PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Improving diagnostic antimicrobial stewardship in respiratory tract infections: a protocol for a scoping review investigating point-of-care testing programs in community pharmacy
AUTHORS	Saha, Sajal K; Promite, Shukla; Botheras, Carly L.; Manias, Elizabeth; Mothobi, Nomvuyo; Robinson, Suzanne; Athan, Eugene

VERSION 1 – REVIEW

REVIEWER	Zha, Lei Xi'an Jiaotong-Liverpool University
REVIEW RETURNED	30-Nov-2022

GENERAL COMMENTS	The present manuscript is a well-designed and written protocol, which will help address interesting questions regarding implementing POCT tests in clinical pharmacies. There are only minor suggestions that authors might take into consideration: 1) In 5. assessing the quality of studies part, it is suggested to name out which tools would be used clearly; 2) Regarding data analysis, it is helpful to mention clearly how to address results adjusted with different variables in different studies. Anyway, it is a well-written and transparent protocol for an interesting and valuable scoping review.

REVIEWER	Puente-Maestu, Luis Hospital Geenral Universitario Gregorio Marañón, Respiratory Medicine
REVIEW RETURNED	13-Dec-2022

GENERAL COMMENTS	Rather than a proposal for a review of a single topic, this paper describes a framework for a set of different reviews around the tests intended to guide the selection of proper antibiotic therapy in primary care for pharyngeal infections. As it is a proposal the reviewer favors to give the authors the benefit of the doubt regarding some of the 5 different objectives. Particularly the cost effectiveness of the implementation and development of such programs. For which, I am afraid, there will not be enough good quality information. From the methodological point of view, the main issues are: 1) Apart from RCT, other studies are planned to be included. This will greatly reduce the internal validity of the results. 2) The authors do not plan to blind those who will select the studies from certain information that potentially could introduce selection bias such as the institution, authors or even the results of the specific studies. Moreover, those who will select the studies seems to be implicated in the analysis of their results.

	3) It is true that it is difficult to define the quality of a study, nonetheless the authors should describe the minimums of quality they are going to accept, such as size, bias minimization and so on. 4) They do not state if they are going to introduce quality as a ponderation criterion. 5) The authors do not describe the statistical model they are going to use to combine the results/data of the studies they plan to include, even if it will depend on the heterogeneity of the studies. 6) The authors do not describe how they are going to evaluate the heterogeneity. For example, at first sight it seems questionable to pool together interventions based on PCR with interventions based on microbiological tests particularly if they intend to perform a metanalysis which will be already burdened with the heterogeneity of the designs, quality and sample sizes. Specific: 1. Page 10 line 27: “A data extraction template will be created and validated by data extractors”. As this is a relevant step for the study, this reader wonders how this will be achieved. The authors should add a brief comment, particularly on which will be the validation criterion and the gold standard for validation. Defining the quality of a study is a controversial issue among RCT, but in this case studies with other designs are going to be included as well. In addition, not all the papers may provide all the information required in such questionnaires. It will be also interesting to know how they will manage the scenario in which the template does not meet the expectations of the investigators. This reader wonders whether what the authors want to say with the term “validation” is just that the template will be double checked to assure it allows to register all the relevant information that will be tried with the first few papers to see that it does or else just a second “senior” investigator will look at the papers to see if all the information was thoroughly and correctly collected. 2. Page 10, line 55 “evidence-based risk assessment tool specific to study design of randomized controlled trial or non-randomized controlled trial” the authors need to describe the tool or quoting a reference where it is described. 3. Page 11, line 37 “POCT services and its characteristics” that should include the type and brand of the test used, since not all have the same sensitivity and specificity and the sample employed if available nasopharyngeal or oropharyngeal. 4. Page 12, line 13 “Continuous variables will be recorded with mean difference and 95% CI”. Be sure that the authors of the primary sources checked the normality assumption, if not median and interquartile range would be a better descriptor. Be aware thar relative risk are preferred to measure the effects of interventions. 5. Page 12, line 32 “The other effect measures include”. The authors must keep in mind that hypotheses based on secondary variables must be considered either as exploratory hypotheses or the alpha error must be adjusted according to the number of statistical variables and no longer can be 0,05. 6. Page 12, line 56 “help pharmacists’ clinical decision making”. While clinical decisions made by pharmacists may occur in some countries, they might be even illegal in others, and certainly not recommended, particularly with drugs that require a medical prescription such as antibiotics. 7. Page 13, line 8 While the current philosophy assumes that reducing the use of antibiotics can’t be anything but good, what can be true in a broad sense, the authors need to be neutral in the

	interpretation of “cost-effectivity of reducing antibiotic use” (and in the selection of studies too as it was said before) 8. Since what matters to the clinical is the success of the intervention or no-intervention (i.e antibiotic treatment, even delayed, or not- antibiotic treatment) in the concept of success it must be included the time to recovery and the consequences of failure(GP usually have to face decisions on individual people from information that only has been addressed in population studies) and the costs should include the need for a closer control in the case of deciding to wait and see. I wonder if this information will be available. 9. I wonder how the QUALY will be measured. It is easy to measure utility in chronic diseases, but much more difficult in acute ones. Besides, it is difficult to grasp which are the expectations of finding papers addressing the impact of the interventions they want to analyze in the cost and QUALY along the patient lifetime of rheumatic fever, or rheumatic heart disease. 10. Page 13, line 18 Data will be analyzed using an implementation science framework, Consolidated Framework for Implementation Research (CFIR) to present reported implementation challenges and opportunities to inform design of future implementation study. Factors influencing implementation of POCT programs in community pharmacies by inner and outer contexts”. This seems a totally different issue for which regulatory as well as the type of health system may have influence. I am not sure if this goal can be achieved from analyzing RCT or other experimental contexts that do not reflect the real clinical practice.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Lei Zha, Xi'an Jiaotong-Liverpool University
Comments to the Author:
The present manuscript is a well-designed and written protocol, which will help address interesting questions regarding implementing POCT tests in clinical pharmacies.
Thanks so much for highlighting the importance of the work.
There are only minor suggestions that authors might take into consideration: 1) In 5. assessing the quality of studies part, it is suggested to name out which tools would be used clearly.
We added the risk assessment tools, the Cochrane risk assessment tool and ROBINS-I risk assessment tool which will be used to assess the quality of RCTS and NRCTs respectively.
2) Regarding data analysis, it is helpful to mention clearly how to address results adjusted with different variables in different studies. Anyway, it is a well-written and transparent protocol for an interesting and valuable scoping review.

Data analysis section (section 6) has been amended. All changes and additions have been marked in red.

Reviewer: 2
Dr. Luis Puente-Maestu, Hospital Geenral Universitario Gregorio Marañón
Comments to the Author:
Rather than a proposal for a review of a single topic, this paper describes a framework for a set of different reviews around the tests intended to guide the selection of proper antibiotic therapy in

primary care for pharyngeal infections. As it is a proposal the reviewer favors to give the authors the benefit of the doubt regarding some of the 5 different objectives. Particularly the cost effectiveness of the implementation and development of such programs. For which, I am afraid, there will not be enough good quality information.

This is a scoping review but not a systematic review therefore it covers a broad ranges evidence (e.g., effectiveness, feasibility, and implementation challenges) on a single topic of POCT programs in community pharmacy to improve safe antimicrobial use in RTIs. We strongly agree that there may not have good quality evidence on the cost effectiveness of the implementation and development of such programs. This is why, this research aims to know the scope and breadth of evidence on cost-effectiveness in the literature to inform future research and policy directions for routine use in community pharmacy.

From the methodological point of view, the main issues are:
1) Apart from RCT, other studies are planned to be included. This will greatly reduce the internal validity of the results.
We map out the breadth of evidence in the literature on the topic and examine how research is conducted and what methodologies have been employed on this topic. However, summary results will be presented by study design. Given enough RCTs are found, and if those are meta-analysable, we will conduct subgroup analysis to report results by RCTs and NRCTs.

2) The authors do not plan to blind those who will select the studies from certain information that potentially could introduce selection bias such as the institution, authors or even the results of the specific studies. Moreover, those who will select the studies seems to be implicated in the analysis of their results.
We reported that three reviewers (SKS, SP and CB) will independently screen titles and abstracts and review full text using predefined inclusion and exclusion criteria in the Covidence systematic review software. Discrepancies will be resolved over discussion among the three reviewers. This approach will prevent selection bias. In this process, all voting by reviewers is blinded, meaning that reviewers will be unable to see others votes until they've cast their own, and vice versa.

3) It is true that it is difficult to define the quality of a study, nonetheless the authors should describe the minimums of quality they are going to accept, such as size, bias minimization and so on. 4) They do not state if they are going to introduce quality as a ponderation criterion.
We added the risk assessment tools, the Cochrane risk assessment tool and ROBINS-I risk assessment tool which will be used to assess the quality of RCTS and NRCTs respectively.

5) The authors do not describe the statistical model they are going to use to combine the results/data of the studies they plan to include, even if it will depend on the heterogeneity of the studies. 6) The authors do not describe how they are going to evaluate the heterogeneity. For example, at first sight it seems questionable to pool together interventions based on PCR with interventions based on microbiological tests particularly if they intend to perform a metanalysis which will be already burdened with the heterogeneity of the designs, quality and sample sizes.

Statistical model that will be used to combine results has been mentioned and revised. In determining the effectiveness of POCT program, given adequate RCTs and meta-analysable data are available, a random effects model will be used to measure the pooled estimates of POCT intervention effect. The effect will be reported utilising risk ratio and 95% CI. Forest plots, and I2 statistics will measure across-study heterogeneity. Subgroup analyses will determine the sources of heterogeneity [e.g., POCT strategies, implementation approaches, sample size, design, study quality]. Summary statistics will be used to measure combined effect of the selected studies. Descriptive summary of the results will be generated. In Section 6, all changes and additions related to data analysis are marked in red.

Specific:
1. Page 10 line 27: “A data extraction template will be created and validated by data extractors”. As this is a relevant step for the study, this reader wonders how this will be achieved. The authors should add a brief comment, particularly on which will be the validation criterion and the gold standard for validation. Defining the quality of a study is a controversial issue among RCT, but in this case studies with other designs are going to be included as well. In addition, not all the papers may provide all the information required in such questionnaires. It will be also interesting to know how they will manage the scenario in which the template does not meet the expectations of the investigators. This reader wonders whether what the authors want to say with the term “validation” is just that the template will be double checked to assure it allows to register all the relevant information that will be tried with the first few papers to see that it does or else just a second “senior” investigator will look at the papers to see if all the information was thoroughly and correctly collected.

The aim of the scoping review is to create a descriptive results summary which addresses the scoping review's objectives, and ideally answers the questions of the review. Authors will develop a data extraction form which will be pilot tested by the data extractors. The process will confirm that the extraction form has captured all the relevant information required for analysis and reporting. The Extractors’ feedback will be used to refine the form and finalise its usability and completeness. Duplicate data extraction will be occurred independently and any disagreements if remains will be addressed through discussion. The third reviewer will be approached if a consensus is not made.

2. Page 10, line 55 “evidence-based risk assessment tool specific to study design of randomized controlled trial or non-randomized controlled trial” the authors need to describe the tool or quoting a reference where it is described.
Revised

3. Page 11, line 37 “POCT services and its characteristics” that should include the type and brand of the test used, since not all have the same sensitivity and specificity and the sample employed if available nasopharyngeal or oropharyngeal.
Revised

4. Page 12, line 13 “Continuous variables will be recorded with mean difference and 95% CI”. Be sure that the authors of the primary sources checked the normality assumption, if not median and interquartile range would be a better descriptor. Be aware thar relative risk are preferred to measure the effects of interventions.
Amended

5. Page 12, line 32 “The other effect measures include”. The authors must keep in mind that hypotheses based on secondary variables must be considered either as exploratory hypotheses or the alpha error must be adjusted according to the number of statistical variables and no longer can be 0,05.
Amended

6. Page 12, line 56 “help pharmacists’ clinical decision making”. While clinical decisions made by pharmacists may occur in some countries, they might be even illegal in others, and certainly not recommended, particularly with drugs that require a medical prescription such as antibiotics. Country wise pharmacy practice and policy varies to the use of POCT. We believe that published study would get ethics approval before testing the POCT intervention in pharmacy. Our study would reflect how many countries articles are coming from, which country POCT use is growing, and we will have an opportunity to seek pharmacy rights on POCT use of those countries while reporting the

review for publication.

7. Page 13, line 8 While the current philosophy assumes that reducing the use of antibiotics can't be anything but good, what can be true in a broad sense, the authors need to be neutral in the interpretation of "cost-effectivity of reducing antibiotic use" (and in the selection of studies too as it was said before)
The author team is consisting of doctors, a pharmacist, microbiologists, epidemiologists, and POCT expert whose collective inputs and review of results will confirm the neutral interpretation of the study results. The study will follow scientific methodologies and tools as described to avoid bias at any level.

8. Since what matters to the clinical is the success of the intervention or no-intervention (i.e antibiotic treatment, even delayed, or not- antibiotic treatment) in the concept of success it must be included the time to recovery and the consequences of failure(GP usually have to face decisions on individual people from information that only has been addressed in population studies) and the costs should include the need for a closer control in the case of deciding to wait and see. I wonder if this information will be available.

The outcomes, time to recovery and the consequences of failure, if reported in the selected study will be reported.

9. I wonder how the QUALY will be measured. It is easy to measure utility in chronic diseases, but much more difficult in acute ones. Besides, it is difficult to grasp which are the expectations of finding papers addressing the impact of the interventions they want to analyze in the cost and QUALY along the patient lifetime of rheumatic fever, or rheumatic heart disease.
We would seek if the selected study used any decision analytic model to estimate the cost-effectiveness of POCT, compared with standard care, in targeted RTI populations. The reported incremental cost-effectiveness ratios of POCT testing per quality-adjusted-life-year (QALY) gained and per antibiotic prescription avoided will be descriptively summarised and reported.

10. Page 13, line 18 Data will be analysed using an implementation science framework, Consolidated Framework for Implementation Research (CFIR) to present reported implementation challenges and opportunities to inform design of future implementation study. Factors influencing implementation of POCT programs in community pharmacies by inner and outer contexts". This seems a totally different issue for which regulatory as well as the type of health system may have influence. I am not sure if this goal can be achieved from analysing RCT or other experimental contexts that do not reflect the real clinical practice.
Lessons learned from the trials are helpful to develop and design the future implementation trials. We strongly believe that reporting implementation challenges and opportunities from identified studies would guide future implementation trial design. Apart from RCTs/NRCTs, surveys or qualitative studies exploring the perceptions of pharmacists regarding POCT implementation will be useful evidence to know the individual, social, health system and policy issues influencing POCT implementation in community pharmacy. The implementation science framework will scientifically guide our reporting by considering the country, context, and health system issues. In doing so, evidence gaps in the literature will be better known.

VERSION 2 – REVIEW

REVIEWER	Zha, Lei Xi'an Jiaotong-Liverpool University
REVIEW RETURNED	28-Jan-2023

GENERAL COMMENTS	The authors have addressed my questions well.

REVIEWER	Puente-Maestu, Luis Hospital Geenral Universitario Gregorio Marañón, Respiratory Medicine
REVIEW RETURNED	17-Jan-2023

GENERAL COMMENTS	No further comments