The effects of the primary health care providers’prescription behavior interventions to improve the rational use of antibiotics: a systematic review

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Abstract

Background: Irrational antibiotic use, especially at primary health care institutions accelerates the spread of antibiotic resistance (ABR). It is important to systematically review the effects of interventions at the primary health care to give evidence for future studies about interventions of providers' antibiotic prescriptions. A systematic review was conducted to explore the effects of interventions targeted to the primary health care providers for improving the rational use of antibiotics.

Methods: The literatures were searched in Ovid Medline, Web of Science, PubMed, Cochrane Library, and two Chinese databases with a time limit from January 1st, 1998 to December 1st, 2018. Only articles in the English and Chinese language were considered. Studies had to be the design of randomised control trial, controlled before-and-after studies or interrupted time series. Outcomes had to measure the change in providers' behaviors. The Cochrane Collaboration criteria was used to assessed the risk of bias of the studies by two reviews. Narrative analysis was performed.

Results: Of 4422 studies identified**,** we included 17studies. Most studies were conducted in the Europe or the United States and 4 of the studies were conducted in low-income and-middle-income countries (LMICs). Most studies had moderate to high risk of bias. There was moderate-strength evidence that interventions targeted at primary health care providers' prescription behaviors were associated with decreases in antibiotic prescribing and promote the rational use of antibiotic.

Conclusions: Provider-targeted interventions in primary health care could decrease the antibiotic prescription and promote the providers' behaviours of irrational use of antibiotic However, we cannot compare the effects between different interventions because of heterogeneity of interventions and outcomes.

Background

Antibiotic resistance (ABR) is a growing public health problem,[1] leading to a delay in the administration of effective therapy, increased costs, morbidity and mortality.[2] It is estimated that about 80 percent antimicrobials were prescribed at primary care institutes in the world.[3] The World Health Assembly issued a separate motion on ABR in 1998 for the first time, and put forward a comprehensive management proposal for ABR.[4] In the same year, the World Health Organization (WHO) issued a report on the global monitoring of ABR and proposed to promote the rational use of antibiotic worldwide.[5] One key element of curtailing the emergence and spread of ABR has been to focus on healthcare providers' prescribing behaviours to ensure they are using antibiotic prudently.[6]

According to previous studies, although many countries have been successful in reducing prescribing of antimicrobials, primary care is still responsible for the majority of antibiotics prescribed to people.[7] A 2017 Cochrane review examined the effectiveness of interventions designed to improve health professionals' antibiotic prescribing practices for hospital inpatients. The review noted that antimicrobial stewardship interventions can safely reduce unnecessary antibiotic use in hospitals.[8] The interventions are typically classified as educational intervention, audit and feedback, health policy change strategies, organizational or professional financial incentives for antibiotic prescribing.[8] Several reviews also reported positive effects of hospital antibiotic stewardship interventions on the types of structural (e.g. new technology for rapid microbiology testing or measurement of inflammatory markers), persuasive (e.g. expert audit of prescriptions and feedback advice to prescribers),enabling (e.g. guidelines or education on antibiotic use) and restrictive (e.g. expert approval for use of certain antibiotics).[9,10] A Cochrane review had evaluated the impact of interventions on reducing the incidence of antimicrobial resistant pathogens, but it included the intervention of any professional intervention and a patient-based intervention. [11] An overview of reviews of Cochrane reported the Clinician-targeted interventions in primary care, it only focused on the acute respiratory infections and there are eight reviews in the overview.[12] Another systematic review concluded the government policy interventions to reduce human antimicrobial use. However, there are insufficient studies to explore the effectiveness of interventions to decrease antibiotic prescribing and promote the antibiotic prescribing behaviours from the perspective of primary health providers, limited recommendations for outpatients are offered. As most antibiotic prescribing practices occur among outpatients, we attempted to explore the effects of interventions targeted to the primary health care providers for improving the rational use of antibiotics.

Methods

The review protocol including the complete search strategy has been registered at the PROSPERO international prospective register of systematic reviews (CRD:42019146631).

Search strategy

We searched the following databases from January 1st, 1998 to December 1st, 2018: The databases of Ovid Medline, Web of Science, PubMed and Cochrane Library were searched for relevant studies published in English, and the databases of China National Knowledge Infrastructure (CNKI) and WANFANG database were searched for Chinese language studies. The Chinese databases were searched using the following terms (in Chinese): ‘prescription’, ‘community’, ‘primary health’, ‘outpatient’, ‘rural doctors’ ‘village doctors’ ‘intervention’, ‘antimicrobial’, ‘antibacterial’ and ‘antibiotic’. The combination of the following and related terms was used to search at Ovid Medline, Web of Science, PubMed and Cochrane Library: population (‘community’, ‘ambulatory care’, ‘family medicine’ , ‘family practitioner’, ‘primary health’, ‘office visits’, ‘general practice’, ‘primary care’, ‘outpatient’), outcomes (‘antibiotic’ ‘antimicrobial’, ‘antibacterial’), intervention (‘stewardship’, ‘education’, ‘audit and feedback’, ‘health policy change strategies’, ‘information system’). Synonyms and search strategies were from other relevant systematic reviews and the controlled vocabulary of databases. Identification of relevant studies was carried out by one researcher and checked by two other researchers. Additional studies were identified by cross-referencing. Moreover, we consulted experts for additional literatures.

Inclusion and exclusion criteria

We included studies according to PICOS (population, intervention, comparison, outcome and study design) characteristic. Population: the participants refer to the physicians at outpatient clinics, general practitioners, rural doctors; the patients we included were not specified (e.g. respiratory tract infections or urinary tract infections). Intervention: the studies were about promoting the antibiotic rational use and the interventions were targeted at primary health care providers. We referred Cochrane Effective Practice and Organisation of Care (EPOC) taxonomy (EPOC 2015) [13]to include interventions of educational, audit and feedback, reminders and health policies changes. Outcomes: the primary outcome was the changes in antibiotic prescribing behaviors of providers, include the changes in antibiotic prescribing rate, the odds ratio of antibiotic prescribing, the percentage of prescriptions of specific antibiotic or prescribing appropriateness. Study design: the design of the studies had to be randomized controlled trials (RCTs), interrupted times series (ITS) or controlled before-and-after studies.

Articles were excluded if they focused on microbiology; were non-research articles such as reviews, meeting reports, policy briefs; or did not focus on outpatient antibiotic prescription. Titles and abstracts were independently screened for eligibility by two authors. In order to maintain agreement, the two researchers evaluated the quality of studies by reading the full-text article.

Data extraction and analysis

We used the data extracted forms from the Cochrane Handbook for Systematic Reviews. The following information was extracted from each included article: first author and year of publication, study design, setting, country, participants, intervention details, target illness , duration and outcomes measures. Narrative synthesis was used due to the great heterogeneity among the included studies.

Quality assessment

We assessed the risk of bias based on the Cochrane Collaboration criteria (Higgins 2011).[14] We used these eight standard criteria for RCTs: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting and no risk of bias from other sources. We used two additional criteria that the Cochrane Effective Practice and Organization of Care (EPOC) Group specifies (EPOC 2009): baseline characteristic similarity, adequate protection against contamination.

We used seven criteria for non-randomized trial (NRT): the intervention is independent of other changes, the shape of the intervention effect is pre-specified, the intervention is unlikely to affect data collection, knowledge of the allocated interventions is adequately prevented during the study, the outcome data are incomplete, selective reporting, and other bias.

The Cochrane Collaboration criteria was used to assessed the risk of bias of the studies by two reviews. The disagreements between reviewers' judgements had been resolved by discussion and consensus.

Results

The process of study identification and inclusion is shown in Figure 1. A total of 4422 articles were identified as relevant. After reviewing the abstracts and full texts, 17 studies were included, of which, 16 were in English and 1 was in Chinese.

Study characteristics

Population

Of the 17 studies, ten were conducted in Europe,[15-24]four in China,[25-28] three in the USA.[29-31] Table 1 provides a summary of the key characteristics of each included study. All of the interventions were targeted at a specific population group (General practitioners, primary care physicians). These studies focus on patients who were diagnosed as respiratory tract infections, urinary tract infections, upper respiratory tract infections and not specified.

Intervention

Diverse interventions were employed in the included studies, five of which mainly evaluated the educational interventions, i.e., educational material, guideline, training sessions; four used audit and feedback interventions including peer review about the prescribing, monitoring and feedback on prescribing behaviors; three used health policy change strategies including public report prescription, changing of payments method and attach the antibiotic use with bonus promotion; and the other five employed health information system supported interventions (reminders), which were clinic-supported decision making system and providing online guideline materials.

Outcomes measured

The most frequently measured outcome was antibiotic prescribing rate. 13 of the studies measured a change in antibiotic prescription rate or the odds ratio of antibiotic prescribing.[15,16,17,20-27,29,30,31] The antibiotic prescription rate defined as the proportion of prescriptions for specific disease that include at least one antibiotic. One of the studies measured the impact of interventions on the rate per 1000 registered patients dispensed one or more 4C antimicrobial prescriptions (co-amoxiclav, cephalosporins, fluoroquinolones and clindamycin).[18] One of the studies measured the effect on prescriptions of penicillins for respiratory tract infections (RTIs) and one on proportion of prescriptions for recommended.[19] One of the Chinese studies measured the effect on changes in types of antibiotics.[28] Akke Vellinga used the proportion of antimicrobial prescribing according to guidelines for urinary tract infection to measure the changes of providers prescription behaviors.[21]

Study design

There were nine cluster random control trials,[15-17,19,21,23-25,29] two matched-pair cluster-randomized trials,[26,27] two RCTs,[22,31] two before and after intervention studies,[20,28] one quasi-experimental trial[30] and one interrupted time series study.[18]

Risk of bias assessment

The risk of bias was considered low if all criteria were scored as low, medium if less three criteria were scored as medium or high, and high if more than three criteria were scored as medium or high.[32] For the 13 RCT studies, the risk of bias was medium (four studies[15,21,23,27]) or high (nine studies[16,17,19,22,24-26,29,31]), the main risk of the studies was that we did not know how the random sequence generated, and the blinding of participants and personnel. For the four NRTs, the risk of the bias was medium (one studies[18]), high (three studies[20,28,30]), and the main risk was the interventions were not independent of other changes. (Figure 2 and Figure 3)

Effect of interventions

Our research found that 11 of the 17 studies reported reductions of antibiotic prescribing rate with the largest effect size reaching 37% of antibiotic prescribing for upper respiratory tract infections (URTIs) in children. Three studies found the promotion in providers' prescribing behaviours like the providers' increasing of proportion of antimicrobial prescribing according to guidelines. The other three studies did not find a significant difference in the prescribing rate between the intervention and the control group. The findings of included studies measuring changes in antibiotic prescribing are summarized in Table 2.

Educational interventions

Five of the studies that used education interventions and four of the studies reported improvements in providers' behaviours of antimicrobial prescribing. Most provider educational interventions were multifaceted and included clinical guidelines, feedback, peer-review meetings, communications skills training, or workshops on C-reactive protein rapid test. The greatest improvement was one ITS study reported by Virginia Hernandez who evaluated the implementation of a range of educational material on British local general practices use of antimicrobials.[18] After 6, 12 and 24 months, there was a highly significant and sustained decrease in 4 antimicrobials prescribing, by 33.5% (95% CI –26.1 to –40.9), 42.2% (95% CI –34.2 to –50.2) and 55.5% (95% CI –45.9 to –65.1) respectively (P value was not reported). Three of the RCT studies were respectively implemented in China, Belgium and Switzerland. The Chinese study had an intervention effect of –29% (95% CI –42 to –16; p=0·0002), on antibiotic prescribing rate between the intervention group and the control group.[25] The Swiss study increased the use of recommended antibiotics (penicillins) for RTIs and UTIs with an effect of 11.1% (P=0.01).[19]A Belgic study reported by Marieke B Lemiengre found that point-of-care C-reactive protein test without guidance is not an effective strategy to reduce antibiotic prescribing for non-severe acute infections in children in primary care (AOR:1.01(0.57 to 1.79，P<0.1).[23] A before-after quality assurance study in Spain[20] show that the full intervention and partial intervention group were both received the educational interventions on RTI guidelines, but the full intervention group were provided the workshop on rapid tests. The study show that full intervention group had a lower odds ratio of antibiotic prescribing of 0.50 (95% CI: 0.44-0.57, p < 0.001) compared to partial intervention group 0.99 (95% CI: 0.89-1.10).

Audit and feedback interventions

Four studies evaluated the effects of audit and feedback to primary healthcare providers, all of which are RCTs. All of the audit and feedback interventions had a positive effect of promoting antibiotic prescribing behaviors of providers.

A cluster-RCT study in Germany[15] enrolled 104 general practitioners (GPs) to receive the intervention visited by peers focused on the communication within the encounter about antibiotic prescribing. After the intervention, the absolute reduction of prescription of an antibiotic was 11.7% ($P<0.001$) and 9.8% ($P=0.001$) after 6 weeks and 12 months of the intervention. Jeffrey S. Gerber had evaluated the effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians.[29] They find that broad-spectrum antibiotic prescribing in pediatric primary care practices decreased from 26.8% to 14.3% among intervention practices vs from 28.4% to 22.6% in controls ($P=0.1$). Two study in Netherlands, one to reduce antibiotic prescribing for respiratory tract symptoms in primary care[22], the author reported a result that the prescription rates for acute symptoms of the respiratory tract in the intervention group fell from 27% to 23%, whereas the control group's rose from 29% to 37% ($P<0.05$) after nine months of the peer review interventions. The other to improve antibiotic prescribing quality by audit/feedback intervention embedded in the primary care practice accreditation[24].There were significant differences between intervention and control practices in the changes in dispensed antibiotics/1000 registered patients (first year: 27.6% versus 20.4%, $P=0.002$; second year:24.3% versus +2%, $P=0.015$),

Health policy change strategies

Three of the policy change interventions were implemented in Chinese rural areas, two of which are matched-pair cluster-randomized trials and one before and after study. All the health policy change interventions had a positive effect of promoting antibiotic prescribing behaviors of primary health care providers.

One policy intervention in Ningxia province changed New Cooperative Medical Scheme (NCMS) payments to township health centers and village posts from fee-for-service to a capitated budget with pay-for-performance.[27] And the results suggested that capitation with pay-for-performance led to a reduction of approximately 15 percent in antibiotic prescriptions ($P<0.05$). The other matched-pair cluster-randomized trial was undertaken in Hubei province[26], they public reported (PR) indicators about physicians' antibiotic prescribing like percentage of prescriptions requiring antibiotics. PR resulted in a 9-percentage point (95% CI −17 to −1) reduction in the use of oral antibiotics (adjusted RR =39%, $P=0.027$). In another study in Zhejiang province, China, they had carried out a control before and after study.[28] They took prescribing check results as an important indicator of physicians' professional promotion and bonus performance. The control before and after study also found out a promotion of antibiotic prescribing in outpatient department of primary health centers. They found that the outcomes of combined application of antibiotic decreased by 9.89% (P<0.05) and the use of antibiotics for injection reduced 11.42% (P<0.05) at primary care outpatient.

Information system supported interventions

In the five of the information supported interventions, three of the interventions had a positive effect on promoting antibiotic prescribing behaviors of primary health care providers.

A study including 603,409 patients did by Martin C. Gulliford[17] evaluated the effectiveness of electronically delivered decision support tools at reducing antibiotic prescribing for RTIs, and reported a reduction in proportion of consultations with antibiotics prescribed of 1.85% (95% CI, 0.10%-3.59%, P = 0.38).The reason may be the intervention was activated when a medical code was entered by the physician, but some family physicians enter data only after the consultation has ended and the patient has left the consultation room. A quasi experimental design[30] with nine intervention practices and 61 control practices in the Practice Partner Research Network used clinical decision support system (CDSS) intervention. A CDSS embedded in an electronic health record（EHR）had a substantial decreasing of 17.7% (P<0.0001) on changing the overall prescribing of broad-spectrum antibiotics (e.g. macrolide antibiotic) among pediatric and adult patients. Meeker, D. used suggested alternatives and accountable justification based on EHR[31], and peer comparison interventions and they reported that accountable justification and peer comparison as behavioral interventions resulted in lower rates of inappropriate antibiotic prescribing for RTIs. The antibiotic prescribing rate for antibiotic-inappropriate acute respiratory tract infection decreased 5%,7.1% and 5.3% respectively at intervention 1 ,2 and 3 group(P<0.01) compared to control group.

A cluster-RCT of 30 practices in Irish general practice integrated a reminder into the patient management software suggested first-line treatment.[21] An increase in proportion of antimicrobial prescribing according to guidelines for urinary tract infection was observed in the intervention arms (arm A increased 24.5% ,P<0.001 and arm B increased 18.4%, P<0.001) relative to control. Another cluster randomized controlled trial in England[16] used a web-based clinician-focused clinical rule to reduce antibiotic prescribing for children presenting to primary care with acute respiratory tract infection and cough, the author reported that the prescribing rate among the control children in the study was even lower with the intervention group decreased 12% and control group decreased 21% (P=0.018) because of the different recruitment.

Discussion

Main findings of this study

This review found evidence that interventions of educational,audit and feedback, policy change interventions and information system reminders could achieve reductions in antibiotic prescribing or promote the rational use of antibiotic by guidelines at primary health care. Only three of the studies did not reported a reduction in antibiotic prescribing rates, which of them are Educational interventions could achieve a more significant reductions in antibiotic prescribing by combining with other strategies like financial incentives or providing rapid C-reactive protein test. The policy change interventions were more common in in LIMICs (China), and the intervention had a good effect of decreasing the antibiotic prescribing rate or increasing the recommend antibiotic use. The information system supported intervention didn't work at the most time. The same type intervention may produce different effect in different settings. However, we cannot make general recommendations to guide the selection of antibiotic stewardship interventions due to limitations of the included studies, including the low quality of studies, under-representation of certain settings, heterogeneity of the interventions

Strengths and limitations

This review is important because we evaluated the effect of primary health care provider targeted interventions and provided an evidence-based material for the researchers. There are many reviews on the effectiveness of antibiotic stewardship of inpatients, however, few were focus on the outpatients. A key strength of this review is that only studies with a control group

,ITS or control before and after studies were included and therefore are more likely to represent true changes.

There are limitations to the methods employed in this review. Firstly, we only identified studies that publicized, so the results may be affected by publication bias although not all interventions were statistically significant. The effect sizes from the included studies in this review may be misleading because published trials are more likely to demonstrate positive and larger intervention effects. Secondly, most of the studies identified were from the US, Europe and China which may be suggestive of this bias, or may also reflect the current evidence base. Third, study designs of included studies were complex and heterogeneous, making it is a challenging to judge the quality of study, we judged 35% of the risk of bias as unclear since many studies provided not enough information to judge the risk of bias as 'no risk' or 'high risk.

Findings in relation to other research

In a systematic review conducted by Dimitri M. Drekonja of antimicrobial Stewardship in Outpatient Settings, the author concluded that low- to moderate-strength evidence suggests that antimicrobial stewardship programs in outpatient settings improve antimicrobial prescribing without adversely effecting patient outcomes and the intervention types will also affect the outcomes.[33] This result was in line with our study. Our research found the primary health care providers' prescription behavior interventions association with reductions in antibiotic prescribing and the rational use of antibiotic, this is consistence with the research conducted by Alike W van der Velden. They evaluated the effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections, and reported a reduction of 11.6% of antibiotic prescription.[34] Another review shows that just delivering guidelines is not enough to restrict antibiotic prescribing and the need to intensify educational material by adding another element to create a multiple intervention.[28] this review find the same results that multiple interventions containing at least educational material for the physician' were most often effective.[35] For the audit and feedback interventions, our study finds this strategy have a good effectiveness on promoting the antibiotic prescribing, which is consistent with the study of Davey P.[6] Policy changed interventions are merely seen in previous studies.

Previous systematic review concluded that computer interventions, educational sessions, collaboratively developed guidelines and training videos were effective in changing practice of pediatricians, and that multifaceted and computer interventions worked best.[36] One result of that computer interventions reduced antibiotic prescribing by 4% and 34% has some differences with our study. The systematic review of interventions in health care professionals to improve treatment in children with upper respiratory tract infections have some differences in the design of ours. 2 of our 4 included studies were focus on urinary tract infections, and not limited in children. That might because this kind of intervention cannot affect the prescriber's behaviors directly. Stewardship interventions in outpatient usually aim to change individual prescriber's behavior. This behavior is influenced by social norms, attitudes and beliefs.[37]

Recommendations for future research

The situation that few of current studies mentioned how the random sequence generated and the protesting of contamination. Future research should focus on the design and methodology of high-quality RCTs. We find that there were few studies reported the sustainable effect of the interventions, studies should aim for longer periods of follow-up. Future studies of the quality of intervention implementation are needed, and the interventions should more attention on the elements of providers' behaviors. More research is needed to assess the primary health care on irrational use of antibiotic.

Conclusions

Our review demonstrated that there have been few studies describing antibiotic improving interventions targeted at provider at primary care in LIMCs. It is hard to compare the studies because the included studies had heterogeneous study designs and different settings. There was moderate-strength evidence shows that provider-targeted interventions can decrease the antibiotic prescribing and promote the rational use of antibiotic. Except the two information system supported interventions[16 17] and one educational interventions, [23]the other types of interventions had a moderate or strong effect of antibiotic prescribing reduction or promotion of antibiotic rational use.

Declarations

Transparency declarations

None to declare.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors give their authorization to publish the article.

Availability of data and material

Lu Yao and Qiang Sun had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Data will be provided under request to the first authors.

Competing interests

The authors declare that they have no competing interests.

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Author contributors

YL designed the study, screened the paper, extracted and analysed data, wrote the manuscript and approved the final manuscript as submitted. JY wrote the manuscript, interpreted the data and approved the final manuscript. TZ reviewed the revised manuscript and approved the final manuscript as submitted. RT screened the paper, extracted the data and approved the final manuscript. DY designed the study, reviewed the revised manuscript and approved the final manuscript as submitted.LS designed the study, reviewed the revised manuscript and approved the final manuscript as submitted. SW screened the paper, extracted the data and approved the final manuscript. QS designed the study, reviewed the revised the manuscript and approved the final manuscript as submitted.

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Abbreviations

LMICs: Low-income and-Middle-Income Countries; ABR: Antibiotic Resistance; CNKI: China National Knowledge Infrastructure; PICOS: Population, Intervention, Comparison, Outcome and Study design; WHO: World Health Organization;EPOC: Effective Practice and Organisation of Care; RCTs :Randomized Controlled Trials; ITS :Interrupted Times Series; NRT: Non-Randomized Trial; RTIs: Respiratory Tract Infections; URTIs: Upper Respiratory Tract Infections; GPs: General Practitioners; NCMS: New Cooperative

Medical Scheme; PR: Public Reported; CDSS: Clinical Decision Support System; EHR: Electronic Health Record.

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Tables

Table 1 Basic characteristics of included studies (n=17)

Study ID	Study design	Country	Participants	Setting	Intervention details	Target illness	duration
Educational interventions							
Carles Llor,2014	before-after quality assurance study	Spain	General practitioners (GPs) registered all patients with RTIs for 15 days in winter 2008	Primary Care centres in Spain	Meetings with the presentation and discussion of the results, and several training meetings on RTI guidelines, workshops on point-of-care tests -rapid antigen detection tests and C-reactive protein rapid test.	RTIs	1 year
Xiaolin Wei,2017	cluster-RCT	China	Participants attended a township hospital as an outpatient, were aged between 2 and 14 years old, and were given a prescription of upper respiratory tract infection	25 township hospitals within the rural, low-income province of Guangxi in western China	Clinical guidelines; monthly peer-review meetings, integrated within routine monthly administrative meetings, during which doctors' antibiotic prescribing rates were assessed; we developed leaflets and a video educating caregivers about antibiotics.	Upper respiratory tract infections	6 months
Virginia Hernandez Santiago,2015	interrupted time series	United Kingdom	408058 residents of the Tayside region of Scotland	Local general practices clinics	Practices received a range of educational material, specific feedback on their own use of antimicrobials; the local Antimicrobial Management Team gave specific advice to general practices	not specified	5 years
Lemiengre, M. B. 2018	cluster-RCT	Belgium	169 FPs started recruitment and 3288 acute infectious episodes	Clinician practices	(1) a point-of-care C-reactive protein test (POC CRP); (2) a brief intervention to elicit parental concern combined with safety net advice (BISNA); (3) both POC CRP and BISNA;	ARTIs (acute respiratory tract infections)	1 year
David Hu¨rlimann,2014	cluster-RCT	Switzerland	16863 cases with RTIs and 4245 cases with lower UTIs per year	140 primary care physicians in Switzerland	Printed guidelines for antibiotic prescription in RTIs and UTIs; individual feedback on antibiotic prescribing behaviour	RTIs and UTIs	16 months
Audit and							

feedback interventions							
Attila Altiner,2007	cluster-RCT	Germany	104 GPs in North-Rhine and Westphalia-Lippe	Regional GPs clinics	GPs in the intervention group were visited by GP peers in their clinics	RTIs	6 weeks/1 year
Jeffrey S. Gerber,2013	cluster-RCT	USA	162 clinicians participated.	A network of 25 pediatric primary care practices	One 1-hour on-site clinician education session (June 2010) followed by 1 year of personalized, quarterly audit and feedback of prescribing for bacterial and viral ARTIs or usual practice.	ARTIs (acute respiratory tract infections)	1 year
Ineke Welschen,2004	RCT	Netherlands	patients presenting with acute symptoms of the respiratory tract	Peer review groups (general practitioners) in the region of Utrecht	Group education meetings; monitoring and feedback on prescribing behavior; group education for assistants of general practitioners and pharmacists; Education materials for patients	acute symptoms of the respiratory tract	1 year
van der Velden 2016	cluster-RCT	Netherlands	169 general practitioners	88 primary care practices participating	GP education, audit/feedback and patient information	ARTI	10–12 months
health policy change strategies							
Lianping Yang,2014	A matched-pair cluster-randomized trial	China	public residents in 20 participating primary care organisations	QJ city of Hubei province, involving 20 primary care organisations	Public reporting on antibiotic prescribing for URTIs	upper respiratory tract infections	1 year
Winnie Yip,2014	A matched-pair cluster-randomized trial	China	twenty-eight towns centers and posts	Twenty-eight towns in Ningxia province	This study’s policy intervention changed NCMS payments to township health centers and village posts from fee-for-service to a capitated budget with pay-for-performance.	not specified	3 years
Li Xiaoxia,2017	control before and after	China	Heads of different departments of primary health centers	17 primary health centers in Jiande, China	Prescribing check results as an important indicator of professional promotion and bonus performance; feedback and audit on primary center	not specified	3 months

information system supported interventions					doctors prescribing.		
Martin C.Gulliford,2014	cluster-RCT	United Kingdom	Individual patients included all those aged 18 to 59 years who were registered with the trial practices.	445 family practices	The decision support tools were installed remotely at the intervention arm practices and delivered during consultations	Urinary Tract Infections	1 year
Akke Vellinga,2016	cluster-RCT	Ireland	A total of 920 patients with suspected urinary tract infection	30 eligible practices in Irish Primary Care	All practices received a workshop to promote consultation coding for urinary tract infections; a reminder integrated into the patient management software suggested first-line treatment;	urinary tract infection	14 months
Mainous, A. G. 2013	quasi-experimental trial	USA	27 physicians, six nurse practitioners and six physician’s assistants volunteered to participate in this study.	Nine intervention practices and 61 control practices	Quarterly EHR based audit and feedback, ‘best-practice’ dissemination during meetings of practice representatives and practice site visits for academic detailing, performance review, and CDSS training.	ARTIs	15 months
Peter S Blair,2017	cluster-RCT	England	542 Children (aged 3 months to <12 years) with acute cough and respiratory tract infection (RTI)	32 general practices' clinics	A web-based clinician-focused clinical rule to predict risk of future hospitalisation and a printed leaflet with individualised child health information for carers, safety-netting advice and a treatment decision record.	RTIs	1 year
Meeker, D.2016	RCT	USA	248 enrolled clinicians	47 primary care practices	suggested alternatives presented electronic order sets; accountable justification prompted clinicians to enter free-text justifications for prescribing	ARTIs	18 months

		antibiotics; peer comparison	

Table 2 antibiotic prescribing changes among these included studies

First author, year	Primary outcome(s)	Change in intervention group	Change in control group	Effect size (95% CI)	P value
Educational interventions					
Carles Llor,2014	change in the odds ratio of antibiotic prescribing (full intervention group)			0.50 (0.44 to 0.57,)	p < 0.001
	change in the odds ratio of antibiotic prescribing (partial intervention group)			0.99 (0.89 to 1.10)	NR
Xiaolin Wei,2017	Antibiotic prescription rate	-42%	-5%	-29%	<0.001
	the multiple antibiotic prescription rate	-6%	6%	1%	0.57
	the broad-spectrum antibiotic prescription rate	-10%	-5%	-4%	0.3
	the intravenous antibiotic prescription rate	-6%	0	-8%	0.07
Virginia Hernandez Santiago,2015	the rate per 1000 registered patients dispensed one or more 4C antimicrobial prescriptions after 6 months of the intervention			-33.5% (–26.1% to –40.9%)	NR
	After 12 months of the intervention			-42.2%(–34.2% to –50.2%)	NR
	After 24 months of the intervention			-55.5%(–45.9% to –65.1%)	NR
David Hu¨rlimann,2014	The percentage of prescriptions of penicillins for all treated RTIs	11.8%	0.7%	11.1%	0.01
	the percentage of trimethoprim/ sulfamethoxazole prescriptions for all uncomplicated lower UTIs treated with antibiotics	13.3%	2.7%	10.6%	0.01
Lemiengre, M. B. 2018	Change in immediate antibiotic prescribing (intervention group of POC CRP vs. control)			1.01（0.57 to 1.79）	<0.1
	Change in immediate antibiotic prescribing (intervention group of BISNA vs. control)			2.04 (1.19 to 3.50).	<0.1
	Change in immediate antibiotic prescribing (intervention group both POC CRP and BISNA vs. control)			1.17 (0.66 to 2.09)	<0.1
Audit and feedback interventions					
Attila Altiner,2007	the ORs for the prescription of an antibiotic (after 6 weeks of the intervention)	0.58 (0.43 to 0.78), p<0.001	1.52(1.19 to 1.95), p=0.001		
	the ORs for the prescription of an antibiotic	0.72 (0.54	1.31(1.01		

	(after 12 months of the intervention)	to 0.97), p=0.028	to 1.71), p=0.044		
Ineke Welschen,2004	Antibiotic prescription rates for acute symptoms of the respiratory tract	-4%	8%	-12%	<0.05
Jeffrey S. Gerber,2013	Rates of broad-spectrum antibiotic prescribing for bacterial ARTIs	-13%	-6%	-7%	=0.1
van der Velden 2016	changes in dispensed antibiotics/1000 registered patients (first year)	-7.6%	-0.4%	-7.2%	=0.002
	changes in dispensed antibiotics/1000 registered patients (second year)	-4.3%	2%	-6.3%	=0.015
health policy change strategies					
Li Xiaoxia,2017	changes in types of antibiotics changes in drug administration of antibiotics changes in combined application of antibiotic				<0.01
Winnie Yip,2014	Change in antibiotic prescription rates at township health centers	:6.6%	8.4%	-15%	<0.05
	Change in antibiotic prescription rates at village posts	-6.0%	10%	-16%	<0.05
Lianping Yang,2014	Percentage of prescriptions requiring antibiotics for upper respiratory tract infections;	-3.02%;	-0.54%	-2.48%	=0.419
	Percentage of prescriptions requiring two or more antibiotics	1.93%	5.65%	-3.72%	=0.049
information system supported interventions					
Martin C.Gulliford,2014	Proportion of consultations with antibiotics prescribed			-1.85% (0.1% to 3.59%)	=0.38
	the rate of antibiotic prescribing for respiratory tract infections			-9.69% (0.75% to 18.63%)	=0.34
Akke Vellinga,2016	proportion of antimicrobial prescribing according to guidelines for urinary tract infection (arm A vs. control)	22.8%	-1.70%	24.5%	<0.001
	proportion of antimicrobial prescribing according to guidelines for urinary tract infection (arm B vs. control)	16.7%	-1.70%	18.4%	<0.001
Peter S Blair,2017	Antibiotic prescribing rates for children’s RTIs	-12%	-21%	9%	=0.018
Mainous, A. G. 2013	Prescribing of broad-spectrum antibiotics rate	-16.60%	1.10%	-17.70%	<0.0001

Meeker, D.2016	The antibiotic prescribing rate for antibiotic-inappropriate acute respiratory tract infection (intervention1 vs. control)	-16%	-11%	-5%	<0.01
	The antibiotic prescribing rate for antibiotic-inappropriate acute respiratory tract infection (intervention 2 vs. control)	-18.1%	-11%	-7.1%	<0.01
	The antibiotic prescribing rate for antibiotic-inappropriate acute respiratory tract infection (intervention3 vs. control)	-16.3%	-11%	-5.3%	<0.01

Figures

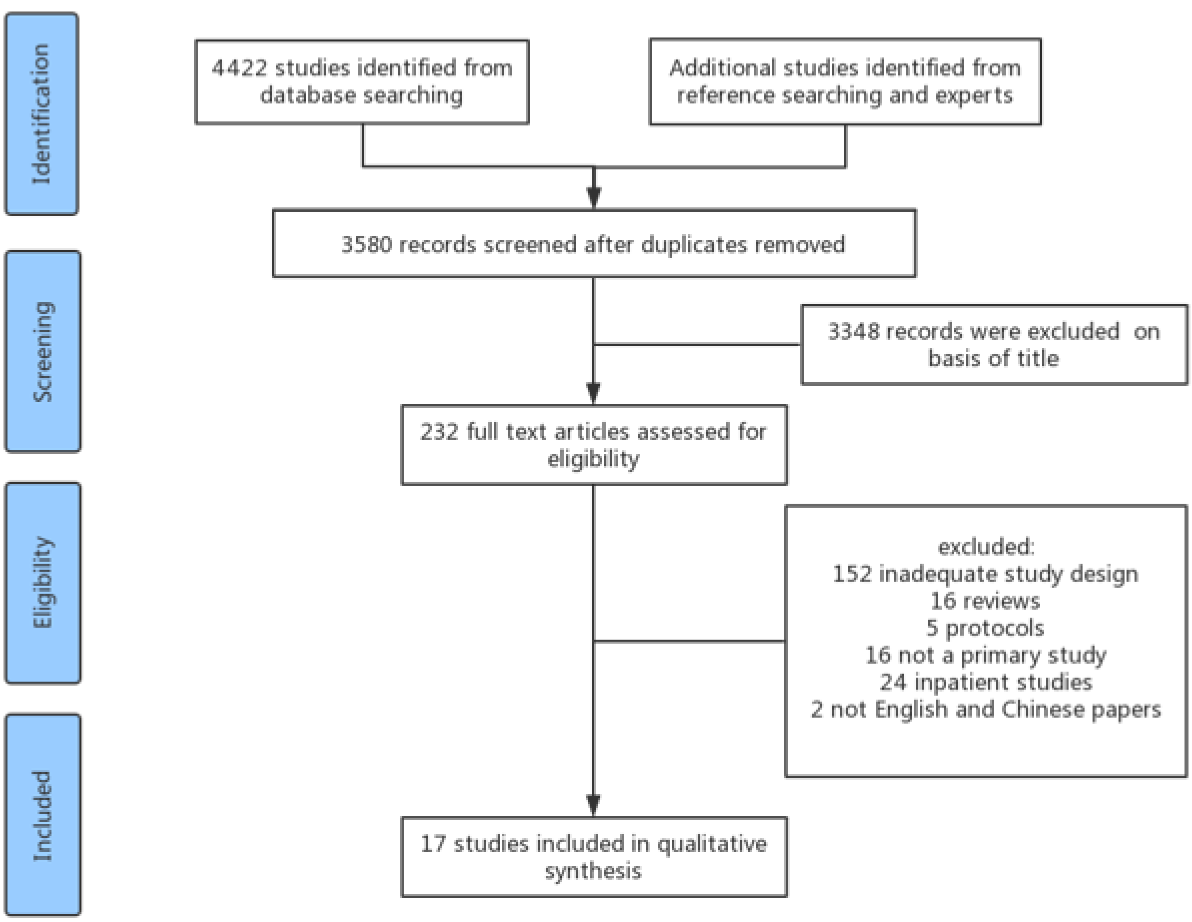

Figure 1

Flow diagram of systematic review screening

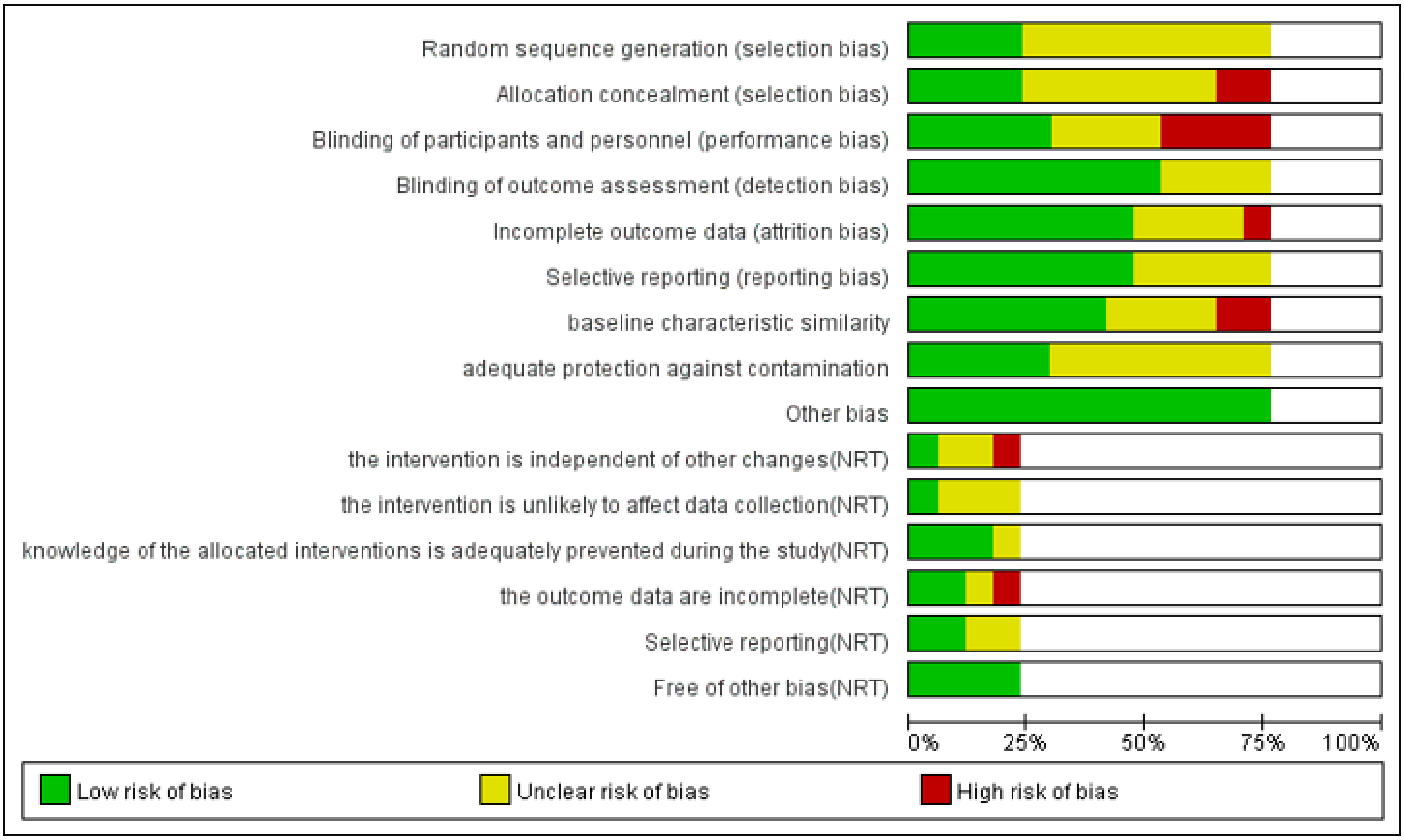

Figure 2

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Blank sections in this graph are due to use of different ROB criteria for RCT versus ITS studies.

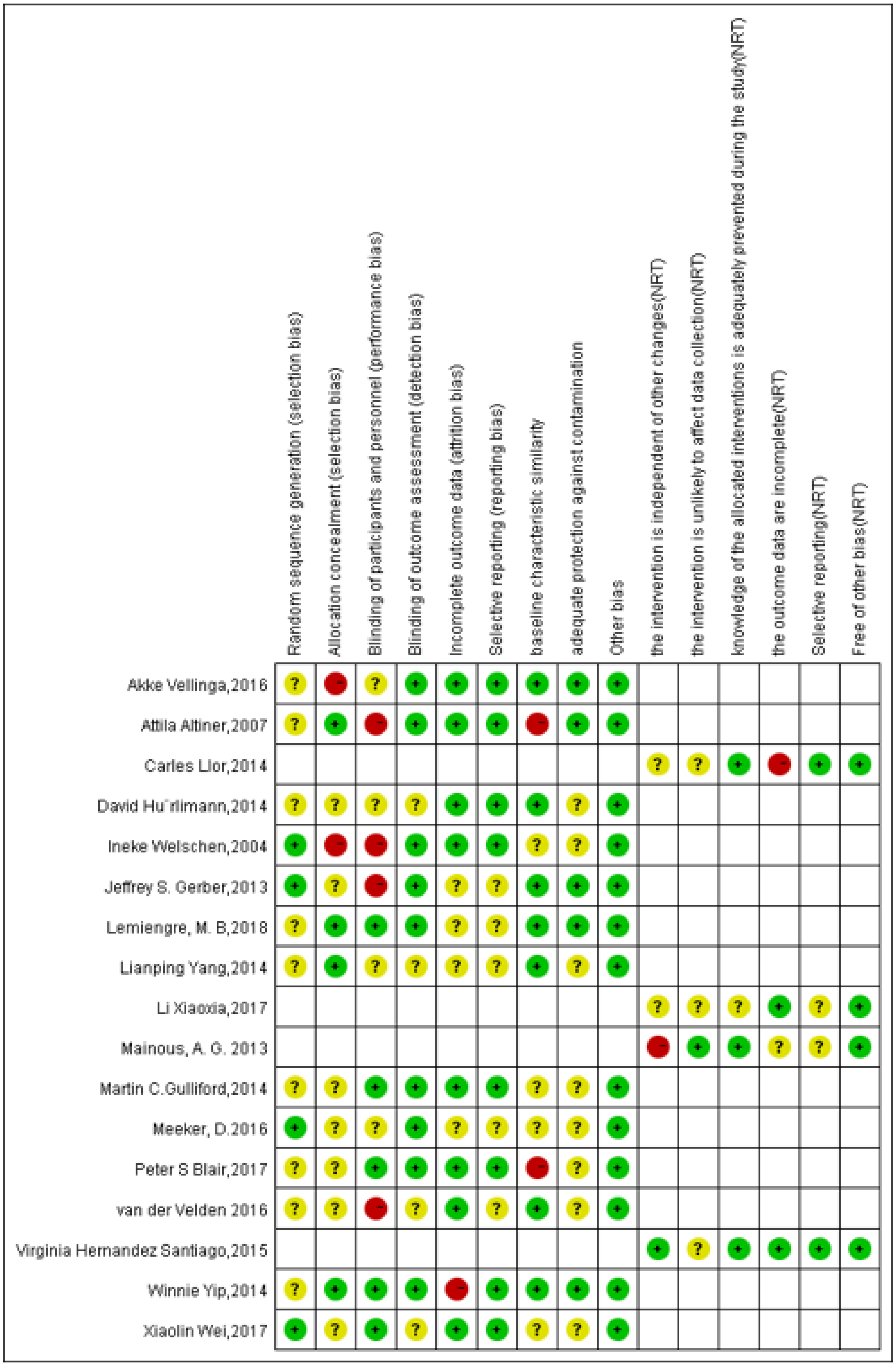

Figure 3

Risk of bias summary: the yellow circles mean the unclear risk of bias or the author did not mention the bias, the green circles mean the low risk of bias, the red circles mean the high risk of bias.

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