Effect of unifaceted and multifaceted interventions on antibiotic prescription control for respiratory diseases: a systematic review of randomised controlled trials

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Abstract

Background

The global health system is improperly using antibiotics, particularly in the treatment of respiratory diseases. We aimed to examine the effectiveness of implementing a unifaceted and multifaceted intervention for unreasonable antibiotic prescriptions.

Methods

Relevant literature published in the databases of Pubmed, Embase, Science Direct, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Journal Full-text (CNKI) and Wanfang was searched. Data were independently filtered and extracted by two reviewers based on a pre-designed inclusion and exclusion criteria. The Cochrane collaborative bias risk tool was used to evaluate the quality of the included randomised controlled trials studies.

Results

A total of 1,074 studies were obtained of which 58 were included in the systematic review. Fifty-one studies reported positive results, that is, the primary results in the intervention groups were superior to those in the control groups. The remaining 7 studies had negative or partially negative results. In 19 studies the outcome variable was the antibiotic prescription rate with detailed reports of the number of prescriptions being further analyzed, of which 17 involved educational interventions for doctors, including: (1) Online training using email, web pages and webinar, (2) Antibiotic guidelines for information dissemination measures by email, postal or telephone reminder, (3) Training doctors in communication skills, (4) Short-term interactive educational seminars, and (5) Short-term field training sessions. Seventeen studies of interventions for health care workers also included: (6) Regular or irregular assessment/audit of antibiotic prescriptions, (7) Prescription recommendations from experts and peers delivered at a meeting or online, (8) Publicly reporting on doctors' antibiotic usage to patients, hospital administrators, and health authorities, (9) Monitoring/feedback prescribing behavior to general practices by email or poster, and (10) Studies involving patients and their families (n = 9). Seventeen randomised controlled trials were rated as having a low risk of bias while 2 randomised controlled trials were rated as having a high risk of bias.

Conclusion

The combination of education, prescription audit, prescription recommendations from experts, public reporting, prescription feedback and patient or family member multifaceted interventions can effectively reduce antibiotic prescription rates in health care institutions. Moreover, adding multifaceted interventions to educational interventions can control antibiotic prescription rates and may be a more reasonable method.

Registrations:

This systematic review was registered in PROSPERO, registration number: CRD42020192560.

Background

The discovery of antibacterial drugs is an important milestone in the history of human medical science. The emergence of antibiotics has changed the outcome of infections, thereby extending people's life expectancy[1]. However, in the past decade, 50% of the world's antibiotic prescriptions have been misused to treat coughs and colds, and many of these prescriptions have no indications for antibiotic use[2]. According to our previous research[3], most unreasonable antibiotic prescriptions are used to treat these uncomplicated respiratory infections caused by viruses, which is common in many countries of the world[4−9]. Therefore, if unchecked, globally, over 700,000 people will die in the next few years as a result of overuse and misuse of antibiotics and this figure could rise to 10 million by 2050, surpassing cancer as the leading cause of death[10, 11]. Previous studies have shown that implementing unifaceted or multifaceted interventions for medical staff, patients and caregivers can effectively reduce antibiotic misuse and thus curb antibiotic resistance[12, 13]. There are two Cochrane Systematic Reviews on interventions to improve antibiotic prescribing; one is in the ambulatory care setting[14] and the other is among hospital inpatients[15]. The ambulatory care review has not been updated since 2005 but more recent systematic reviews have been published about interventions in primary care, especially for respiratory diseases[12, 13, 16] and care homes[17]. They focused specifically on primary care institutions and physicians, or systematic reviews of educational interventions. There is strong evidence that educational interventions improve antibiotic prescribing but more evidence is required about the effectiveness of supplementing education with additional intervention elements and on the sustainability of interventions in a wider range of studies and study subjects. The antibiotic prescription rate (APR) is the main outcome indicator of interventions to control antibiotic prescriptions in those studies[15, 16].

To further confirm the effectiveness of various interventions on antibiotic prescription misuse and overuse in respiratory diseases, we used the Cochrane systematic review method to evaluate published results of relevant randomized controlled trials (RCTs) to provide a reference for relevant decision-makers.

Materials And Methods

Protocol and registration

This systematic review was conducted using the PRISMA reporting guidelines[18] and was registered in PROSPERO with registration number CRD42020192560.

Inclusion criteria

The inclusion criteria of this study were based on the full-text information available in the English and Chinese literature databases and also included the following:

(1) The study objective focused on respiratory diseases;

(2) RCTs of intervention and control groups with measurements collected both before and after the intervention;

(3) Intervention targets were medical staff (general practitioners, physicians, nurses), patients and caregivers;

(4) The interventions were clearly described.

Exclusion criteria

(1) Cross-sectional studies, cohort studies, case-control studies;

(2) Systematic reviews, intervention protocols and letters;

(3) Duplicate studies.

Selection strategy and information sources

A systematic literature search was conducted in PubMed, Embase, Science Direct, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese Journal Full-text (CNKI) and Wanfang databases. The search period was from the time of construction of the database to June 1, 2020. We collected published studies in English or Chinese evaluating the effectiveness of antibiotic prescription interventions. Keywords and search terms used included ("Antibiotic prescription" or "Antimicrobial prescription") and ("Intervention") and ("Respiratory"). Appendix 1 contains an example of the search strategy. Data were independently filtered and extracted based on the pre-designed inclusion and exclusion criteria.

Study setting

Referring to Vodicka[19] and Roque[12], study settings included: (1) Primary care (PC); (2) Hospital care (HP); (3) Health care center (HCc); (4) Pharmacy (PA); (5) Nursing home (NH); and (6) Clinical Practices center (CPc).

Study Design

Study designs included: (1) Cluster randomized controlled trial (cRCT); (2) Randomized controlled trial (RCT); (3) RCT/cRCT & factorial design (FD), where the authors implemented a RCT/cRCT for patients to receive 0, 1, 2,or 3 interventions in a factorial design.

Primary outcomes and findings

The primary outcomes and findings of studies were adapted from Roque[12, 20]. The primary outcomes included: (1) Antibiotic prescription rate (APR); (2) Knowledge, attitude and practice (KAP); (3) Quality of clinical practice (QCP), which were hospitalizations, symptom duration/severity, incidence, mortality; and (4) Inappropriate rate of antibiotic (IRA). The primary findings included: (+) positive findings (±), negative findings (−), both positive and negative (±).

Summary of APR for respiratory diseases

In the RCT studies we included, we performed a more detailed analysis if the outcome variable was the APR (defined as antibiotic prescriptions/total prescriptions ×100%) and there was a detailed prescription quantity report or it could be inferred indirectly from the literature.

Risk of bias assessment

The first two authors (YC, ZZC) read the abstracts of all uncertain studies and the full-text of all studies that were still uncertain. A final agreement to include or exclude the studies was done after discussion of the discrepancies. The risk of bias in the included studies was independently assessed according to the "Cochrane systematic reviewer's manual"[21]. There are 7 items in the criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome bias (attrition bias), selective reporting (reporting bias) and other bias. The bias risk assessment scoring criteria for each study were: “low risk” when all items were rated “low” or one or two of them were “unclear”. If one or more items were rated "high" and more than one "unclear", it was rated as "high risk". RevMan 5.3 software was used to show the results.

Results

The search and selection process is shown in Fig. 1. A total of 1,074 studies were obtained, of which 335 were excluded after reading the title and abstract. The remaining 739 studies were further screened by reading the full-text, of which 671 were excluded: 121 because they were treatment or drug intervention trials, 17 because they were antibiotic cost-benefit analysis studies, 116 because they were systematic reviews or cohort studies such as non-RCTs, 323 because they were observational studies (cross-sectional studies, and case-control studies), 97 because they were duplicate studies, and 7 studies because the full-text could not be accessed. Finally, 68 studies were included in the systematic review. In 22 studies, the outcome variable was APR and included detailed reports of the number of antibiotic prescriptions.

Basic characteristics of the included studies

As shown in Table 1, of the 58 studies included, 28[22–49] were cluster randomized controlled trials (cRCT), 21[50–70] were randomized controlled trials (RCT), 9 [71–79]were factorial design RCT/cRCT. Forty-four[22–27, 30, 32–43, 48–51, 53–57, 59–61, 65–73, 76–79] studies were conducted in primary care settings (including general practice clinics, family practices and township hospitals) and there were 7[31, 44, 46, 47, 58, 62, 63] hospital-based studies. Seven studies[28, 29, 45, 52, 64, 74, 75] were conducted in other settings including a health care center, pharmacy. General practitioners (GPs) were participants of 28[24, 26, 30, 32, 34, 36, 37, 39, 40, 42, 46, 50, 51, 53, 54, 56, 60, 61, 63, 65–67, 69, 70, 73, 76–78] intervention studies. Participants in the other 30 studies included: (1) Physicians (n = 9)[23, 27, 33, 43, 45, 49, 59, 71, 74], doctors (n = 2)[58, 75] clinicians (n = 4)[38, 44, 68, 79], pharmacists (n = 4)[31, 52, 59, 70] and staff (n = 2)[29, 64] of day-care centers; (2) Family physicians (FPs, n = 2)[41, 48]; (3) Health providers (HPs, n = 3)[25, 28, 35];which were faculties at a clinical practices center; (4) Nurses or nurse practitioners (n = 1)[33]; (6) All kinds of patients, caregivers and inhabitants (n = 13)[22, 23, 29, 30, 33, 37, 47, 49, 55, 57, 62, 72, 73]. Forty one studies[22, 25–30, 34–36, 39, 40, 42–48, 50, 51, 54, 56–58, 61, 63, 65–70, 72–79] were for respiratory diseases in all patients, and the remaining 19 studies were of children (n = 14)[23, 24, 29, 32, 33, 37, 38, 49, 52, 55, 59, 62, 64, 71] and adults (n = 3)[41, 53, 60]. Fifteen studies had intervention periods of less than one year. Fifty nine studies had positive results (+, The primary results in the intervention groups were superior to those in the control groups). Seven studies[43, 47, 55, 56, 60, 64, 71] had negative (-) or partially negative (±) results. The outcome variable for 32[24–27, 30, 33–37, 39–51, 54, 58, 60, 63, 66, 69, 70, 74, 79] studies was APR but details were available for the intervention groups and control groups in only 19 studies (Table 2)

Table 1
Basic characteristics of the 58 studies

Study	Design (a)	Settings (b)	Diseases (c)	Participants (d)	Patients	Duration	Primary Outcome (e)	Primary findings (f)
Zwar N et al. Australia 1999[51]	RCT	PC	URTIs	GPs	All	unclear	APR	(+)
Mainous AG et al. USA 2000[71]	RCT & FD	PC	Pediatric RTIs	Physicians	Children	5 months	PRE	(−)
Chalker J et al. Vietnam 2002[52]	RCT	PA	ARTIs	Pharmacists	Children	1 year	KAP	(+)
Macfarlane J et al. England 2002[53]	RCT	PC	ARTIs	GPs	Adults	Unclear	PRE	(+)
Wilson EJ et al. Australia 2003[54]	RCT	PC	ARTIs	GPs	All	2 years	APR	(+)
Coenen S, et al. Belgium 2004[36]	cRCT	PC	ARTIs	GPs	All	4 months	APR	(+)
Ineke W, et al. Netherland 2004[70]	RCT	PC	RTIs	GPs & Pharmacists	All	10 months	APR	(+)
Paul L et al. UK 2005[72]	RCT & FD	PC	LRTIs	Patients	All	5 years	QCP	(+)
Samore MH et al. USA 2005[73]	RCT & FD	PC	ARTIs	GPs & Inhabitants	All	21 months	PRE	(+)
Gonzales R, et al. USA 2005[74]	RCT & FD	HCc	ARTIs	Physicians	All	Unclear	APR	(+)
Taylor JA et al. USA 2005[55]	RCT	PC	URTIs	Caregivers	Children	1 year	QCP	(−)
Fairall L.R et al. UK 2005[22]	cRCT	PC	RTIs	Patients (≥ 15)	All	3 months	QCP	(+)
Hedin K et al. Sweden 2006[64]	RCT	HCc	IDs	Staffs & Parents	Children	Unclear	KAP & PRE	(−)
Jeroen AS et al. Netherlands 2007[46]	cRCT	HP	CAP&COPD	GPs	All	10 months	APR	(+)
Chowdhury AKA et al. Bangladesh 2007[75]	RCT & FD	HCc	ARTIs	Doctors	All	unclear	PRE	(+)
Altiner A, et al. Germany 2007[30]	cRCT	PC	RTIs & others	GPs & Patients	All	1 year	APR	(+)
Metlay JP, et al. USA 2007[44]	cRCT	HP	ARTIs	Clinicians & Patients	All	Unclear	APR	(+)
Monette J, et al. Canada 2007[45]	cRCT	HCc	RTIs & others	Physicians	All	8 months	APR	(+)
Finkelstein JA et al. USA 2008[23]	cRCT	PC	RTIs	Patients & Physicians	Children	3 years	PRE	(+)
Susan H et al. UK 2008[77]	RCT & FD	PC	URTIs	GPs	All	unclear	KAP	(+)
Smeets HM et al. Netherlands 2009[56]	RCT	PC	RTIs	GPs	All	1 year	PRE	(−)
Nick AF. et al. UK 2009[38]	cRCT	PC	ARTIs	Clinicians	children	unclear	QCP	(+)
Fabienne CB. et al. US 2010[33]	cRCT	PC	ARTIs	Physicians & NPs	Patients < 18 years	6 months	APR	(+)
Christopher CB. et al. UK 2012[34]	cRCT	PC	unclear	GPs	All	1 year	APR	(+)
Llor C, et al. Spain 2012[50]	RCT	PC	RTIs	GPs	All	Unclear	APR	(+)
Jenkins TC et .al USA 2013[65]	RCT	PC	ARTIs	GPs	All	1 year	PRE	(+)
Angoulvant F et al. France 2013[62]	RCT	HP	ARTIs & UTIs	Caregivers	Children	6 months	KAP	(+)
Milos V et al. Sweden 2013[69]	RCT	PC	URTIs	GPs	All	5 months	APR	(+)

Study	Design (a)	Settings (b)	Diseases (c)	Participants (d)	Patients	Duration	Primary Outcome (e)	Primary findings (f)
Philippe LC, et al. France 2013[66]	RCT	PC	RTIs	GPs	All	30 months	APR	(+)
Little P et al. UK 2013[78]	RCT & FD	PC	ARTIs	GPs	All	3 months	PRE	(+)
Gerber JS et al. US 2013[24]	cRCT	PC	ARTIs	GPs	Children	1 year	APR	(+)
Hoye S. et al. UK 2013[42]	cRCT	PC	RTIs	GPs	All	1 year	APR	(+)
Gjelstad S, et al. Norway 2013[39]	cRCT	PC	ARTIs	GPs	All	Unclear	APR	(+)
Meeker D et al. USA 2014[68]	RCT	PC	ARTIs	Clinicians	All	12 weeks	IRA	(+)
Chen Y, et al. China 2014[35]	cRCT	PC	URTIs	HPs	All	2 months	APR	(+)
Gulliford MC, et al. England 2014[41]	cRCT	PC	RTIs	FPs	Patients (18–59)	6 months	APR	(+)
Yang L, et al. China 2014[25]	cRCT	PC	URTIs	HPs	All	Unclear	APR	(+)
Little P et al. England 2015[57]	RCT	PC	RTIs & IDs	Patients	All	16 weeks	QCP	(+)
Hürlimann D, et al. Switzerland 2015[43]	cRCT	PC	RTIs & URTIs	Physicians	All	2 years	APR	(±)2
Treweek S et al. England 2016[76]	RCT & FD	PC	URTIs	GPs	All	Unclear	KAP	(+)
Meeker D et al. USA 2016[79]	cRCT & FD	PC	ARTIs	Clinicians	All	18 months	APR	(+)
Little P et al. England 2016[67]	RCT	PC	RTIs	GPs	All	20 weeks	QCP	(+)
Ferrat E, et al. France 2016[63]	RCT	HP	RTIs	GPs	All	4.5 years	APR	(+)
Qiu JG, et al. China 2016[58]	RCT	HP	RTIs	Doctors	All	Unclear	APR	(+)
Velden AW, et al. Netherlands 2016[26]	cRCT	PC	RTIs	GPs	All	1 year	APR	(+)
Vervloet M, et al. Netherland 2016[48]	cRCT	PC	RTIs	FPs	All	3 months	APR	(+)
Hoa, et al. Vietnam 2017[59]	RCT	PC	ARTIs	Physicians & Pharmacists	Children	7 months	KAP	(+)
Blair PS et al. England 2017[32]	cRCT	PC	ARTIs	GPs	Children	Unclear	PRE	(+)
Lee MHM, et al. Singapore 2017[60]	RCT	PC	URTIs	GPs	Patients (≥ 21)	Unclear	APR	(-)
Tang YQ, et al. China 2017[27]	cRCT	PC	URTIs	Physicians	All	Unclear	APR	(+)
Wei XL, et al. China 2017[49]	cRCT	PC	URTIs	Physicians & Caregivers	Children (2–14)	6 months	APR	(+)
Shen XR et al. China 2018[61]	RCT	PC	RTIs & others	GPs	All	1 year	KAP	(+)
Temime L et al. USA 2018[28]	cRCT	NHs	IDs	HPs	All	1 year	QCP and APRs	(+)
Azor-Martinez E et al. Spain 2018[29]	cRCT	HCc	RTIs	Staffs & Caregivers & Children (0–3)	Children	8months	QCP	(+)
Dekker ARJ, et al. England 2018[37]	cRCT	PC	RTIs	GPs & Caregivers	Children	Unclear	APR	(+)
Gulliford MC, et al. England 2019[40]	cRCT	PC	RTIs	GPs	All	1 year	APR	(+)
Ashiru-Oredope D et al. UK[31]	cRCT	HP	RTIs	Pharmacists	All	1 month	QCP	(+)
van de Maat JS et al. Holland 2020[47]	cRCT	HP	RTIs	Children (1–60 months)	All	9 months	APR	(−)

1. (a) Design: cRCT: Cluster randomized controlled trial; RCT: Randomized controlled trial; FD: Factorial design.
2. (b) Setting: PC: Primary care; HP: Hospital; HCc: Health care center; PA: Pharmacy; (c) Disease: URTIs: Upper respiratory tract infections; LRTIs: Lower respiratory tract infections; RTIs: Respiratory tract infections; ARTIs: Acute respiratory tract infections; IDs: Infectious diseases; UTIs: Urinary tract infections; TB: Tuberculosis; COPD: Chronic obstructive pulmonary disease; CAP: Community-acquired pneumonia.
3. (d) Participants: GPs: General practitioners; FPs: Family physicians; HPs: Health providers; PPs: Practice providers; NPs: Nurses or nurse practitioners.
4. (e) Outcome: APR: Antibiotic prescription rate; KAP: Knowledge, attitude and Practice; QCP: Quality of clinic practice; PRE: Prescription evaluation; IRA: Inappropriate Rate of antibiotic.
5. (f) Primary findings: (+): Positive findings; (−): Negative findings; (±): Positive and negative findings, (±) 1: Academic detailing led to a significant reduction in unnecessary antibiotic prescribing, sending an educational email is invalid; (±)2: The guidelines, coupled with sustained personal feedback, did not reduce APR but increased the use of recommended antibiotic. (±) 3: A multifaceted intervention reduced antibiotic prescribing for bronchitis/bronchiolitis but not upper respiratory tract infections.

Intervention of APR studies

Table 2 shows intervention studies in which the outcome variable was APR. A total of 19 RCTs were included in the review, including 1[58] published in Chinese and 18[25–27, 30, 35–37, 39–41, 43–45, 48, 49, 60, 63, 70] in English. The studies involved a total of 1,853,829 prescriptions from 11 countries: China[25, 27, 35, 49, 58],, the United States[44], England[37, 40, 41], Canada[45], Norway[39], Germany[30], Netherlands[26, 48, 70], Singapore[60], Switzerland[43], France[63] and Belgium[36] (940,567 in the intervention group and 913,262 in the control group). Fifteen studies[25–27, 30, 35–37, 39–41, 43–45, 48, 49] were designed using cluster sampling. Fifteen [25–27, 30, 35–37, 39–41, 43, 48, 49, 60, 70] were interventions implemented at a primary care/community setting, 5[26, 30, 40, 43, 63] mentioned that the duration of the intervention was more than 1 year while 7[35, 36, 41, 45, 48, 49, 70] mentioned that the duration of the intervention was less than 1 year. Four[35, 36, 39, 60] of the study's control groups received a partial intervention. One study[60] had a negative result which may be due to the fact that the interventions were targeted only at patients. Therefore, the authors suggested that future research should be aimed at GPs. Two studies had negative and positive results: Hürlimann[43] advocated use of an intervention that included providing guidelines for the treatment of the diseases and providing sustained, regular feedback (twice a year) on individual physicians' antibiotic prescribing behavior over a two-year period, which did not reduce the APR, but increased the use of recommended antibiotics. Routine guidelines and long personal feedback intervals (twice yearly) may be the reason why the intervention was not so effective. Magin showed that a multifaceted intervention (online modules that included guidelines and communication skills and a face-to-face educational session) could reduce antibiotic prescribing for bronchitis/bronchiolitis but not upper respiratory tract infections. The study had a non-random sampling design that resulted in contamination in the control group resulting in no significant difference in the outcomes.

Table 2
Basic characteristics of the 19 APR studies

Author	Year	Country	Sample size included in the study (antibiotic prescriptions / total prescriptions)		Research design	Settings	Participants	Duration	Control group intervention·	Primary findings
			Intervention group	Control group						
Coenen S, *et al*[36]	2004	Belgium	80/292	115/401	Cluster sampling Random allocation	PC	GPs	4 months	Partial intervention	(+)
Ineke W, *et al*[70]	2004	Netherland	60/261	39/105	Random allocation	PC	GPs and pharmacists	10 months	-	(+)
Altiner A, et al[30]	2007	Germany	289/787	596/920	Cluster sampling Random allocation	PC	GPs and patients	1 year	-	(+)
Metlay J.P, et al[44]	2007	USA	483/1510	637/1342	Cluster sampling Random allocation	HP	Clinicians and patients	Unclear	-	(+)
Monette J, et al[45]	2007	Canada	309/1326	154/431	Cluster sampling Random allocation	HCc	Physicians	8 months	-	(+)
Gjelstad S, et al[39]	2013	Norway	21 246/66 757	23 307/66 501	Cluster sampling Random allocation	PC	GPs	Unclear	Partial intervention	(+)
Chen Y, et al[35]	2014	China	568/831	299/446	Cluster sampling Random allocation	PC	HPs	2 months	Partial intervention	(+)
Gulliford MC, et al[41]	2014	England	34313/317717	32569/285692	Cluster sampling Random allocation	PC	FPs	6 months	-	(+)
Yang L, et al[25]	2014	China	11184/12774	9824/10369	Cluster sampling Random allocation	PC	HPs	Unclear	-	(+)
Hürlimann D, et al[43]	2015	Switzerland	15952/41580	13654/45737	Cluster sampling Random allocation	PC	Physicians	2 years	-	(±)
Ferrat E, et al[63]	2016	France	9916/70830	17708/106036	Random allocation	HP	GPs	4.5 years	-	(+)
Qiu JG, et al[58]	2016	China	107/150	143/150	Random allocation	HP	Doctors	Unclear	-	(+)
Velden AW, et al[26]	2016	Netherlands	895/3461	974/3421	Cluster sampling Random allocation	PC	GPs	1 year	-	(+)
Vervloet M, et al[48]	2016	Netherland	8677/53829	14603/94767	Cluster sampling Random allocation	PC	FPs	3 months	-	(+)
Lee MHM, et al[60]	2017	Singapore	94/457	81/457	Random allocation	PC	GPs	Unclear	Partial intervention	(-)

Author	Year	Country	Sample size included in the study (antibiotic prescriptions / total prescriptions)		Research design	Settings	Participants	Duration	Control group intervention·	Primary findings
			Intervention group	Control group						
Tang YQ, et al[27]	2017	China	14649/17021	13219/14937	Cluster sampling Random allocation	PC	Physicians	Unclear	-	(+)
Wei XL, et al[49]	2017	China	943/2351	1782/2552	Cluster sampling Random allocation	PC	Physicians and caregivers	6 months	-	(+)
Dekker ARJ, et al[37]	2018	England	102/475	176/531	Cluster sampling Random allocation	PC	GPs and Caregivers	Unclear	-	(+)
Gulliford MC, et al[40]	2019	England	37601/348158	40099/278467	Cluster sampling Random allocation	PC	GPs	1 year	-	(+)

Interventions of included APR studies

Table 3 shows the categories of interventions included in the APR studies. Seventeen[26, 27, 30, 35–37, 39–41, 43–45, 48, 49, 58, 63, 70] of the 19 studies involved educational interventions, including: (1) online training using email, web pages and webinars containing guidelines and communication skills[36, 37, 40], (2) antibiotic guidelines for information dissemination measures by email, postal or telephone reminder[27, 35, 36, 40, 41, 43–45, 58, 63], (3) training doctors in communication skills[27, 30, 37, 41, 45, 48, 70], (4) short-term interactive educational seminars[26, 39, 40, 44, 49, 58, 63, 70] and (5) short-term field training sessions[26, 39, 44, 49, 58, 63, 70], the latter two types of training methods were generally face-to-face (on-site) interventions and the duration was usually hours or days of diagnostic and drug guidances, rapid testing method, of which 5[40, 44, 58, 63, 70] studies comprehensively used more than 2 educational interventions, and all of these studies had positive results.

Seventeen studies of interventions for health care workers also included: (6) regular or irregular assessment/audit of antibiotic prescriptions[39, 40, 45, 49, 58, 70], and (7) prescription recommendations from experts and peers delivered at a meeting or online[26, 30, 36, 41, 44, 45, 48]. Vervloet[48] implemented a prescription recommendation in an Electronic Prescribing System (EPS). When a family physician tried to prescribe an antibiotic to a patient with RTI, the EPS immediately prompted an alert with the message "no prescription", and if the doctor still wanted a prescription, a pop up window containing the message "delayed prescription" would appear. After acknowledging these two electronic alerts, the doctor could write a prescription. (8) Two studies[25, 27] reported publicly on doctors' antibiotic usage to patients, hospital administrators, and health authorities. The report contained APR, injection for APR, cost and peer ranking. (9) Nine studies reported moniotoring/feedback prescribing behaviour to GPs by email or poster (the prescribing behaviour of individual physicians for 6 months or one year)[26, 27, 39, 40, 43–45, 48, 70].

Among the studies of interventions, 9[25, 26, 30, 37, 40, 44, 49, 60, 70] involved patients and their families, including the distribution of leaflets and brochures on the rational use of antibiotics, the installation of multimedia education systems or poster/video in waiting rooms, and the use of flyers and posters. One[60] of the studies involved only patients and family members.

Table 3
Categories of interventions included in the 19 studies

Author (year)	**Health care worker**								
Educational intervention					(6) Prescription audit	(7) Prescription recommendations from experts†	(8) Public reporting	(9) Prescription feedback	Brochure
(1) Online training	(2) Distribution of educational materials	(3)Communication skill	On-site intervention*						
			(4) Short-term interactive education seminar	(5) Short-term field training					
Coenen S(2004) [36]	√	√					√		
Ineke W (2004) [70]			√	√	√	√			√
Altiner A (2007) [30]			√				√		
Metlay JP (2007) [44]		√		√	√		√		√
Monette J(2007) [45]		√	√			√	√		√
Gjelstad S (2013) [39]				√	√	√			√
Chen Y(2014) [35]		√							
Gulliford MC(2014) [41]		√	√				√		
Yang L(2014) [25]								√	
Hürlimann D(2015) [43]		√							√
Ferrat E (2016) [63]		√		√	√				
Qiu JG (2016) [58]		√		√	√	√			
Velden AW (2016) [26]				√	√		√		√
Vervloet M (2016) [48]			√				√		√
Lee MHM (2017) [60]									
Tang YQ (2017) [27]		√	√					√	√
Wei XL (2017) [49]				√	√	√			
Dekker ARJ (2018) [37]	√		√						

Author (year)	Health care worker							
Gulliford MC (2019)[40]	√	√		√	√			√

Risk of bias

As shown in Fig. 2, seventeen studies[25–27, 30, 35–37, 39–41, 43, 44, 48, 49, 60, 63, 70] were rated as having a low risk of bias while 2[45, 58] were rated as having a high risk of bias. Figure 2 shows the risk of bias assessment for each criterion. Among the 19 studies, 1[58] in the “Random Sequence Generation” section were determined to have a high risk of bias as the one did not describe the sampling method. Although the study stated itself as using a randomized approach, the process described by it is more likely to be grouped according to the availability of interventions. One study was identified as having a high risk of bias in the “Blinding of outcome assessment”[45] section due to a lack of random sampling and unblinded nature. Fifteen studies[26, 27, 30, 36, 37, 39–41, 43–45, 48, 58, 60, 63] showed an unclear risk of bias in 5 domains: allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome bias, and other bias. Only four[25, 35, 49, 70] of the studies were low risk of bias in all domains. In the domain of "Allocation concealment", 10 studies[26, 30, 37, 39–41, 43, 44, 48, 58] were judged as having unclear risks of bias. The main reason is that no information was provided about the process of generating random sequences in these studies. This can lead to selection bias. In the domain of " Blinding of participants and personnel ", 9 studies[26, 27, 30, 37, 39, 41, 44, 58, 63] were judged as having unclear risks of bias. The reason is that there was not enough information to determine "low risk" or "high risk." There may be a risk of performance bias. In the domain of "blinding of outcome assessment”, 7 studies[26, 36, 39, 41, 43, 48, 58] were judged to have "unclear risk of bias" due to lack of information. Detection bias is likely to arise. In the domain of “incomplete outcome bias”, 1 study[44] was judged to have an unclear risk of bias because it did not provide a random number of people and lacked data. This has the potential to create attrition bias. Finally, in the domain of "Other bias," 8 studies[26, 27, 36, 43, 45, 48, 58, 60] were judged to have unclear risk of bias because these authors did not provide enough information to determine whether there was a significant risk of bias.

Discussion

Our findings indicate that the majority (44, 76%) of RCTs on antibiotic prescriptions for RTIs were conducted in primary health care settings. GPs and physicians were the main subjects of the intervention. Forty-one studies (71%) did not have a specific population with the diseases and twenty-one studies (36%) had intervention periods of less than 1 year. There were 32 studies that had an APR as the outcome variable. Patient-only, long feedback intervals, non-random sampling and non-blind nature of the intervention may have led to negative results and a high risk of bias.

A further analysis of 19 studies in which the outcome variable was APR found that all but one were multifaceted interventions. Educational methods were the most common interventions. Among them, the distribution of antibiotic guidelines to doctors, short training sessions of one to several days and training in doctors' communication skills were the most common educational interventions, and they were often used in combination. In addition, interventions for health care workers included monitoring and feedback of doctors' prescribing performance to them, auditing or evaluating the rationality of prescriptions, and prescribing recommendations from experts or via an electronic prescribing system. On the basis of the above interventions, some were added to the intervention of patients or caregivers. However, it is important to note that patients cannot be given an intervention alone, or the intervention may face ineffective results. In addition, we originally planned to do a meta-analysis of 19 RCTsthe study objects were the medical records of the intervention group and the control group after the intervention. The risk difference (RD) of APR of the two groups was combined, and the combined effect value and 95% confidence interval (CI) were calculated. However, even when the random impact model was used, the heterogeneity was still significant (I^2 = 99%), so a sensitivity analysis and subgroup analysis were conducted. After the sensitivity analysis, we attempted to conduct a subgroup analysis on factors such as cluster or non-cluster, random or non-random, study area, intervention methods, duration of intervention and randomness, to explore the causes of heterogeneity. RD (relative deviation) was used to control the confounders. Nevertheless, the high heterogeneity of all subgroups led us to perform a descriptive review of the literature. These 19 RCTs studies investigated a wide range of interventions targeted at both clinicians and patients (education, guidelines, prescriber feedback, patient pamphlets, etc.). This makes it very difficult to meta-analyse and to interpret the results as it's unclear exactly which intervention targeted at which groups and in what setting is having the impact on prescribing. It also explains why there are such high rates of heterogeneity.

We identified the final 19 RCTs using a risk of bias tool[21]. Most (17) of the studies were low risk, but 15 of them had an "unclear risk of bias" due to insufficient information. Therefore, we hope that future studies will follow standard RCT procedures (e.g. SPIRIT 2013 Checklist)[80] to conduct trials and write manscripts.

In summary, multifaceted feedback interventions were used in most of the included studies. Therefore, the education and training of doctors in prescribing antibiotics should be strengthened, organized medical staff should delve deep into the rules and regulations of antibiotics, and make full use of pharmacology, pharmacokinetics, pharmacodynamics, and other relevant knowledge to issue prescriptions[81, 82]. On this basis, various feedback interventions can be added, such as communication between experts and peers, prescription audits, and ranking of doctors in the same department. In addition, interventions can improve the awareness of patients and their families toward antibiotics, such as providing them with brochures and leaflets, displaying posters in the waiting rooms, installing a multimedia education system in waiting areas, and encouraging patients to communicate more with their physicians about the use of antibiotics. Dekker[37] and Metlay[44] adopted certain intervention measures for patients and their families based on educational intervention measures for medical staff. Altiner[30] studied patients and their families based on using feedback intervention for medical staff, and the degree of reduction of antibiotic utilization was significantly higher than in other studies. Therefore, according to education and training interventions, feedback interventions were used to influence the prescribing behavior of doctors and improve the cognition of patients and their families about antibiotics. This multifaceted behavioral feedback intervention might be a more rational approach to antibiotic prescription control. In terms of policymaking, health administration departments should introduce regulations and relevant policies on the administration of antibiotics to strictly control the use of antibiotics. These departments can take strong administrative interventions against the unreasonable use of antibiotics, for example, patients or consumers could only obtain antibiotics from the pharmacies based on prescriptions, and doctors can prescribe antibiotics in a hierarchical manner.

Our study has certain limitations. First, like most systematic reviews, there is a possibility of publication bias. We analyzed only 58 of the studies with basic characteristics, and 19 of the studies further focused were all positive outcomes. We concluded from these 19 studies that multifaceted interventions are more effective in reducing antibiotic prescription rates. Furthermore, some studies were not included due to incomplete data and non-randomization. This limitation may have reduced the objectivity of the results to a certain extent. Second, there were different degrees of quality differences in the design of the included studies, which may have affected our results. Third, these studies were conducted in different countries. The policies and management systems of antibiotic use differ by country, thus there was a risk of information bias. Fourthly, we only focused on the APR, but did not pay attention to the rational evaluation of antibiotics.

This systematic review found that combination of education, prescription audit, prescription recommendations from experts, public reporting, prescription feedback and patient or family member interventions and other multifaceted feedback interventions can effectively reduce the rate of antibiotic prescriptions and promote the rational use of antibiotics. However, due to the above limitations, we can only conclude that adding multifaceted feedback interventions to education interventions may be a more reasonable control method. In the future, more studies need to be included to obtain more accurate information.

Additional file

Additional file 1: PRISMA 2009 Checklist.

Additonal file 2: An example of a search strategy (Pubmed database search strategy)

Abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials;

APR: Antibiotic prescription rate;

CNKI: Chinese Journal Full-text;

RD: Risk difference;

CI: Confidence interval;

RCTs: Randomized Controlled Trials;

RTIs: Respiratory tract infections

RCTs: randomized controlled trials;

PC: Primary care;

HP: Hospital care;

HCc: Health care center;

PA: Pharmacy;

NHs: Nursing homes;

CPc: Clinical Practices center

cRCT: Cluster randomized control trial;

RCT: Randomized controlled trial;

FD: Factorial design;

KAP: Knowledge, Attitude and Practice (KAP);

QCP: Quality of clinic practice;

PRE: Prescription evaluation

IRA: Inappropriate rate of antibiotic;

URTIs: Upper respiratory tract infections;

LRTIs: Lower respiratory tract infections;

ARTIs: Acute respiratory tract infections;

IDs: Infectious diseases;

UTIs: Urinary tract infections;

TB: Tuberculosis;

COPD: Chronic obstructive pulmonary disease;

CAP: Community-acquired pneumonia;

GPs: General practitioners;

FPs: Family physicians;

HPs: Health providers;

PPs: Practice providers;

NPs: Nurses or nurse practitioners.

Declarations

Conflict of Interest

All authors have no conflicts of interest to declare.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Authors' contributions

All authors made substantial contributions to the development of the trial, and read and approved the final manuscript. YC, ZZC, GHY designed the trial. XZ drafted the manuscript, and YC and ZZC completed data extraction, statistical analysis and data interpretation. GHY and LT participated in the concept, data interpretation and manuscript revision. YC is responsible for data integrity and accuracy of data analysis.

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Ethical approval

This study was approved by the Academic Committee of Guizhou Medical University. All participants provided written informed consent

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Figures

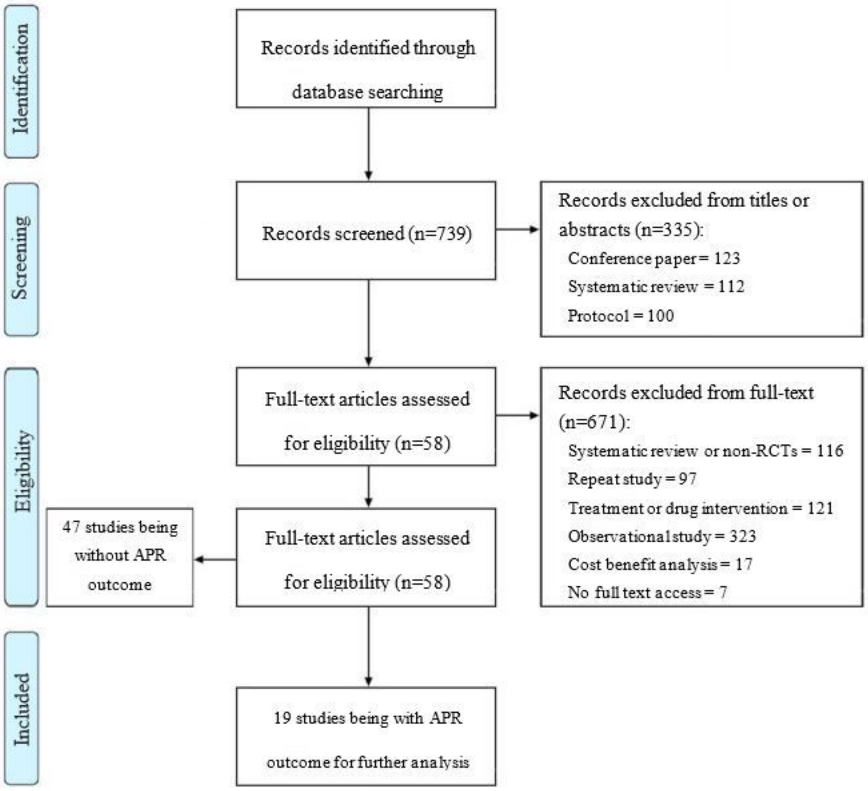

Figure 1

PRISMA screening flow chart

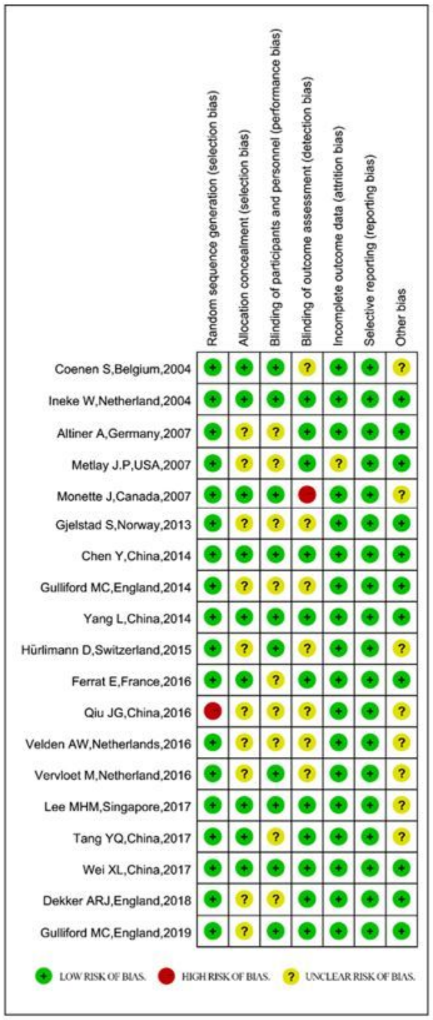

Figure 2

Risk of bias summary

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2009checklist.doc
- Pubmeddatabasesearchstrategy289.csv