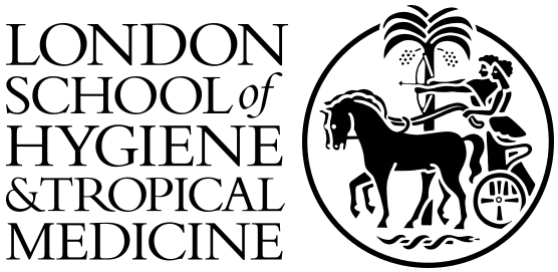

Educational interventions to reduce childhood antibiotic prescribing for upper respiratory infections: systematic review and meta-analysis

AUTHORS: Yanhong Hu, M.D, MPH,[a] John Walley FFPH, MComH,[b] Roger Chou, MD,[c] Joseph D Tucker, MD, PhD,[d] Joseph I Harwell, M.D, FAAP, FIDSA,[e] Xinyin Wu, PhD,[a] Jia Yin, MPH,[a] Guanyang Zou, MPHil,[f] Xiaolin Wei PhD, FFPH.[g a]

[a] The Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong (CUHK), Hong Kong, China
[b] International Public Health, COMDIS-HSD, Nuffield Centre for International Health, LIHS, University of Leeds, Leeds, UK
[c] Medical Informatics & Clinical Epidemiology, Oregon Health & Science University, USA
[d] UNC Project-China, Guangzhou, China and International Diagnostics Centre, London School of Hygiene and Tropical Medicine, London, UK
[e] Clinton Health Access Initiative, 383 Dorchester Avenue, Suite 400, Boston, MA 02127, USA
[f] Nuffield Centre for International Health and Development, University of Leeds, UK (Based in China), Shenzhen, China
[g] Dalla Lana School of Public Health, University of Toronto, 155 College Street, Ontario, M5T 3M7, Canada

KEYWORDS

Educational intervention, childhood upper respiratory infection, antibiotic prescription, systematic review, Meta-analysis

ABBREVIATIONS

URIs-upper respiratory infections	RCTs-randomized controlled trials
APR-antibiotics prescription rate	OR-Odds Ratio
CI-confidence interval	ICC- intra-cluster correlation coefficients

Dr. Yanhong Hu designed the study, screened the candidate papers, extracted and analyzed data, wrote the manuscript and approved the final manuscript as submitted. Prof. John Walley wrote the manuscript, interpreted the data and approved the final manuscript. Prof Joseph I Harwell wrote the manuscript, interpreted the data and approved the final manuscript. Prof. Roger Chou reviewed the revised manuscript and approved the final manuscript as submitted. Prof. Joseph D Tucker reviewed the revised manuscript and approved the final manuscript as submitted. Mr. Guangyang reviewed the revised the manuscript and approved the final manuscript as submitted. Dr. Xinyin Wu reviewed the revised the manuscript and approved the final manuscript as submitted. Ms. Jia Yin reviewed the revised the manuscript and approved the final manuscript as submitted. Prof. Xiaolin Wei designed the study, extracted data, analyzed and interpreted the results, wrote the manuscript and approved the final manuscript as submitted.

Address correspondence to Prof. Xiaolin Wei, PhD, FFPH, Dalla Lana School of Public Health, University of Toronto, 155 College Street, Ontario, M5T 3M7, Canada. Email: xiaolin.wei@utoronto.ca.

FINANCIAL DISCLOSURE: The authors have no financial relationships relevant to this article to disclose.

FUNDING: MRC welcome trust – Funding reference number: MR/M022161/1.

PROSPERO registration number: CRD42015029255. (http://www.crd.york.ac.uk/PROSPERO)

CONFLICT OF INTEREST: The authors declare that there are no conflicts of interest.

Abstract

Context

Antibiotics are over-prescribed for children with upper respiratory infections (URIs), leading to unnecessary expenditures, adverse events and antibiotic resistance.

Objective

To assess whether interventions can reduce antibiotic prescription for childhood URIs and identify what factors impact intervention effectiveness.

Data sources

MEDLINE, EMBASE, Google Scholar, Web of Science - Global Health, WHO website, United States CDC website and The Cochrane Central Register of Controlled Trials (CENTRAL) were searched by August 2014.

Study selection

Cluster or individual patient randomized controlled trials (RCTs) and non-randomized controlled trials examining interventions to change antibiotic prescription rates (APR) for children with URIs were selected for meta-analysis. Educational interventions for clinicians and/or parents were compared with usual care.

Results

Of 6074 studies identified, thirteen were included. All were conducted in high-income countries. Educational interventions were associated with lower APR versus usual care (OR 0.65 (95% confidence interval [CI] 0.49-0.86, P<0.001). A patient-clinician communication approach was the most effective type of intervention, with a pooled OR 0.41 (95% CI 0.20-0.83; P<0.001) for clinicians and a pooled OR for parents 0.26 (95%CI 0.08-0.91; P=0.04) compared with usual care. Compared with usual care, educational interventions that targeted both clinicians and parents were more effective than interventions for either group alone OR of 0.52 (95% CI 0.35-0.78; P=0.002).

Conclusion

Educational interventions are effective in reducing antibiotic prescribing for childhood URIs. Interventions targeting both clinicians and parents are more effective than those for either group alone. The most effective interventions address patient-clinician communication. Studies in low-middle income countries are needed.

Word (249)

Introduction

Worldwide, inappropriate medication use is a major problem. According to the World Health Organization (WHO) 50% of medicines are prescribed, dispensed or sold inappropriately, while 50% of patients take their medicines incorrectly.[1] Inappropriate antibiotic use can lead to antibiotic resistance, resulting in difficult or impossible to treat infections.[2] Antibiotic resistance is more common in countries with high rates of antibiotic prescription.[2]

Childhood upper respiratory infections (URIs) are very common, but are usually viral and self-limiting. Nevertheless prescribing antibiotics for childhood URIs is highly prevalent.[3] Antibiotic resistance is frequently observed in young children and more invasive infections occur in this vulnerable population.[4] In Asia, every two minutes a child under five years of age dies from antibiotic–resistant infections.[5]

There are two main factors influencing inappropriate antibiotic use for childhood URIs - clinician prescribing and parent knowledge, attitude and demand.[6] Educational interventions addressing these factors could reduce inappropriate antibiotic use. A Cochrane review showed that interventions involving physicians/pharmacists could reduce antibiotic prescription rates.[7] However this review did not assess specifics of interventions (e.g., intervention type, the intervention target, intensity). Conflicting results were seen with parental interventions. One review found that parental interventions can influence knowledge and behavior, reducing consultation rates by 13% to 40%.[3] However, another review showed that caregiver education may not be effective.[8] Many published studies are descriptive, involving both adults and children with various diseases.[9-12] This study aims to analyze the effectiveness of different intervention approaches, targeting different groups (clinicians, parents or both) and whether other factors – study setting, study design, study period - influence effectiveness for reducing antibiotic prescribing for childhood URIs.

Methods

Search strategy

We searched MEDLINE, EMBASE, Google scholar, Web of Science, Global Health, WHO website, United States CDC website and The Cochrane Central Register of Controlled Trials (CENTRAL) from 1980 to December 2015 for published articles without language restriction. Search terms included URIs, respiratory infections (RI), education, antibiotic prescription/prescribing, children/pediatric and antibiotic prescription rates. Two independent reviewers screened candidate studies using a structured form based on the PRISMA 2009 four-phase flow diagram.

Study selection

We included studies according to PICOS (population, intervention, comparison, outcome, setting) characteristics by following professional interventions in the Effective Practice and Organization of Care group (EPOC) scope.[13]

Population We included studies of children (<=18 years of age) diagnosed with any URI including rhinitis, sinusitis, pharyngitis, tonsillitis, acute otitis media or URI as a general category. To reduce misclassification bias, for studies that classified URI and these aforementioned specific categories as separate, we included all patients as they should be classified under the category of "URI" in our analysis.

Intervention - Approaches for targeting clinicians, featuring: 1) Antibiotic prescription rate (APR) feedback; 2) Update and/or reinforcement of national guidelines; 3) Promoting delayed prescriptions; 4) Clinician-parent communication skills training and workshops. Intervention methods included: 1) Face to face training such as seminars, workshops or group discussion by trained peer leaders; 2) Indirect training, which included online workshops or pop-up messages through software or printed information related to appropriate antibiotic use. Approaches for targeting parents included: 1) Printed educational materials including leaflets/pamphlet or

posters; 2) Mass media such as video, radio and newspapers; 3) Clinician-patient communication, which included facilitating patient health literacy, explaning appropriate antibiotic use by clinicians.

Comparator We included prospective studies with an intervention group compared to a control with usual care. Study designs were (clustered) randomized controlled trials and non-randomized controlled trials including cohort experimental studies.

Outcome Studies with antibiotic prescription expressed either as a rate (%) or as numbers per person-time were included. APR was defined as the number of children who were prescribed one or more antibiotic classes divided by the total number of children assessed for URIs during a designated interval.

Setting Studies from all geographic regions were eligible for inclusion. Study sites were included if they cared for children either in primary care/general practice or in specialty clinics.

Quality assessment

Quality was determined by two independent reviewers using the Cochrane risk of bias tool[13], including domains related to sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, intervention contamination, seasonal data collection and reporting of clustering coefficient. Each item outcome was categorized as high risk, low risk or unclear risk according to information provided. Disagreements between reviewers were resolved by discussion and consensus.

Data extraction

For the characteristic table, we extracted the following variables: study design, setting, follow up duration, children age, participants, details of interventions (target group, intervention content for clinician and parents, intervention technics), details of the comparator and outcome measures. To calculate the intervention group APR odds ratio (OR) we extracted the number of children or visits prescribed any antibiotic from both groups

as well as the total number of children or visits in each group. For studies that were designed as cluster randomized controlled trials (RCTs), we also extracted the intra-cluster correlation coefficients (ICCs) to adjust for design effect according to the Cochrane handbook.[13] Furthermore, for studies with unknown ICC, we estimated from similar trials or by an approximated ICC.[13 14] Studies with more than one control or time point were treated as if controls and time points were independent of each other.[15]

Analysis

Only studies with a calculable or reported APR were included into the meta-analysis. OR and 95% confidence interval (CI) were used to measure the effectiveness of intervention compared to usual care. Overall p value was used for the interaction between intervention and the estimates. We pooled studies using a Bayesian random-effects model to account for variations across RCTs in populations, interventions, settings and other factors during meta-analyses.[16 17] Heterogeneity across studies was evaluated using the I^2 test. To explore heterogeneity source, meta-regressions were conducted for each potentially influential factor (target group, follow-up duration, region, design, year). For cluster studies additional factors (ICC reported or unreported, number of clusters, whether sites were pediatric clinics) were included. We also conducted a sensitivity analysis on individual studies to identify potential effects of outliers. For studies designed as cluster RCTs, we conducted another sensitivity analysis on ICC factors to determine if design effect influenced study outcome. According to the Cochrane handbook we selected three different ICC values (0.004, 0.02 and 0.2) for this sensitivity analysis. [18] For studies with more than one control group and time point within a study we also compared the result by merging effects within each study.[15] Finally, we used a funnel plot with Egger's regression test to assess for publication bias ($p<0.1$). All analyses used STATA version 13.

Results

Description of included interventions

Of 6074 articles, 373 were accessed with full text. After exclusions 12 articles were eligible for meta-analysis (see Figure 1).

Of the 12 studies included into this systematic review and meta-analysis, seven were cluster RCTs, three were non-randomized controlled trials and two were individual RCTs. One study had two control groups; one had 4 outcomes with 3 different follow-up durations and one follow-up (12 months, 24 months, 36 months, 48 months). Six studies were conducted in the United States (US), two in Israel, two in Norway, and one each in United Kingdom (UK), Iran, and Canada. Eight of 12 were conducted in primary care or general practices and the remaining four studies were conducted in pediatric practices. The study year ranged from 2000 to 2014, with follow-up duration lasting from one to 12 months. Finkelstein 2001[18] had two outcomes for age 3-36 months and 36-72 months. Gonzales 2005[19] had two control groups with one located near to the intervention site and the other far from it. Regev-Yochay 2011[20] had 4 time point outcomes for different intervention types - year one was workshops for determinants of reducing antibiotic prescriptions, year two focused on patient-clinician communication, year three involved workshops for APR feedback and year four was for follow-up after intervention. The cluster numbers ranged from two to 286 units, and the number of participating clinicians and registered patients ranged from 27 to 578 and 81 to 97699, respectively (Table 1). Nine articles were found to have low risk of bias, three had high risk (see Table 2).

Intervention effects, all studies (Figure 2)

Based on heterogeneity we used random-effects to deal with differences among studies. We combined the control groups and combined the different time point outcomes within studies. The pooled OR of APR for the intervention group was 0.65 (95% CI 0.49-0.86; P=0.003). However, significant heterogeneity was observed (I^2=66%) as a result of differences in design, population, and intervention details.

Effects of intervention strategies (Figure 3)

Among the clinician interventions four of nine studies used guidelines for respiratory infections and two used APR feedback to clinicians. Delayed prescription was used in one study. Three studies used patient-clinician communication skills training. Training and workshops lasted from 40 minutes to two days. Training lasted <1 day in 6 studies and >1 day for the remaining 3. Printed leaflets/posters were used in three of eight studies involving parents. Three studies used patient-clinician communication intervention. Two studies used video in waiting areas, lasting five to eight minutes.

Meta-analysis showed that the pooled OR for all types of interventions with clinicians was 0.65 (95% CI 0.54-0.79; I^2=44%), for patient-clinician communication approach was 0.41 (95% CI 0.20-0.83; I^2=73%), for APR feedback was 0.65 (95% CI 0.49-0.87; I^2=0%), for delayed prescription was 0.86 (95% CI 0.65-1.13;n=1), for guideline use was 0.68 (95% CI 0.53-0.88; I^2=21%). Though there were overlaps in 95% CI, testing for subgroup interaction was insignificant (p=0.2).

For intervention types with parents, the pooled OR for all was 0.55 (95% CI 0.36-0.84; I^2=36%), for video was 0.86 (95% CI 0.56-1.31; I^2=0%), for leaflets/posters the pooled OR was 0.74 (95% CI 0.49-1.12; I^2= 0%), for patient-clinician conmmunication was 0.26 (95% CI 0.08-0.91; I^2=86%). No significant subgroup difference was found.

Effects of interventions through targeted group, study design, study year, follow-up duration and intensity of intervention and ICC report (Table 3)

When studies were grouped according to the intervention target, four studies targeting clinicians achieved a pooled OR of 0.88 (95% CI 0.67-1.16; I^2=73%). Three studies targeting parents achieved an OR of 0.50 (95% CI 0.10-2.51; I^2=80%). A total of five studies that had interventions targeting both groups achieved a pooled OR of 0.52 (95% CI 0.34-0.79; I^2=50%).

For studies with different designs, the pooled OR for all RCTs (including cluster RCTs) was 0.56 (95% CI 0.41-0.78; I^2 =74%). Non-randomized controlled trials had similar pooled OR 0.84 (95% CI 0.61-1.17; I^2 =0%). Five

studies were conducted in 2010s and seven were in 2000s. The pooled OR was for studies conducted in 2000s was 0.59 (95% CI 0.36-1.00; I^2 =66%) and for studies in 2010s was 0.66 (95% CI 0.49-0.89; I^2 =72%).

For studies with different follow-up durations, six had follow-up durations from 1-6 months, with a pooled OR of 0.62 (95% CI 0.43-0.90, I^2 =77%) while the pooled OR for the other six studies with follow-up durations from 7-12 months was 0.59 (95% CI 0.45-0.79, I^2 =17%). For the nine face to face training studies the pooled RR was 0.77 (95% CI 0.65-0.92; I^2=36%), while three studies with written or online training had a pooled OR of 0.38 (95% CI 0.21-0.70; I^2=44%). However subgroup interaction here was significant (p=0.03).

When evaluating only cluster trials, the results were similar to including all studies. Studies that reported ICC achieved a pooled OR 0.52 (n= 4, 95% CI 0.33-0.84; P= 0.007; I^2=76%) while studies with unreported ICC had a higher OR 0.81 (n=5, 95% CI 0.67-0.98; I^2=13%). Pediatric clinical settings achieved a pooled OR of 0.61 (95% CI 0.47-0.79; I^2=0%), which was similar to non-pediatric settings 0.60 (95% CI 0.43-0.85; I^2=74%).

Meta regression

To explore factors that might contribute to heterogeneity between studies, we also conducted meta-regressions on target group, follow-up duration, study design, study setting and study years, respectively for all included studies. However, none of these factors were associated with between-study heterogeneity. Also when only considering cluster studies, none of these variables or additionally, ICC reported or unreported or study setting were associated with between-study heterogeneity.

Sensitivity analysis

We used three different ICCs to assess all cluster studies (ICC=0.04; ICC=0.02; ICC=0.2) without a reported ICC according to the following factors: target of intervention, study design, follow-up duration and study year for all studies and only cluster studies. Results were consistent across the three ICCs.

Sensitivity analysis on individual studies revealed that there was no change in heterogeneity after omitting any of the included articles.

Publication bias

Results from Egger's regression test revealed publication bias was not significant (p=0.214)

Discussion

We have found that clinician-parent communication intervention appeared to have the strongest effect compared to other approaches. APR feedback and updated guidelines were effective in reducing APR for childhood URIs. Targeting both clinicians and parents was more effective compared with targeting either group alone. Among cluster trials, those with reported ICC had a stronger effect. None of the following factors: intervention target, follow-up duration, design, years, clinical setting, and reported or unreported ICC were associated with residual variation due to heterogeneity. This is probably due to the presence of multiple sources of heterogeneity as well as difficulty in measuring sources of heterogeneity. However, heterogeneity declined by subgroup, with heterogeneity for intervention with clinicians at 44% while that for interventions with parents was 36%.

Previous systematic reviews were conducted to explore the effectiveness of interventions to reduce irrational antibiotic prescription in both adults and children with various diseases.[3 4 7 21-24] The advantages of our review over others is that we focus on a specific population (children) and condition (URI) and stratified analyses according to the type of intervention, which enriched the existing literature as most of the previous studies were descriptive. Additionally, very few studies describe intervention approaches. We found that the lowest pooled ORs were seen in the clinician-parent communication approach, This is consistent with the review by Davey [11] et al for hospital inpatients. Davey found that clinician-targeted intervention using interactive meetings appeared more effective than didactic lectures, improved laboratory resources and consultation with specialists.

Combined interventions were found to be more effective than a single intervention alone [7 22 25 26]. This review and prior research reached similar conclusions, in particular that the involvement of both physicians and parents was most effective. Vodicka [24] and Boonacker [26] both examined interventions to improve childhood antibiotic

prescription for respiratory infections. However, neither review used meta-analysis to measure relative risk. Both concluded that multifaceted interventions can reduce antibiotic use, however providing printed materials and targeting only parents had limited effects, which is consistent with our results. A review conducted by Thoolen showed that education to decrease inappropriate antibiotic use was not effective despite increased patient knowledge, which is contrary to the findings from Arnold [7] and our analysis. We found the pooled OR for targeting parents was 0.50 though it was statistically insignificant with a higher I^2. In these studies, the change in knowledge was the primary outcome, while very few studies had data for APR that could be included into the meta-analysis. Nevertheless education for parents could have a synergistic effect with clinician training and further reduce APR.[28]

For cluster RCTs, within-study variation can also influence the effect through variation at the cluster level.[29] We observed a stronger effect in studies where ICC was reported. A study that reports the ICC may have been more carefully designed with more consideration of study design.

Our review has several strengths. First, to our knowledge, this is the first study to examine the effect of interventions through APR, which is ultimately the desired effect. Second, sensitivity analysis with 3 different ICC found trends to be consistent. Sensitivity analysis on excluding cluster non-randomized controlled trails had similar results, suggesting the study design had limited effect on the results. This suggests results were reliable. Third, the two studies with the widest confidence intervals targeted both clinicians and parents, and both were cluster RCTs. This may actually have led to under-estimation of the effect of this type of intervention, making the result more conservative. Fourth, we evaluated the association between interventions and APR under subgroups of 1) different approaches to clinicians and parents respectively; 2) study design and 3) study settings rather than just the overall effect, thus making our findings more specific.

In terms of limitations, Firstly, non-randomized controlled trials had a higher selection bias than RCTs, while cluster RCTs had cluster level selection bias, although we calculated the cluster RCT studies ICC to adjust for design effects. It is impossible to avoid the nature of the existing selection bias within studies. Secondly, most of

the studies we reviewed had multifaceted interventions, which were mixed to maximize the effect, making it difficult to evaluate individual components. At the same time, prescription is not a single clinician behavior, but is influenced by different factors. This also increases the complexity of study design, which made data analysis complex and we could not analyze which intervention component is superior to the other. As no study provided feedback on the intervention implementation, it is difficult to know which component might contribute the most. Thirdly, no study was from a developing country, which limits generalizability.

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For policy makers, we hope we have better characterized the optimal intervention design. Future efforts should focus on an interactive approach that includes both parents and clinicians, in addition to providing clinicians with information through feedback on their APR and guidelines. Communications skills between clinicians and parents should also be enhanced. Education for parents might facilitate improved communication.

Future studies of the quality of intervention implementation are needed. Given the variability in the content and intensity of a given type of intervention, more research is needed to understand optimal content/intensity. This is needed for children especially, given the frequency of URI in this population and the paucity of available proven therapies. There is a need to evaluate future interventions in the context of continuously improving diagnostics and therapeutics. More evidence on intervention sustainability is needed and the acceptance of interventions should be further explored based on the local context, resources and cost-effectiveness studies. The interventions in these trials should be studied against a theoretical framework of health behavior change. Given the extent of antibiotic overuse in developing countries, further studies of interventions in these settings are needed.

Words (3024)

Acknowledgements

We thank Yiwen Huang the former research assistant from COMDIS-HSD, Nuffield Centre for International Health Shenzhen office for the contribution to literature review and earlier version of drafting, Professor Robbie Foy from Leeds Institute of Health Science, University of Leeds and Dr. Rebecca King from Nuffield Centre for International Health and Development, University of Leeds for their comments and reviews of this manuscript.

What is already known on this subject?
Antibiotic resistance is a global public health crisis, due in part to over-prescribing of antibiotics, which is common for childhood URIs. Systematic reviews show interventions with providers reduce antibiotic prescription, but with conflicting results about interventions with parents. Little is known about the relative benefits of each intervention, and no meta-analyses have been published.

What the study adds:
In order to reduce antibiotic prescription for childhood URIs, the most effective interventions involve both clinicians and parents. Improved communication between clinicians and parents is an essential part of antibiotic stewardship for childhood URIs.

Table 1. Basic characteristics of the included studies (n=12)

Study ID	Design	Settings/ No of clusters	Follow-up duration	Children age	Participants	Intervention	Control	Outcomes
Esmaily 2010*[#31]	cRCT	Iran/ 110 clusters	3 months	Not described	112 general practitioners (GPs)	*Target:* Clinicians *Approach:* peer leaders training *Content:*principle of rational antibiotic use (guideline) *Technic:*16 hours workshop	Control: lecture based training with traditional teaching method	% prescriptions with antibiotics intervention: 61% to 63% Control: 59% to 60%
Finkelstein 2001*[#18] (outcome for age 3-36 months, outcome for 36-72 months	cRCT	US/ 12 clusters	12 months	3 months to 72 months	157 practice clinicians; 13460 patients	*Target:* Both clinicians and parents *Approach to clinicians:* update guideline, peer leaders training *to parents*: leaflets/posters;	No educational intervention and no feedback	The rate of antimicrobial prescribing per person year in the Intervention: decreased by 41% control: decreased by 33%

						Technic: 90 minutes' small group education		
Francis 2009*[32]	cRCT	UK/ 61 clusters	7 months	6 months to 14 years	108 practice clinicians; 558 patients	*Target:* Both clinicians and parents *Approach to both:* *Content:* patient-clinician communication *Technic* :40 minutes online training	Usual care	Antibiotics were prescribed at the index consultation 19.5% in the intervention group and 40.8% in the control group
Gerber 2013*[#33]	cRCT	US/ 18 clusters	12 months	1-10 years	162 practice clinicians	*Target:* Clinicians *Content:* updated guidelines; APR feedback *Technic:* 1 hour clinical training	No education and prescribing feedback	For acute sinusitis broad spectrum prescriptions in intervention: decreased from 38.9% to 18.8% Control: decreased from 40.0% to 33.9%
Gjelstad 2013*[34]	cRCT	Norway/ 79 clusters	6 months	<18 years	382 practice clinicians	*Target:* Clinician *Approach:* peer leaders training; *Content:* Delayed prescriptions *Technic:*One day seminar	Control: received intervention targeting appropriate drug use but not antibiotics	APR: Intervention: decreased from 33.2% to 31.85 Control: increased from 33.4% to 35%
Gonzales 2005[19](two control groups)	Cluster non- randomized controlled trial	US/ 7 clusters	3 months	0-17 years	578 practice clinicians	*Target:* Both Clinician and parents *Approach* *to clinicians: Content:* APR feedback, *to parents:* Leaflets/posters *Technic:* Mail the information	Physician education only, two controls: local and distance practices	Adjusted antibiotic prescription rates: Distant control increased from 38% to 39% Local control decreased from 39% to 37% Intervention decreased from 34% to 30%
Juzych 2005[35]	Cluster non- randomized controlled trial	US/ 4 clusters	5 months	<15 years	30 clinic physicians; 15 internists	*Target:* Clinician *Approach: Content:* clinical guideline; *Technic:* half day education	No educational interventions	Change in antibiotic prescription rate in Intervention: reduced by 35.2% Control: increased by 6.5%
Legare 2012*[36]	cRCT	Canada/ 9 clusters	5 months	8 months - 9 years	149 physicians; 359 eligible	*Target:* Both clinician and parents *Approach:* peer leaders training; Patient-clinician	Usual care	% patients deciding to use antibiotics Intervention: decreased from 40% to

					patients	communication *Technic:* two hours online workshop		27.1% Control: increased from 36.8% to 65.5%
Pshetizky 2003[37]	RCT	Israel	3 months	3 months to 4 years	2 primary care clinics 81 parents	*Target:* Parents *Approach: content:* Patient-clinician communication *Method:*short explanation	No brief explanation given to parents	Parents administered antibiotics to their children in Intervention: 37% Control: 63%
Regev-Yochay 2011*[20](4 follow-up time points outcomes)	cRCT	Israel/ 50 clusters	12, 24, 36, 48 months	<18 years	Primary care pediatricians; 97699 registered children	*Target:* Both clinician and parents *Approach to clinicians:* *Year1:* peer leaders training *content:*guideline ; *Technic:*2 days workshop, *Year2*: *content:*Patient-clinician communication ; *Technic:*workshop *Year3*: APR feedback; *Technic:*workshop *to parents* : leaflets/poster;	No intervention	APRs reduced by 22% in the control group, by 40% in the intervention group
Taylor 2005[8]	RCT	US	12 months	<24 months	Pediatricians in Seattle Parents of 499 eligible children	*Target:* Parents *Approach:* Videos	Parents received educational leaflets regarding effective injury prevention	Total no. of prescriptions for antibiotics in Intervention: 2.2±2.6 Control: 2.5±2.9
Wheeler 2001[39]	Non-randomized controlled trial	US	9 months	<19 years	5 pediatric practices; 9 physicians; 771 parents	*Target:* Parents *Approach: Videos* Leaflets/posters	A control video on the dangers of stimulant use played to parents in the waiting areas;	APR for viral infection reduced from 6.8% to 4.2% in the intervention

Note: * Studies in which the number of children were prescribed any antibiotics from both groups, as well as the total number of children in each group were recalculated after adjustment for design effect (DE). # For CRCTs that had no ICCs reported, we estimated from similar study as supported by the evidences from Adams et al. in their article "Patterns of intra-cluster coORelation from primary care research to inform study design and analysis".

Table 2. Summary of risk of bias of included studies (n=12)

Study ID	*Sequence generation*	*Allocation concealment*	*Blinding participants and personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective outcome reporting*	*Other bias*	*Summary of risk of bias*
Gerber 2013	+	+	-	-	?	+	?	Low risk
Gjelstad 2013	+	+	?	?	+	?	+	Low risk
Juzych 2005	-	+	+	?	+	+	?	High risk
Esmaily 2010	-	+	+	+	+	+	+	Low risk
Pshetizky 2003	+	+	+	?	+	-	+	Low risk
Taylor 2005	+	+	+	?	+	+	?	Low risk
Wheeler 2001	-	-	-	?	+	-	-	High risk
Legare 2012	+	+	-	+	+	-	?	Low risk
Francis 2009	+	+	-	+	+	+	+	Low risk
Gonzales 2005	-	+	-	?	+	+	?	High risk
Regev-Yochay 2011	+	?	-	?	+	+	+	Low risk
Finkelstein 2001	+	+	+	?	+	+	+	Low risk

Note: + = Low risk, ?= Unclear risk, -= high risk; Other bias: possible intervention contamination, recruitment bias, data collection bias.

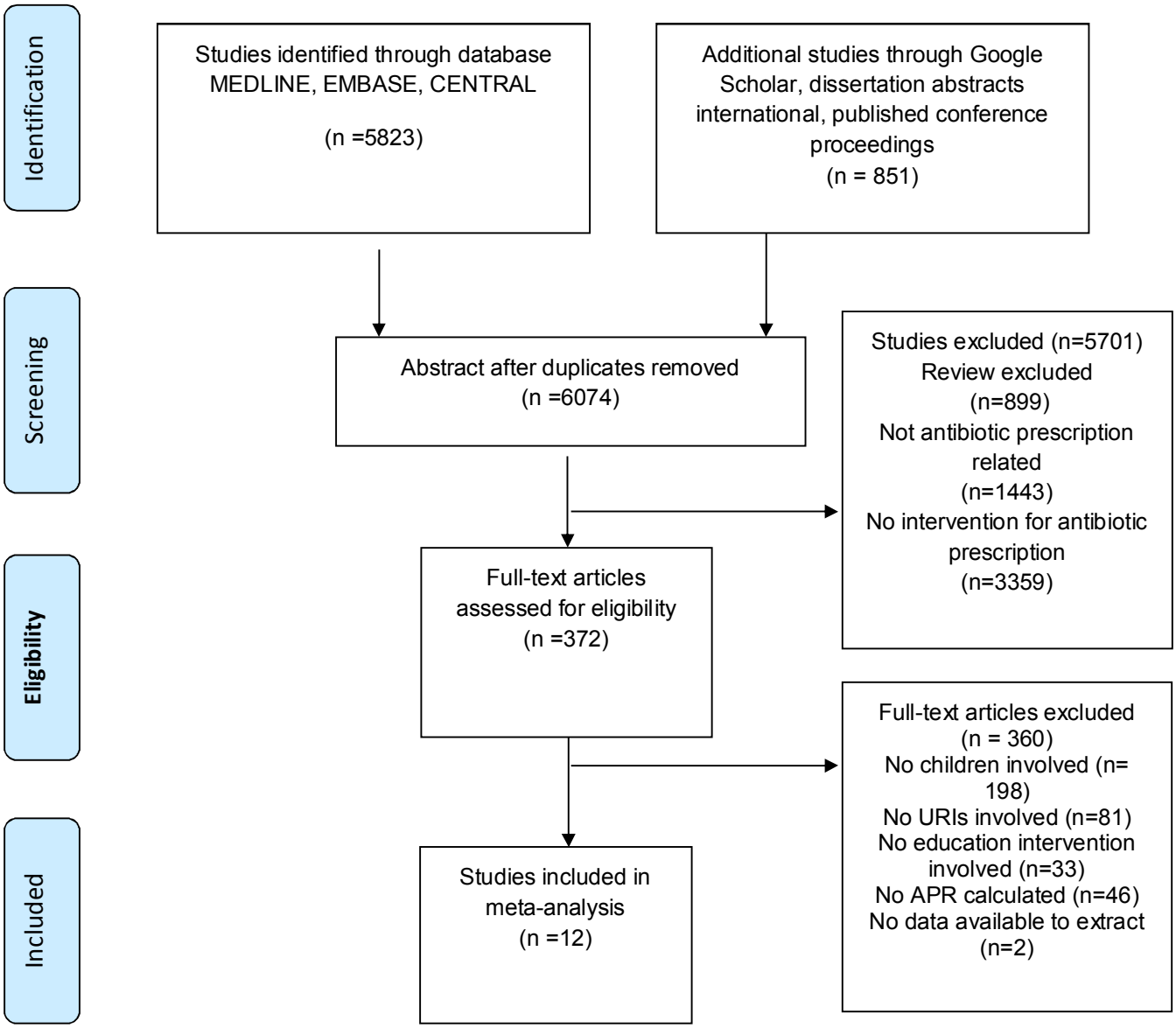
Table 3. Results of meta-analysis of all included studies

			Heterogeneity	
Subgroup	No of study	OR (95% CI)	I^2	p
Overall	12 *	0.65(0.49,0.86)	66%	<0.001
Study target				
Clinicians	4	0.88(0.67,1.16)	73%	0.010
Parents	3	0.50(0.10,2.51)	80%	0.007
Both	5	0.52(0.34,0.79)	50%	0.009
Study design				
cRCT	9	0.56(0.41,0.78)	74%	<0.001
Non-R control trial	3	0.84(0.61,1.17)	0%	0.551
Follow-up duration				
1-6 months	6	0.62(0.43,0.90)	77%	<0.001
7-12 months	6	0.59(0.45,0.79)	17%	0.300
Intervention intensity				
<1 day	9	0.52(0.33,0.81)	66%	0.04

≥ 1 day	3	0.79(0.64,0.98)	50%	0.13
Intervention method[@]				
Face to face training	6	0.77(0.65,0.92)	36%	0.160
Non face to face training	3	0.38(0.21,0.70)	44%	0.170
ICC report *				
ICC reported	4	0.52(0.33,0.84)	76%	0.006
No ICC reported	5	0.81(0.67,0.98)	13%	0.330
Study year				
2000s	7	0.59(0.35,1.00)	66%	0.007
2010s	5	0.66(0.49,0.89)	72%	0.006
Clinical settings				
Pediatric clinic	4	0.61(0.47,0.79)	0%	0.470
Non-pediatric clinic	8	0.60(0.43,0.85)	74%	<0.001

*ICC report studies only included the cluster studies . [@] Intervention method used only for the studies targeting clinicians.

Figure 1. Summary of included and excluded relevant articles in the review process.



Note: CENTRAL= the Cochrane Central Register of Controlled Trials.

Figure 2. Pooled relative risk (OR) and 95% confidence interval (CI) for reducing antibiotic prescription on childhood URIs

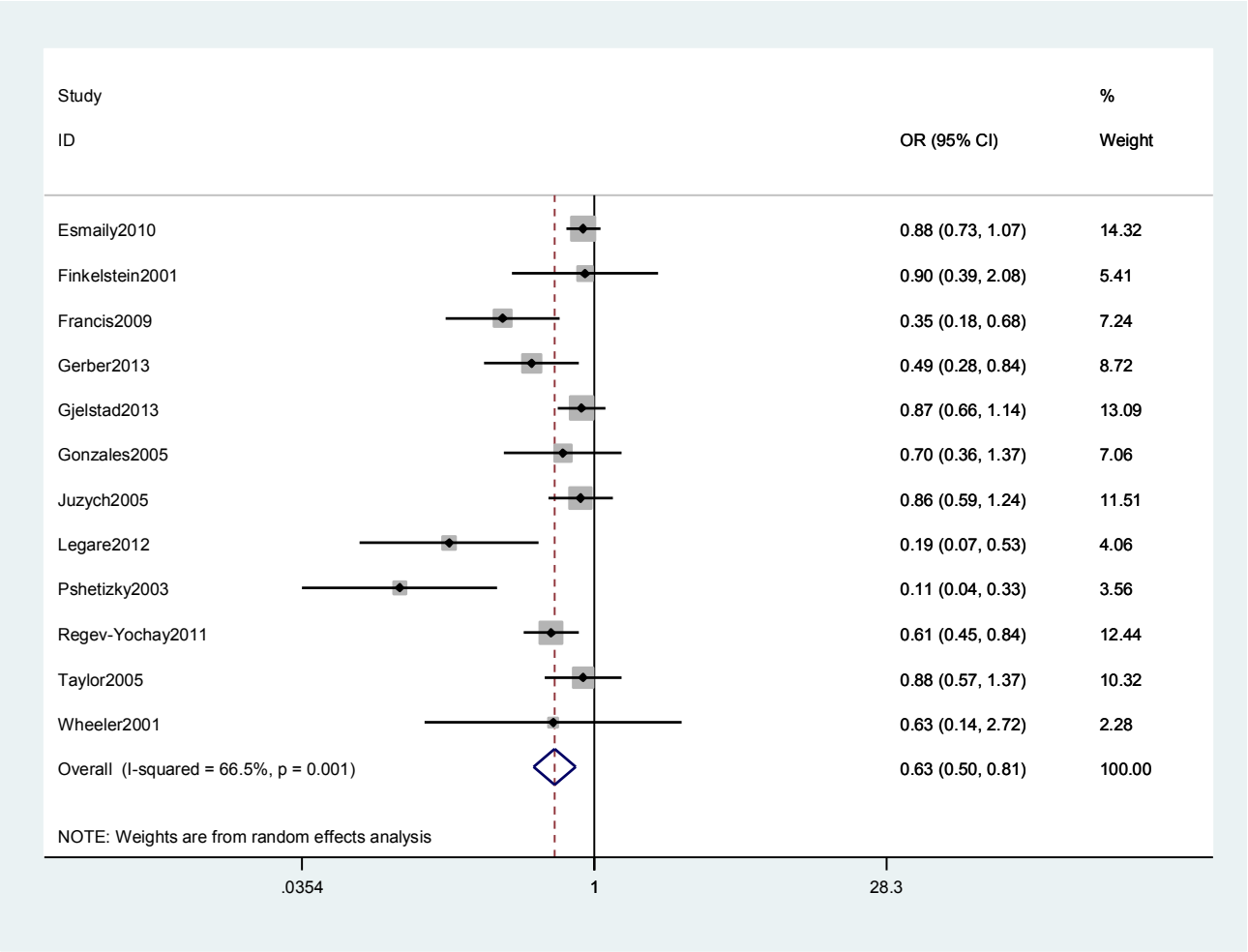
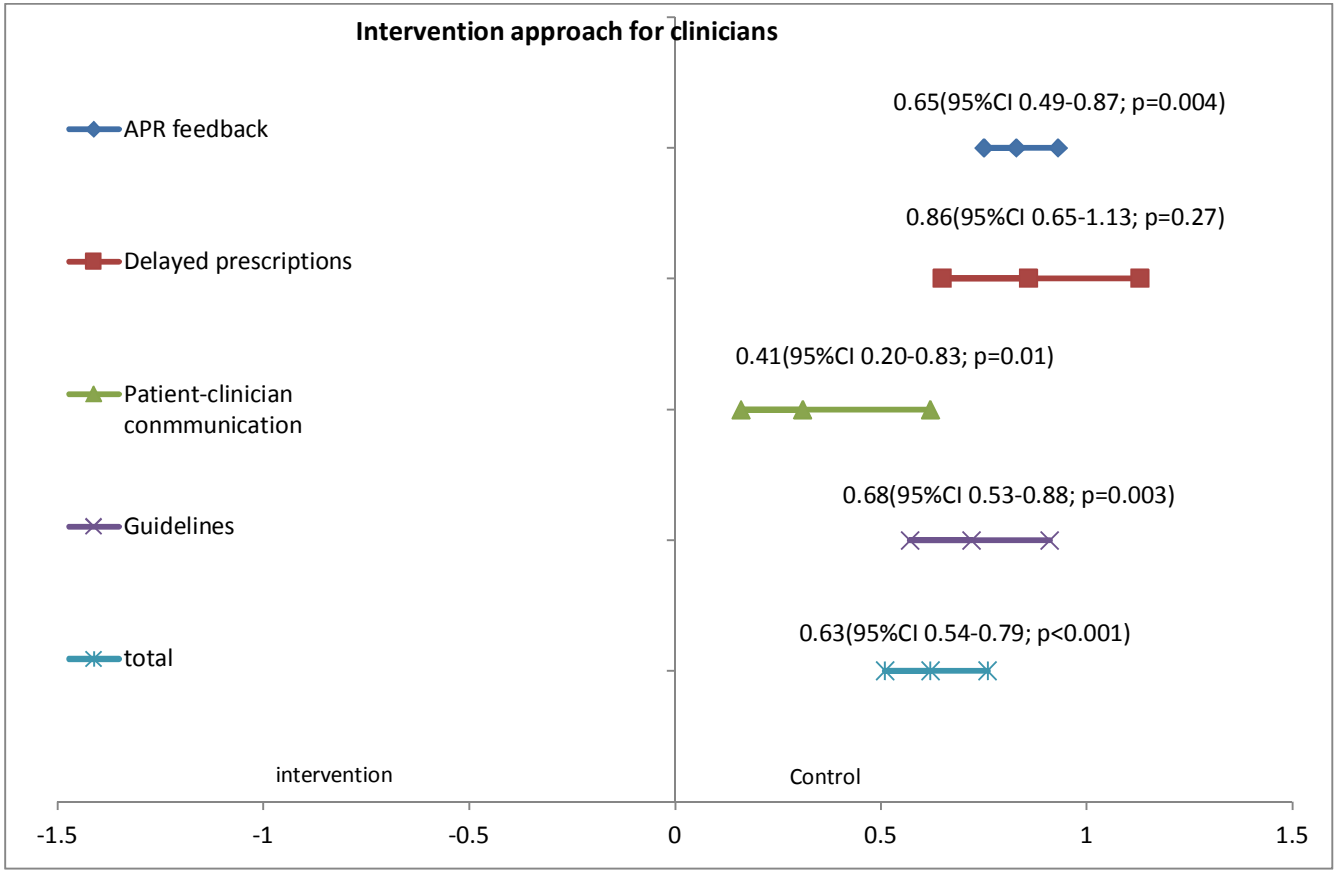
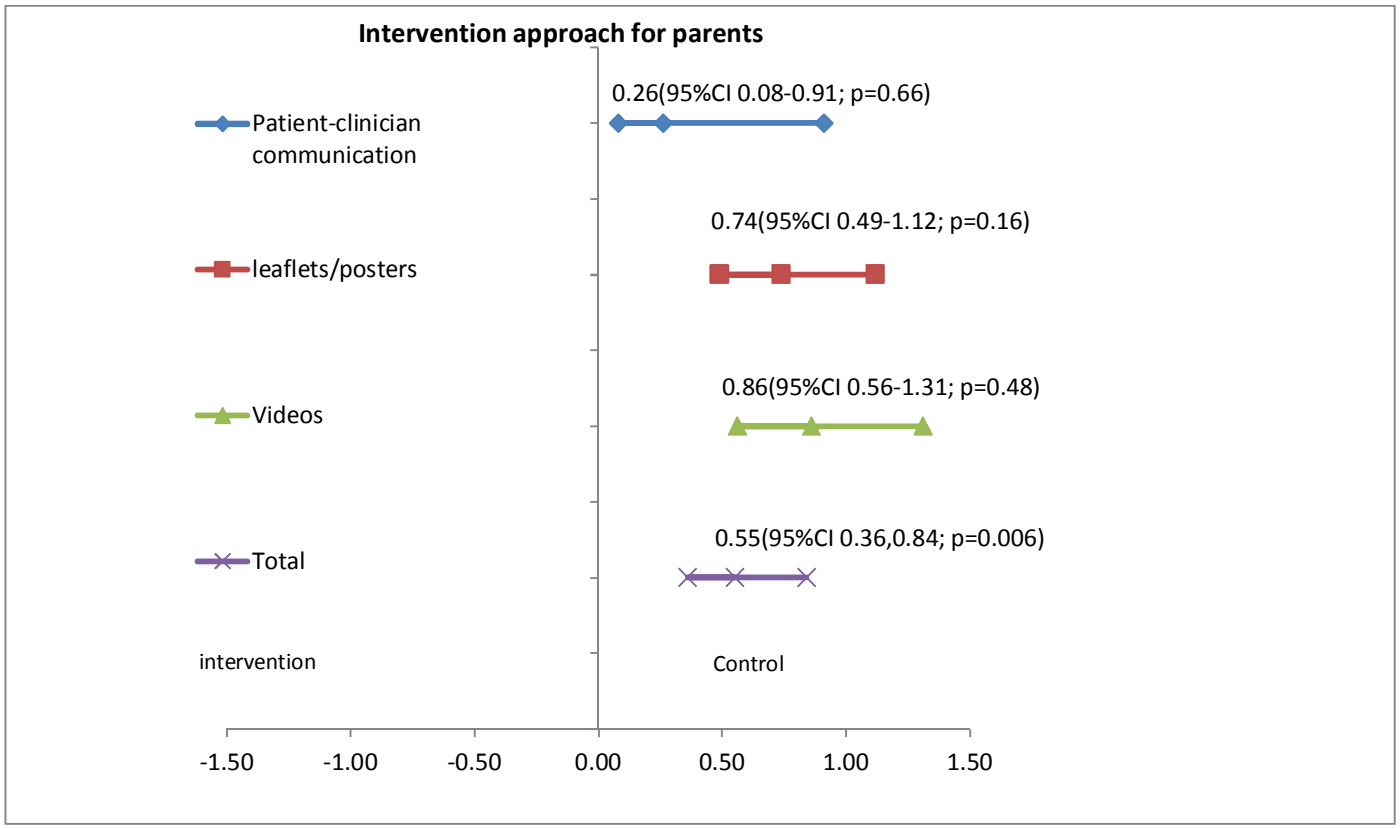


Figure 3. Forest plot results across different intervention types for clinicians and parents.



p= test for overall effect.



p= test for overall effect.

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