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Drug Management Program

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Interventions and strategies to improve the use of antimicrobials in developing countries: a review

Drug Management Program

Management Sciences for Health
Arlington, VA, United States of America

World Health Organization

A BACKGROUND DOCUMENT FOR THE WHO GLOBAL STRATEGY FOR CONTAINMENT OF ANTIMICROBIAL RESISTANCE

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Contents

Abbreviations and acronyms

AB	antibiotic
ARCH	Applied Research for Child Health [Project]
ARI	acute respiratory infection
C	control group
CCM	community case management
CHWs	community health workers
Dx	diagnosis
E	experimental group
EDP	essential drugs program
HCs	health centres
ICIUM	International Conference on Improving the Use of Medicines
INRUD	International Network for Rational Use of Drugs
NIS	Newly Independent States
PHC	primary health care
PP&C	pre-, post-measurements with comparison
RCT	randomized control trials
RPM	Rational Pharmaceutical Management [Project]
Rx	prescription
Rxg	prescribing
STDs	sexually transmitted diseases
STGs	standard treatment guidelines
TS&C	time series with comparison
TS-C	time series without comparison
Tx	treatment
USAID	United States Agency for International Development
USP	United States Pharmacopeia
UTI	urinary tract infections
WHO/DAP	World Health Organization Action Programme on Essential Drugs

Background

A significant force driving the spread of antimicrobial resistance is the inappropriate use of antimicrobials in primary care and hospital settings. This is related to overprescribing as well as inappropriate selection and dosing of antibiotics by health care providers, unfettered access to antimicrobials by consumers, and a failure to adhere to clinically desirable treatment regimens. Consequently, interventions focusing on health providers have been widely recommended and implemented. These include educational interventions that aim to change behaviour by changing people's knowledge (e.g. formal education, seminars, training, distribution of literature, academic detailing), managerial interventions that aim to guide behaviour (e.g. formulary lists, treatment guidelines, clinical supervision systems, audit, and feedback), and regulatory interventions that define what is required and legal (e.g. professional licensing, registration, practice laws). However, not all the proposed interventions have been rigorously tested to determine their impact on the use of antimicrobials. Hence, it is likely that many lessons learned already, both positive and negative, are being repeated, some at a cost that must be questioned in light of the results.

Some efforts have been made to promote refinement of the state-of-the-art of drug use intervention research in general. In 1997 the Rational Pharmaceutical Management (RPM) Project, the Applied Research for Child Health (ARCH) Project, the International Network for Rational Use of Drugs (INRUD), the United States Pharmacopeia (USP), and the WHO Action Programme on Essential Drugs (WHO/DAP) cosponsored the First International Conference on Improving the Use of Medicines (ICIUM). The conference identified key topics for research on improving prescribing and dispensing practices, improving community use of medicines, and developing effective pharmaceutical policies and regulations. Also recognized was the need for innovative interventions to improve malaria case management and well-designed interventions in hospitals and private sector settings.

In 1998 RPM received funds from the United States Agency for International Development (USAID), through the global initiative to slow the emergence of antimicrobial resistance, to conduct a technical review that would refine and update current knowledge of the effectiveness of interventions aimed at the use of antimicrobials. This activity is within the mandate of RPM's technical leadership programme. The partners for this activity are INRUD Ghana and the Harvard University Drug Policy Group.

This review serves as a springboard to further work on interventions to improve the use of antimicrobials. To the extent that there are still many gaps in our understanding of the determinants of drug use in general and antimicrobials in particular, our understanding of why some interventions appear to be more effective than others is also not complete. More rigorous design, implementation, and follow-up of intervention research can greatly assist in closing these gaps. Health care planners, managers, and practitioners can benefit greatly from this information by quickly identifying the most appropriate strategies to improve drug use in their contexts and expect reasonable improvements in the use of antimicrobials, and, ultimately, a reduction in the rates of resistance.

1. Introduction

The use of antimicrobials[1] has contributed to the dramatic fall in morbidity from communicable and infectious diseases over the last 50 years globally (e.g. UNIDO, 1980; WHO, 1988, 1996; Kunin et al., 1990; Richardson, 1992), as to increasingly high levels of expenditure on and consumption of antimicrobials. A substantial proportion of the total drug budget in many countries is dedicated to antibiotics and they are often the largest single group of drugs purchased in developing countries. However, despite the vast advancements brought about since the development of antibiotics and antimicrobials, their widespread availability and use have had several negative implications on global health care, among these the inappropriate use by health care providers and consumers and the increase of drug resistance. The primary economic implication of resistance on the diminishing efficacy of antibiotic treatment includes the need to rely on more expensive drugs that may be practically unaffordable for most primary health care programmes.

In developing countries, relatively high levels of availability and consumption have led to disproportionately higher incidence of inappropriate use and greater levels of resistance compared to developed countries (WHO, 1988, 1996). Surveys on antibiotic use in these settings show antibiotics prescribed in 35 to 60% of clinical encounters although appropriate in less than 20% (Trostle, 1996). A recent comparative analysis of inappropriate prescribing by physicians and other professional personnel in 12 developing countries also highlighted an unnecessarily high proportion (25 to 75%) of patients receiving antibiotics during clinical visits (Hogerzeil et al., 1993). These indicate the continuing need to curb the irrational, or inappropriate, use of antimicrobial agents and to identify effective interventions to improve drug use.

[1] The terms antimicrobial and antibiotic are often used interchangeably. Antibiotics are natural substances that inhibit the growth of bacteria or kill them directly. In practice, though, most commercial antibiotics have been chemically altered or enhanced, producing antimicrobials.

Inappropriate drug use is characterized by any of the following: overprescription (prescribing drugs when none are needed clinically); omission (when required drugs for certain conditions are not prescribed); the use of inappropriate dosages (too high or too low); incorrect duration (too short or too long); incorrect selection (mismatch between organisms); unnecessary expense (the selection of newer and more expensive drugs when older, cheaper drugs are clinically adequate); and unnecessary risk (use of injections or intravenous antibiotics when oral forms would be suitable). Participants in drug use decisions include not only clinically trained health care providers, and authorized and other dispensers, but also consumers who engage in self-initiated purchasing of drugs without contact with prescriber or dispenser and the use of drugs left over from previous treatments. For antimicrobials, these characteristics of inappropriate drug use cause particular concern for the development of resistance.

There is a strong correlation between inappropriate prescribing and inappropriate self-medication (Greenhalgh, 1987), but generally drug use within these groups is rooted in a complex and multilayered mix of medical, psychosocial, cultural, economic, and even geopolitical factors. Within this complex, a number of factors have been associated with suboptimal use of antibiotics, particularly within the context of prescribing and dispensing health care provider groups. These include (1) insufficient prescriber knowledge about differential diagnosis, the kinds of conditions treatable with antibiotics and appropriate therapies for bacterial infections; (2) patient demands and preferences for treatment, sometimes real, sometimes based on misperceptions by health providers; (3) fear of loss of economic incentives due to patient dissatisfaction arising from non-response to perceived patient demands; (4) fear of negative clinical outcomes in the absence of therapy; (5) influence of social and cultural norms or opinion leaders on practice; (6) promotional pressures of pharmaceutical companies; and (7) wish to maximize profits. To a lesser

extent, inadequate drug supply infrastructure, inappropriate or outdated treatment guidelines, lack of access to correct clinical information, and work environment factors also contribute in varying measure to inappropriate use of antibiotics by prescribers and dispensers. Attempts to improve antibiotic use should aim to identify the key factors that promote overuse, such as those described above, and develop interventions that address the identified factors.

Despite the volume of studies that describe inappropriate drug use in general, and antimicrobial drug use in particular, there is relatively little known about effective strategies to improve the use of antimicrobials in the developing country context. A recent study evaluated strategies to improve general medication use in primary care in 56 developing countries (Ross-Degnan et al., 1997). Although this review did not concentrate on antimicrobial drug use, it did show that the most common practice addressed by the interventions was the prescribing of antibiotics, with 76% of the studies focusing directly or indirectly on improving antibiotic use. The desired outcome for most of the studies reviewed was typically a reduction in unnecessary prescribing of antibiotics, although in interventions that sought to improve compliance with treatment guidelines of specific diseases such as acute respiratory infections, an increase in the prescribing of a preferred antibiotic was the desired outcome.

This paper aims to follow up on the above-referenced review by focusing specifically on evaluating interventions aimed at improving antimicrobial use in developing countries. It is hoped that the understanding gained through this exercise will not only identify gaps in our knowledge about the effectiveness of interventions, but also serve as a guide in the development of research agendas and applications of results to address antimicrobial use in these regions.

2. Objectives

The overall objective of this review was to survey published and unpublished interventions to improve the use of antimicrobials in developing countries and evaluate the evidence of their effectiveness. Within this general aim were three specific objectives. First, the review set out to select interventions that meet minimum methodological criteria for validity in study design and compare their experiences in terms of settings, target conditions and populations, and outcome measures. Second, it aimed to identify the interventions that appear to be most effective in improving antimicrobial prescribing and dispensing and other outcomes of antimicrobial use by health care providers, and to assess their level of impact. Finally, it aimed to identify critical gaps in current knowledge about interventions and on measuring their impact on antimicrobial use specifically in developing country settings.

3. Methodology

3.1 Search strategy

A database of published and unpublished intervention studies on improving antimicrobial use by health care providers in developing countries was generated using three main search strategies. First, a search was conducted for abstracts, posters, journal articles, reports, reviews, and newsletters reporting interventions to improve the use of antimicrobial drugs by health care providers. The search was conducted on the WHO/DAP website, the computerized INRUD database, and the programme and abstract book of ICIUM. Next, a search on general medical health literature was conducted using the computerized retrieval system MEDLINE (1966–1999). The search was for articles with the keywords "antimicrobial", "antibiotic", "antibiotic use", or those that referred to the name of any individual antibiotic. The initial collection was then limited to articles about drug utilization, or prescribing, and those whose title implied an intervention because of the use of action words like "reducing", "improving", and so on. Established canned strategies aimed at accomplishing such screens were used in this selection process. Penultimately, the search was limited to articles from Africa, Latin America, and Asia.[1] Finally materials of interest, especially from the Newly Independent States (NIS) and Eastern Europe, were requested from individual researchers and organizations known to be involved in research on improving the use of drugs. These were identified through RPM contacts in the NIS, including the Russian Federation, the Republic of Moldova, Ukraine, and Hungary, in addition to the MEDLINE and INRUD bibliographical searches. Data were extracted by one researcher only, and the authors were not approached.

This initial broad collection of studies on antimicrobial use was then narrowed down to the current selection of 36 studies using the following inclusion criteria:

- Studies from the following geographical areas: Africa, Asia, Latin America, and the Newly Independent States and Eastern Europe
- Studies targeted at public and private sector health care providers, which were divided into three main categories: (1) clinically trained health providers, which included physicians and other authorized prescribers such as nurses, clinical officers, medical aides, and health workers; (2) authorized dispensers, which included pharmacists and counter attendants; and (3) other dispensers such as drug sellers and variety storekeepers
- Studies focusing on antibiotic use on the following target conditions: respiratory infections (otitis media, pharyngitis, sinusitis, no-pneumonia cough/bronchitis, pneumonia, and purulent rhinitis/common cold), gastrointestinal conditions (acute watery diarrhoea, such as cholera and non-cholera, and bloody diarrhoea), skin infections, hospital infections (systemic prophylaxis, wound infections), fever, genitourinary infections (urinary tract infections [UTI], and sexually transmitted diseases [STDs])
- Studies using the following study designs: randomized control trials (RCT), before and after measurements with a comparison group (PP&C), and time series with or without a comparison group (TS&C, TS-C)

3.2 Criteria for methodological adequacy

The stated study designs were preselected for a number of reasons. Generally within the context of the experimental design, the RCT is the ideal paradigm for providing valid scientific evidence. This is because it has the strength of eliminating confounding variables by the process of randomization. However RCTs and experimental designs are often not feasible when studying

[1] These included countries not on the Organization for Economic Cooperation and Development list of industrialized countries for 1998.

human groups. In real-life settings it is often impossible to assign people at random to two groups or to maintain a control group. Therefore experimental designs are often replaced by quasi-experimental designs. With these designs at least one characteristic of a true experiment is missing either randomization or the use of a separate control group. However it always includes manipulation of an independent variable that serves as the intervention. Studies that use strong quasi-experimental designs such as before and after studies with control groups and time series studies with or without comparison groups are generally considered to be adequate for guiding policy (Campbell and Stanley, 1963; Cook and Campbell, 1979; Varkevisser et al., 1991).

3.3 Measuring study effects and effect size

Five main outcome measures were identified for assessing change in antibiotic use: changes in health care provider knowledge of antibiotic use (diagnosis, therapy), changes in prescribing and administration of antibiotics, changes in clinical outcome, changes in patient factors (satisfaction, improved knowledge on illness and drugs, changes in mortality, duration or severity of illness), and changes in cost of antibiotic use.

The interventions included in this review took place in different countries and health settings, used different approaches and methodologies, targeted different audiences and practices, and measured different outcomes. In order to evaluate the relative effectiveness of these different intervention strategies it was important to develop a metric for comparing effect sizes across studies that took into account the heterogeneity of study dynamics. A systematic process for summarizing relative effect sizes in all included studies was therefore developed.

This involved firstly outlining all the outcomes identified by authors as the targets for their intervention(s). In order to indicate the magnitude of effects of an intervention, the outcome measures within this outlined group for which the study achieved a significant positive change were identified (e.g. reduction in antibiotic prescribing, increase in number of cases treated according to a treatment guideline, or a reduction in disease-specific mortality). All outcome measures were then converted to a scale where positive change was indicated by positive numbers.

The procedure for calculating effect size depended on how study outcomes were measured. Generally, outcome measures reported within the studies were expressed as percentages (e.g. percentage of patients receiving an injection), mortality rates (e.g. deaths per 1000 live births in children under five), performance scores (e.g. a knowledge index), or numerical scores (e.g. number of cases treated according to a treatment guideline). For outcomes measured as percentages, effect size was computed as the relative gain in the intervention group, calculated as the net difference between the percentage improvement in the intervention group and the percentage improvement in the comparison group.[1] For outcomes measured as mortality rates, performance scores, or numerical scores, the changes before and after intervention were converted into percentages by dividing the absolute changes (post-intervention) by baseline values.[2]

For studies using time series or repeated measures without comparison groups, effect size was calculated as percentage improvement between the stable pre-intervention percentage and the stable post-intervention percentage; short-term shifts in percentage immediately before or after an intervention were discounted as transitory effects.

It is important to note that the taxonomy of interventions used in this study was developed by MSH and is used in many developing countries. However, in other parts of the world studies tend to use the taxonomy developed by the Effective Practice and Organization of Care (EPOC) group of the Cochrane Collaboration.

[1] Effect size = $(\%POST–\%PRE)_{intervention} – (\%POST–\%PRE)_{control}$

[2] Effect size = $((\%POST–\%PRE) / PRE)_{intervention}) – ((\%POST–\%PRE) / PRE)_{control})$

4. Results

4.1 Overview of results

There were 36 studies meeting the inclusion criteria. A comprehensive summary of results outlining the characteristics of all selected interventions and their key measured outcomes is presented in Appendix 1. Each study in Appendix 1 has a number in the first column. This number is used for reference in the tables. An overview of results indicates the following:

1. The selected studies were distributed over three geographical regions: Asia, Africa, and Latin America.[1] The majority of studies (20) reviewed were carried out in Asia. Distribution of remaining studies in Africa and Latin America was 10 and 6, respectively. The majority of studies were carried out in the early to mid-1990s. Three studies (one Latin American and two African) were carried out in the 1980s.

2. The majority of studies (31) were conducted in public primary health care (PHC) facilities, of which 11 were also carried out in the community. Three studies were carried out in hospitals and two in private sector pharmacy/drugstore settings. Table 1 presents the distribution of studies across geographical areas and study settings.

3. In terms of methodology employed, 12 studies were randomized controlled trials (RCTs), 16 were pre-post-measurements with a comparison group studies (PP&C), and the remaining eight were time series studies, of which three employed comparison groups (TS&C) and five did not (TS-C) (Table 2).

4. The types of interventions tested were broken down into four main categories: (1) educational, (2) combined educational and managerial, (3) managerial, and (4) an economic intervention. The definition of an educational intervention is one in which "prescribers are persuaded by providing information or knowledge for them" (*Managing Drug Supply*, 1997, p. 466). The educational intervention may be face-to-face interventions, trainings, seminars, workshops, or provision of written material. A managerial intervention is one in which "prescribers are guided in the decision-making process." This guidance may take the form of providing standard treatment guidelines, limited procurement lists, supervisory and monitoring visits, and so on. A mixed educational and managerial intervention provides both guidance and persuasion. Lastly, an economic intervention provides a different economic incentives environment.

   The categories for these interventions are described in Table 2 and then subcategorized with results in Tables 3a, 3b, and 3c. The distribution of interventions per category is 13 educational interventions, 18 combination educational/managerial interventions, four managerial interventions, and one economic intervention strategy. In addition, two of the combined managerial and educational interventions had a purely managerial intervention as well.

5. The studies targeted three main groups of health care providers: (1) prescribers, which included physicians and paramedics (e.g. nurses, clinical officers, trained community health workers); (2) dispensers, including pharmacists and counter attendants, and other dispensers such as drug sellers and general or variety storekeepers; and (3) populations within communities. Table 4 presents the distribution of studies by targeted health care providers, health conditions, and practices. Twenty-two of the studies targeted physicians, 25 targeted paramedics, nine targeted community health workers, two targeted pharmacists and drug sellers, and 11 targeted the community.

6. There were three main health conditions targeted by the studies: 18 targeted acute respiratory infections (ARI), 13 targeted gastrointestinal con-

[1] Despite an active search for published and unpublished interventions to improve use of antibiotics in Eastern Europe and the Newly Independent States, none were found that met the study criteria.

ditions (particularly diarrhoea), and six worked with malaria. Three studies investigated other specific health conditions, namely hypertension and urinary tract infections, in addition to the main ones. Six studies focused on health worker practices (such as injection and rational drug use) across a broad range of health conditions (Table 4).

7. Outcomes measured by the studies fell into five categories: changes in health providers' knowledge of antibiotic use, prescribing and administration practices, dispensing practice, patient factors, and drug costs. One study focused on the cost of drugs as the main outcome measure. The outcomes focused on here for the sake of improved antimicrobial use are percentage of change in antibiotic use, percentage of change in correct dose prescribed, under-five mortality rates, and malaria prevalence.

8. Thirty-one of the 36 studies reported the results of the intervention. Twelve studies reported at least one large impact (>30% improvement in a targeted outcome relative to control), 12 reported moderate impact (10–30% improvement), and seven had very low or no impact (<10%) (Table 5).

TABLE 1. **INTERVENTIONS ACROSS GEOGRAPHICAL AREAS AND STUDY SETTINGS**

		Study settings			
Geographical area		**Hospital**	**Public PHC facilities**	**Private sector pharmacies/drugstores**	**Community**
Type of intervention	**Total no. of studies**	3	31 [2]	2	[11]
Asia	20 [3]	1	18	2	[7]
Educational			4 (*1,3,8,13*)	1(*12*)	
Man./Edu.		1 (*16*)	10 (*15,17,18,19,21, 25,26,28,29,30*)	1(*23*)	7 (*15,17,21,25,26,28,29*)
Managerial			3 (*19,32,34*)		
Economic			1 (*36*)		
Africa	10 [1]	2	9	0	[2]
Educational			2 (*2,9*)		
Man./Edu.			6 (*14,20,22,24,27,31*)		2 (*22,27*)
Managerial		2 (*33,35*)	1 (*24*)		
Economic					
Latin America	6 [2]	0	6	0	[2]
Educational					
Man./Edu.			6 (*4,5,6,7,10,11*)		2 (*10,4*)
Managerial					
Economic					

Notes: Number inside ( ) denotes reference number of study in Appendix 1. Number in [ ] denotes number of studies that cover this intervention as well as their main one.

TABLE 2. **DISTRIBUTION OF STUDIES BY TYPE OF INTERVENTION AND DESIGN**

		Type of Intervention				
Study design		**Educational**	**Educational/Managerial**	**Managerial**	**Economic**	**Total**
RCT		4 (*1,2,4,13*)	6 (*14,18,24,27,30,31*)	2 (*24,32,33*)	0	12
PP&C		7 (*3,5,6,9,10,11,12*)	7 (*15,19,20,21,23,25,29*)	1 (*19,35*)	1 (*36*)	16
TS	&C	0	3 (*16,26,28*)	0	0	3
	–C	2 (*7,8*)	2 (*17,22*)	1 (*34*)	0	5
Total		**13**	**18**	**4**	**1**	**36**

Notes: RCT = randomized controlled trial, PP&C = pre, post with comparison, TS + or – C = time series with or without control. Number inside ( ) denotes reference number of study in Appendix 1.

TABLE 3A. **STUDIES BY IDENTIFIED CATEGORIES AND SUBCATEGORIES OF INTERVENTION TYPES**

Educational intervention	No. interventions	Alone		In combination	
		Ref.	Eff.	Ref	Eff.
Newsletters	3	*1*	[6%]	*3,12*	[18%] [ns]
Face to face	2	*13*	[17%]	*3*	[18%]
Workshop interactive	4	*2,5*	[ns], [36%]	*3, 6*	[18%], [27-29-45%****]
Seminars	2	*13*	[10%]	*1*	[6%]
Trainings	8	*4,7*	[9%] [17%]	*4,10*	[18%], [ns]
		8,9	[21-6%**], [ns]	*11,12*	[37-20%***], [ns]
Community education	3	*4*	[-1%]	*4,10*	[18%], [ns]
Peer review	4			*2,6*	[ns], [27-29-45%****]
				10,11	[ns], [37-20%***]
Evaluations	1			*6*	[27-29-45%]
Media	1			*10*	[ns]
Total	**28**	**10**		**18**	

** effect reduced after 3 months to 9 months.
*** effect reduced after 6 months.
**** effect enhanced from training to peer review to evaluation.
[ ] brackets show results of equivalent intervention.
ref. reference.
ns non-significant at 95% level.

TABLE 3B. **STUDIES BY IDENTIFIED CATEGORIES AND SUBCATEGORIES OF INTERVENTION TYPES**

Educational and managerial interventions methods	Reference	Nos.	Results			Prevalence malaria
			Antibiotic use	<5 Mortality	Correct dose	
Consensus STGs	*14*	1	[+ 8% (controls + 18%)]			
STGs and training	*19,23,24*		[+ 85%] [+12%] [-1%]			
	31	4	[- 3% adults, + 49% children]			
	25	1		[-54%]		
STGs, training, and mass education	*25,26*	2		[-55%] [-49%]		
STGs, mass education, and printed materials	*15*	1		[-30%]		
STGs, supervision, and training	*18,23, 24,*	3	[-64%][+5%] [0%]			
	29	1		[-38%]		
Consensus STGs, supervision, trainings, mass education, and provision of drugs and materials	*17*	1	[-22%]		[+69%]	
Supervision and training	*22,30*	2	[-29%], 30 results poorly presented			
	21,27,28	3		[-29%] [-13%] [-28%]		
Supervision and training and provision of drugs	*20*	1				[-48%]
Regulation, training, and advocacy	*16*	1	Looked at number of drugs used and number on essential drugs list. Results showed improvement then decline.			
Total number		**21**	**10**	**8**	**1**	**1**

Note: Reference 18 showed plus 62% without training; reference 24 showed plus 6% with STGs alone.
Brackets show results of equivalent intervention.

TABLE 3C. **STUDIES BY IDENTIFIED CATEGORIES AND SUBCATEGORIES OF INTERVENTION TYPES**

Managerial interventions	**Reference number**	**Total number**	**Effect**	
			Reduction AB use	**Following STG**
STG	*24*	1	[6%]	
STG plus discussion	*19*	1	[-10%]	
STG plus discussion, plus audit and review	*19*	1	[-24%]	
Audit and review	*33, 35*	2	[dk], [dk]	
Supervision, audit, and review	*32*	1	[ns]	[14%]
Surveys, audit supervision, making plans	*34*	1	[-32%]	

Economic interventions	**Reference number**	**Total number**	**Effect**	
			Reduction AB use	**Following STG**
Change from flat fee to item fee	*36*	1	[-7%]	

Note: Brackets show results of equivalent intervention.
ns non-significant at 95% level.
dk don't know.

TABLE 4. **DISTRIBUTION OF STUDIES BY TARGETED HEALTH CARE PROVIDERS, HEALTH PROBLEMS, AND PRACTICES**

	Intervention targets: Health conditions and health care provider practices					
Intervention targets: Health care providers	**ARI [18]**	**Diarrhoea [13]**	**Malaria [6]**	**Other specific conditions* [3]**	**General health conditions** [6]**	**Practices*** [6]**
PRESCRIBERS						
Physicians [22]	11 (*2,4,7,8,11,14, 16,19,26,30,32*)	10 (*2,3,5,6,10,13, 14,18,24,30*)	4 (*2,14,24,33*)	3 (*14,16,33*)	5 (*1,31,32,34,36*)	6 (*24,31,32, 34,35,36*)
Paramedics [25]	10 (*2,7,8,14,15,16, 21,26,27,30*)	6 (*2,3,13,14,24,30*)	5 (*2,9,14, 24,33*)	3 (*14,16,33*)	6 (*1,17,31, 32,34,36*)	6 (*24, 31,32, 34,35,36*)
CHWs [9]	7 (*15,21,25,26, 27,28,29*)	1 (*22*)	1 (*20*)	0	0	0
DISPENSERS						
Pharmacists [1]	0	1 (*12*)	0	0	0	0
Drug sellers/ storekeepers [2]	1 (*23*)	2 (*12,23*)	0	0	0	0
USERS						
Community [11]	8 (*4,15,21,25,26, 27,28,29*)	2 (*10,22*)	1 (*20*)	0	0	1 (*17*)

Notes: 1. Number inside ( ) denotes reference number of study in Appendix I targeting different health care providers, health conditions, and health provider practices.
2. Number in [ ] in column headings denotes total number of studies that targeted ARI, diarrhoea, malaria, other specific conditions, general health conditions, and practices. Number in [ ] in far left column indicates total number of studies that targeted physicians, paramedics, CHWs, pharmacists, drug sellers/storekeepers, and the community.

* Lack of appetite, urinary tract infection, hypertension, trivial infections.
** AB use, prescribing for all conditions.
*** Health worker performance, drug-selling behaviour.

TABLE 5. **PERCENTAGE MAGNITUDE OF IMPROVEMENT BY TYPE OF INTERVENTION CONCENTRATING ON THE FOLLOWING OUTCOMES: USE OF ANTIMICROBIALS, DOSE OF ANTIMICROBIALS, UNDER-5 MORTALITY RATE**

	Greatest effect change in outcome measure							
Types of intervention	**<10%**	**10–20%**	**21–30%**	**31–40%**	**41–50%**	**>50%**	**Excluded results**	**Total no. of studies**
Educational	3 (*1,9,10*)	5 (*2,3,4,7,13*)	1 (*8*)	2 (*5,6*)	1 (*11*)	0	1 (*12*)	13
Educational/ Managerial	3 (*14,24,31*)	2 (*23,27*)	3 (*15,22,28*)	2 (*21,29*)	2 (*20,26*)	4 (*17,18,19,25*)	2 (*16,30*)	18
Managerial	[1] (*24*)	1 (*32*)	[1] (*19*)	1 (*34*)	0	0	2 (*33,35*)	4 [2]
Economic	1 (*36*)	—	—	—	—	—	—	1
Total effect change by intervention type	7 [1]	8	4 [1]	5	3	4	5	36 [2]

Notes: [ ] includes studies that have been categorized under a different section as well. Numbers in italics and parentheses refer to studies as numbered in Appendix 1.

4.2 Analysis of results

Throughout this analysis, numbers in parentheses denote the reference number of the relevant study. The studies that these reference numbers refer to can be found in Appendix 1.

4.2.1 Types of interventions tested

The classification of the interventions was based on the predominant strategy they employed to influence the use of antibiotics by health care providers. It is important to note that while this system presented homogenized categories of intervention studies (e.g. educational or managerial) each intervention had distinct characteristics. For example, while interventions may have applied the same intervention modalities (a training seminar, or development of treatment guidelines) they were likely to have applied different study designs and varying levels of timeframe, intensity, or sophistication. Several interventions, both within and between intervention group types, applied varied multiple strategies. However, classifying the interventions by predominant strategy used enabled a clear presentation of the range of tested strategies aimed at improving the use of antibiotics. The distribution of studies by type of intervention and study design is presented in Table 2. The distribution of studies by primary intervention type and subcategories of interventions with degree of effect is presented in Table 3a–c. As many studies employed multiple interventions, the number of interventions is greater than the number of studies.

Educational interventions were tested in 13 studies (Table 3a). Within these 13 studies there were 10 intervention groups that had a single intervention, of which eight were some kind of training course, seminar, or workshop. One single intervention was community education and one the distribution of a newsletter. In addition there were 18 strategies used in combination with each other. Trainings were combined with community education (*4*) as well as media coverage and peer review (*10*). Face-to-face education was combined with interactive workshops and newsletters (*3*). Seminars and trainings were combined with a newsletter (*1*, *12*), and newsletters were combined with interactive workshops and trainings were combined with peer review (*2*, *6*, *10*, *11*).

Eighteen studies involved some combination of educational and managerial strategy and were thus categorized separately (see Tables 2 and 3b). Ten of these had a community case management approach for improving the treatment of pneumonia (nine studies) and malaria (one study). Overall standard treatment guidelines (STGs) and supervision were the most common interventions: five studies combined providing STGs with training (*19*, *23*, *24*, *25*, *31*), one had a consensual STG building exercise alone (*14*), whereas another combined that with supervision, training, mass education, and conditional supply of drugs and equipment (*17*). Three studies had STGs and mass education, one combining with printed material (*15*) and two combining with training (*25*, *26*). Supervision was combined with training in five (*21*, *22*, *27*, *28*, *30*) and with an STG in addition (18), and with drugs in addition (*20*). One combined regulations with

advocacy and training (*16*). Thus of the 18 study interventions in this section, 14 used STGs and 11 used supervision as managerial interventions combined with 16 using some form of training.

Four studies and two interventions in other studies used purely managerial interventions (Tables 2 and 3c). Audit and review was the most common intervention. It was used alone in two (*33*, *35*), combined with supervision in one (*32*), and used in addition to surveys and planning in one (*34*) and with STGs and discussion in another (*19*). STGs (*24*) with discussions (*19*) made up the others.

The final category of interventions reviewed was economic. Only one study fell under this category (*36*). It focused mainly on the impact of differential drug pricing on prescribing practices and on patients' ability to remember dosing schedules according to the number of dispensed drug items. Although this may be considered to be a managerial intervention, because the intervention was geared less on guiding behaviour and more on providing incentives for behaviour change, it is worthwhile considering this as a separate category.

4.2.2 Targets of interventions: Health care providers, health problems, and practices

The interventions targeted a broad range of health care providers and three major health problems. Some studies targeted health care providers' practices, such as injection use or polypharmacy, across a range of different health problems.

Physician practices were the predominant focus in a majority of the studies (n=22), while the practices of paramedics such as nurses and clinical officers were the target of 25 studies (Table 4). Nine studies targeted some type of community worker, such as village health workers or midwives. The dispensing practices of pharmacists and counter attendants were the subjects studied in one study, while practices of other dispensers such as community drug sellers and storekeepers were studied in another. Lastly, in addition to targeting health care providers, five studies focused on the health and drug use behaviours of communities at which the interventions were targeted.

Overall, 17 studies focused on the treatment of ARI, 14 on diarrhoea, and six on malaria. Only three studies addressed other specific health conditions in addition to one or more of the aforementioned health problems. These were namely hypertension (*14*), urinary tract infection (*16*), and trivial infections (*33*). In addition, six focused on general health conditions and health worker practices.

The most common practice addressed by all the studies was the prescribing of antibiotics in the treatment of ARI, diarrhoea, and malaria. The desired outcome was a change in inappropriate prescribing of antibiotics. In all cases other than for ARI, the desired outcome was a reduction in use as well as in two studies an improvement in dose (*2*, *17*). However, for ARI, very often the goal was to increase the use of antibiotics in children suspected of having pneumonia. The effectiveness of these was measured by looking at the total under-five mortality rate in seven (*15*, *21*, *25*, *26*, *27*, *28*, *29*) and antibiotic use in two (*18*, *31*).

Other prescribing practices including polypharmacy and the use of injections also received some attention, but as they were not directly concerned with antimicrobials we will not consider them further here.

Other important prescribing practices influencing the rational use of drugs, such as the choice of appropriate classes of drugs, of appropriate drugs within a therapeutic class, or the cost-effectiveness of prescribing were not addressed in the studies reviewed.

4.2.3 Outcomes measured

The principal outcomes of interest in the majority of studies were prescribing practices in antibiotic use. Twenty-five of the studies focused on improvement in health care providers' prescribing practices of antibiotics as the major targeted outcome. One focused on the cost of the drugs (*30*), one on treatment according to STGs without measuring antibiotics in particular as well (*32*), and another looked at various prescribing parameters (*16*) (Appendix 1).

Changes in patient outcomes were the second most frequent focus of studies. Of the eight studies that measured this, seven focused on reducing child mortality due to ARI (*15*, *21*, *24*, *26*, *27*, *28*, *29*) and one collected outcome data on the prevalence of malaria in the community (*20*). All of these studies used community case management approaches.

The remaining study, apart from prescribing indicators, targeted patient knowledge on dosing schedules of dispensed drugs (*36*).

Although the majority of interventions were predominantly or partly educational, improvement in knowledge, an implicit consequence of training

or education, was not a major outcome measure targeted by studies. Specific gains in knowledge by health care providers were measured in only six of the studies. Diagnostic skill, another crucial intermediate factor influencing appropriate prescribing practice and arising from improved knowledge, was largely ignored by studies that explicitly measured improved knowledge.

Dispensing practices were the foci of two studies. These studies concentrated on changes in dispensers' knowledge of diarrhoea and ARI treatment (*12*, *23*). Neither of these studies examined the impact of improved dispensing practices on patient outcomes. Improved knowledge and motivation, as well as clinically effective use of drugs, have been identified as some of the crucial changes in patient outcomes arising from appropriate dispensing encounters (Ross-Degnan et al., 1997).

4.2.4 Impacts of interventions

The overall impacts of the interventions on improving at least one targeted outcome was high (Table 5). Of the studies reviewed, 31 reported results from which evaluation of impacts could be made: 12 reported at least one large impact with relevance to antimicrobials (>30% improvement) after implementation of interventions, 12 reported moderate impacts (10–30%), and seven of the interventions had very low impact (<10%). There were five studies for which impacts could not be determined due to incomplete presentation of results included (*12, 16*, *30*, *33*, *35*).

4.3 Evaluating the effectiveness of intervention strategies

4.3.1 Educational interventions

Educational interventions were mainly tested in 13 of the studies (Table 3a). But throughout the 13 studies reviewed there were 28 different educational interventions, of which 10 were a single intervention and 18 were in combination with other educational interventions. We can see from Table 3a that the effectiveness of these single educational interventions was varied. Newsletters alone promoted a 6% change (1). Face-to-face interventions (*13*) promoted a 17% change in the numbers of antibiotics prescribed. Interactive workshops did not show a significant effect in one intervention (*2*) and a 36% change in another (*5*). Seminars helped a 10% change (*13*), whereas trainings caused a 21%, 17%, 9%, and non-significant effect in four different studies (*4*, *7*, *8*, *9*). However, when the effect in study 8 was measured a few months later, the effect was reduced to 6%. An effort in community education (*4*) showed no effect.

Two or more educational interventions together sometimes produced added effect and sometimes did not. When a seminar was added to newsletters (*1*), no greater effect was shown than with newsletters alone (6%). Newsletters in combination with face-to-face education and an interactive workshop (*3*) showed an 18% change, compared to face-to-face alone (*13*), which produced a 17% change. In combination with a training (*12*) and seminars (*1*), newsletters caused no change at all. When an interactive workshop was followed by peer review and then evaluation (*6*) the effect went on increasing from 27% to 29% to 45%. Although community education was not effective alone in study 4, in combination with a training the effect was greater (18%) in the same study, although in study 10 where media and peer review were added to a community education, no effect was found.

The most successful three educational interventions with changes of over 30% reported were all targeting treatment of ARI and diarrhoea in the Mexico Ministry of Health and Social Security health systems. They were, in order of effectiveness, studies 6, 11, and 5. The first was a combination of interactive workshops, peer review, and evaluation; the second a combination of training and peer review; and the third was just an interactive workshop. Interestingly the other intervention with an interactive workshop showed no significant change (*2*). Study 6 achieved both short-term (three months) and long-term (18 months) improvements, whereas the effect of study 11 deteriorated over time, showing perhaps the sustainability of ongoing evaluations.

The level of impact of these studies appeared also to be influenced by the type of facilitator used during the guideline workshops. Greater improvement in practice, for example antibiotic use in ARI, was achieved when national opinion leaders facilitated the guideline workshops (-28.8%) or the facilitation was by health facility staff opinion leaders (-30.6%), compared to facilitation by health system administrators at the state level (-15.5%). This method had a sustainability problem as state-level interventions proved more cost-effective because of their greater scope (Appendix 1).

The next most effective study was a training intervention (*8*) with a 21% effect, but the effect deteriorated to 6% after six months.

Five studies reported reduction of antibiotic use by between 10 and 20% (*2*, *3*, *4*, *7*, *13*). Three of them (*2*, *7*, *13*) had single training, face-to-face education, or interactive workshop interventions, and two had combinations with a newsletter or community education.

Two reported reductions of around 7% (*1*, *10*). They used newsletters and group seminars in one case and intensive community education and doctor training in another. In study 1, Agunawela et al. tested the distribution of five newsletters on five different issues on proper antibiotic use with and without training seminars for prescribers. Both interventions had small but nonsignificant positive impacts on antibiotic use. In study 10, Paredes-Solari et al. used media-oriented approaches (video, market broadcasts) and printed educational materials targeted at the community, in addition to face-to-face visits and dissemination of educational materials for physicians to educate both groups on diarrhoea treatment. These approaches had minimal impact on general drug use for diarrhoea and antibiotic use specifically. Subsequent focus groups with medical officers highlighted possible reasons for the ineffectiveness of the study, including the failure of the training to address key issues such as misunderstandings about drug efficacy or patient preference for injections.

Three showed little effect (*2*, *9*, *12*), even though one used a multimethod workshop, one carried out in-service training, and one trained private pharmacists. In study 2, they used multimethod training covering standard treatment guidelines for ARI, diarrhoea, and malaria. This width may have been the reason for the minimal impact in antibiotic use, although they achieved an impact on improving dosage.

Five studies with moderate impacts focused on a single health problem; either ARI (*4*, *8*) or diarrhoea (*3*, *10*, *13*).

One study compared multimethod refresher training and community education with just refresher training, or just community education (*4*). Researchers found that reductions in community antibiotic use were twice as large (18.8%) with the combined strategy compared to just retraining (8.8%), whereas community education alone had minimal impact.

Another study (Santoso, 1996) compared face-to-face education with a seminar. The face-to-face showed a greater change in antibiotic use (17% versus 10%) but the opposite was true for antidiarrhoeal use where the greater change was in the seminar group. This may, however, be explained by the higher initial level of use.

4.3.2 Combined managerial and educational approaches

Eighteen of the studies were categorized as testing combined educational and managerial interventions (see Table 3b and Appendix 1).

Ten of them, as stated before, used a community case management (CCM) approach where both health workers and the community were targeted. The predominant focus of these studies using CCM intervention strategies was the reduction of childhood mortality due to ARI and malaria through the training of community health workers (CHWs), other health providers, and the community. The two that measured percentage of antibiotic use showed dramatic increases — +85% and +49% in children (studies 19 and 31, respectively). Of the seven that measured child mortality, four showed results over 30% (*15*, *25*, *26*, *29*), two between 25 and 30% (*21*, *28*), and one of 13% (*27*). The study that concentrated on malaria prevalence showed an effect of 48% reduction (*20*).

The remaining eight studies, apart from the 10 mentioned above, showed varied results. Three showed great effect. One with a combination of many different methods (consensus STGs, supervision, trainings, mass education, and conditional provision of drugs and equipment showed a 22% decline in antibiotic prescription and a 69% improvement in antibiotic dose (*17*). Another (22) by combining a multimethod workshop for CHWs and the community with follow-up supervision attained a 29% decrease in antibiotic use. Study 18 concentrated on diarrhoea treatment and dissemination of printed STGs and achieved a large drop in antibiotic use (64%).

For three other intervention studies, consensual STGs (14) or STGs with training plus or minus supervision (*23*, *24*) were not very effective. The first (*23*) was dealing with private drug sellers, who have a strong economic motive to not prescribe rationally, and the second (*24*) tested three strategies within three intervention groups for dissemination of new STGs to health facilities in six districts. The first strategy focused on simple dissemination of the STG booklet during a visit to collect data to measure the WHO drug use indicators. The second combined the dissemination of the booklet with follow-up feedback of baseline performance data and targeted training on identi-

fied problems; and the third combined dissemination of the manual with feedback, training, and additional monthly supervisory visits over a six-month period. Across all 16 indicators tested, including prescribing practice, antibiotic use, and percentage treated according to STGs, the following results were found: simple dissemination had no effect, targeted on-site training had consistent positive effects on performance, and supervision sometimes resulted in additional improvement. The behaviours upon which supervision seemed to have an impact were those that were observable and quantifiable during supervisory visits, such as consulting and dispensing times, or adequacy of drug labelling.

The successful interventions almost all included regular supervision and other administrative/managerial strategies such as drug supply management. Most CCM interventions reviewed here also shared a number of characteristics with successful training interventions such as a focus on a single health problem, multimethod and multisession training approaches, and practical skills orientation. These strategies were also typically reinforced through concurrent community and health worker education.

4.3.3 Managerial approaches

Managerial approaches actually all included some educational work, sometimes through feedback and sometimes through participatory formulations of STGs. One of the managerial studies (*34*) reported a large reduction in injection use (56%) and a large reduction in antibiotic use (32%). Their intervention involved surveys, audit, supervision, and including the medical staff in making plans. In the managerial arm of study 19, the effect of introducing an STG with discussion showed a 10% reduction, but when audit and review were added the reduction increased to 24%.

The studies reporting the largest impacts (of improving at least one outcome measure by over 50%) focused predominantly on improving existing public sector supervisory systems (*32*, *34*). In (*32*), Kafle and colleagues, for example, developed improved guidelines for supervision and monitoring, which were then used by district and public health officers within their various district health posts. The results of supervision and monitoring were incorporated into audits and feedback to prescribers. This strategy yielded a moderate impact of a 19.8% increase of cases treated according to the STGs. The average consulting time was increased by over 50%. In an innovative variation of the supervisory strategy, one study in Indonesia implemented a self-monitoring system in which health centre staff, trained and facilitated initially by district staff, sampled their own prescription records on a monthly basis (Sunartono et al., 1995). The data gathered were then used to track three simple drug use indicators, namely number of drugs prescribed, percentage antibiotic use, and percentage injection use. Over an 18-month period, the number of drugs per prescription declined by 26%, antibiotic use was reduced by 32%, and injection use declined by 56%.

4.3.4 Economic interventions

Only one study reviewed has looked at the effect of charging mechanisms on prescribing practices. Holloway and Gautam (1997) showed that charging by banded items moderately reduces the frequency of prescribing antibiotics and injections compared to charging a flat fee.

5. Discussion

It is remarkable the few numbers of acceptable studies performed in this area. Only 36 studies were found covering all developing countries. Considering the huge problems with antibiotic use in developing countries and the variety of conditions and settings, it is clear that our level of knowledge is not great. However, from these studies we can draw some conclusions about effectiveness of different strategies.

5.1 Effectiveness of different types of interventions

Based on the results of the review, a number of assertions can be made about interventions that are effective in improving antimicrobial use by health care providers in developing countries, as well as those that have proved ineffective.

- Firstly, educational/training interventions, whether conducted in large or small groups, can successfully improve targeted antibiotic prescribing outcomes by an average of 20% or more, if they are well designed. The characteristics of training strategies that have the greatest impact on outcome measures include use of multiple training modalities (such as lectures, group problem-solving, role playing, and practical skills orientation); repeated sessions; single problem focus; on-site training; and use of opinion leaders or district-level staff as trainers. However, where measured, these improvements are not necessarily sustainable over time.
- Secondly, the use of group process approaches among health workers has great potential for improving prescribing practices. Strategies that encourage peer review and peer group commitment to treatment standards, preferably developed by target group or continuing group involvement in peer monitoring, appear to create and sustain change. The group process approach also appears to have a moderate impact on drug use behaviours within patient and community groups when group process encounters between community members and health workers are participatory and interactive. The strategy that seems to achieve low impact on practice, when used alone, is the use of individual involvement in the development and definition of treatment norms.
- Thirdly, supervision or performance monitoring using indicators or simple protocols in combination with audit and feedback of performance indicators to prescribers has proved to be highly effective in improving specific practices. Combining these approaches with the peer group development of new guidelines or the improvement of existing ones, or active dissemination of guidelines through staff training, has also resulted in considerable improvement in compliance with treatment guidelines. Overall some ongoing activity such as supervision, data feedback, or peer review is needed to sustain the intervention effect.
- A strategy that has consistently failed to cause measurable improvements in behaviour is the simple dissemination of printed clinical guidelines or unbiased drug information.
- Finally, the community case management approach has produced clear evidence of effectiveness in reducing child mortality from ARI or diarrhoea. The combination of single health problem focus, multimethod, and multisession training approaches with simultaneous supervision and drug supply management and concurrent community and health worker education has the practical advantage of addressing the multiple dynamics of child health and childhood diseases. A critical issue that was neglected by all but one of the studies using the CCM approach is the impact of the approach on health care providers' prescribing practice, particularly with the treatment of ARI, and the implication of this on their treatment of other health problems or on long-term patterns of community antibiotic use. Since the desired outcome of the compliance with WHO ARI guidelines (used by all the studies) was an increase in the pre-

scribing of preferred antibiotics, could compliance with ARI treatment guidelines lead to increased prescribing and use of antibiotics for other conditions and encourage the development of antibiotic resistance? The possibility of such carry-over effects demands examination.

5.2 Neglected issues

5.2.1 Settings

The majority of studies were carried out in public health settings, leaving private sector practices virtually unexamined.

Drug sellers. More than 80% of people when sick use drug sellers or pharmacists but only two of these studies address drug shops. Of the two studies that did concentrate on private pharmacies, Podhipak et al (*12*) with an educational intervention showed very small changes whereas Kafle (*23*) showed some positive effect.

Hospital inpatients. Only three studies addressed hospitals directly. Given the volume and cost of antimicrobials used in inpatient settings, and the risk of the development of resistant organisms, the dearth of hospital-based studies is remarkable. The development of multiple drug resistance to such bacteria as *Pseudomonas*, *Streptococcus aureus*, *Enterococci*, and *Staphylococcus aureus* is a cause of serious infections in hospitalized patients. Treating antimicrobial-resistant infections generally requires the use of more expensive or more toxic drugs and can result in longer hospital stays. Alternatives can not only be more expensive but can also not be approved for use in special populations, such as children, rendering management of an otherwise common infection difficult.

Private sector doctors in outpatient settings. No studies addressed this part of the health sector.

Patient and community use. Apart from the community case management interventions for ARI, in the relatively rare occurrence that drugs are prescribed correctly in the right dose we know nothing of the compliance of the public in taking the prescribed drugs.

In particular we have no examples of case studies to find the determinants of poor use and any examples of interventions to change this. Thus very little is known about whether and under what circumstances interventions directed at prescribers and dispensers and changes in their practices result in better patient outcomes.

Dispensing encounters, for example, have been identified as crucial mediums for educating patients and motivating them to use drugs in clinically effective ways (Ross-Degnan et al., 1997). In this context, it would be useful to know how improved communication from dispensers influences intermediate patient variables such as knowledge about disease and treatment, satisfaction with treatment, and eventual compliance with recommended therapy.

These points only serve to highlight gaps in the sample of studies, emphasizing their narrow focus on a few types of inadequate use outcome measures.

5.2.2 Conditions

The majority of studies focused on three health conditions: ARI, diarrhoea, and malaria. Although it is recognized that these are a major cause of death in children, other important conditions for which antimicrobials are used include tuberculosis, hepatitis B, various sexually transmitted diseases, and AIDS. In fact, by 1990, nearly every common pathogenic bacterial species had developed varying degrees of antimicrobial resistance. Knowledge of all the conditions for which antibiotics may be used may contribute to the development of strategies to improve diagnosis and disease management, as well as the development of guidelines and other interventions.

5.2.3 Cost-effectiveness

With the exception of one study that highlighted the cost-effectiveness of the small group training over the formal seminar (Santoso, 1996), none of the studies assessed the cost-effectiveness of their interventions. In order to select among different possible strategies for improving similar antibiotic use problems as well as justifying the use of a particular intervention strategy over another within the health system, data on cost-effectiveness is essential. The development of simple standardized approaches can aid the collection of data on cost-effectiveness and the selection of other feasible and relevant effectiveness measures.

5.3 Limitations of this review

While this review has highlighted the relative strengths and weaknesses of selected interventions and their impacts on antimicrobial use, it is important to note that like the majority of literature reviews, it has a number of methodological limitations.

Firstly, this collection of intervention strategies is not exhaustive, despite intensive attempts to create a comprehensive database of relevant studies. The exclusive focus on studies obtained from MEDLINE and only two key institutional archives necessarily excludes studies reported or published in other contexts.

Secondly, the availability and quality of evaluation studies on activities targeted at improving antimicrobial use affect the proportions that end up in reviews such as these. Generally, the impacts of countless activities such as training courses, development of drug formularies and bulletins, and drug supply improvements are not known because they are often not evaluated. For those that get evaluated, a substantial number of attempts employ inadequate research designs that affect the validity of findings. This review set a specified inclusion criteria for research designs based on knowledge on methodologically accepted designs. While this strategy was used to obviate the more comprehensive process of reviewing all studies and then evaluating the evidence of only those with acceptable designs, it resulted in the exclusion of studies that may well have provided critical background and supplementary information on the research area. Furthermore the more comprehensive process may have had the advantage of building a strong documented case for evaluating only studies with acceptable designs, by highlighting the failings of methodologically inadequate studies. Ten studies that matched all inclusion criteria except for appropriate research design were excluded from the final selection process for this review.

Finally, conducting a comparative analysis of interventions with diverse objectives, strategies, and outcomes is a problematic process. The majority of selected interventions in this review are multidimensional and the process of homogenizing distinct modalities into broad categories ("community case management" or "group process") for the purposes of comparison presents problems for comprehensive analysis. Furthermore, while the development of a metric to compare effect sizes across studies is helpful, it is a technically and conceptually limiting way of measuring the absolute magnitude or the importance of studies documenting multiple impacts.

Limitations notwithstanding, this review has highlighted critical information on interventions to improve the use of antibiotics by health care providers in developing countries.

6. Conclusion

The issues of antimicrobial misuse are of global concern, not least because of the spreading and developing resistance of most common bacteria to most inexpensive generic antibiotics. Therefore, methods to improve their use in a sustainable and cost-effective way are of crucial importance.

However, exploring interventions to improve antimicrobial use is, in fact, exploring methods applicable to the wider issues of rational drug use for acute care drugs. This review has shown that the same lessons are learned and therefore we need to build on the work already done. The major findings of this paper are not essentially different from the review of all interventions for all drug use prepared for the International Conference on Improving Use of Medicines (Ross-Degnan, 1997).

Answers are urgently needed to the crucial question: If I am a manager in a health area, what interventions can I use to improve antibiotic use? This review has helped answer that in some respects, but not in others. Within the public sector there are a range of possibilities, although issues of cost-effectiveness have not been addressed. However, in the private sector, the community, private pharmacies, and hospitals, there is almost no information and a clear need for further research exists.

Appendix 1

Characteristics of intervention studies

Reference and number	Region	Design	Target group	Target condition	Setting	Sample size	Intervention (characteristics)	Outcome measures	Size of effect
EDUCATIONAL INTERVENTIONS									
Angunawela et al. (1991)	Asia	RCT	Prescribers	AB use for all conditions	Public sector: OPDs in PHC units	15 OPDs (2 IG,1 CG): 43 prescribers (E1-12, E2-16, C-15)	E1.5 newsletters on 5 different issues on proper AB use,	% AB use	ΔE1: 31.5%→24.1%= -7.4%
							E2.reinforced by group seminar (1 3-hr session per 7-8) (E2)		ΔE2:38.8%→31.5%= -7.3% (ΔC:32.2%→31.8%=-0.4%)
1									
Bexell et al. (1996)	Africa	RCT	Prescribers, physicians, clinical officers	Pre-scribing practice re malaria, diarrhoea & ARI	Public sector: PHC facilities (Lusaka, Zambia)	16 PHC : 8E, 8C 26 prescribers in each group	2-day multimethod training seminars: group self-audit, case studies, individual homework, group work, lectures	Correct drug given	ΔE: 52.5%→69% = 16.5% ΔC: 43%→57% = 14%
								Correct dosage given	ΔE: 43% →57% = 14% ΔC: 41% →38% = -3%
								Use of anti-biotics	ΔE: 48.9%→49.1%= +0.2% ΔC: 46.6%→48.5%= +1.9%
2								Use of injections	ΔE: 11.9%→12.6%= +0.7% ΔC: 13.1%→11.2%= -1.9%
Gani et al. (1995)	Asia	PP&C	Prescribers, physicians, paramedics	Acute diarrhoea	Public health centres	95 Prescribers 37E from 3 districts 58C from 5 districts	Workshop on clinical management and communication. Distri-bution of leaflets and scientific literature for face-to-face encoun-ters with physicians	% AB prescribed	ΔE:46%→28% = + 18% ΔC: 32%→32% = 0%
								% ORS prescribed	ΔE: 35%→53% = +18% ΔC: 51%→48% = -3%
3									
Gonzales Ochoa et al. (1996)	Latin America	RCT	Prescribers (physicians) community	ARI	Health clinics	4 health areas (A,B,C,D): 10 clinics per area	Area A (E1): refresher training programme & comm. ed.	% AB use in community for mild ARI	ΔE1: 26.6%→7.8% = -18.8%
							Area B (E2): refresher training		ΔE2: 20.6%→11.7% = -8.8%
							Area C (E3): comm. ed.		ΔE3: 11.4%→12.3% = +0.9%
4							Area D (C): control		ΔC: 19.6%→20.3% = + 0.7%
Guiscafre et al. (1988)	Latin America	PP&C	MDs	Diarrhoea	2 PHCs	69 MDs (36E; 33C)	Workshop using active participative edu-cating techniques	% use of antibiotics	ΔE: 76.3%→40.6% = -35.7%
								% use of restrictive diets	ΔE: 33.5%→62.3% = +28.8%
5								% use of ORT	ΔE: 53.5%→88.3% = +34.8%
Gutierrez et al. (1994)	Latin America	PP&C	Physicians	Diarrhoea	PHC units of Min. of Health & Social Security (Mexico City)	40 physicians (20E, 20C)	1. Baseline study of Rxg practices of MDs	% AB use	ΔE: 78.8%→39.3% = -39.5%
							2. Multimethod training workshop	% use of restrictive diets	ΔE: 47.3%→12.4% = -34.9%
							3. Post-workshop evaluation		
							4. Peer review to discuss Tx behaviour of MDs	% ORT use	ΔE: 31.4%→58.4% = +27%
6									

Reference and number	Region	Design	Target group	Target condition	Setting	Sample size	Intervention (characteristics)	Outcome measures	Size of effect
EDUCATIONAL INTERVENTIONS									
6 (cont'd)							5. Mid-term evaluation at 2 months 6. Long-term evaluation at 6, 12, and 18months	% cases treated according to algorithm	(after workshop) ΔE: 31.3%→60.5% = +29.2% (after peer review committee) ΔE: 31.3%→76.5% = +45.2% [no modification of Rxg behaviour or cases Txd according to algorithm in C throughout study]
Hugh and Corrales (1996) **7**	Latin America	TS-C	MDs, paramedics	ARI	Public health centres at municipal level	Physicians at each health centre in 5 municipalities	MDs trained to facilitate process of improving ARI diagnosis and Tx in municipalities	% AB use	ΔE: 48.8%→31.4% = -17.4%
Naivalulevu (1990) **8**	Asia	TS	Prescribers, physicians, paramedics	ARI	Public sector: all health centres in Western regional division	All health facilities (~2000 ARI cases)	Training workshops on ARI case management	% AB use for ARI	At 3 months: 43%→22% = -21% At 9 months: 43%→37% = -6%
Ofori-Adjei and Arhinful (1996) **9**	Africa	PP&C	Medical assistants (MAs)	Malaria	Public health centres	60 MAs 20 with early training E1; 20 with later training E2; 20 with no training C	In service training in malaria treatment using case histories and case presentations	% use of chloroquine (CQ) injection % of std. WHO CQ dose for 2-year-old	ΔE1:17.0%→15.9%= -1.1% ΔE2:16.9%→15.6%= -1.3% ΔC: 19.9%→18.3%= 1.6% ΔE1: 191%→203 = +12% ΔE2: 198%→169% = -29% ΔC: 185%→135% = -50%
Paredes-Solari et al. (1996) **10**	Latin America	PP&C	Physicians, community	Diarrhoea	Periurban area in Lima, Peru	2 periurban areas	Intensive community intervention (video, market broadcasts, print materials), plus face-to-face visits, booklets, & Rx pads for MDs	Drug use for diarrhoea (all cases) % AB use (all cases) Drug use for diarrhoea (case seeing MD)	ΔE: 43.1%→33.3% = -9.8% ΔC: 48.8%→41.95 = -6.9% ΔE: 25.5%→17.9% = -7.6% ΔC: 29.3%→21.4% = -8.9% ΔE: 94.6%→84.9% = -9.7% ΔC: 92.4%→91.9% = -0.5%
Perez-Cuevas et al. (1996) **11**	Latin America	PP&C	MDs	ARI	Public PHC facilities	4 Mexican Social Security Institute [I] (32E; 36C) 14 Min. of Health [S] (33E; 18C)	Workshop (1wk 2hr daily sessions) using interactive educational techniques co-facilitated by physician instructors who received 1wk training, followed by peer review	% AB use (6 month follow-up) % following STG (18 month follow-up)	ΔS/E: 85.2›48.1% = -37.1% ΔS/C: 97.1%›86.5% = -10.6% ΔI/E: 68.8%›49.1% =19.7% ΔI/C: 95.7%›96.9% =+1.2% ΔS/E: 35.7%›40.9% = +5.2% ΔS/C: 30.5%›31.0% = +0.5% ΔI/E: 30.0%›54.2% =+24.2% ΔI/C: 19.0%›21.0% =+12.0%
Podhipak et al. (1993) **12**	Asia	PP&C	Pharmacists, drug sellers	Diarrhoea	Private sector drugstores (Bangkok)	3 subdistricts (300 drugstores) E: 120 type-1 DS, 60 type-2 DS C: 50 type-1 DS, 60 type-2 DS	3-hour training course for pharmacists (educational material w/ follow-up call for non-attendees) Educational material by mail w/ follow-up call for drug sellers	% changes in pharmacists and drug sellers Rxg ORS, antibiotics and anti-diarrhoeal drugs for diarrhoea and dysentery	Results NS although a standard effective % change indicated some practices showed slight yet favourable change in sample groups. Antibiotics and anti-diarrhoeal drug uses were slightly changed (unfavourably in some instances)

Reference and number	Region	Design	Target group	Target condition	Setting	Sample size	Intervention (characteristics)	Outcome measures	Size of effect
EDUCATIONAL INTERVENTIONS									
Santoso (1996 **13**	Asia	RCT	MDs, paramedics	Diarrhoea	District health cenres	90 HCs in 6 districts. 30 face-to-face int.; 30 formal seminar; 30 C	1. Face-to-face small group intervention on appropriate diarrhoeamanagement 2. Two hr seminars on same subject	% antimicrobial use % antidiarrhoeal use Change in levels of knowledge re diarrhoea Tx	ΔE1:77.4%→60.4%=-17.0% ΔE2: 82.3%→72.3%= -10% ΔC: 82.6%→79.3% = -3.3% ΔE1: 20.3%→12.5%= -7.8% ΔE2: 48.5%→27% = -21.5% ΔC: 21.1%→20.7% = -0.4% ΔE1: 4.79→7.55 ΔE2: 4.37→7.44 C: no data
EDUCATIONAL / MANAGERIAL									
Agyepong et al. (1996) **14**	Africa	RCT	Physicians, paramedics	Malaria, ARI, diarrhoea, hypertension	PHC facilities	30 urban PHC facilities (15E, 15C)	Develop consensus Tx norms in workshops with staff of each H facility facilitated by experts	% AB use % injection use % generic drug Rxg	ΔE: 53.4 %161.7 % =+8.3% ΔC: 43.4%→61.0% =+17.6% ΔE: 45.4%→41.7% = -3.7% ΔC: 43.4%→46.8%=[+5.4%] ΔE: 75.2%→84.0% = +8.8% ΔC: 83.5%→82.1% = -1.4%
Bang et al. (1990) **15**	Asia	PP&C	Paramedics, village health workers, traditional birth attendants	Pneumonia	Public sector: PH centres (Gadchi-roli, India)	2 PH centres within contiguous area of 120 villages	Mass education on childhood pneumonia and case management, training to aid recognition of childhood pneumonia and Tx w/ co-trimoxazole	Pneumonia-specific childhood mortality (rate/1000) Infant mortality (rate/1000) Total under-five mortality	Post: E - 8.09 C - 17.5 Post: E - 89 C - 121 Post: E - 28.5 C - 40.7
Carandang et al. (1997) **16**	Asia	TS+C	Prescribers	ARI, UTI	Private and public hospitals (Metro Manila, Philippines)	10 gov't hospitals, 10 private tertiary and secondary hospitals	Point 1: Advocacy, education, and distribution of information Point 2: Full implementation with penalties Point 3: Period of sustainability/levelling off	(1) Av No. drugs/case (2) % Rx generic drugs (3) % drugs in EDL (4) % drug Rxd as single agent	(1) higher in private hosps. (2) and (3) w/ respect to both ARI and UTI increased during advocacy, monitoring and sanctions but declined over time—higher in gov't hosps. No variation in (4) between type of hosp, but higher in ARI. Results NS.
Chalker and Phuong (1997) **17**	Asia	TS	Health workers	Antibiotic prescribing	Public PHC facilities (Commune health stations)	217 PHC facilities in 12 districts (pop 1.6 million)	HWs retrained and assisted in making STGs and short EDLs plus regular supervision by district staff	% patients receiving antibiotics % patients receiving adequate AB doses	67.7%→45.3 = -22.4% 29.9%→98.4% = +68.5%
Chowdhury et al. (1995) **18**	Asia	RCT	Prescribers, physicians	Diarrhoea	Public sector Thana health complexes (THC)	18 THCs (72 doctors; 4/THC) E1 (STG), E2 (STG and small group training), C	E1. Dissemination of printed STG for diarrhoea management and treatment E2. Brief small group training ORS corners set up in all THCs during intervention period.	% treated according to STG % receiving antibiotics	ΔE1: 29.3%→91.1% =+61.8% ΔE2: 22.8%→95.3% = +72.5% ΔC: 31.1%→85.5% = +54.7% ΔE1: 70.1%→8.9% = -61.2% ΔE2: 65.0%→1.1% = -63.9% ΔC: 66.3%→15.3% = -51.0%

Reference and number	Region	Design	Target group	Target condition	Setting	Sample size	Intervention (characteristics)	Outcome measures	Size of effect
EDUCATIONAL / MANAGERIAL									
Chowdhury, et al. (1996) **19**	Asia	PP&C	Physicians	ARI	Thana (sub-district) health complexes	E (1 THC) C (1 THC)	ARI case management [auditing and analysing of prescriptions for ARI served by the doctors]	Average no. drugs used	ΔE: 3.48→2.10 = +1.38 ΔC: 3.68% [post]
								% prescribers following STG	ΔE: 7.0%→94% = +87% ΔC: 9.0% [post]
								Antibiotic use	ΔE: 10.0%→95.0% = +85% ΔC: 9.8% [post]
								Prescribers using drugs from EDL	ΔE: 55.0%→93.0% = +38% ΔC: 57.0% [post]
								Generic prescribing	ΔE: 51.5%→81.0% = +29.5 ΔC: 48% [post]
								Mortality rate	ΔE: 10%→1.6% = -8.4% ΔC: 12.0% [post]
Delacollete et al. (1996) **20**	Africa	PP&C	CHWs, community	Malaria	Rural health zone	E (13 000 pop; 12 CHWs) C (14000 pop)	Malaria case management (training CHWs, drug supply, supervision)	Mean prev. acute malaria	ΔE: 143→74 = -48.3% ΔC: 121→109 = -9.9%
								% untreated cases	ΔE: 31%→24% = -7% ΔC: 20%→28% = +8%
Fauveau et al. (1992) **21**	Asia	PP&C	Paramedics, CHWs	ARI	Rural sub-district	E: 1/2 district (110 CHWs) C: 1/2 district	ARI case management (training of CHWs and paramedic supervisors, bi-weekly home visits, home Tx, referral)	ARI< 5 mortality rate (/1000)	ΔE: 4.7→3.2 = -31.9% ΔC: 6.5→6.1 = -6.2%
								ARI< 1 mortality rate (/1000)	ΔE: 13.0→9.1 = -31.5% ΔC: 15.5→16.0 = +3.2%
Hetta and Lundstrom (1984) **22**	Africa	TS-C	CHWs, community	Diarrhoea	Community rural districts	All CHWs in 2 rural health districts	4-day multimethod (drama, audio demos, flipcharts, handbills, educational demos) on Tx / prevention of diarrhoea plus follow up supervision	% sulfonamide use	ΔE: 51%→22% = -29%
								% ORS use	ΔE: 50%→72% = +22%
Kafle (1998) **23**	Asia	PP&C	Drug retailers	Diarrhoea, ARI	District drug retail shops (Nepal)	352 retailers from 12 districts, 4 study groups E1,E2,E3,C	(1) Small group face-to-face training [E1] plus reinforcement material [E2] (2) Audit feedback via mail [E3]	Referral practices	**Diarrhoea:** ΔE3: 5.8→5.0 = -0.8 ΔC: 2.3→11.3 = +9 **ARI:** ΔE1: 15.5→27.0 = +11.5 ΔC: 4.6→16.3 =+ 11.7
								Dispensing practices: % antimicrobial dispensed	**Diarrhoea:** ΔE1= 58.3→39.2 = -19.1 ΔC= 59.3→30.0 = 29.3 **ARI:** ΔE1: 15.5→27.0 = +11.5 ΔE2: 18.6→28.8 = +10.2 ΔE3: 17.5→22.2 = +4.7 ΔC: 31.5→17.5 = -14
								Knowledge (of severe dehydration in diarrhoea)	ΔE2: 5.8→38.4= 32.6 ΔC: 15.1→21.0 = 5.9
								(of severe ARI-pneumonia)	ΔE1: 42.8→63.1 = +20.3 ΔC: 51.1→46.5 = +4.6 [NS results not shown].

Reference and number	Region	Design	Target group	Target condition	Setting	Sample size	Intervention (characteristics)	Outcome measures	Size of effect
EDUCATIONAL / MANAGERIAL									
Kafuko et al. (1996) **24**	Africa	RCT	Prescribers, physicians, paramedics	Diarrhoea, malaria, Rxg and dispensing for all conditions	126 district health units (HUs) from 4 regions of Uganda	E1: 42 HUs E2: 29 HUs E3: 14 HUs C: 42 HUs	Dissemination of national standard treatment guidelines alone (E1) plus timely feedback and target training of health workers (E2); plus 6 month support supervision (E3)	# drugs Rxd % cases given antibiotics % treated according to NSTGs	ΔE1: 2.37→2.45 = +3.4% ΔE2: 2.35→2.09 = -11.1% ΔE3: 2.39→2.14 = -10.5% ΔC: 2.45→2.45 = -0.0% ΔE1: 51.6→57.8 = + 6.2% ΔE2: 51.7→50.7 = - 1% ΔE3: 54.3→54.3 = 0.0% ΔC: 53→58 = +5.0% ΔE1: 24.8 %→32.3% = +7.5% ΔE2: 24.0%→52.0% = +28.0% ΔE3: 21.4%→55.2% = +33.8% ΔC: 24.8%→29.9% = + 5.1%
Khan et al. (1990) **25**	Asia	PP&C	CHWs	ARI	Community	38 villages (31 E1, 7C which crossed over in year 2 as E2)	ARI case management training workshops, plus community education through CHWs.	ARI < 5 mortality rate (/1000)	ΔE1: 8.6→4.0 = -53.5% ΔC: 14.4→14.5 = +1.5% ΔE2: 14.5→6.5 = -55.2%
Lucero et al. (1994) **26**	Asia	TS+C	Physicians, paramedics, CHWs	ARI	Public sector, PHC. Communities on island of Bohol	8 municipalities E: 4 municipalities C: 4 municipalities	3 bi-annual ARI case management training workshops plus community education through CHWs (and assisting midwives)	All cause < 5 mortality rate (/1000 person-yr)	ΔE: 18.5→9.5 = -48.6% ΔC: 16.5→12.5 = -24.2
Mtango et al. (1986) **27**	Africa	RCT	CHWs, paramedics	ARI	Community	72 villages (36 E, 36 C which crossed over as E2 during phase II of intervention)	ARI case management programme (training CHWs, household visits [6-8 wks], home Tx, referral, training HC and dispensary workers to strengthen services at referral level)	Pneumonia < 5 mortality rate (/1000)	ΔE1 post = 32.4→29.2 ΔC/E2 post 40→35.0 = -12.8%
Pandey et al. (1991) **28**	Asia	TS+C	CHWs	ARI (pneumonia)	Communities, households with children under 5 (in Jumla District)	18 subdistricts	ARI case management programme (CHW small group training, household visits every 2 wks, home Tx, biweekly supervisory visits)	All cause < 5 mortality rate (/1000) Pneumonia <5 mortality rate (/1000)	RR in yr 3 = 0.72 = -28% RR in yr 3 = 0.70 = -30%
Reddaiah et al. (1991) **29**	Asia	PP&C	CHWs (multi-purpose workers)	ARI	Public PHC facilities (Ballabgarh block, Haryana State)	1E (~ 5000 under-5s) & 1C (~9000 under-5s) community	Pilot ARI case management programme (train CHWs, monthly refresher, immunization)	All cause < 5 mortality rate (/1000) ARI < 5 mortality rate (/1000)	ΔE: 30.3→18.9 = -37.6% ΔC: 20.4→18.5 = -9.3% ΔE: 5.0→3.7 = -26.0% ΔC: 4.4→5.0 = +13.6%
Widyastuti et al. (1997) **30**	Asia	RCT	Physicians, paramedics	ARI, diarrhoea	Primary health care facilities	20 HCs and auxiliary HCs in 3 intervention and 2 control districts	– Drug use training for physicians and paramedics (interactive problem-solving and problem-based learning – polypharmacy, antibiotics, injection use) – Supervision (integrated team	Per-case cost saving after intervention	E (ARI) - 59% E (Drh) - 68% C (ARI) - 10% C (Drh) -7% [results poorly presented]

Reference and number	Region	Design	Target group	Target condition	Setting	Sample size	Intervention (characteristics)	Outcome measures	Size of effect
EDUCATIONAL / MANAGERIAL									
30 (cont'd)							approach, integrated supervisory guidelines on drug use/management indicators)		
Wiedenmayer (1996)	Africa	RCT	Prescribers	Prescribing practices	Public sector facilities	20 health facilities (10 E; 10 C)	New STGs distributed via introductory and continuing education workshops for in-service charges.	% injections % AB Rxd % AB Rxd in children <5 w/ diarrhoea % compliance with STG % correct prescribing	30%→32.7% = 2.7% 38.3%→35.3% = 3% 25.6%→75% = 49.4% 73.7%→76.3% = 2.6%
31									
MANAGERIAL INTERVENTIONS									
Chowdhury (1996) (ALSO M&E)	Asia	RCT	Physicians	ARI	H facilities	24 H facilities (8E, 8C)	Visit to disseminate and discuss ARI STG (E1)	% receiving AB for ARI	ΔE1: 85.9%→75.7% = -10.2%
19							with Rx audit and review (E2)		ΔE2: 91.8%→67.8% = -24.0% ΔC: 89.3%→81.5% = -7.8%
Kafle et al. (1995)	Asia	RCT	Prescribers	Prescribing	Public PHC facilities	E (3 districts) C (6 districts) 7 health posts per district	Supervision/monitoring by district health office/provincial health office 1 & 3 months after baseline using guidelines developed by research team	% cases treated according to STG average consulting time (in secs.)	ΔE:26.9→40.5= +13.6 ΔC: 28.4→22.2 = -6.2 ΔE: 121→141 = +20 ΔC: 178→132 = -46
32							Audit/feedback to prescribers post supervision	% cases with injection, antibiotics	Some improvement but NS
Kafuko et al. (1996) (ALSO M&E)	Africa	RCT	Prescribers, physicians, paramedics	Diarrhoea, malaria, Rxg and dispensing for all conditions	126 district health units from 4 regions of Uganda	E1: 42 HUs E2: 29 HUs E3: 14 HUs C: 42 HUs	Dissemination of national standard treatment guidelines alone (E1)	# drugs Rxd	ΔE1: 2.37→2.45 = +3.4% ΔE2: 2.35→2.09 = -11.1% ΔE3: 2.39→2.14 = -10.5% ΔC: 2.45→2.45 = -0.0%
							plus timely feedback and target training of health workers (E2)	% cases given antibiotics	ΔE1: 51.6→57.8 = + 6.2% ΔE2: 51.7→50.7 = - 1% ΔE3: 54.3→54.3 = 0.0% ΔC: 53→58 = +5.0%
							plus 6-month support supervsion (E3)	% treated according to national standard treatment guidelines	ΔE1: 24.8 %→32.3% = +7.5% ΔE2: 24.0%→52.0% = +28.0% ΔE3: 21.4%→55.2% = +33.8% ΔC: 24.8%→29.9% = +5.1%
24									
Ogwal-Okeng et al. (1997)	Africa	RCT	Physicians, paramedics	Malaria, trivial infections	Regional referral and teaching hospitals	7 hospitals	Feedback of baseline and interim survey results via face-to-face discussion with prescribers	Freq. antimicrobial use No. drugs prescribed per case	Results not adequately presented
33							Evaluation of hospitals	No. antimicrobials prescribed per case	

Reference and number	Region	Design	Target group	Target condition	Setting	Sample size	Intervention (characteristics)	Outcome measures	Size of effect
MANAGERIAL INTERVENTIONS									
Sunartono et al. (1995) **34**	Asia	TS-C	MDs, paramedics	Injection antibiotic use, polypharmacy	Public health centre	29 public health centres	1. Monthly survey of cases on 3 prescribing indicators 2. Monthly observation of paramedics' clinical encounters by managers 3. Monthly interviews with patients 4. Monthly discussion about findings Develop and implement process for monthly self-monitoring of Rxg practice indicators	Change in prescribing: % use of injections % use of antibiotics % use of polypharmacy	 76%→20% = -56% 63%→31% = -32% 4.2%→3.1% = -1.1%
Thuo (1997) **35**	Africa	PP&C	Prescribers	Rational drug use	Inpatient care settings (hospitals)	Not clearly stated	E: feedback on analysis of treatment records C: participatory discussions	No. of antibiotics per patient No. of injections per patient	Tables unhelpful
ECONOMIC INTERVENTIONS									
Holloway and Gautam (1997) **36**	Asia	PP&C	Prescribers, community	Rational drug use	Public PHC facilities (Eastern Nepal)	30 health posts (HPs) and 3 hospitals in 3 districts. E1(9HPs, 1Hosp) E2 (10HPs, 1 Hosp) C (11 HPs, 1 Hosp)	Baseline: all districts charged flat fee covering full course of all drugs E1: 1-band item fee E2: 2-band item fee C-flat fee	1. INRUD/ WHO Rxg indicators: a. No. items per Rx b. % Rx w/ ABs c. % Rx w/ injections d. % Rx conforming to STG 2.% patients able to remember dosing schedules per number of dispensed items	 DE1: 2.6 Æ 1.8 = -0.8 DE1: 2.5 Æ 2.0 = -0.5 DC: 2.7 Æ 2.7 = 0 DE1: 56.8 Æ 49.7 = -7.1% DE2: 53.5%Æ46.2% =-7.3% DC: 57.6%Æ65.7% =+8.1 DE1: 6.9%Æ14.2%=-2.7% DE2: 25.2%Æ15%=-10.2% DC: 22.5%Æ19.8%=-2.7% DE1: 1.5% Æ48.7%= +17.1% DE2: 31.2% Æ47.7% = +16.5 DC: 23.5% Æ26.2% = +2.7% 1 item: E1-76%; E2-78%; C-74% 2 items: E1-65%; E2-54%; C-66% 3 items: E1-36%; E2-34%; C-48%

AB – antibiotic; **ARI** – acute respiratory infection; **CG** – control group; **CHWs** – community health workers; **DS** – drugstore; Dx – diagnosis; **ED** – essential drugs; **EDL** – essential drugs list; **EDP** – essential drugs programme; **EG** – experimental group; **H** – health; HCs – health centres, health posts, etc.; **IG** – intervention group; **NS** – non-significant; **OPD** – outpatient department; **ORS** – oral rehydration salts; **Paramedics** – nurses, clinical officers, medical assistants, etc.; **Rx** – prescription; **Rxg** – prescribing; **STG** – standard treatment guideline; **Tx** – treatment.

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