Interventions for the prevention of cardiovascular diseases: a protocol for a systematic review of economic evaluations in low-income and middle-income countries

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ABSTRACT

Introduction: Low-income and middle-income countries (LMICs) are experiencing a growing disease burden due to cardiovascular and other chronic non-communicable diseases. Interventions for the control of these diseases are paramount; however, these countries are faced with competing health and financial needs. There is an urgent need for quality evidence on cost-effective strategies to address these chronic diseases. We aim to synthesise the current literature on economic evaluations of interventions for primary and secondary cardiovascular disease prevention in LMICs.

Methods and analysis: A systematic review of studies (published and unpublished) in LMICs up to 30 October 2016 will be conducted. The following databases will be searched: PubMed/MEDLINE, EMBASE, SCOPUS, CINAHL, Web of Science, EconLit, NHS Economic Evaluations Database (NHS EED). Data sources specific to African literature, such as the WHO AFROLIB, Africa Index Medicus and African Journals online (AJOL) as well as grey literature, will also be searched. 2 reviewers shall independently screen potential articles for inclusion and disagreements shall be resolved by consensus. Quality appraisal of studies shall be done using Drummond’s checklist for economic evaluation of studies. A descriptive synthesis of the evidence obtained is planned. The primary outcomes will be costs per life years gained or unit of clinical outcome, cost per quality-adjusted life years or disability-adjusted life years. This systematic review protocol has been prepared according to the Preferred Reporting Items for Systematic reviews and Meta-analyses for Protocols (PRISMA-P) 2015 statement.

Ethics and dissemination: Ethics approval is not required considering that this is a protocol for a systematic review of published studies. Results from this review will be disseminated via conference presentations and peer-reviewed journal publications.

Trial registration number: CRD42016043510.
incidence of cardiovascular events (ischaemic heart disease and strokes) in individuals at risk but who have not yet developed overt or clinical CVD. Efforts aimed at preventing recurrent clinical events (ischaemic heart disease, stroke) in individuals with established CVD is known as secondary prevention. Studies have demonstrated the beneficial impacts of pharmacological interventions in primary and secondary prevention of CVD, though with caveats for population-based interventions. The need for economic assessment of these studies to identify those which have best value for money is paramount. Owing to finite financial resources akin to these countries, and growing healthcare needs, it is almost inevitable for governments, health policy and decision makers to make choices via balancing costs and health benefits of intervention programmes geared towards addressing these health problems. Suhrcke and colleagues previously suggested that evidence for economic evaluation of CVD interventions was accumulating but still scarce in low-income and middle-income countries (LMICs). Efforts in a review later by Schroufi and colleagues on cost-effectiveness studies conducted in low-income settings up to January 2011. Preliminary searches suggest that since then, there have been more studies assessing costs and consequences of interventions for the prevention of CVD. We propose a systematic review which will synthesise all studies carried out thus far until October 2016 reporting economic evaluations of CVD in low-income and middle-income settings and hence provide overall updated evidence on which interventions provide maximum health benefits with limited costs.

Objectives
The objective of this review is to identify and provide a comprehensive synthesis of interventions for primary and secondary prevention of CVD delivered to populations in LMICs (as defined by the current World Bank classification), all through until October 2016.

Review question
The proposed review will aim to address the following questions:
1. What are the costs and costs relative to the outcome measure of interventions for CVD prevention in LMICs from various perspectives (individual patients and their families, healthcare providers and society)?
2. What are the contexts that are conducive to lower cost and increase the effectiveness of interventions for CVD prevention?

METHODS
This review protocol is registered in the PROSPERO International Prospective Register of systematic reviews (Registration Number: CRD42016043510) and has been prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P) 2015 statement.

Criteria for considering studies for the review
Inclusion criteria
A. Study population: studies involving adults (age ≥18 years) living in LMICs.
B. Intervention type: studies reporting on interventions for either primary or secondary prevention of CVD.
C. Setting: primary (randomised control trials and observational studies) or modelling studies conducted in LMICs.
D. Comparator: studies identifying how the interventions were compared, either with respect to current practice or the ‘do nothing’ scenario.
E. Outcome measures: the outcomes of interest would be: cost per life year gained or per unit clinical outcome, cost per quality-adjusted life years (QALYs) or cost per DALYs.
F. Study designs: studies reporting full economic evaluations (cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), cost-utility analysis (CUA)) shall be considered. This would include empirical as well as modelling studies.
G. Language: studies reported in English and French.

Exclusion criteria
A. Study setting: any studies conducted in high-income countries and duplicate publications of the same material will be excluded. If a study has been published in more than one journal, only the most complete and recent version will be considered.
B. Study types: narrative reviews, letters to the editor, case reports, editorials or any other lacking explicit information and methods will be excluded.

Data sources and search strategy
The following databases will be searched: PubMed/MEDLINE, EMBASE, SCOPUS, Web of Science, EconLit, NHS Economic Evaluations Database, and Cochrane Library, Centre for Reviews and Dissemination (CRD) database, WHO AFROLIB and Africa Index Medicus (AIM). An elaborate and comprehensive search strategy will be designed for maximum sensitivity combining relevant terms, country and regional names to obtain the maximum possible number of studies. Table 1 shows the proposed PubMed search strategy which shall be adapted to other databases. If a country has changed its name over time, both names will be included in the search. We will also search the reference list of articles for potential articles of interest for inclusion.

Grey literature
We will contact authors, experts in the field, conference websites and research organisations for relevant material. This will be done via emails. In the event of no
response after repeated attempts to contact authors via email for relevant information, the said study shall be excluded.

**Study records**

**Data management**

All studies identified shall be imported to EndNote V.7.4 software for de-duplication of records. After this, all studies shall be uploaded into Rayyan QCRI, which is an internet-based program that facilitates collaboration between investigators during the screening and selection of studies to be finally included in the review. Prior to screening of studies, investigators shall develop a tool according to the eligibility criteria to guide the selection process.

**Screening**

Two reviewers (LNA and LV) will independently select studies that meet inclusion criteria. Titles and abstracts shall first be screened following inclusion criteria set a priori for relevance. Full texts of potentially eligible studies shall then be obtained and further screened for relevance using the predetermined tool for final eligibility for inclusion. Any disagreements shall be resolved by consensus. In case there is unclear or ambiguous information on studies, the corresponding authors shall be contacted via email to request clarification. The reasons for exclusion of any studies shall be documented and a flow chart shall be presented of the entire review process.

**Data extraction**

Two reviewers (LNA and LV) shall independently extract data from the final full texts of eligible studies using a predetermined data extraction sheet. Any disagreements or inconsistencies shall be resolved by consensus.

**Data items**

We shall extract the following data from included studies: author and year of publication, study setting,
geographical region, study design, type of preventive intervention (primary vs secondary; pharmacological vs non-pharmacological), intervention target (individual vs population), time horizon of intervention, effect size (relative risk) associated with intervention, CVD risk factor targeted (single vs multiple), type of economic evaluation or method (CEA, CUA, CBA), modelling technique used, outcome measure (cost per unit of clinical outcome, QALYs or DALYs), economic perspective, uncertainty analysis.

Risk of bias and quality appraisal
The quality of included studies will be rated independently by two reviewers (LNA and LV) using the checklist (table 2) for economic evaluations produced by Drummond. This checklist contains 35 questions (with yes, no and not clear as responses) divided into three sections. The quality rating will then be reported and ranked using the National Institute for Health and Care Excellence (NICE) scale from ‘++’ for good-quality, ‘+’ for moderate-quality, and ‘−’ for low-quality studies, indicating
the lowest to highest risk of bias, respectively. For decision modelling studies, we shall use Philip’s checklist for critical appraisal. Discrepancies will be resolved by consensus. Inter-rater agreement on screening, data abstraction and quality assessment will be assessed using Cohen’s κ statistic. We plan to present a table showing risk of bias and quality rating of included studies.

Data synthesis
We plan to do an amalgamation of our findings while answering our research questions. In a descriptive fashion, we shall present and discuss the studies overall by geographical regions, according to type (primary vs secondary) of CVD prevention, intervention target, CVD risk factor (single vs multiple) assessed as well as perspective (patient, healthcare provider, societal) for economic evaluation. We shall classify studies according to economic evaluation (CEA, CUA, CBA) performed and also discuss the origin of data used in evaluation (intervention effect size and estimates of effectiveness, estimates of costs, resource usage, epidemiological data). For comparison, included studies shall be summarised (in tabular form) showing currency and year used for analysis, interventions assessed, their costs, incremental cost-effectiveness ratio and cost-effectiveness as reported by the authors in the study.

Reporting this review
The resulting systematic review will be reported according to the PRISMA 2009 statement. Flow diagrams shall be used to demonstrate the study selection process detailing reasons for exclusion at each stage. The search strategy and quality appraisal tool will be published as online supplementary material.

Potential amendments
We do not envisage any further amendments to this protocol. However, in case of any changes, the amendment shall be detailed out in the final report.

Conclusion
Low-income settings are disproportionately affected by the current CVD epidemic, with the highest rates of premature deaths. Most of these countries similarly carry the largest burden of communicable diseases. With their mostly finite financial resources, and competing health needs, there is thus an urgent need for cost-effective strategies in these countries to address the disease burden. This review will update previous efforts by Shroufi and colleagues and Suhreke and colleagues by providing current evidence on economic evaluations of interventions for CVD prevention to inform policy and decision makers in LMICs.

Ethics and dissemination
Considering that systematic reviews are based on available published data, this review would therefore not need any formal ethical approval. Results of this systematic review will be disseminated via conference presentations and peer-reviewed publications.

Contributors
LNA conceived the paper and wrote the first draft. JLV provided revisions to the manuscript. All authors read and approved the final manuscript. LNA is the guarantor of the review.

Competing interests
None declared.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data sharing statement
All data for this manuscript are included in the submission.

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REFERENCES