 out of 367 (40.6%) patients were eligible for throat swab testing. Of these, only 36 out of 149 (24.2%) were positive for group A streptococci. Antibiotics were supplied to 9.8% (n=36 out of 367) of all patients accessing the service.
Gulliford 2014 Electronic health records for intervention research: a cluster randomized trial to reduce antibiotic prescribing in primary care (eCRT study)	Cluster RCT	General practice: 104 practices, 603,409 patients (aged 18 to 59) with RTIs	1) Decision support tools (electronically delivered and remotely installed, accessed during the consultations) 2) Control (usual care)	Proportion of consultations for RTIs with antibiotics prescriptions	SSE Reduction in proportion of consultations with antibiotics prescriptions of 1.85% (95% CI, 0.10% to 3.59%, P = 0.038) and in the rate of antibiotics prescriptions for RTIs (9.69%; 95% CI, 0.75% to 18.63%, fewer prescriptions per 1,000 patient-years, P = 0.034).

First author, year, title (study name)	Study design	Setting and participants	Interventions and comparators	Outcomes measured	Key results (on effectiveness of interventions on antibiotics prescription or use) (The initials SSE and green shading indicate statistically significant effects)
Little 2014 Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial	RCT	General practice: 25 practices, 889 patients (aged 3) with RTIs	4 delayed prescribing strategies: 1) Re-contact for antibiotics 2) Post-dated prescription 3) Collection of prescription 4) Antibiotics prescription given to patient 5) No antibiotics prescription	Symptom severity; antibiotics use; patients' beliefs in effectiveness of antibiotics use; secondary: comparison of delayed prescription strategies with immediate antibiotics	Modest and non-significant difference between the randomised delayed prescribing groups in antibiotics use (26%, 37%, 37%, 33%, 39%; 4.96, P = 0.292). 97% of patients given immediate antibiotics used them but with no benefit for symptom severity or duration.
Little 2013a Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial (GRACE INTRO)	Cluster RCT	General practice: 246 practices, 4,264 patients with RTIs	1) Training in the use of CRP POCT 2) Training in enhanced communication skills 3) Combined training in the use of CRP and in enhanced communication skills 4) Control (usual care)	Antibiotics prescriptions; secondary: re-consultations; new signs; hospital admission; symptom severity and duration	SSE Antibiotics prescribing was lower with CRP POCT training than without (33% versus 48%, adjusted risk ratio 0.54, 95% CI 0.42 to 0.69) and with enhanced communication skills training than without (36% vs 45%, 0.69, 0.54 to 0.87). The combined intervention (CRP POCT plus communication skills training) was associated with the greatest reduction in prescribing rate (CRP risk ratio 0.53, 95% CI 0.36 to 0.74, p less than 0.0001; enhanced communication 0.68, 0.50 to 0.89, p=0.003; combined 0.38, 0.25 to 0.55, less than 0.0001).
Little 2013b Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management)	Cluster RCT	General practice: 21 practices, 631 patients (aged 3 and over) with a sore throat	1) Delayed prescription to be collected after 3 to 5 days if symptoms are not better or get worse 2) Clinical score (FeverPAIN) 3) Rapid antigen test (RADT; rapid streptococcal antigen detection test) used with clinical score (FeverPAIN)	Patient-reported symptom severity; duration of symptoms; patient-reported antibiotics use	SSE 1) In delayed prescription group, 75 out of 164 (46%) patients used antibiotics. 2) In the clinical score group antibiotics use (60 out of 161) was 29% lower (adjusted risk ratio 0.71, 95% CI 0.50 to 0.95; p=0.02). 3) In the RADT plus clinical score group antibiotics use (58 out of 164) was 27% lower (0.73, 0.52 to 0.98; p=0.03).
Butler 2012 Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in	Cluster RCT	General practice: 68 practices, 263 GPs	1) Communication skills training (including a practice seminar, online training and practising consulting skills) 2) Control (usual care)	Antibiotics items dispensed per 1000 practice patients in the year after the intervention, adjusted for the previous year's dispensing; secondary:	SSE Antibiotics dispensed decreased by 14.1 in the intervention group but increased by 12.1 in the control group, a net difference of 26.1. After adjustment for baseline dispensing rate, this

First author, year, title (study name)	Study design	Setting and participants	Interventions and comparators	Outcomes measured	Key results (on effectiveness of interventions on antibiotics prescription or use) (The initials SSE and green shading indicate statistically significant effects)
primary care: practice based randomised controlled trial (STAR)				re-consultations; hospital admissions; costs.	amounted to a 4.2% (95% CI 0.6% to 7.7%) reduction in total oral antibiotic dispensing for the year in the intervention group relative to the control group (p=0.02).
Francis 2009 Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial	Cluster RCT	General practice: 61 practices, 558 children (6 months - 14 years) with RTIs	1) Training in the use of interactive booklet on RTIs and use of the booklet in consultations 2) Control (usual care)	Proportion of children re-consulting during 2 week follow-up; secondary: antibiotics use; future consulting intentions; parental satisfaction; reassurance; enablement.	SSE Antibiotics were prescribed at index consultation to 19.5% of children in the intervention group and 40.8% of children in the control group (absolute risk reduction 21.3%, 95% CI 13.7 to 28.9), p less than 0.001). A significant difference was still present after adjusting for clustering (odds ratio 0.29; 0.14 to 0.60).
Little 2005 Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial	RCT	General practice: 37 GPs, 807 patients (aged 3 and above) with cough as the main symptom	1) Patient leaflet (information on natural history of lower RTI addressing patient concerns) 2) No patient leaflet X 3) Immediate antibiotics prescription 4) No antibiotics prescription 5) Delayed prescription (on request if symptoms don't resolve after 14 days)	Symptom severity and duration; patient-reported antibiotics use.	SSE Fewer patients in the delayed prescribing and no antibiotics prescription groups used antibiotics compared with the immediate antibiotics group (20%, 16%, 96%, respectively; p=0.001). 57% patients used antibiotics in the no leaflet group compared with 55% in the leaflet group (p=0.58).
Macfarlane 2002 Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet	RCT	General practice: 3 practices, 259 adults (aged 16 and over) with acute bronchitis	Patients judged to not need antibiotics: 1) Delayed prescription plus verbal reassurance (prescription given to patients with advice to use it if they got worse) 2) Delayed prescription plus verbal reassurance plus leaflet (on natural course of lower RTI symptoms, pros and cons of antibiotics use)	Antibiotics use in the next 2 weeks; re-consultation for the same symptoms in the next month.	SSE Fewer patients who received leaflet took antibiotics compared with those who did not receive the leaflet: 49 (23.1%) v 63 (29.7%) out of 212, risk ratio 0.76, 95% CI 0.59 to 0.97, p=0.04. 44 out of 47 (93.6%) patients judged to need antibiotics and given immediate antibiotics prescription took antibiotics.

First author, year, title (study name)	Study design	Setting and participants	Interventions and comparators	Outcomes measured	Key results (on effectiveness of interventions on antibiotics prescription or use) (The initials SSE and green shading indicate statistically significant effects)
			3) Patients judged to need antibiotics and given immediate AP		
Cox 2001 Is it possible to decrease antibiotic prescribing in primary care? An analysis of outcomes in the management of patients with sore throats	Pre-post	General practice: 1 practice, 785 patients (aged 2 plus) with a sore throat as the main complaint	1) Old protocol for management of sore throats in practice 2) Revised evidence-based protocol for management of uncomplicated sore throats (focused on low antibiotics use)	Antibiotics prescriptions; patient acceptability; recovery; consultation rates.	SSE Antibiotics prescriptions decreased from 56% to 19% during the study (p less than 0.0001).
Dowell 2001 A randomised controlled trial of delayed antibiotic prescribing as a strategy for managing uncomplicated respiratory tract infection in primary care	RCT	General practice: 22 practices, 191 adults (aged over 16) with cough	1) Immediate antibiotics prescription 2) Delayed prescription (patients asked to wait a week before deciding whether to collect the prescription from reception)	Symptom duration; prescription uptake; patient satisfaction; patient enablement; subsequent consultation rates.	In delayed prescription group, 45% (43 out of 95) patients picked up their prescription; 35% (12 out of 34) waited 7 days as asked.
Little 2001 Pragmatic randomised controlled trial of 2 prescribing strategies for childhood acute otitis media	RCT	General practice: 65 practices, 315 children (6 months to 10 years) presenting with otitis media	1) Immediate antibiotics prescription plus advice sheet, 2) Delayed prescription plus advice sheets (patients asked to collect the prescription after 72 hours if no improvement)	Symptom resolution; absence from school or nursery; paracetamol consumption; collection of prescription; reported antibiotics use.	132 out of 134 (98.5%) participants who were given an immediate antibiotics prescription reported using antibiotics at some stage during the illness compared to 36 out of 150 (24%) participants in the delayed prescription group.
McNulty 2000 Primary care workshops can reduce and rationalize antibiotic prescribing	Pre-post	General practice: 84 practices	1) Workshops on antibiotics prescribing (1.5 to 2 hour, including presentation of a poster, discussion of new antibiotics prescribing guidelines, key messages) 2) Microbiology tutorials in practices 3) Control (no intervention)	Dispensed antibiotics.	SSE 51 practices offered workshops decreased antibiotics prescribing by 3.4%, compared with 2.2% decrease in 33 practices not offered workshops (p=0.09). Broad-spectrum antibiotics prescriptions declined by 15.4% in practices receiving workshops, compared with a 6.5% increase in practices with tutorials (p=0.002). Use of narrow-spectrum antibiotics (encouraged) did not change in workshop practices, but decreased by 12% in tutorials practices (p=0.003).

Appendix G. Comparison of national and research interventions

Nationally implemented interventions included in the previous AMR project

(Note: here only interventions targeting prescribers and community pharmacists are reported; see the AMR project report for other included and excluded interventions)

Guidelines

1. AMS Competencies
2. UK 5 year AMS (UK 5 year AMR strategy 2013 to 2018
3. NG15 (NICE Guideline 15, AMS: systems and processes for effective antimicrobial medicine use, 2015)
4. NG63 (NICE Guideline 63, AMS: changing risk-related behaviours in the general population, 2017)
5. NG79 (NICE Guideline 79, Sinusitis (acute): antimicrobial prescribing, 2017)
6. NG84 (NICE Guideline 84, Sore throat (acute): antimicrobial prescribing, 2018)
7. NICE QS61 (NICE Quality Standard 61, Infection prevention and control, 2014)
8. NICE QS121 (NICE Quality Standard 121, Antimicrobial stewardship, 2016)
9. NICE CG69 (NICE Clinical Guideline 69, Respiratory tract infections (self-limiting): prescribing antibiotics, 2008)
10. PHE managing infections (2010, last updated 2018)
11. RPS AMS quick reference guide (2017)

Data monitoring and feedback

12. Public Health England Fingertips website
13. PrescQIPP website
14. Chief Medical Officer (CMO) letters to highest-prescribing practices

Clinical scores

15. Centor clinical scoring tool or criteria (for acute sore throat)
16. FeverPAIN clinical scoring tool or criteria (for acute sore throat)

Training and resources

17. TARGET toolkit website and resources
18. CPPE AMR module
19. STAR module
20. MARTI (Managing Acute Respiratory Tract Infections) module

21. HEE (Health Education England) video for GPs
22. The Learning Pharmacy on antibacterials
23. UKPA-RPS (UK Clinical Pharmacy Association, Royal Pharmaceutical Society) and Professional practice curriculum

Awareness campaigns

24. ABG (Antibiotic Guardian pledge scheme)
25. AB Action
26. TYB (Treat Yourself Better with Pharmacist Advice)

Table G1. Mapping of national and research interventions

Intervention	Targeted at prescribers	Targeted at community pharmacy staff	Identified in the AMR project	Identified in the ENACT project
1. AMS Competencies	✓		✓	
2. UK 5 year AMS strategy	✓		✓	
3. NG15 (guideline)	✓	✓	✓	
4. NG63 (guideline)	✓	✓	✓	
5. NG79 (guideline)	✓		✓	
6. NG84 (guideline)	✓		✓	
7. NICE QS61 (quality standards)	✓		✓	
8. NICE QS121 (quality standards)	✓		✓	
9. NICE CG69 (guideline)	✓		✓	
10. PHE managing infections (guideline)	✓		✓	
11. RPS AMS quick reference guide		✓	✓	
12. PHE Fingertips (data)	✓		✓	
13. PrescQIPP (data)	✓		✓	
14. CMO letters to prescribers	✓		✓	✓ Hallsworth 2016, effective
15. CENTOR (clinical score)	✓		✓	

Intervention	Targeted at prescribers	Targeted at community pharmacy staff	Identified in the AMR project	Identified in the ENACT project
16. FeverPAIN (clinical score)	✓		✓	✓ Little 2013b, effective (with or without RADT)
17. TARGET toolkit	✓		✓	✓ McNulty 2018, effective
18. CPPE AMR module (training)	✓	✓	✓	
19. STAR e-module (training)	✓		✓	✓ Butler 2012, effective
20. MARTI e-module	✓		✓	
21. HEE video GPs	✓		✓	
22. The Learning Pharmacy (training)		✓	✓	
23. UKPA/RSP	✓		✓	
24. Antibiotic Guardian (campaign)	✓	✓	✓	
25. Antibiotic Action (campaign)	✓		✓	
26. Treat Yourself Better with Pharmacist Advice (campaign)		✓	✓	
27. Electronic decision support tools	✓		No	✓ Gulliford 2014, effective -Blair 2017, not effective
28. CRP POCTs (with and without enhanced communication skills)	✓		No	✓ Little 2013a, effective -Ward 2018, not effective
29. POC throat swabs		✓	No	Thornley 2016 (no data on effectiveness)
30. Training and using interactive booklet with patients	✓		No	✓ Francis 2009, effective
31. Evidence-based practice protocol for	✓		No	✓ Cox 2001, effective

Intervention	Targeted at prescribers	Targeted at community pharmacy staff	Identified in the AMR project	Identified in the ENACT project
management of sore throats				
32. Workshops on antibiotic prescribing	✓		No	✓ McNulty 2000, effective