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Improving the Prescription and Use of Antibiotics in Low and Middle-Income Countries: How effective and cost-effective are behaviour change interventions?

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Complete List of Authors:	Batura, Neha; University College London, Institute for Global Health Cuevas, Carla; UCL Centre for Global Health Economics Khan, Mishal; London School of Hygiene and Tropical Medicine Wiseman, Virginia; The University of New South Wales, School of Public Health and Community Medicine; LSHTM, Health Ecoomics
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Systematic Review Protocol: Improving the Prescription and Use of Antibiotics in Low and Middle-Income Countries: How effective and cost-effective are behaviour change interventions?

Neha Batura, Carla Cuevas, Mishal Khan, Virginia Wiseman

Neha Batura (corresponding author)
Institute for Global Health
University College London
30 Guilford Street
London WC1 1EH
United Kingdom
Email: n.batura@ucl.ac.uk

Carla Cuevas
UCL Centre for Global Health Economics
Email: carla.cuevas.15@alumni.ucl.ac.uk

Mishal Khan
London School of Hygiene and Tropical Medicine
Email: mishal.khan@lshtm.ac.uk

Virginia Wiseman
London School of Hygiene and Tropical Medicine and University of New South Wales
Email: virginia.wiseman@lshtm.ac.uk

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Abstract

Introduction: Antibiotic resistance endangers effective prevention and treatment of infections and places significant burden on patients, families, communities and healthcare systems. Low- and middle-income countries (LMICs) are especially vulnerable to antibiotic resistance, owing to high infectious disease burden, and limited resources for treatment. High prevalence of antibiotic prescription and use due to lack of provider's knowledge, prescriber's habits, and perceived patient needs further exacerbate the situation. Interventions implemented to address inappropriate prescription and use of antibiotics in LMICs must address different determinants of antibiotic resistance through sustainable and scalable interventions. The aim of this protocol is to provide the methods that will identify behaviour change interventions implemented in LMICs to improve prescription and use of antibiotics; and appraise their effectiveness and cost-effectiveness.

Methods and analysis: Two databases (Web of Science, and PubMed) will be searched based on a strategy developed in consultation with an essential medicines and health systems researcher. Additional studies will be identified using the same search strategy in Google Scholar. To be included, a study must describe a behaviour change intervention and use experimental design to estimate effectiveness and/or cost-effectiveness in a LMIC. Following systematic screening of titles, abstracts and keywords, and full-text appraisal, data will be extracted using a customized extraction form. Studies will be categorised by type of behaviour change interventions and experimental designs. A meta-analysis or narrative synthesis will be used as appropriate along with an appraisal of quality of studies using the GRADE checklist.

Ethics and dissemination: No individual patient data is used, so ethical approval is not required. The systematic review will be disseminated in a peer-reviewed journal and presented at a relevant international conference.

Systematic review registration: PROSPERO **CRD42017075596**

Keywords: Antibiotic resistance, behaviour change, systematic review, protocol, public health

Strengths and limitations of this study

Strengths:

- The proposed systematic review, to our knowledge, that focuses solely on low- and middle-income countries which are especially vulnerable to antibiotic resistance

- This study will focus on behaviour change interventions only and will be rooted in behaviour change theory in order to identify potential policies that can support implementation and delivery of the intervention functions appropriate for these settings

Limitations:

- It is anticipated that the effectiveness and cost-effectiveness outcomes of the included data might be too heterogeneous to conduct a meta-analysis; if so, a narrative synthesis of evidence will be carried out.

Introduction

Antibiotic resistance (ABR) is recognized as one of the greatest threats to human health [1, 2]. It endangers the effective prevention and treatment of a range of infections as it often results in prolonged illness, and consequently, patients remain infectious for a longer time [3]. There is an increased risk of spreading resistant microorganisms to others [4, 5]. Owing to resistance to first-line drugs, alternative and more expensive and lengthy treatment procedures must be used, placing a strain on the healthcare system [6–8]. This also adds to the burden on individuals, their families and communities who bear higher direct and indirect costs of care [4, 5, 9, 10]. While ABR has predominantly been a clinical problem in hospital settings, there is increasing evidence that indicates that resistant organisms have also been detected at the primary care level [11].

A significant force driving the spread of ABR is the inappropriate use and prescription of antimicrobials in primary care and hospital settings [7, 12]. Low- and middle-income countries (LMICs) are especially vulnerable, owing to a high burden of infectious diseases and limited resources to treat them [13–15]. A complex range of determinants of the inappropriate use of antibiotics have been identified in LMIC settings including: lack of provider knowledge [7, 14, 16–18]; prescriber's habit [7, 17, 18]; limited availability of independent, non-pharmaceutical industry, sources of information about the effects of medicines [17]; lack of continuing medical education and supervision [17, 19–21]; pharmaceutical promotion [17, 21]; short doctor-patient-dispenser interaction time [1, 17]; peer pressure [2, 17, 18, 22, 23]; perceived and real patient demand [17, 18, 24]; lack of diagnostic support tools [1, 17], economic incentives to prescribers and or dispensers [17, 18, 25]; inappropriate medicine supply [17, 18, 26]; and the ways in which patients and community members use or consume prescribed medicines by community members [18].

Interventions to tackle these different determinants must be a key part of any strategy to address ABR (WHO 2015). Recently published systematic reviews have identified a a range of interventions that could improve antibiotic stewardship [6, 27–29]. These interventions include the use of printed educational materials [6, 27], audit and feedback [6, 27], interactive educational meetings [6, 27], didactic lectures, compliance with antibiotic guidelines [28], reinforcement of existing guidelines [28], physician reminders to improve the prescription and use of antibiotics [6, 27], and the importance of guideline development [28] as means for improving the use and prescription of antibiotics. Another set of interventions uses mass media communication campaigns to reach both the public and prescribers in nationwide campaigns or more targeted interventions [29]. The majority of studies included in the reviews used data from interventions implemented in high-

income settings. Only 26 of the 221 studies included in the review by Davey et al [27], four of the 39 studies included in the review by Arnold et al [6], and one of the 14 included studies [29] were set in LMICs. The review by Charani et al [28] did not include any interventions set in LMICs.

The studies included in all four reviews appraised both single and multi-faceted interventions, and overall, multi-faceted interventions that had more than one component were more effective in the improvement of antibiotic use and prescribing, [1, 6, 17, 22, 29]. All studies included in these reviews were set in the health facilities (ambulatory and inpatient) and did not include any interventions implemented in the community setting. Moreover, only two reviews included behaviour change interventions [28, 30]. None of these reviews provided any estimates of costs of delivery, or cost-effectiveness of the implemented interventions. This leaves a considerable knowledge gap for LMICs where resistance to antibiotics is growing at an alarming rate [16, 25] .

This systematic review will summarise, and critically appraise the evidence on behaviour change interventions implemented to improve the prescription and use of antibiotics in LMICs, by:

1. Identifying behaviour change interventions implemented in LMICs to improve the prescription and use of antibiotics in in-patient and out-patient settings;
2. Synthesizing the available evidence to determine the effectiveness and cost-effectiveness of the implemented interventions;
3. Appraise the quality of the studies included in the review using criteria set in the GRADE checklist [31];
4. Identifying the intervention components that are most strongly associated with effectiveness and cost-effectiveness; and
5. Identifying knowledge gaps to guide future research in this area.

Methods

Population, interventions & outcomes:

For the review, we will consider peer-reviewed and published studies that evaluate the effectiveness and cost effectiveness of behaviour change interventions to improve the prescription and use of antibiotics in LMICs. We follow Michie et al's, definition of behaviour change – "a coordinated sets of activities designed to change specified behaviour patterns"(pp 1) [32]. We will consider Interventions targeting health care workers (including doctors, nurses, pharmacists, and support staff), patients and community, and we will review all primary and secondary outcomes relating to antibiotic use and prescription.

Inclusion and exclusion criteria:

Based on Michie et al's behaviour change wheel (BCW) that the authors propose, we will include those interventions that focus on education; training; modelling; enablement; persuasion; incentivisation; coercion; restriction; and environmental restructuring. [32].

The BCW is a layered framework (Figure 1) [32]. At the centre of this framework is the COM-B model that recognises that behaviour is part of an interacting system involving multiple components that include capability', 'opportunity', 'motivation' and 'behaviour'. This allows for the investigation of a situation by defining the problem, specifying the target behaviour, and identifying changes needed. The next circle contains the intervention functions such as training, enablement, education that might be necessary to address the gaps identified by the COM-B model. The outer most circle of the BCW is built on categories of policy that can potentially support the implementation and delivery of the intervention functions appropriate for the setting (Figure 1).

[Insert Figure 1 here]

We will include studies that evaluate the interventions within the framework of a randomized controlled trial (RCTs), interrupted time series (ITS), controlled before-after (CBA), or a quasi-experimental design, as the experimental design allows rigorous testing and establishment of causal relationships, and the ruling out of alternative causes [33]. We will include studies undertaken in countries classified as LMIC using the World Bank's 2016 country classification [34] . The complete list of countries can be found in Appendix 1. The review will comprise articles published between 1990 and 2017, reflecting the period over which debate around appropriate use of antibiotics gained momentum [35].

Studies written in languages other than those that the authors are proficient in (English, Spanish, French and Portuguese) will be excluded. Finally, we will also exclude conference abstracts, trial protocols, and previous systematic reviews as well as non-peer reviewed publications of programme or intervention evaluation.

Search strategy:

The study team (NB, CC, MK and VW) will define the search terms to be used. These will be categorised into different domains, based on the research question (Table 1). These domains are: population, interventions, outcomes and countries. The process will be iterative, as key search terms

might change throughout the process. One researcher, CC will conduct a comprehensive search for peer-reviewed articles using three online research databases Web of Science, MEDLINE and PubMed. CC will use the same set of key words to search for studies in Google Scholar, and screen the first 100 hits for peer-reviewed articles that might have been missed in the previous database searches. NB and MK will handsearch the references of the final included studies to capture additional studies that fit the inclusion criteria.

Table 1. Proposed keywords for systematic review search strategy

Population – drugs	antibiotic*; antimicrobial*; "anti-bacterial agents"; antibacterial; anti-bacterial
Interventions	"behavioural intervention*", "behavioral intervention*", "behaviour intervention", "behavior intervention", "behaviour change", "behavior change", "behaviour modification", "behavior modification", "training", "supervision", "education", "knowledge", "feedback", "audit", "reminders", "modelling", "modeling", "enablement", "persuasion", "incentivisation", "incentivization", "coercion", "restriction", "environmental restructuring", "guidelines", "stewardship", "law enforcement", "policy", "governance"
Outcomes	"use", "rational use", "irrational use", "inappropriate use", "appropriate use", "appropriate treatment", "treatment", "prescription", "adequate prescription", "prescri*", "knowledge", "prophylactic use", "prophilaxys", "effectiveness", "cost effectiveness", "cost-effectiveness", "economic evaluation", "costs", "costing", "cost effectiveness analysis", "cost-effectiveness analysis", "cost benefit analysis", "cost-benefit analysis", "cost utility analysis", "cost-utility analysis", "utilization", "utilisation", "drug use", "medicine use", "essential medicine*", "drug information", "drug therapy", "consumption", "prescribing practices", "prescribing behaviour", "prescribing behavior"
Countries	"low and middle income countr*", "low income countr*", "middle income countr*", LMIC*, "developing countr*", Afghanistan, Benin, Burkina Faso, Burundi, Central African Republic, Chad, Comoros, Democratic Republic of Congo, Eritrea, Ethiopia, The Gambia, Guinea, Guinea Bissau, Guinea-Bissau, Haiti, Democratic People's Republic of Korea, Korea, Liberia, Madagascar, Malawi, Mali, Mozambique, Nepal, Niger, Rwanda, Senegal, Sierra Leone, Somalia, South Sudan, Tanzania, Togo, Uganda, Zimbabwe, Armenia, Bangladesh, Bhutan, Bolivia, Cabo Verde, Cambodia, Cameroon, Republic of Congo, Congo, Cote d'Ivoire, Djibouti, Arab Republic of Egypt, Egypt, El Salvador, Ghana, Guatemala, Honduras, India, Indonesia, Kenya, Kiribati, Kosovo, Republic of Kyrgyz, Kyrgyz, Lao PDR, Lao, Lesotho, Mauritania, Federated States of Micronesia, Micronesia, Moldova, Mongolia, Morocco, Myanmar, Burma, Nicaragua, Nigeria, Pakistan, Papua New Guinea, Philippines, Samoa, Sao Tome and Principe, Solomon Islands, Sri Lanka, Sudan, Swaziland, Arab Republic of Syria, Syria, Tajikistan, Timor-Leste, Timor Leste, East Timor, Tonga, Tunisia, Ukraine, Uzbekistan, Vanuatu, Vietnam, West Bank and Gaza, Republic of Yemen, Yemen, Zambia, Albania, Algeria, American Samoa, Angola, Argentina,

	Azerbaijan, Belarus, Belize, Bosnia and Herzegovina, Botswana, Brazil, Bulgaria, China, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Equatorial Guinea, Guinea, Ecuador, Fiji, Gabon, Georgia, Grenada, Guyana, Islamic Republic of Iran, Iran, Iraq, Jamaica, Jordan, Kazakhstan, Lebanon, Libya, Republic of Macedonia, Macedonia, Malaysia, Maldives, Marshall Islands, Mauritius, Mexico, Montenegro, Namibia, Palau, Panama, Paraguay, Peru, Romania, Russian Federation, Russia, Serbia, South Africa, St Lucia, St Vincent and the Grenadines, Suriname, Thailand, Turkey, Turkmenistan, Tuvalu, Venezuela RB, Venezuela
Terms within each row are separated by OR Terms across each row are separated by AND Limited to publications related to Humans Limited to publications since January 1990 to 2017	

Data analysis and synthesis

The search results will be extracted into Mendeley 1.17.11 and checked for duplicates, which will be removed. One researcher from the review team (CC) will initially screen all titles and abstracts retrieved from the literature search. If there is uncertainty around whether certain studies should be included, the other team members (NB, MK, and VW) will independently appraise these studies to resolve the uncertainty. Following this initial screening phase, one researcher (CC) will review the full text of the papers to ensure that all inclusion criteria are met. We will exclude any studies not meeting one or more of the inclusion criteria. If there is uncertainty around the inclusion of studies at this stage, a second round of appraisal might be required by other team members (NB, MK). Any outstanding disputes will be resolved by VW. The selection process will be summarised in a flow chart that will also document the number of excluded studies, and reasons for exclusion. Studies published in Spanish, French or Portuguese included after a reading of the full text will be translated by CC into English and made available for the team to discuss.CC will extract the data into a data extraction form in Excel designed by the team to capture details about the authors, country setting, study design, description of intervention package, indicators and results.

Once the data have been extracted, we will categorise studies according to the different types of behaviour change interventions using the BCW. Interventions will be assessed as either single- or multi-faceted, level of effectiveness and/or cost-effectiveness, and generalisability of results. Given that the included studies might have different evaluation designs, we will analyse the results for RCT, ITS, CBA, quasi-experimental studies separately. We anticipate a high degree of heterogeneity amongst study outcomes as interventions will be tailored to specific behaviours, populations and country settings. If there is some degree of homogeneity in the outcomes assessed across all or a

sub-set of included studies, we will conduct a meta-analysis of effect with sub-group analysis, otherwise a narrative synthesis strategy will be used. Careful consideration will also be given to publication bias across studies and selective reporting within studies.

Finally, we will conduct an appraisal of the quality of the included studies using the GRADE checklist [31], which has been widely used by the World Health Organization, Cochrane Collaboration, Agency for Healthcare Research and Quality (USA) and National Institute of Health and Care Excellence (UK) [36]. This checklist explicitly evaluates the quality of the evidence and the strengths and weaknesses of the recommendations that follow [37].

Discussion

The extent of the adverse impacts of ABR are widely known, and recognised as a global public health concern. Timely and appropriate interventions and programmes need to be implemented to alleviate its harmful impact on people, communities, and health systems. This review will be one of the first to focus on interventions designed to improve the use of antibiotics in LMICs. Our findings, which will be contrasted with available literature on the topic, will help inform the design of future interventions and will be of international interest to public health, primary healthcare professionals, policy-makers and patients. This is especially helpful at a time when global monitoring of antibiotic and antimicrobial resistance is on the rise and LMIC governments are being tasked with developing evidence-based national strategies and action plans that include interventions to control resistance to antibiotics and antimicrobials.

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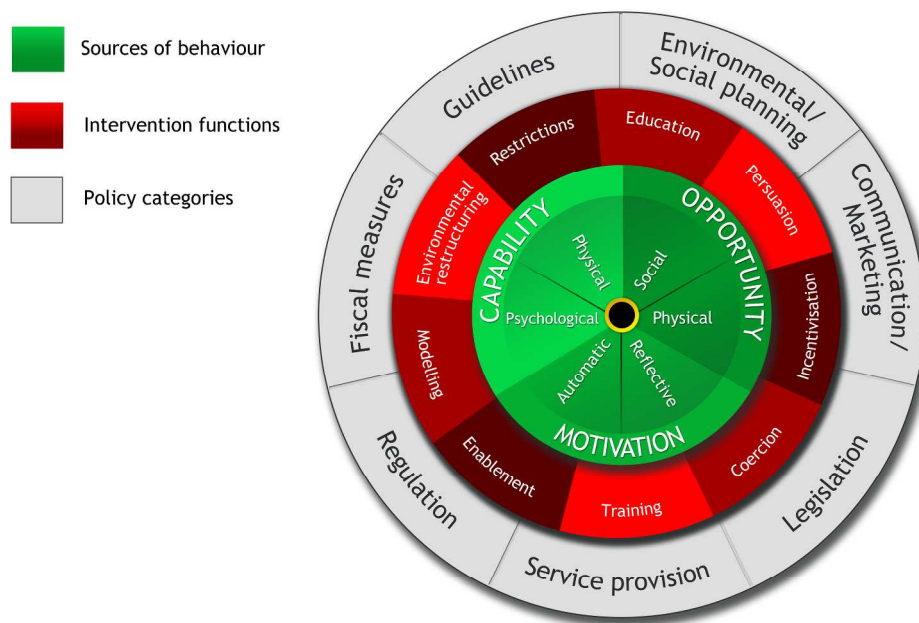
Figure legend:
Figure 1: Behaviour change wheel

Authors' contributions: All authors contributed equally to the design of the study. NB and CC drafted the manuscript, with support from MK and VW. VW is the guarantor of the review

Competing interests statement: The authors have no competing interests

Source: Michie et al, 2011

Figure 1: Behaviour change wheel

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Appendix 1: World Bank Country Classification 2016

Low Income Countries (31)

Afghanistan; Benin; Burkina Faso; Burundi; Central African Republic; Chad; Comoros; Democratic Republic of Congo; Eritrea; Ethiopia; The Gambia; Guinea; Guinea-Bissau; Haiti; Democratic People's Republic of Korea; Liberia; Madagascar; Malawi; Mali; Mozambique; Nepal; Niger; Rwanda; Senegal; Sierra Leone; Somalia; South Sudan; Tanzania; Togo; Uganda; Zimbabwe

Lowe-middle Income Countries (52)

Armenia; Bangladesh; Bhutan; Bolivia; Cabo Verde; Cambodia; Cameroon; Republic of Congo; Cote d'Ivoire; Djibouti; Arab Republic of Egypt; El Salvador; Ghana; Guatemala; Honduras; India; Indonesia; Kenya; Kiribati; Kosovo; Republic of Kyrgyz; Lao PDR; Lesotho; Mauritania; Federated States of Micronesia; Moldova; Mongolia; Morocco; Myanmar; Nicaragua; Nigeria; Pakistan; Papua New Guinea; Philippines; Samoa; São Tomé and Principe; Solomon Islands; Sri Lanka; Sudan; Swaziland; Arab Republic of Syria; Tajikistan; Timor-Leste; Tonga; Tunisia; Ukraine; Uzbekistan; Vanuatu; Vietnam; West Bank and Gaza; Republic of Yemen; Zambia

Upper-middle Income Countries (56)

Albania; Algeria; American Samoa; Angola; Argentina; Azerbaijan; Belarus; Belize; Bosnia and Herzegovina; Botswana; Brazil; Bulgaria; China; Colombia; Costa Rica; Cuba; Dominica; Dominican Republic; Equatorial Guinea; Ecuador; Fiji; Gabon; Georgia; Grenada; Guyana; Islamic Republic of Iran; Iraq; Jamaica; Jordan; Kazakhstan; Lebanon; Libya; Republic of Macedonia; Malaysia; Maldives; Marshall Islands; Mauritius; Mexico; Montenegro; Namibia; Palau; Panama; Paraguay; Peru; Romania; Russian Federation; Serbia; South Africa; St. Lucia; St. Vincent and the Grenadines; Suriname; Thailand; Turkey; Turkmenistan; Tuvalu; Venezuela

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned	7,8

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		limits, such that it could be repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

How effective and cost-effective are behaviour change interventions in improving the prescription and use of antibiotics in low and middle-income countries? A protocol for a systematic review

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Primary Subject Heading:	Global health
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Keywords:	Antibiotic resistance, Behaviour change, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Public health < INFECTIOUS DISEASES, Systematic review

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How effective and cost-effective are behaviour change interventions in improving the prescription and use of antibiotics in low and middle-income countries? A protocol for a systematic review

Neha Batura, Carla Cuevas, Mishal Khan, Virginia Wiseman

Neha Batura (corresponding author)
Institute for Global Health
University College London
30 Guilford Street
London WC1 1EH
United Kingdom
Email: n.batura@ucl.ac.uk

Carla Cuevas
UCL Centre for Global Health Economics
Email: carla.cuevas.15@alumni.ucl.ac.uk

Mishal Khan
London School of Hygiene and Tropical Medicine
Email: mishal.khan@lshtm.ac.uk

Virginia Wiseman
London School of Hygiene and Tropical Medicine and University of New South Wales
Email: virginia.wiseman@lshtm.ac.uk

Abstract

Introduction: Antibiotic resistance endangers effective prevention and treatment of infections and places significant burden on patients, families, communities and healthcare systems. Low- and middle-income countries (LMICs) are especially vulnerable to antibiotic resistance, owing to high infectious disease burden, and limited resources for treatment. High prevalence of antibiotic prescription and use due to lack of provider's knowledge, prescriber's habits, and perceived patient needs further exacerbate the situation. Interventions implemented to address inappropriate prescription and use of antibiotics in LMICs must address different determinants of antibiotic resistance through sustainable and scalable interventions. The aim of this protocol is to provide a comprehensive overview of the methods that will be used to identify and appraise evidence on the effectiveness and cost-effectiveness of behaviour change interventions implemented in LMICs to improve prescription and use of antibiotics.

Methods and analysis: Two databases (Web of Science, and PubMed) will be searched based on a strategy developed in consultation with an essential medicines and health systems researcher. Additional studies will be identified using the same search strategy in Google Scholar. To be included, a study must describe a behaviour change intervention and use experimental design to estimate effectiveness and/or cost-effectiveness in a LMIC. Following systematic screening of titles, abstracts and keywords, and full-text appraisal, data will be extracted using a customized extraction form. Studies will be categorised by type of behaviour change intervention and experimental design. A meta-analysis or narrative synthesis will be conducted as appropriate along with an appraisal of quality of studies using the GRADE checklist.

Ethics and dissemination: No individual patient data is used, so ethical approval is not required. The systematic review will be disseminated in a peer-reviewed journal and presented at a relevant international conference.

Systematic review registration: PROSPERO **CRD42017075596**

Keywords: Antibiotic resistance, behaviour change, systematic review, protocol, public health

Strengths and limitations of this study

- To our knowledge, this is the first review to focus solely on low- and middle-income countries, which are especially vulnerable to antibiotic resistance, and will contribute to strengthen the evidence on effective interventions to improve prescription and use of antibiotics in these settings.

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- This study will focus on behaviour change interventions, using the Behaviour Change Wheel to systematically classify interventions.
- Studies written in multiple languages (English, Spanish, French and Portuguese) will be considered.
- The GRADE checklist will be used to assess quality and strength of the evidence.
- Effectiveness and cost-effectiveness outcomes of the included data might be too heterogeneous to conduct a meta-analysis; if so, a narrative synthesis of evidence will be conducted.

Introduction

Antibiotic resistance (ABR) is recognized as one of the greatest threats to human health [1, 2]. It endangers the effective prevention and treatment of a range of infections as it often results in prolonged illness, and consequently, patients remain infectious for a longer time [3]. There is also an increased risk of spreading resistant microorganisms to others [4, 5]. Owing to resistance to first-line drugs, alternative and more expensive and lengthy treatment procedures must be used, placing a strain on the healthcare system [6–8]. This adds to the burden on individuals, their families and communities who bear higher direct and indirect costs of care [4, 5, 9, 10]. While ABR has predominantly been a clinical problem in hospital settings, there is increasing evidence that resistant organisms are prevalent at the primary care level [11].

A significant force driving the spread of ABR is the inappropriate use and prescription of antimicrobials in primary care and hospital settings [7, 12]. Low- and middle-income countries (LMICs) are especially vulnerable, owing to a high burden of infectious diseases and limited resources to treat them [13–15]. A complex range of determinants of the inappropriate use of antibiotics have been identified in LMIC settings including: lack of provider knowledge [7, 14, 16–18]; prescriber's habit [7, 17, 18]; limited availability of independent, non-pharmaceutical industry, sources of information about the effects of medicines [17]; lack of continuing medical education and supervision [17, 19–21]; pharmaceutical promotion [17, 21]; short doctor-patient-dispenser interaction time [1, 17]; peer pressure [2, 17, 18, 22, 23]; perceived and real patient demand [17, 18, 24]; lack of diagnostic support tools [1, 17], economic incentives to prescribers and or dispensers [17, 18, 25]; inappropriate medicine supply [17, 18, 26]; and how patients and community members use or consume prescribed medicines [18].

Interventions to tackle these different determinants must be a key part of any strategy to address ABR [12]. Recently published systematic reviews have identified a range of interventions that could improve antibiotic stewardship [6, 27–29]. These interventions include the use of printed educational materials [6, 27], audit and feedback [6, 27], interactive educational meetings [6, 27], didactic lectures, compliance with antibiotic guidelines [28], reinforcement of existing guidelines or their development, if previously non-existent [28], and physician reminders to improve the prescription and use of antibiotics [6, 27] as means for improving the use and prescription of antibiotics. Another set of interventions uses mass media communication campaigns to reach both the public and prescribers in nationwide campaigns or more targeted interventions [29]. The majority of studies included in the reviews used data from interventions implemented in high-

income settings. Only 26 of the 221 studies included in the review by Davey et al [27], four of the 39 studies included in the review by Arnold et al [6], and one of the 14 included studies [29] were set in LMICs. The review by Charani et al [28] did not include any interventions set in LMICs.

The studies included in all four reviews appraised both single and multi-faceted interventions. Overall, multi-faceted interventions (more than one intervention component) were more effective in the improvement of antibiotic use and prescribing, [1, 6, 17, 22, 29]. All studies included in these reviews were set in the health facilities (ambulatory and inpatient), and did not include any interventions implemented in the community setting. Moreover, only two reviews included behaviour change interventions [28, 30]. None of these reviews provided any estimates of costs of delivery, or cost-effectiveness of the implemented interventions. This leaves a considerable knowledge gap for LMICs where resistance to antibiotics is growing at an alarming rate [16, 25] .

The aim of this protocol is to provide a comprehensive overview of the methods that will identify behaviour change interventions implemented in LMICs to improve prescription and use of antibiotics; and appraise their effectiveness and cost-effectiveness through a systematic review of available evidence. The proposed review will summarise, and critically appraise the evidence on behaviour change interventions implemented to improve the prescription and use of antibiotics in LMICs. Specifically, the objectives of the review are to:

1. Identify behaviour change interventions implemented in LMICs to improve the prescription and use of antibiotics in in-patient and out-patient settings;

2. Synthesize the available evidence to determine the effectiveness and cost-effectiveness of the implemented behaviour change interventions, using the framework outlined by the Behaviour Change Wheel [31];

3. Appraise the quality of the studies included in the review using criteria set in the GRADE checklist [32];

4. Identify the intervention components that are most strongly associated with effectiveness and cost-effectiveness; and

5. Identify knowledge gaps to guide future research in this area in the content of health promotion and health system interventions.

Methods

Population, interventions & outcomes:

For the review, we will consider peer-reviewed and published studies that evaluate the effectiveness and cost effectiveness of behaviour change interventions to improve the prescription and use of antibiotics in LMICs. We follow Michie et al's, definition of behaviour change – "a coordinated sets of activities designed to change specified behaviour patterns"(pp 1) [31]. We will consider interventions targeting health care workers (including doctors, nurses, pharmacists, and support staff), patients and community, and we will review all primary and secondary outcomes relating to antibiotic use and prescription.

Inclusion and exclusion criteria:

Based on Michie et al's behaviour change wheel (BCW) that the authors propose, we will include those interventions that focus on education; training; modelling; enablement; persuasion; incentivisation; coercion; restriction; and environmental restructuring. [31].

The BCW is a layered framework (Figure 1) [31]. At the centre of this framework is the COM-B model that recognises that behaviour is part of an interacting system involving multiple components that include capability', 'opportunity', 'motivation' and 'behaviour'. This allows for the investigation of a situation by defining the problem, specifying the target behaviour, and identifying changes needed. The next circle contains the intervention functions such as training, enablement, education that might be necessary to address the gaps identified by the COM-B model. The outer most circle of the BCW is built on categories of policy that can potentially support the implementation and delivery of the intervention functions appropriate for the setting (Figure 1).

[Insert Figure 1 here]

We will include studies that evaluate interventions within the framework of a randomized controlled trial (RCTs), interrupted time series (ITS), controlled before-after (CBA), or a quasi-experimental design, as the experimental design allows rigorous testing and establishment of causal relationships, and the ruling out of alternative causes [33]. We will include studies undertaken in countries classified as LMIC using the World Bank's 2016 country classification [34] . The complete list of countries can be found in Appendix 1. The review will comprise articles published between 1990 and 2017, reflecting the period over which debate around appropriate use of antibiotics gained significant momentum [35].

Studies written in languages other than those that the authors are proficient in (English, Spanish,
French and Portuguese) will be excluded. Finally, we will also exclude conference abstracts, trial
protocols, previous systematic reviews, and non-peer reviewed publications of programme or
intervention evaluation.

Search strategy:

The study team (NB, CC, MK and VW) will define the search terms to be used. These will be
categorised into different domains, based on the research question (Table 1). These domains are:
population, interventions, outcomes and countries. The process will be iterative, as key search terms
might change throughout the process. Two researchers from the review team (CC and NB) will
independently conduct comprehensive searches for peer-reviewed articles using two online
research databases: Web of Science, and PubMed. They will use the same set of key words to search
for studies in Google Scholar, and screen the first 100 hits for peer-reviewed articles that might have
been missed in the previous database searches. They will handsearch the references of the final
included studies to capture additional studies that fit the inclusion criteria.

Table 1. Proposed keywords for systematic review search strategy

Population – drugs	antibiotic*; antimicrobial*; "anti-bacterial agents"; antibacterial; anti-bacterial
Interventions	"behavioural intervention*", "behavioral intervention*", "behaviour intervention", "behavior intervention", "behaviour change", "behavior change", "behaviour modification", "behavior modification","training", "supervision", "education", "knowledge", "feedback", "audit", "reminders", "modelling", "modeling", "enablement", "persuasion", "incentivisation", "incentivization", "coercion", "restriction", "environmental restructuring", "guidelines", "stewardship", "law enforcement", "policy", "governance"
Outcomes	"use", "rational use", "irrational use", "inappropriate use", "appropriate use", "appropriate treatment", "treatment", "prescription", "adequate prescription", "prescri*", "knowledge", "prophylactic use", "prophilaxys", "effectiveness", "cost effectiveness", "cost-effectiveness", "economic evaluation", "costs", "costing", "cost effectiveness analysis", "cost-effectiveness analysis", "cost benefit analysis", "cost-benefit analysis", "cost utility analysis", "cost-utility analysis", "utilization", "utilisation", "drug use", "medicine use", "essential medicine*", "drug information", "drug therapy", "consumption", "prescribing practices", "prescribing behaviour", "prescribing behavior"
Countries	"low and middle income countr*", "low income countr*", "middle income countr*", LMIC*, "developing countr*", Afghanistan, Benin, Burkina Faso, Burundi, Central African Republic, Chad, Comoros, Democratic Republic of Congo, Eritrea, Ethiopia, The Gambia, Guinea, Guinea Bissau, Guinea-Bissau, Haiti, Democratic People's Republic of Korea, Korea, Liberia, Madagascar, Malawi, Mali, Mozambique, Nepal, Niger, Rwanda, Senegal, Sierra Leone, Somalia, South Sudan, Tanzania, Togo, Uganda, Zimbabwe, Armenia, Bangladesh, Bhutan, Bolivia, Cabo Verde, Cambodia, Cameroon, Republic of Congo,

	Congo, Cote d'Ivoire, Djibouti, Arab Republic of Egypt, Egypt, El Salvador, Ghana, Guatemala, Honduras, India, Indonesia, Kenya, Kiribati, Kosovo, Republic of Kyrgyz, Kyrgyz, Lao PDR, Lao, Lesotho, Mauritania, Federated States of Micronesia, Micronesia, Moldova, Mongolia, Morocco, Myanmar, Burma, Nicaragua, Nigeria, Pakistan, Papua New Guinea, Philippines, Samoa, Sao Tome and Principe, Solomon Islands, Sri Lanka, Sudan, Swaziland, Arab Republic of Syria, Syria, Tajikistan, Timor-Leste, Timor Leste, East Timor, Tonga, Tunisia, Ukraine, Uzbekistan, Vanuatu, Vietnam, West Bank and Gaza, Republic of Yemen, Yemen, Zambia, Albania, Algeria, American Samoa, Angola, Argentina, Azerbaijan, Belarus, Belize, Bosnia and Herzegovina, Botswana, Brazil, Bulgaria, China, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Equatorial Guinea, Guinea, Ecuador, Fiji, Gabon, Georgia, Grenada, Guyana, Islamic Republic of Iran, Iran, Iraq, Jamaica, Jordan, Kazakhstan, Lebanon, Libya, Republic of Macedonia, Macedonia, Malaysia, Maldives, Marshall Islands, Mauritius, Mexico, Montenegro, Namibia, Palau, Panama, Paraguay, Peru, Romania, Russian Federation, Russia, Serbia, South Africa, St Lucia, St Vincent and the Grenadines, Suriname, Thailand, Turkey, Turkmenistan, Tuvalu, Venezuela RB, Venezuela
Terms within each row are separated by OR	
Terms across each row are separated by AND	
Limited to publications related to Humans	
Limited to publications since January 1990 to 2017	

Data analysis and synthesis:

The search results will be extracted into Mendeley 1.17.11 and checked for duplicates, which will be removed. CC and NB will independently screen all titles and abstracts retrieved from their literature searches. If there is uncertainty around whether certain studies should be included, the other team members (MK and VW) will independently appraise these studies to resolve the uncertainty. Following this screening phase, one researcher (CC) will review the full text of the papers to ensure that all inclusion criteria are met. We will exclude any studies not meeting one or more of the inclusion criteria. If there is uncertainty around the inclusion of studies at this stage, a second round of appraisal will be undertaken by MK. Any outstanding disputes will be resolved by VW. The selection process will be summarised in a flow chart that will also document the number of excluded studies, and reasons for exclusion (Figure 2). Studies published in Spanish, French or Portuguese included after a reading of the full text will be translated by CC into English and made available for the team to discuss. CC will extract the data into a data extraction form in Excel designed by the team to capture details about the authors, country setting, study design, description of intervention package, indicators and results.

[Insert Figure 2 here]

Once the data have been extracted, we will categorise studies according to the different types of behaviour change interventions using the BCW. Interventions will be assessed as either single- or multi-faceted, level of effectiveness and/or cost-effectiveness, and generalisability of results. Given that the included studies might have different evaluation designs, we will analyse the results for RCT, ITS, CBA, quasi-experimental studies separately. We anticipate a high degree of heterogeneity amongst study outcomes as interventions will be tailored to specific behaviours, populations and country settings. If there is some degree of homogeneity in the outcomes assessed across all or a sub-set of included studies, we will conduct a meta-analysis of effect with sub-group analysis, otherwise a narrative synthesis strategy will be used [36]. Careful consideration will also be given to publication bias across studies and selective reporting within studies.

Finally, we will conduct an appraisal of the quality of the included studies using the GRADE checklist [32], which has been widely used by the World Health Organization, Cochrane Collaboration, Agency for Healthcare Research and Quality (USA) and National Institute of Health and Care Excellence (UK) [37]. This checklist explicitly evaluates the quality of the evidence and the strengths and weaknesses of the recommendations that follow [38].

Patient and public Involvement:

Patients and/or public are not involved in this study.

Discussion

The extent of the adverse impacts of ABR are widely known, and recognised as a global public health concern. Timely and appropriate interventions and programmes need to be implemented to alleviate its harmful impact on people, communities, and health systems. This review will be one of the first to focus on interventions designed to improve the use of antibiotics in LMICs. The results will be of direct benefit to governments and donors who are seeking to respond to the threat of ABR by developing evidence-based national strategies and action plans that include priority interventions to control resistance to antibiotics and antimicrobials. This review will provide a comprehensive overview of available evidence on both the effectiveness and cost-effectiveness of interventions that will aid priority-setting and investment decisions.

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Figure legend
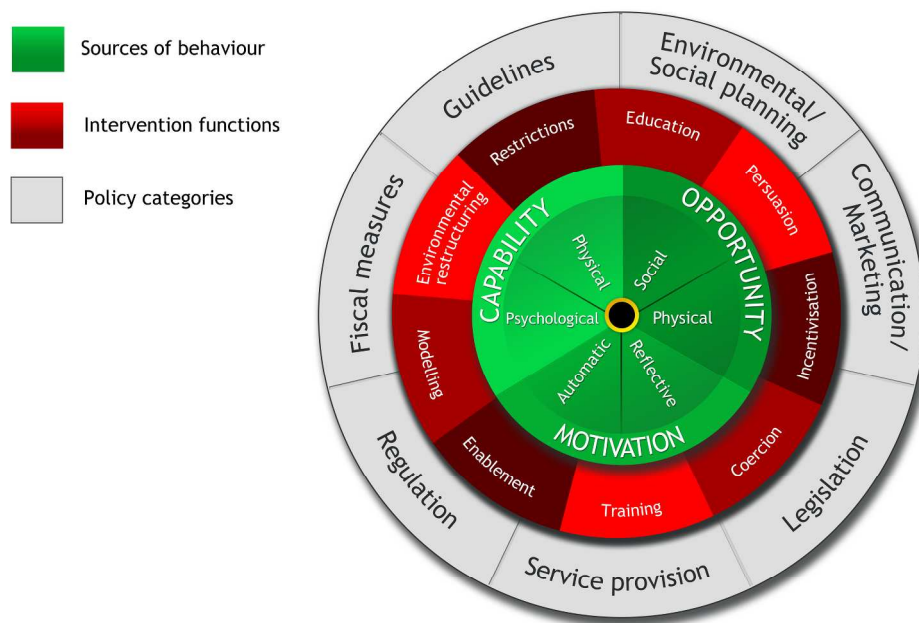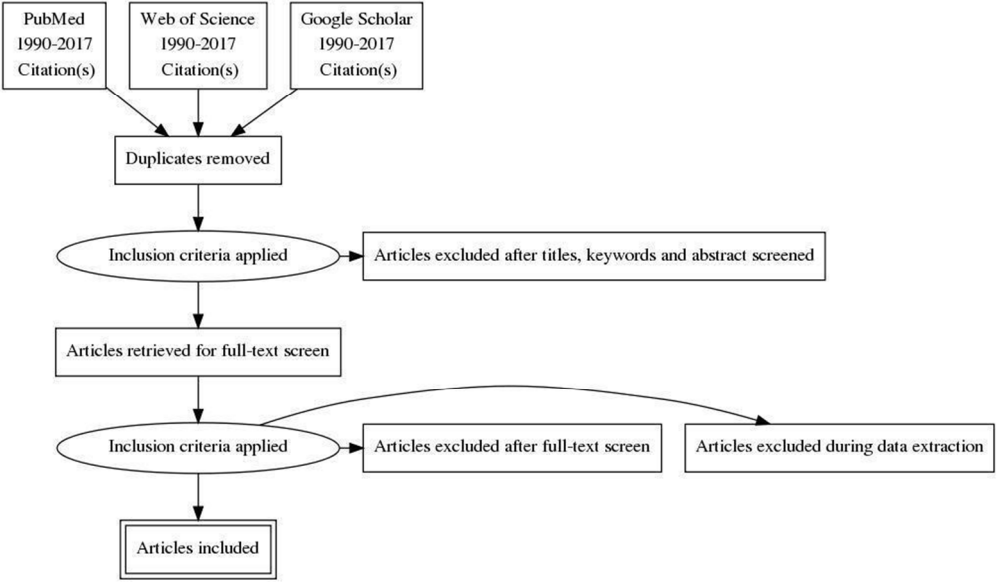Figure 1: Behaviour change wheel
Figure 2: Flow diagram

Authors' contributions: All authors contributed equally to the design of the study. NB and CC drafted the manuscript, with support from MK and VW. VW is the guarantor of the review.

Funding statement: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests statement: The authors have no competing interests.

Source: Michie et al, 2011

Figure 1: Behaviour change wheel

250x176mm (300 x 300 DPI)

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Figure 2: Flow diagram

85x50mm (300 x 300 DPI)

Appendix 1: World Bank Country Classification 2016

Low Income Countries (31)

Afghanistan; Benin; Burkina Faso; Burundi; Central African Republic; Chad; Comoros; Democratic Republic of Congo; Eritrea; Ethiopia; The Gambia; Guinea; Guinea-Bissau; Haiti; Democratic People's Republic of Korea; Liberia; Madagascar; Malawi; Mali; Mozambique; Nepal; Niger; Rwanda; Senegal; Sierra Leone; Somalia; South Sudan; Tanzania; Togo; Uganda; Zimbabwe

Lowe-middle Income Countries (52)

Armenia; Bangladesh; Bhutan; Bolivia; Cabo Verde; Cambodia; Cameroon; Republic of Congo; Cote d'Ivoire; Djibouti; Arab Republic of Egypt; El Salvador; Ghana; Guatemala; Honduras; India; Indonesia; Kenya; Kiribati; Kosovo; Republic of Kyrgyz; Lao PDR; Lesotho; Mauritania; Federated States of Micronesia; Moldova; Mongolia; Morocco; Myanmar; Nicaragua; Nigeria; Pakistan; Papua New Guinea; Philippines; Samoa; São Tomé and Principe; Solomon Islands; Sri Lanka; Sudan; Swaziland; Arab Republic of Syria; Tajikistan; Timor-Leste; Tonga; Tunisia; Ukraine; Uzbekistan; Vanuatu; Vietnam; West Bank and Gaza; Republic of Yemen; Zambia

Upper-middle Income Countries (56)

Albania; Algeria; American Samoa; Angola; Argentina; Azerbaijan; Belarus; Belize; Bosnia and Herzegovina; Botswana; Brazil; Bulgaria; China; Colombia; Costa Rica; Cuba; Dominica; Dominican Republic; Equatorial Guinea; Ecuador; Fiji; Gabon; Georgia; Grenada; Guyana; Islamic Republic of Iran; Iraq; Jamaica; Jordan; Kazakhstan; Lebanon; Libya; Republic of Macedonia; Malaysia; Maldives; Marshall Islands; Mauritius; Mexico; Montenegro; Namibia; Palau; Panama; Paraguay; Peru; Romania; Russian Federation; Serbia; South Africa; St. Lucia; St. Vincent and the Grenadines; Suriname; Thailand; Turkey; Turkmenistan; Tuvalu; Venezuela

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned	7,8

		limits, such that it could be repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-9
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8-9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8-9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

How effective and cost-effective are behaviour change interventions in improving the prescription and use of antibiotics in low and middle-income countries? A protocol for a systematic review

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How effective and cost-effective are behaviour change interventions in improving the prescription and use of antibiotics in low and middle-income countries? A protocol for a systematic review

Neha Batura, Carla Cuevas, Mishal Khan, Virginia Wiseman

Neha Batura (corresponding author)
Institute for Global Health
University College London
30 Guilford Street
London WC1 1EH
United Kingdom
Email: n.batura@ucl.ac.uk

Carla Cuevas
UCL Centre for Global Health Economics
Email: carla.cuevas.15@alumni.ucl.ac.uk

Mishal Khan
London School of Hygiene and Tropical Medicine
Email: mishal.khan@lshtm.ac.uk

Virginia Wiseman
London School of Hygiene and Tropical Medicine and University of New South Wales
Email: virginia.wiseman@lshtm.ac.uk

Abstract

Introduction: Antibiotic resistance endangers effective prevention and treatment of infections, and places significant burden on patients, families, communities and healthcare systems. Low- and middle-income countries (LMICs) are especially vulnerable to antibiotic resistance, owing to high infectious disease burden, and limited resources for treatment. High prevalence of antibiotic prescription and use due to lack of provider's knowledge, prescriber's habits, and perceived patient needs further exacerbate the situation. Interventions implemented to address the inappropriate prescription and use of antibiotics in LMICs must address different determinants of antibiotic resistance through sustainable and scalable interventions. The aim of this protocol is to provide a comprehensive overview of the methods that will be used to identify, and appraise evidence on the effectiveness and cost-effectiveness of behaviour change interventions implemented in LMICs to improve the prescription and use of antibiotics.

Methods and analysis: Two databases (Web of Science, and PubMed) will be searched based on a strategy developed in consultation with an essential medicines and health systems researcher. Additional studies will be identified using the same search strategy in Google Scholar. To be included, a study must describe a behaviour change intervention; and use an experimental design to estimate effectiveness and/or cost-effectiveness in a LMIC. Following systematic screening of titles, abstracts and keywords, and full-text appraisal, data will be extracted using a customized extraction form. Studies will be categorised by type of behaviour change intervention and experimental design. A meta-analysis or narrative synthesis will be conducted as appropriate, along with an appraisal of quality of studies using the GRADE checklist.

Ethics and dissemination: No individual patient data is used, so ethical approval is not required. The systematic review will be disseminated in a peer-reviewed journal and presented at a relevant international conference.

Systematic review registration: PROSPERO CRD42017075596

Keywords: Antibiotic resistance, behaviour change, systematic review, protocol, public health

Strengths and limitations of this study

- This study will focus on behaviour change interventions, using the Behaviour Change Wheel to systematically classify interventions.

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- Studies written in multiple languages (English, Spanish, French and Portuguese) will be considered.

- The GRADE checklist will be used to assess quality and strength of the evidence.

- Effectiveness and cost-effectiveness outcomes of the included data might be too heterogeneous to conduct a meta-analysis; if so, a narrative synthesis of evidence will be conducted.

- Studies may not report process and/or wider contextual factors that could facilitate or act as a barrier to the success of an intervention.

Introduction

Antibiotic resistance (ABR) is recognized as one of the greatest threats to human health [1, 2]. It endangers the effective prevention and treatment of a range of infections as it often results in prolonged illness, and consequently, patients remain infectious for a longer time [3]. There is also an increased risk of spreading resistant microorganisms to others [4, 5]. Owing to resistance to first-line drugs, alternative and more expensive and lengthy treatment procedures must be used, placing a strain on the healthcare system [6–8]. This adds to the burden on individuals, their families and communities who bear higher direct and indirect costs of care [4, 5, 9, 10]. While ABR has predominantly been a clinical problem in hospital settings, there is increasing evidence that resistant organisms are prevalent at the primary care level [11].

A significant force driving the spread of ABR is the inappropriate use and prescription of antimicrobials in primary care and hospital settings [7, 12]. Low- and middle-income countries (LMICs) are especially vulnerable, owing to a high burden of infectious diseases and limited resources to treat them [13–15]. A complex range of determinants of the inappropriate use of antibiotics have been identified in LMIC settings including: lack of provider knowledge [7, 14, 16–18]; prescriber's habit [7, 17, 18]; limited availability of independent, non-pharmaceutical industry sources of information about the effects of medicines [17]; lack of continuing medical education and supervision [17, 19–21]; pharmaceutical promotion [17, 21]; short doctor-patient-dispenser interaction time [1, 17]; peer pressure [2, 17, 18, 22, 23]; perceived and real patient demand [17, 18, 24]; lack of diagnostic support tools [1, 17], economic incentives to prescribers and or dispensers [17, 18, 25]; inappropriate medicine supply [17, 18, 26]; and how patients and community members use or consume prescribed medicines [18].

Interventions to tackle these different determinants must be a key part of any strategy to address ABR [12]. Recently published systematic reviews have identified a range of interventions that could improve antibiotic stewardship [6, 27–29]. These interventions include the use of printed educational materials [6, 27]; audit and feedback [6, 27]; interactive educational meetings [6, 27]; didactic lectures, compliance with antibiotic guidelines [28]; reinforcement of existing guidelines or their development, if previously non-existent [28]; and physician reminders to improve the prescription and use of antibiotics [6, 27] as means for improving the use and prescription of antibiotics. Another set of interventions uses mass media communication campaigns to reach both the public, and prescribers through nationwide campaigns or more targeted interventions [29]. The majority of studies included in these reviews used data from interventions implemented in high-

income settings. Only 26 of the 221 studies included in the review by Davey et al [27], four of the 39 studies included in the review by Arnold et al [6], and one of the 14 included studies in the review by Cross et al [29] were set in LMICs. The review by Charani et al [28] did not include any interventions set in LMICs.

The studies included in all four reviews appraised both single and multi-faceted interventions. Overall, multi-faceted interventions (more than one intervention component) were more effective in the improvement of antibiotic use and prescribing, [1, 6, 17, 22, 29]. All studies included in these reviews were set in the health facilities (ambulatory and inpatient), and did not include any interventions implemented in the community setting. Moreover, only two reviews included behaviour change interventions [28, 29]. None of these reviews provided any estimates of costs of delivery, or cost-effectiveness of the implemented interventions. This leaves a considerable knowledge gap for LMICs where resistance to antibiotics is growing at an alarming rate [16, 25] .

The aim of this protocol is to provide a comprehensive overview of the methods that will identify behaviour change interventions implemented in LMICs to improve the prescription and use of antibiotics; and appraise their effectiveness and cost-effectiveness through a systematic review of available evidence. The proposed review will summarise, and critically appraise the evidence on behaviour change interventions implemented to improve the prescription and use of antibiotics in LMICs. Specifically, the objectives of the review are to:

1. Identify behaviour change interventions implemented in LMICs to improve the prescription and use of antibiotics in in-patient and out-patient settings;

2. Synthesize the available evidence to determine the effectiveness and cost-effectiveness of the implemented behaviour change interventions, using the framework outlined by the Behaviour Change Wheel [30];

3. Appraise the quality of the studies included in the review using criteria set in the GRADE checklist [31];

4. Identify the intervention components that are most strongly associated with effectiveness and cost-effectiveness; and

5. Identify knowledge gaps to guide future research in this area in the content of health promotion and health system interventions.

Methods

Population, interventions & outcomes:

For the review, we will consider peer-reviewed and published studies that evaluate the effectiveness and cost effectiveness of behaviour change interventions to improve the prescription and use of antibiotics in LMICs. We follow Michie et al's, definition of behaviour change – "a coordinated set of activities designed to change specified behaviour patterns" (pp 1) [30]. We will consider interventions targeting health care workers (including doctors, nurses, pharmacists, and support staff), patients and community, and we will review all primary and secondary outcomes relating to antibiotic prescription and use.

Inclusion and exclusion criteria:

Based on Michie et al's behaviour change wheel (BCW), we will include those interventions that focus on education; training; modelling; enablement; persuasion; incentivisation; coercion; restriction; and environmental restructuring. [30].

The BCW is a layered framework (Figure 1) [30]. At the centre of this framework is the COM-B model that recognises that behaviour is part of an interacting system involving multiple components that include capability', 'opportunity', 'motivation' and 'behaviour'. This allows for the investigation of a situation by defining the problem, specifying the target behaviour, and identifying changes needed. The next circle contains the intervention functions such as training, enablement, education that might be necessary to address the gaps identified by the COM-B model. The outer most circle of the BCW is built on categories of policy that can potentially support the implementation and delivery of the intervention functions that are appropriate for the setting (Figure 1).

[Insert Figure 1 here]

We will include studies that evaluate interventions within the framework of a randomized controlled trial (RCTs), interrupted time series (ITS), controlled before-after (CBA), or have a quasi-experimental design, as the experimental design allows rigorous testing and establishment of causal relationships, and the ruling out of alternative causes [32]. We will include studies undertaken in countries classified as LMIC using the World Bank's 2016 country classification [33] . The complete list of countries can be found in Appendix 1. The review will comprise articles published between 1990 and 2017, reflecting the period over which debate around appropriate use of antibiotics gained significant momentum [34].

Studies written in languages other than those that the authors are proficient in (English, Spanish,
French and Portuguese) will be excluded. Finally, we will also exclude conference abstracts, trial
protocols, previous systematic reviews, and non-peer reviewed publications of programme or
intervention evaluation.

Search strategy:

The study team (NB, CC, MK and VW) will define the search terms to be used. These will be
categorised into different domains, based on the research question (Table 1). These domains are:
population, interventions, outcomes and countries. The process will be iterative, as key search terms
might change throughout the process. Two researchers from the review team (CC and NB) will
independently conduct comprehensive searches for peer-reviewed articles using two online
research databases: Web of Science, and PubMed. They will use the same set of key words to search
for studies in Google Scholar, and screen the first 100 hits for peer-reviewed articles that might have
been missed in the previous database searches. They will handsearch the references of the final
included studies to capture additional studies that fit the inclusion criteria.

Table 1. Proposed keywords for systematic review search strategy

Population – drugs	antibiotic*; antimicrobial*; "anti-bacterial agents"; antibacterial; anti-bacterial
Interventions	"behavioural intervention*", "behavioral intervention*", "behaviour intervention", "behavior intervention", "behaviour change", "behavior change", "behaviour modification", "behavior modification" "training", "supervision", "education", "knowledge", "feedback", "audit", "reminders", "modelling", "modeling", "enablement", "persuasion", "incentivisation", "incentivization", "coercion", "restriction", "environmental restructuring", "guidelines", "stewardship", "law enforcement", "policy", "governance"
Outcomes	"use", "rational use", "irrational use", "inappropriate use", "appropriate use", "appropriate treatment", "treatment", "prescription", "adequate prescription", "prescri*", "knowledge", "prophylactic use", "prophilaxys", "effectiveness", "cost effectiveness", "cost-effectiveness", "economic evaluation", "costs", "costing", "cost effectiveness analysis", "cost-effectiveness analysis", "cost benefit analysis", "cost-benefit analysis", "cost utility analysis", "cost-utility analysis", "utilization", "utilisation", "drug use", "medicine use", "essential medicine*", "drug information", "drug therapy", "consumption", "prescribing practices", "prescribing behaviour", "prescribing behavior"
Countries	"low and middle income countr*", "low income countr*", "middle income countr*", LMIC*, "developing countr*", Afghanistan, Benin, Burkina Faso, Burundi, Central African Republic, Chad, Comoros, Democratic Republic of Congo, Eritrea, Ethiopia, The Gambia, Guinea, Guinea Bissau, Guinea-Bissau, Haiti, Democratic People's Republic of Korea, Korea, Liberia, Madagascar, Malawi, Mali, Mozambique, Nepal, Niger, Rwanda, Senegal, Sierra Leone, Somalia, South Sudan, Tanzania, Togo, Uganda, Zimbabwe, Armenia, Bangladesh, Bhutan, Bolivia, Cabo Verde, Cambodia, Cameroon, Republic of Congo,

	Congo, Cote d'Ivoire, Djibouti, Arab Republic of Egypt, Egypt, El Salvador, Ghana, Guatemala, Honduras, India, Indonesia, Kenya, Kiribati, Kosovo, Republic of Kyrgyz, Kyrgyz, Lao PDR, Lao, Lesotho, Mauritania, Federated States of Micronesia, Micronesia, Moldova, Mongolia, Morocco, Myanmar, Burma, Nicaragua, Nigeria, Pakistan, Papua New Guinea, Philippines, Samoa, Sao Tome and Principe, Solomon Islands, Sri Lanka, Sudan, Swaziland, Arab Republic of Syria, Syria, Tajikistan, Timor-Leste, Timor Leste, East Timor, Tonga, Tunisia, Ukraine, Uzbekistan, Vanuatu, Vietnam, West Bank and Gaza, Republic of Yemen, Yemen, Zambia, Albania, Algeria, American Samoa, Angola, Argentina, Azerbaijan, Belarus, Belize, Bosnia and Herzegovina, Botswana, Brazil, Bulgaria, China, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Equatorial Guinea, Guinea, Ecuador, Fiji, Gabon, Georgia, Grenada, Guyana, Islamic Republic of Iran, Iran, Iraq, Jamaica, Jordan, Kazakhstan, Lebanon, Libya, Republic of Macedonia, Macedonia, Malaysia, Maldives, Marshall Islands, Mauritius, Mexico, Montenegro, Namibia, Palau, Panama, Paraguay, Peru, Romania, Russian Federation, Russia, Serbia, South Africa, St Lucia, St Vincent and the Grenadines, Suriname, Thailand, Turkey, Turkmenistan, Tuvalu, Venezuela RB, Venezuela

Terms within each row are separated by OR
Terms across each row are separated by AND
Limited to publications related to Humans
Limited to publications since January 1990 to 2017

Data analysis and synthesis:

The search results will be extracted into Mendeley 1.17.11 and checked for duplicates, which will be removed. CC and NB will independently screen all titles and abstracts retrieved from their literature searches. If there is uncertainty around whether certain studies should be included, the other team members (MK and VW) will independently appraise these studies to resolve the uncertainty. Following this screening phase, one researcher (CC) will review the full text of the papers to ensure that all inclusion criteria are met. Studies not meeting one or more of the inclusion criteria will be excluded. If there is uncertainty around the inclusion of studies at this stage, a second round of appraisal will be undertaken by MK. Any outstanding disputes will be resolved by VW. The selection process will be summarised in a flow chart that will also document the number of excluded studies, and reasons for exclusion (Figure 2). Studies published in Spanish, French or Portuguese will be translated by CC into English and made available for the team to discuss. CC will extract the data into a data extraction form in Excel to capture details about the authors, country setting, study design, description of intervention package, outcome indicators and results.

[Insert Figure 2 here]

Once the data have been extracted, we will categorise studies according to the different types of behaviour change interventions using the BCW. Interventions will be assessed as either single- or

multi-faceted, as well as by the level of effectiveness and/or cost-effectiveness, and generalisability of results. Given that the included studies might have different evaluation designs, we will analyse the results for RCT, ITS, CBA, quasi-experimental studies separately. We anticipate a high degree of heterogeneity amongst study outcomes as interventions will be tailored to specific behaviours, populations and country settings. If there is some degree of homogeneity in the outcomes assessed across all or a sub-set of included studies, we will conduct a meta-analysis of effect with sub-group analysis. Otherwise a narrative synthesis strategy will be used [35]. Careful consideration will also be given to publication bias across studies and selective reporting within studies.

Finally, we will conduct an appraisal of the quality of the included studies using the GRADE checklist [31], which has been widely used by the World Health Organization, Cochrane Collaboration, Agency for Healthcare Research and Quality (USA) and National Institute of Health and Care Excellence (UK) [36]. This checklist explicitly evaluates the quality of the evidence and the strengths and weaknesses of the recommendations that follow [37].

Study dates:

This study is on-going and the anticipated completion date for data extraction is 31 May 2018.

Patient and public Involvement:

Patients and/or public are not involved in this study.

Ethics and dissemination:

As no individual patient data is used in this study, ethical approval is not required. The systematic review's findings will be disseminated in a peer-reviewed journal, and presented at relevant international conferences.

Discussion

The extent of the adverse impacts of ABR are widely known, and recognised as a global public health concern. Timely and appropriate interventions and programmes need to be implemented to alleviate its harmful impact on people, communities, and health systems. This review will be one of the first to focus on interventions designed to improve the use of antibiotics in LMICs. The results will be of direct benefit to governments and donors who are seeking to respond to the threat of ABR by developing evidence-based national strategies and action plans that include priority interventions to control resistance to antibiotics and antimicrobials. This review will provide a comprehensive

overview of available evidence on both the effectiveness and cost-effectiveness of interventions that

will aid priority-setting and investment decisions.

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Figure legend
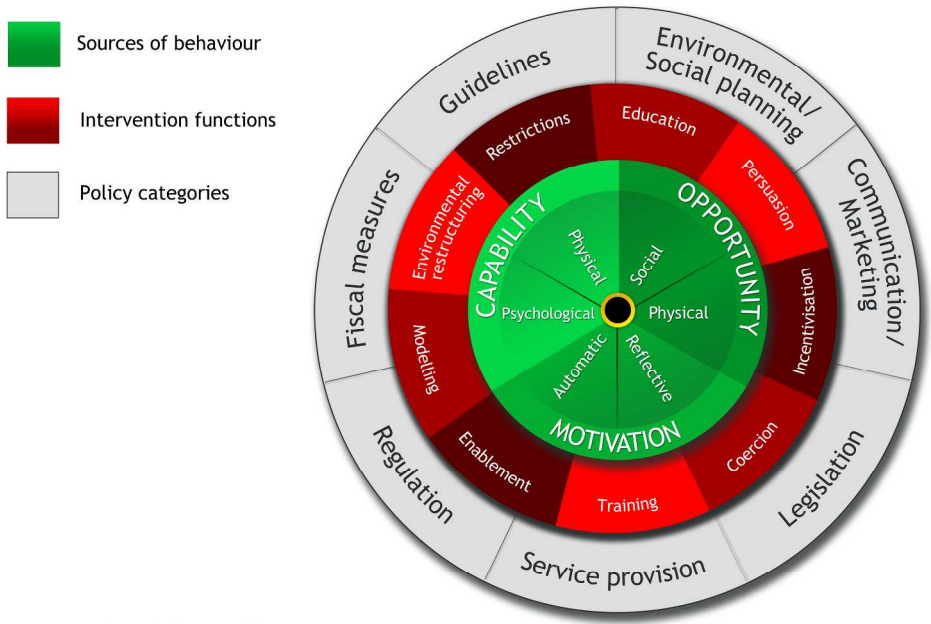Figure 1: Behaviour change wheel (reproduced from Michie et al 2011 [30]).
Figure 2: Flow diagram

Authors' contributions: All authors contributed equally to the design of the study. NB and CC drafted the manuscript, with support from MK and VW. VW is the guarantor of the review.

Competing interests statement: The authors have no competing interests.

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Source: Michie et al, 2011

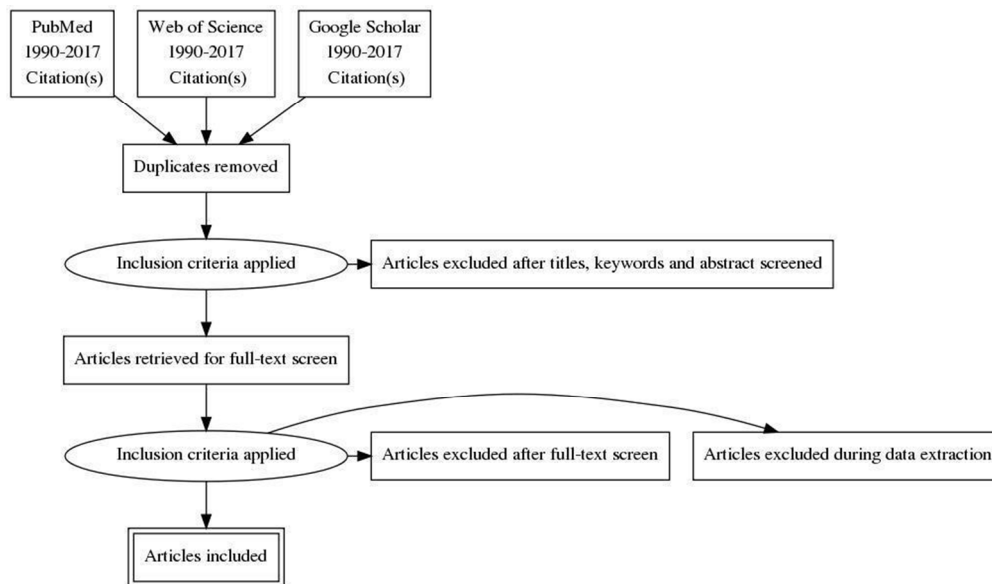Figure 1: Behaviour change wheel

250x176mm (300 x 300 DPI)

Figure 2: Flow diagram

85x50mm (300 x 300 DPI)

Appendix 1: World Bank Country Classification 2016

Low Income Countries (31)

Afghanistan; Benin; Burkina Faso; Burundi; Central African Republic; Chad; Comoros; Democratic Republic of Congo; Eritrea; Ethiopia; The Gambia; Guinea; Guinea-Bissau; Haiti; Democratic People's Republic of Korea; Liberia; Madagascar; Malawi; Mali; Mozambique; Nepal; Niger; Rwanda; Senegal; Sierra Leone; Somalia; South Sudan; Tanzania; Togo; Uganda; Zimbabwe

Lowe-middle Income Countries (52)

Armenia; Bangladesh; Bhutan; Bolivia; Cabo Verde; Cambodia; Cameroon; Republic of Congo; Cote d'Ivoire; Djibouti; Arab Republic of Egypt; El Salvador; Ghana; Guatemala; Honduras; India; Indonesia; Kenya; Kiribati; Kosovo; Republic of Kyrgyz; Lao PDR; Lesotho; Mauritania; Federated States of Micronesia; Moldova; Mongolia; Morocco; Myanmar; Nicaragua; Nigeria; Pakistan; Papua New Guinea; Philippines; Samoa; São Tomé and Principe; Solomon Islands; Sri Lanka; Sudan; Swaziland; Arab Republic of Syria; Tajikistan; Timor-Leste; Tonga; Tunisia; Ukraine; Uzbekistan; Vanuatu; Vietnam; West Bank and Gaza; Republic of Yemen; Zambia

Upper-middle Income Countries (56)

Albania; Algeria; American Samoa; Angola; Argentina; Azerbaijan; Belarus; Belize; Bosnia and Herzegovina; Botswana; Brazil; Bulgaria; China; Colombia; Costa Rica; Cuba; Dominica; Dominican Republic; Equatorial Guinea; Ecuador; Fiji; Gabon; Georgia; Grenada; Guyana; Islamic Republic of Iran; Iraq; Jamaica; Jordan; Kazakhstan; Lebanon; Libya; Republic of Macedonia; Malaysia; Maldives; Marshall Islands; Mauritius; Mexico; Montenegro; Namibia; Palau; Panama; Paraguay; Peru; Romania; Russian Federation; Serbia; South Africa; St. Lucia; St. Vincent and the Grenadines; Suriname; Thailand; Turkey; Turkmenistan; Tuvalu; Venezuela

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-8
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned	7,8

		limits, such that it could be repeated		
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7-9	
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-9	
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-9	
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7-9	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8-9	
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8-9	
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9	
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8-9	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8-9	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8-9	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8-9	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9	

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.