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Effect of unifaceted and multifaceted interventions on antibiotic prescription control for respiratory diseases

A systematic review of randomized 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, China National Knowledge Infrastructure and Wanfang was searched. Data were independently filtered and extracted by 2 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 randomized controlled trials studies.

Results: A total of 1390 studies were obtained of which 23 studies the outcome variables were antibiotic prescription rates with the number of prescriptions and intervention details were included in the systematic review. Twenty-two of the studies involved educational interventions for doctors, including: online training using email, web pages and webinar, antibiotic guidelines for information dissemination measures by email, postal or telephone reminder, training doctors in communication skills, short-term interactive educational seminars, and short-term field training sessions. Seventeen studies of interventions for health care workers also included: regular or irregular assessment/audit of antibiotic prescriptions, prescription recommendations from experts and peers delivered at a meeting or online, publicly reporting on doctors' antibiotic usage to patients, hospital administrators, and health authorities, monitoring/feedback prescribing behavior to general practices by email or poster, and studies involving patients and their families (n = 8). Twenty-one randomized controlled trials were rated as having a low risk of bias while 2 randomized controlled trials were rated as having a high risk of bias. Six studies contained negative results.

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.

Abbreviations: APR = antibiotic prescription rate, CI = confidence interval, GPs = general practitioners, RCT = randomized controlled trial, RD = risk difference.

Keywords: antibiotic prescriptions, randomized controlled trial, respiratory diseases, systematic evaluation

YC, ZC, and XH contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

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] As a result, globally, 4.95 million people died in 2019 from bacterial antimicrobial resistance caused by overuse and misuse of antibiotics. If unchecked, 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 2 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 and meta-analysis methods to evaluate published results of relevant randomized controlled trials (RCTs) to provide a reference for relevant decision-makers.

2. Materials and Methods

2.1. Protocol and registration

This systematic review was conducted using the PRISMA reporting guidelines (Appendix 1, Supplemental Digital Content, http://links.lww.com/MD/H434)[18] and was registered in PROSPERO with registration number CRD42020192560. The study was approved by the Human Trial Ethics (Appendix 2, Supplemental Digital Content, http://links.lww.com/MD/H435) Committee of Guizhou Medical University (Certificate No.: 2019 (148)) in December 27, 2019.

2.2. 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.

2.3. Exclusion criteria

(1) Cross-sectional studies, cohort studies, case-control studies;
(2) Systematic reviews, intervention protocols and letters;
(3) Duplicate studies.

2.4. Selection strategy and information sources

A systematic literature search was conducted in PubMed, Embase, Science Direct, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure and Wanfang databases. The search period was from the time of construction of the database to February 28, 2022. 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 3 (Supplemental Digital Content, http://links.lww.com/MD/H560) contains an example of the search strategy. Data were independently filtered and extracted based on the pre-designed inclusion and exclusion criteria.

2.5. Study setting

Referring to Vodicka et al[19] and Roque et al,[12] study settings included: primary care; hospital care; health care center; and nursing homes.

2.6. Study design

Study designs included: cluster randomized controlled trial and RCT.

2.7. Primary outcomes and findings

The primary outcomes and findings of studies were adapted from Roque et al.[12,20] The primary outcome was APR. The primary findings included: (+) positive findings (±), negative findings (–), both positive and negative (±).

2.8. 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.

2.9. Risk of bias assessment

The first 2 authors (YC and ZC) 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.

2.10. Meta-analysis

We conducted a meta-analysis of all the studies selected for the systematic review, and the 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 2 groups was combined, and the combined effect value and 95% confidence interval (95% CI) were calculated. The *T* test and chi-square test statistics were used to analyze the heterogeneity between the results ($a = 0.05$), a fixed effect model ($P > .05$) or a random effect model ($P \leq .05$) will be determined. If $I^2 < 50\%$, a fixed effect model was used; if $I^2 \geq 50\%$, a random effect model was used. If there was still significant heterogeneity in the research results, a subgroup analysis or a descriptive analysis is required. RevMan 5.3 software was employed for meta-analysis.

3. Results

The search and selection process are shown in Figure 1. A total of 1390 studies were obtained, of which 384 were excluded after reading the title and abstract. The remaining 1006 studies were further screened by reading the full-text, of which 916 were excluded: 190 because they were treatment or drug intervention trials, 25 because they were antibiotic cost-benefit analysis studies, 170 because they were systematic reviews or cohort studies such as non-RCTs, 390 because they were observational studies (cross-sectional studies, and case-control studies), 125 because they were duplicate studies, and 15 studies because the full-text could not be accessed. Finally, of the 91 eligible studies, a total of 23 studies were included in the systematic review and meta-analysis after excluding 68 studies that did not have APR as the outcome variable.

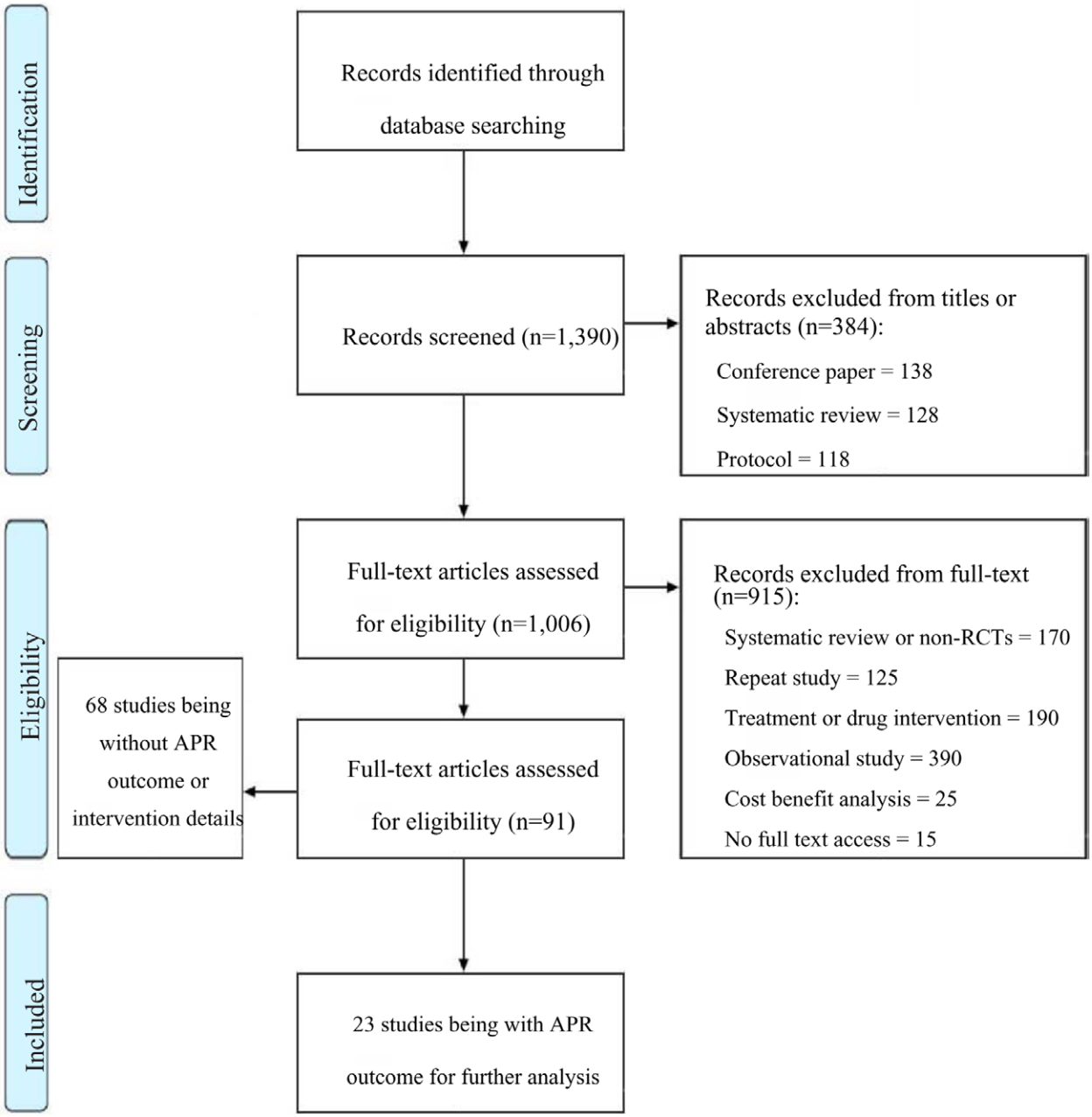

Figure 1. PRISMA screening flow chart. APR = antibiotic prescription, RCT = randomized controlled trial.

3.1. Basic characteristics of the included studies

As shown in Table 1, of the 23 studies included, 17[23–32,34,37–40,42,43] were cluster randomized controlled trial, 6[22,33,35,36,41,44] were RCT. Eighteen[22,23,26–32,34,36–42,44] studies were conducted in primary care settings (including general practice clinics, family practices and township hospitals), 3[24,33,35] hospital-based studies and 1[25] in health care center, and 1[43] in nursing homes. General practitioners (GPs) were participants of 10[22,23,26–28,32,35,36,39,40] intervention studies. Therefore, the authors suggested that future research should be aimed at GPs. Participants in the other 10 studies included: physicians (n = 4),[25,38,43,44] and (n = 2)[24,41]; family physicians (n = 2)[24,41]; health providers (n = 5),[29,30,33,37,42] which were faculties at a clinical practices center; and all kinds of patients (n = 7).[22,26,32,36–39] Fourteen[22,25,27–30,32–35,37,40–42] studies were for respiratory diseases in all patients, and the remaining 10 studies were of children (n = 3),[38,39,44] adults (n = 3),[24,26,36] elderly (n = 1),[43] and patients aged 18 to 65 (n = 2).[23,31] Eighteen[22–27,29,30,32–34,36,38,39,41–44] studies had intervention periods of less than 1 year or unclear.

In Table 2, a total of 23 RCTs were included in the review, including 1[33] published in Chinese and 22[22–32,34–44] in English. The studies involved 396,959/1,911,248 prescriptions (antibiotic prescriptions/the total prescriptions) from 11 countries: China,[29,30,33,37,38] the United States,[24,41,42,44] Netherlands,[22,32,34,43] England,[31,39,40] Canada,[25] Norway,[27] Germany,[26], Singapore,[36] Switzerland,[28] France,[35] and Belgium[23] (187,156/978,472 in the intervention group and 209,803/932,776 in the control group). Four[27,30,36,41] of the study's control groups received a partial intervention. Seventeen studies[22,24–27,29,31–35,37–41,43] had positive results (+, The primary results in the intervention groups were superior to those in the control groups). Two study[23,42] had negative results

Table 1

Basic characteristics of the 23 studies.

Study	Design*	Settings†	Diseases‡	Participants§	Patients	Duration
Ineke W, et al Netherland 2004[22]	RCT	PC	RTIs	GPs and pharmacists and patients	All	9 mo
Coenen S, et al Belgium 2004[23]	cRCT	PC	Acute cough	GPs	Adult (18–65)	2 mo
Metlay JP, et al USA 2007[24]	cRCT	HP	ARTIs	Clinicians and patients	Adult (>18)	4 mo
Monette J, et al Canada 2007[25]	cRCT	HCc	RTIs and others	Physicians	All	3 mo
Altiner A, et al Germany 2007[26]	cRCT	PC	Acute cough	GPs and patients	Adult (≥16)	Unclear
Gjelstad S, et al Norway 2013[27]	cRCT	PC	ARTIs	GPs	All	6 mo
Hürlimann D, et al Switzerland 2014[28]	cRCT	PC	RTIs	GPs	All	2 yr
Yang L, et al China 2014[29]	cRCT	PC	URTIs	HPs	All	Unclear
Chen Y, et al China 2014[30]	cRCT	PC	URTIs	HPs	All	40 d
Gulliford MC, et al England 2014[31]	cRCT	PC	RTIs	FPs	Adult (18–59)	1 yr
Velden AW, et al Netherlands 2015[32]	cRCT	PC	RTIs	GPs and patients	All	1 yr
Qiu JG, et al China 2016[33]	RCT	HP	RTIs	HPs	All	Unclear
Vervloet M, et al Netherland 2016[34]	cRCT	PC	RTIs	FPs	All	6 mo
Ferrat E, et al France 2016[35]	RCT	HP	RTIs	GPs	All	4.5 yr
Lee MHM, et al Singapore 2017[36]	RCT	PC	URTIs	Patients	Adult (≥21)	9 d
Tang YQ, et al China 2017[37]	cRCT	PC	URTIs	HPs and patients	All	1 yr
Wei XL, et al China 2017[38]	cRCT	PC	URTIs	Physicians and caregivers	Children (2–14)	6 mo
Dekker ARJ, et al England 2018[39]	cRCT	PC	RTIs	GPs and caregivers	Children	Unclear
Gulliford MC, et al England 2019[40]	cRCT	PC	RTIs	GPs	All	1 yr
Lily DY, et al USA2020[41]	RCT	PC	ARTIs	Clinicians	All	11 mo
Mann D, et al USA2020[42]	cRCT	PC	ARTIs	HPs	All	7 mo
Tjarda MB, et al Netherlands2021[43]	cRCT	NH	LRTIs	Physicians	Elderly	7 mo
Zahlanie Y, et al USA2021[44]	RCT	PC	RTIs	Physicians	Children	6 mo

**Design*: cRCT = cluster randomized controlled trial, RCT = randomized controlled trial.

†*Setting*: HCc = Health care center, HP = Hospital, NH = nursing homes, PC = primary care.

‡*Diseases*: ARTIs = acute respiratory tract infections, LRTIs = lower respiratory tract infections, RTIs = respiratory tract infections, URTIs = upper respiratory tract infections.

§*Participants*: FPs = family physicians, GPs = general practitioners, HPs = health providers.

Table 2

Basic characteristics of the 23 APR studies.

Author	Year	Country	Sample size included in the study (antibiotic prescriptions/total prescriptions)		Control group intervention·	Primary findings
			Intervention group	Control group		
Ineke W, et al[22]	2004	Netherlands	60/261	39/105	–	(+)
Coenen S, et al[23]	2004	Belgium	80/292	115/401	Partial intervention	(–)
Metlay JP, et al[24]	2007	USA	483/1510	637/1342	–	(+)
Monette J,et al[25]	2007	Canada	309/1326	154/431	–	(+)
Altiner A, et al[26]	2007	Germany	289/787	596/920	–	(+)
Gjelstad S, et al[27]	2013	Norway	21,246/66,757	23,307/66,501	Partial intervention	(+)
Hürlimann D, et al[28]	2014	Switzerland	15,952/41,580	13,654/45,737	–	(±)
Yang L, et al[29]	2014	China	11,184/12,774	9824/10,369	–	(+)
Gulliford MC, et al[31]	2014	England	34,313/317,717	32,569/285692	–	(+)
Chen Y,et al[30]	2014	China	568/831	299/446	Partial intervention	(±)
Velden AW, et al[32]	2015	Netherlands	895/3461	974/3421	–	(+)
Qiu JG, et al[33]	2016	China	107/150	143/150	–	(+)
Vervloet M, et al[34]	2016	Netherlands	9589/23,500	14,603/23,500	–	(+)
Ferrat E, et al[35]	2016	France	9916/70,830	17,708/10,6036	–	(+)
Lee MHM, et al[36]	2017	Singapore	94/457	81/457	Partial intervention	(±)
Tang YQ, et al[37]	2017	China	14,649/17,021	13,219/14,937	–	(+)
Wei XL, et al[38]	2017	China	943/2351	1782/2552	–	(+)
Dekker ARJ, et al[39]	2018	England	102/475	176/531	–	(+)
Gulliford MC, et al[40]	2019	England	37,601/348,158	40,099/27,8467	–	(+)
Lily DY, et al[41]	2020	USA	13,604/25,513	18,352/31,429	Partial intervention	(+)
Mann D, et al[42]	2020	USA	14,723/42,126	20,765/58,447	–	(–)
Tjarda MB, et al[43]	2021	Netherlands	89/162	65/79		(+)
Zahlanie Y, et al[44]	2021	USA	360/433	642/826	–	(±)

Primary findings: (+) = positive findings, (–) = negative findings, (±) = positive and negative findings. The guidelines, coupled with sustained personal feedback, did not reduce APR but increased the use of recommended antibiotic.

We originally planned to do a meta-analysis of 23 RCTs the study objects were the medical records of the intervention group and the control group after the intervention. The RD of APR of the two groups was combined, and the combined effect value and 95% confidence interval 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 age group of patients, cluster or non-cluster, random or nonrandom, study area, intervention methods, duration of intervention and randomness, to explore the causes of heterogeneity. RD was used to control the confounders. Nevertheless, the high heterogeneity of all subgroups led us to perform a descriptive review of the literature.

APR = antibiotic prescription rate, RCT = randomized controlled trial, RD = risk difference.

(–, The primary results in the control groups were superior to those in the intervention groups). Four study[28,30,36,44] had negative and positive results (±, Some of the results were better in the intervention group than in the control group).

3.2. Interventions of included APR studies

Table 3 shows the categories of interventions included in the APR studies. Twenty two[22–35,37–44] of the 23 studies involved educational interventions, including: (1) online training using email, web pages and webinars containing guidelines and communication skills,[23,39–42,44] (2) antibiotic guidelines for information dissemination measures by email, postal or telephone reminder,[23–25,28,33,35,37,38,40,42,43] (3) training doctors in communication skills,[22,25,26,34,38,39] (4) short-term interactive educational seminars,[22,24,27,32,33,35,38,40,42,44] and (5) short-term field training,[22,24,27,32,33,35,38,43,44] the latter 2 types of training methods were generally face-to-face (on-site) interventions and the duration was usually hours or days of diagnostic and drug guidance, rapid testing method, of which 8 studies comprehensively used more than 2 educational interventions, and all of these studies had positive results.

Twenty-three studies of interventions for health care workers also included: (6) regular or irregular assessment/audit of antibiotic prescriptions[22,25,27,32–34,38,40] and (7) prescription recommendations from experts and peers delivered at a meeting or online.[23–26,30–32,34] Vervloet et al[34] implemented a prescription recommendation in an Electronic Prescribing System. When a family physician tried to prescribe an antibiotic to a patient with respiratory tract infections, the Electronic Prescribing System 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 2 electronic alerts, the doctor could write a prescription. (8) Two studies[29,37] 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) Eleven studies reported monitoring/feedback prescribing behavior to GPs by email or poster (the prescribing behavior of individual physicians for 6 months or 1 year).[22,24,25,27–29,32,34,37,40,41]

Among the studies of interventions, 8[22,24,26,29,32,36,38,39] 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[36] of the studies involved only patients and family members.

3.3. Risk of bias

As shown in Figure 2, 21 studies[22–24,26–32,34–44] were rated as having a low risk of bias while 2[25,33] were rated as having a high risk of bias. Figure 2 shows the risk of bias assessment for each criterion. Among the 23 studies, 1[33] 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[25] was identified as having a high risk of bias in the "Blinding of outcome assessment" section due to a lack of random sampling and unblinded

Table 3

Categories of interventions included in the 23 studies.

	Health care worker										Patient or family member		
	Educational intervention												
				On-site intervention*									
Author (yr)	(1) Online training	(2) Distribution of educational materials	(3) Communication skill	(4) Short-term interactive education seminar	(5) Short-term field training	(6) Prescription audit	(7) Prescription recommendations from experts†	(8) Public reporting	(9) Prescription feedback	Brochure	Flyers and posters	Waiting room education
Ineke W (2004)[22]			√	√	√	√			√	√	√	
Coenen S (2004)[23]	√	√					√					
Metlay JP (2007)[24]		√		√	√		√		√	√	√	√
Monette J (2007)[25]		√	√			√	√		√			
Altiner A (2007)[26]			√				√				√	
Gjelstad S (2013)[27]				√	√	√			√			
Hürlimann D (2014)[28]		√							√			
Yang L (2014)[29]								√	√		√	
Chen Y (2014)[30]							√					
Gulliford MC (2014)[31]							√					
Velden AW (2015)[32]				√	√	√	√		√	√		√
Qiu JG (2016)[33]		√		√	√	√						
Vervloet M (2016)[34]			√			√	√		√			
Ferrat E (2016)[35]		√		√	√							
Lee MHM (2017)[36]										√		√
Tang YQ (2017)[37]		√						√	√			
Wei XL (2017)[38]		√	√	√	√	√					√	√
Dekker ARJ (2018)[39]	√		√							√		
Gulliford MC (2019)[40]	√	√		√		√			√			
Lily DY (2020)[41]	√								√			
Mann D (2020)[42]	√	√		√								
Tjarda MB (2021)[43]		√			√							
Zahlanie Y (2021)[44]	√			√	√							

*On-site intervention is a kind of subgroup analysis of intervention measures in this study, including short-term interactive education seminar or short-term field training, which is a type of educational intervention.

†Prescription recommendations are the type of subgroup analysis of interventions in this study, and are recommendations for replacement or non-antibiotic prescriptions from peer exp.

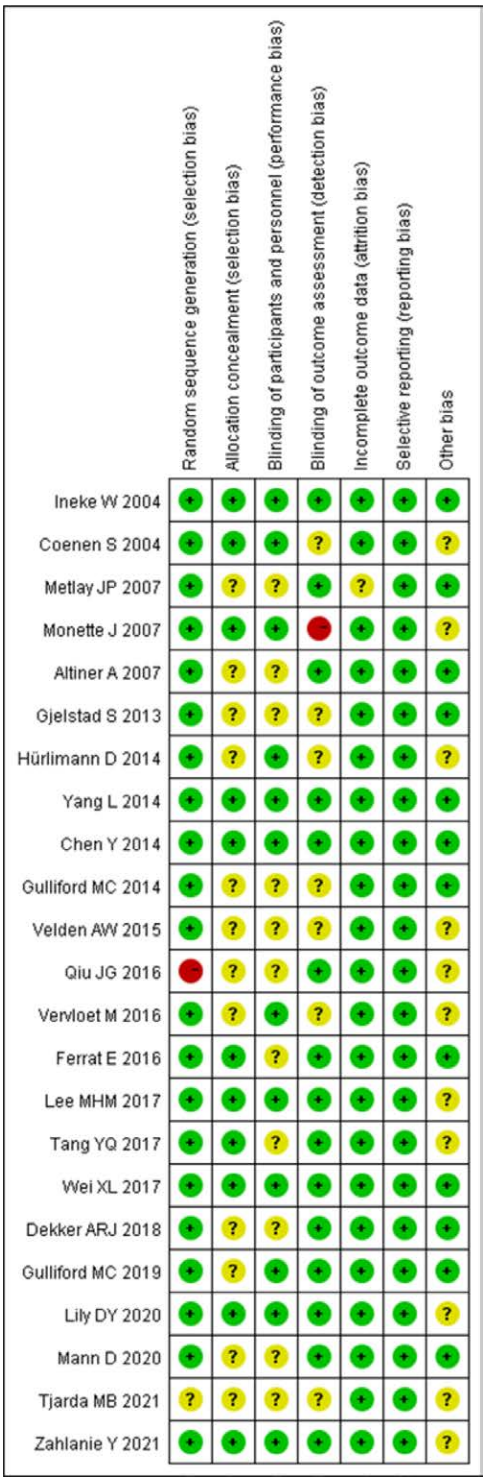

Figure 2. Risk of bias summary.

nature. Nineteen studies[23–28,31–37,39–44] showed an unclear risk of bias in 6 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome bias, and other bias. Only four[22,29,30,38] of the studies were low risk of bias in all domains. In the domain of "Allocation concealment," 12 studies[24,26–28,31–34,39,40,42,43] 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," 11 studies[24,26,27,31–33,35,37,39,42,43] 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[23,27,28,31,32,34,43] 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[24] 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," 11 studies[23,25,28,32–34,36,37,41,43,44] 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.

3.4. Evaluation of publication bias

According to the included studies, the inverted funnel chart was produced, which has poor symmetry and may have publication bias. See Figure 3 for details.

3.5. Meta-analysis

Figures 4 and 5 shows a meta-analysis of 23 studies of antibiotic prescription samples. The heterogeneity test showed that the results of antibiotic prescription interventions were significantly different ($\chi^2 = 4569.23$, $P < .00001$, $I^2 = 99\%$), so a random-effects model was chosen. The results of the combined analysis showed that the RD was significant and favored the experimental group (RD = –0.07.14, 95% CI = –0.0896, –0.0533, $P < .00001$). The rate of antibiotic prescriptions in these studies significantly decreased after the implementation of feedback intervention. However, due to the high heterogeneity ($I^2 = 99\%$), a sensitivity analysis and subgroup analysis were not applicable. The forest plot without summary pooled effect were developed to provide visual information for various magnitudes of effect observed. The APR in these studies decreased after the implementation of feedback intervention, except 4 studies (DH, YC, MHML, and YZ). The results of 4 (SC, YC, MHML, and DM) studies fell on the invalid line, indicating that there was no difference between intervention groups and control groups.

4. Discussion

A total of 1390 studies were obtained of which 23 studies the outcome variables were APR with the number of prescriptions and intervention details were included in the study. In the 23

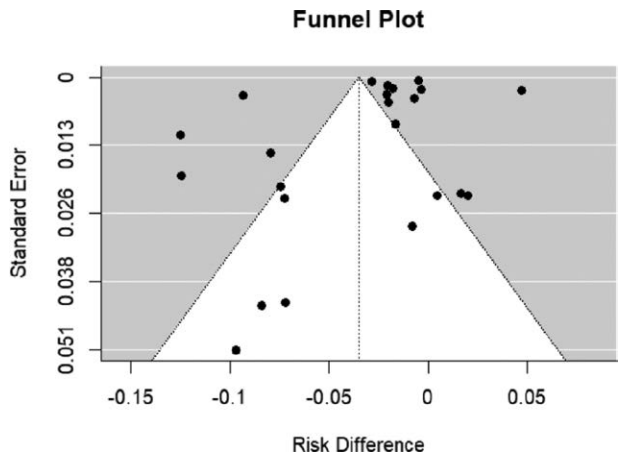

Figure 3. Inverted funnel plot of the effects of interventions on doctors' antibiotic prescription.

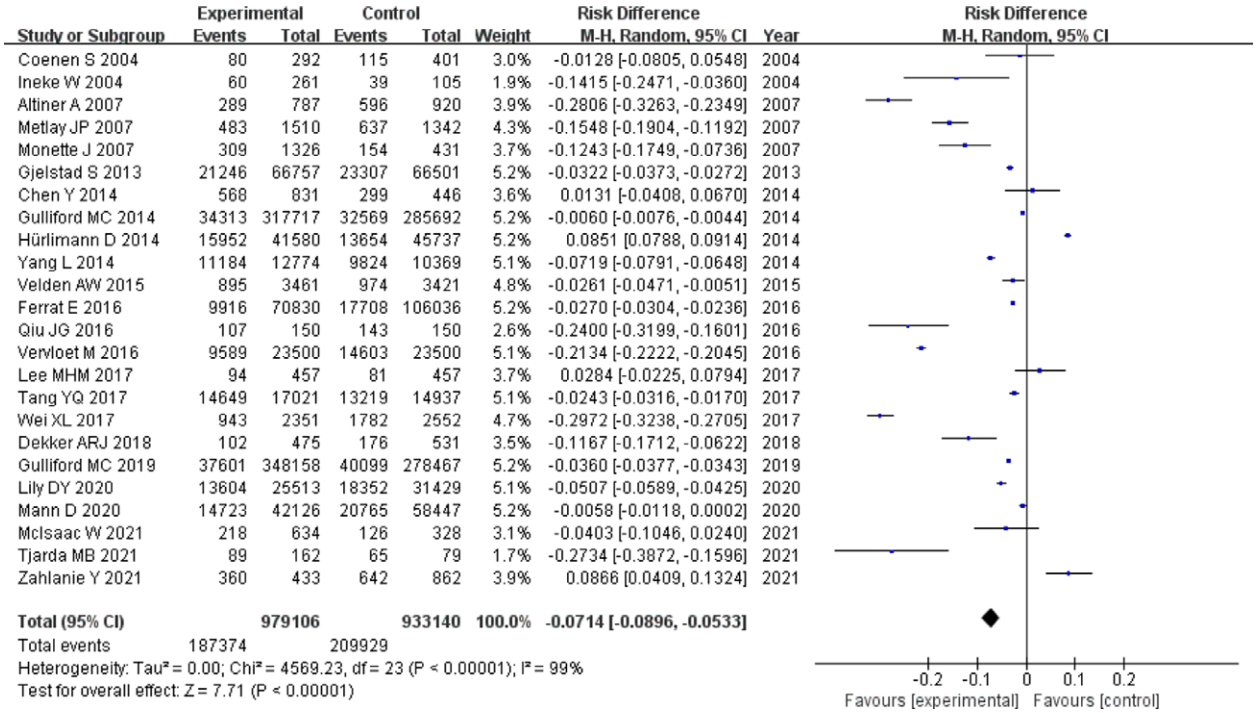

Figure 4. The forest plot of antibiotic prescription (1). CI = confidence interval.

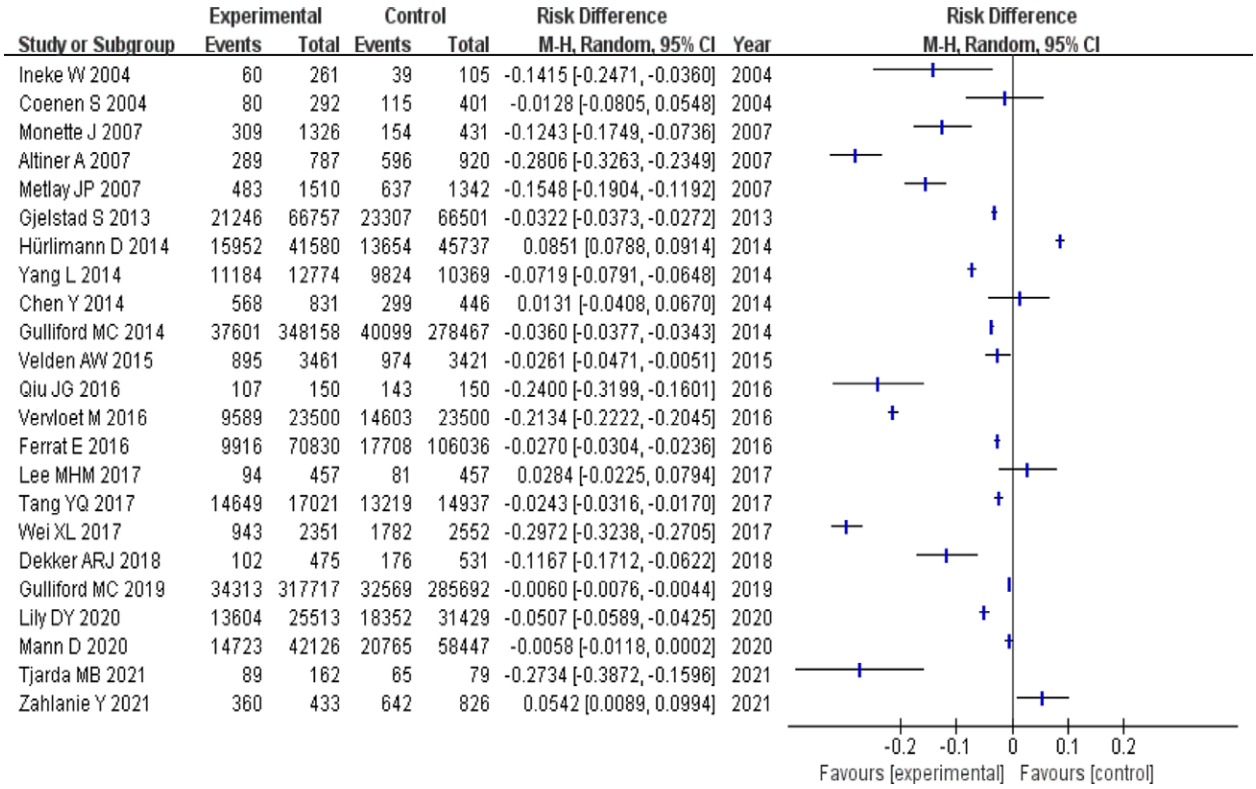

Figure 5. The forest plot of antibiotic prescription (2). CI = confidence interval.

studies that were eventually included, GPs and physicians were the main subjects of the intervention. Fourteen studies (58%) did not have a specific population with the diseases and 13 studies (57%) had intervention periods of less than 1 year. Patient-only, long feedback intervals and non-blind nature of the intervention may have led to negative results and a high risk of bias. Of these studies, 17 (74%) had positive results and 6 (26%) contained negative results.

A further analysis of 23 studies found that all but 2 (YC and MCG) 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.

These 23 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-analysis and to interpret the results as its 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 23 RCTs using a risk of bias tool.[21] Most (21) of the studies were low risk, but 19 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)[45] to conduct trials and write manuscripts.

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.[46,47] 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 et al[39] and Metlay et al[24] adopted certain intervention measures for patients and their families based on educational intervention measures for medical staff. Altiner et al[26] 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.

Of the 24 studies, 6 contained negative results. Four[28,30,36,44] of them were negative and positive (±): Hürlimann et al[28] 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 2-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. Zahlanie et al[44] developed an Pediatric educational intervention. After the intervention, antibiotic prescribing rates were higher in the intervention group (83.1% vs 77.7%; $P = .024$), the treatment course was shorter than that of the control group. The author believed that the problem of small sample size and multifaceted intervention methods need to be improved. Chen et al[30] conducted a 2-month intervention in which educational messages were sent to the intervention group 3 times a week. Antibiotic prescriptions did not change, and prescriptions for other drugs declined. The study said that text messages was more convenient than looking at literature for health workers, but more research is needed to confirm the effectiveness. Lee et al[36] gave patients in the intervention group 9 days of intervention in the form of pamphlets and oral education. The study did not reduce antibiotic prescribing, except among Indian patients. This suggests that intervention in patients alone has no significant effect on reducing antibiotic prescriptions. Two[23,42] of them were negative (–): Coenen's et al[23] interventions in 2002 included a clinical practice guideline for acute cough, an educational outreach visit and a postal reminder. They concluded that the intervention was effective by comparing OR values before and after the intervention [OR_{adj} (95% CI) $5_{0.56}$ (0.36–0.87)]. However, RD or relative risk more interpretable for clinical trials or prospective studies. When RD values of this study were compared, there was no difference between the intervention group and the control group (see Fig. 4 forest plot). Mann et al[42] implemented a clinical decision support tool to guide evidence-based evaluation and treatment of streptococcal pharyngitis and pneumonia. According to the authors, the negative results may be due to the very low adoption and utilization rates of the tool at all clinical sites.

Our study has certain limitations. First, like most systematic reviews, there is a possibility of publication bias as the majority of the studies (17/23) reported positive results. 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.

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Author contributions

All authors made substantial contributions to the development of the trial, and read and approved the final manuscript. YC, XH, and GY designed the trial. YC and HZ drafted the manuscript, and YC and ZC completed data extraction, statistical

analysis, and data interpretation. GY and XZ participated in the concept, data interpretation, and manuscript revision. YC, XF, and WW are responsible for data integrity and accuracy of data analysis.

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