A Comprehensive Systematic Review Protocol of Vaccine Hesitancy in Low- and Middle-Income Countries

Ebenezer Wiafe (weben38@gmail.com)
University of KwaZulu-Natal College of Health Sciences https://orcid.org/0000-0002-0496-5737
Keiyara Rameshwarnath
University of KwaZulu-Natal College of Health Sciences
Danielle Tyler
University of KwaZulu-Natal College of Health Sciences
Simo Mbanjwa
University of KwaZulu-Natal College of Health Sciences
Nazeefah Bux
University of KwaZulu-Natal College of Health Sciences
Ndumiso Mbatha
University of KwaZulu-Natal College of Health Sciences
Tasmiyah Syed
University of KwaZulu-Natal College of Health Sciences
Shweta Devnarain
University of KwaZulu-Natal College of Health Sciences
Kofi Boamah Mensah
Kwame Nkrumah University of Science and Technology Faculty of Pharmacy and Pharmaceutical Sciences
Frasia Oosthuizen
University of KwaZulu-Natal College of Health Sciences
Varsha Bangalee
University of KwaZulu-Natal College of Health Sciences

Protocol

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Abstract

Background: Vaccine hesitancy has presented to public health, especially the fight against vaccine-preventable diseases, a great challenge in promoting global health. In this coronavirus era, it has become important to examine the concept of vaccine resistance, and effect adequate measures to clamp down on vaccine hesitancy. In an attempt to address vaccine hesitancy, some studies have determined the causes of vaccine hesitancy, reported on the reasons why individuals in resource-constraint countries delay and ultimately reject vaccination interventions, and provided evidence on measures that have been successful at reducing vaccine hesitancy. This comprehensive review protocol, which has been developed as a teaching tool, aims to present a stepwise approach to examining these studies.

Methods: The protocol will guide the conduct of the systematic review in an orderly manner and by the allocated number of reviewers: the search strategy development and testing (2); the database search (6); the titles and abstract screening (3); full-text screening (3); the data extraction (7); and the quality assessment of included studies (2). The search strategy has been tested with results in 3 databases from inception to June 30, 2021: MEDLINE via EBSCOhost (n=1364), CINAHL via EBSCOhost (n=91), and Web of Science (n=3472). The included research papers will be reviewed according to the convergent segregated approach as explained in the Joanna Briggs Institute's (JBI) manual.

Conclusion: The review protocol, when successfully applied to conduct the systematic review, will provide some guidance to policy-makers as we tackle coronavirus through vaccination intervention.

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Background

Viruses have plagued humans throughout history, often being responsible for increased mortality and morbidity rates across the globe. The diversity of structure, genetic elements, and replication strategies have made these entities difficult to eradicate [1]. Viruses are resilient and capable of remaining dormant for many years and have been found to withstand harsh conditions such as extreme cold or heat [2]. Viruses do not have metabolic enzymes of their own and are therefore unable to produce proteins [3]. They are obligate organisms, only able to replicate within a host cell. Viruses damage or kill host cells by causing the release of hydrolytic enzymes from lysosomes in the host cell, thus causing infectious diseases such as the common cold, flu, Ebola, HIV/AIDS, Covid-19, amongst many others.

Immunization is an attempt to counteract the fatalities caused by viruses [4]. A vaccine is a weakened form of a pathogenic organism that has been formulated for administration into other organisms. The administration of a vaccine is called vaccination and this process brings about immunity against the pathogen. Immunization is thus the response of the vaccinated organism to the vaccine whereby the organism's immune system identifies the pathogen and produces antibodies against that pathogen to protect that organism from a future infection [5].

The reduction in mortality, morbidity and disability rates globally since the introduction of vaccines presents proof of vaccine efficacy [6]. It has been estimated that over 3 million deaths and 75 000 disabilities are prevented annually by vaccination [7]. High vaccination coverage in a population slows down infection and disease transmission through indirect protection or herd immunity. Herd immunity is "the indirect protection from a contagious infectious disease that happens when a population is immune either through vaccination or immunity developed through previous infection" [8]. This decreases the chances of infections amongst those who are immunocompromised in the community. Many historical diseases such as smallpox, measles, diphtheria, and polio have nearly been eradicated due to vaccination [9].

Successful vaccination programs rely on a high acceptance rate to achieve a reduction in the prevalence and incidence of vaccine-preventable diseases [10]. Despite the exceptional improvement of health through vaccinations, there are still many people who perceive vaccines as unsafe and unnecessary. Consequently, there is an increased delay in the

acceptance or even the rejection of vaccines despite the availability of vaccine services. This is defined as vaccine hesitancy [11]. Vaccine hesitancy is complex and specific, varying across regions, periods, and vaccines [12]. Analyses have been done to understand the complex motives behind vaccine hesitancy and to identify the contributing factors. These include the environment, agent, and host factors that combine to form an epidemiological triad of factors [13].

Environmental factors include information spread via the media, health policies, and social determinants. The "agent" component of the epidemiological triad pertains to the vaccine and disease itself, commenting on the vaccine's safety and efficacy compared to the disease's perceived susceptibility. Host factors are influenced by the education, income levels, experience, and knowledge of the population. The improvement and accessibility of information and communication technologies have promoted the profound expression of vaccine hesitancy [6]. Intense expression of vaccine hesitancy increases the risk of potential vaccine-preventable disease outbreaks, promoting the recurrence of epidemics in the population [10].

There have been multiple studies conducted across the world regarding vaccine hesitancy [14]. A survey conducted in developed countries revealed that possible reasons for vaccine hesitancy included a distrust in health care professionals, previous vaccination experiences, and peer behavior [15]. A United States of America study revealed an increase in the number of measles infections, particularly in homes where vaccination was refused due to non-medical reasons [15]. Other studies emphasized the importance of psychological factors and the perception of high individual risk on vaccine hesitancy [14]. A study conducted in England and Germany revealed that individuals with high income and educational levels were more likely to refuse vaccination, suggesting that socioeconomic and educational factors contribute to vaccine hesitancy [15].

In low- and middle-income countries (LMICs), there have been fewer studies conducted to determine the reasons for vaccine hesitancy. A study from Pakistan reported distrust in the government and vaccine organizations, concerns for personal safety, and conflicts with participant religious beliefs as reasons for vaccine hesitancy [15]. In Africa, many children are not vaccinated despite the availability of vaccination services in their area [16]. The contributing factor to vaccine hesitancy in these regions is the lack of information provided to these families [16]. Therefore, understanding the determinants for vaccine hesitancy in these regions will provide possible techniques for improvement for future endeavors. This will be beneficial, particularly considering the COVID-19 pandemic where the subject of vaccination is imperative.

Review Question

What are the determinants of vaccine hesitancy in LMICs?

Objectives of the Review

1. To determine the causes of vaccine hesitancy.
2. To report on the reasons why individuals in LMICs delay and reject vaccination interventions.
3. To map evidence on successful approaches of reducing vaccine hesitancy.

Methodology

In this critical appraisal and synthesis of evidence, the authors will utilize the mixed-methods approach. This approach has been shown to combine pieces of evidence from qualitative, quantitative, and other mixed-methods studies to successfully provide more seamless and scientific findings on selected topics [17, 18]. Data triangulation, a feature of the mixed-methods approach, has improved the validity of systematic reviews by increasing the scope, depth, and consistency in systematic review methodologies [19]. The methodological approach of this study will permit the use of the qualitative findings to either clarify or contradict the quantitative findings in an explanatory format [20]. The review is expected to

commence in July 2021. The protocol has been registered at the Open Science Framework (Registration DOI: https://doi.org/10.17605/OSF.IO/BVP4S).

Criteria for Studies Inclusion

Interest Population

The review will focus on studies conducted on individuals who are concerned with vaccination activities and programs. The population subgroups will not be limited to:

- Adults (18 years and above) who are potential targets of vaccination programs. For example; travelers who are required by immigration policies to vaccinate against diseases such as yellow fever.
- Children below 18 years, provided parental consent was obtained before their inclusion.
- Healthcare workers, including professionals who are tasked with vaccination.
- Parents/guardians who are to ensure their wards complete vaccination schedules. For example; vaccination schedules targeting childhood vaccine-preventable diseases.
- Vaccination policy-makers. For example; public health professionals who formulate immunization policies for governments and organizations.

The population-specific characteristics of studies that would be included in the review will take into account the age of study subjects, their ethnic backgrounds, and other sociodemographic features of the study subjects.

Phenomenon of Interest

Vaccine hesitancy is the phenomenon of interest for this review. The outright refusal of vaccination interventions and/or the undue delay in accepting vaccination interventions regardless of the availability of immunization services characterizes vaccine hesitancy [21]. Therefore, the research team will consider for inclusion, studies that focused on vaccine hesitancy.

Context of Study

The review will focus on primary vaccine hesitancy studies conducted in low- and middle-income countries according to the World Bank classification. The low- and middle-income countries would include the 29 low-income countries, the 50 lower-middle-income countries, and the 56 upper-middle-income countries. Therefore, the review will consider vaccine hesitancy studies conducted in these 135 countries. The characteristics of the study findings table will reflect these three (3) World Bank income level subgroups and hence, a subgroup analysis will be done [22].

Outcomes of Interest

The facets of vaccine hesitancy that will be studied include; the causes of vaccine hesitancy, the reasons why individuals who reside in LMICs delay and/or reject vaccination services, and the various measures that have been taken by vaccination agencies to address the issue of vaccine hesitancy.

In reporting on the causes of vaccine hesitancy, the review team will screen included studies for causes such as the influx of misleading information about vaccination, the unstable supply of vaccines, poor energy supply which affects cold-chain storage of vaccines, and the poor availability of trained vaccination staff. The reasons behind vaccine hesitancy will be reviewed from the perspective of individuals who are potential targets of vaccination services. Some of the reasons that will be considered include the fear of adverse vaccination reactions, distrust in the effectiveness of vaccines, inconveniencies encountered at vaccination centers, and superstitious beliefs surrounding vaccination services. Measures

that have been successful in addressing vaccine hesitancy will not be limited to education and the adequate supply of vaccines.

Potential studies to be considered

The review team will consider quantitative, qualitative, and mixed-methods primary studies for possible inclusion.

Quantitative studies will not be limited to descriptive studies and cross-sectional studies. All primary studies that are quantitative in their design will be considered. The qualitative arm of the review will consider all forms of interviews, all forms of group discussions included focused-group discussions, observational studies, and other studies that were conducted following the principles of qualitative study design. Primary studies that combined the principles of qualitative and quantitative study designs will constitute the mixed-methods arm.

Criteria for Studies Exclusion

Studies that will be excluded from the review, with grounds of exclusion, include:

- secondary studies including all forms of reviews and overviews.
- editorials, commentaries, conference proceedings, letters to the editor, position statements of organizations, and expert opinions. This is because they are not primary studies.
- book chapters. This is because they do not meet the requirements of primary studies.
- primary studies that are pre-prints or in-press. This is because they have not completed the publication process and hence, have not been rigorously peer-reviewed.
- abstracts only studies. These studies do not have the full component of primary studies suitable for a systematic review.
- primary research articles that do not have abstracts. This is because subjecting such studies to titles and abstracts screening will not be possible.
- studies that were conducted in high-income countries. Including such studies will be contrary to the defined context of the review.
- primary studies that were not reported in the English language. The review team is only fluent in the English language. Therefore, the team will not be able to review studies that were not published in the English language.

Proposed databases and respective search strategies

The review will recruit studies published by journals indexed in Medline, CINAHL, and Web of Science. Except for Web of Science, which will be sourced directly, Medline and CINAHL will be sourced via EBSCOhost. Search strategies for the proposed databases have been developed by EW and reviewed by KBM for the identification of various literature. The preliminary search strategies have been tested by EW and the numerical results of the individual databases have been presented, see Appendix A.

The development of the search strategy took into consideration the PICO framework [23, 24] outlined in the criteria for study inclusion. The keywords of the review also guided the development of the search strategy. The preliminary search strategies were developed according to the three-step procedure employed by Wiafe and his team members (2020) [23].

The application of the search strategies to identify and extract potential studies will be done by KR and DT for Medline, SM and NB for CINAHL, and NM and TS for Web of Science. The reviewer pairs would work independently to improve the quality of the database search, and their results would be pulled by SD in the EndNote reference manager (version X8). The EndNote library manager, SD, will identify and remove duplicates to present a final catalog of search findings for the review. The duration for the database search would span from the inception of the proposed databases to June 30, 2021.

Titles and abstracts screening

The titles and abstracts screening would be done after the identification and removal of duplicates. This activity would be performed independently by three reviewers (KR, DT, and SM). The eligibility criteria would serve as the yardstick for the titles and abstracts screening of studies. Potential studies that will pass this quality assurance stage will thereafter undergo full-text screening. Any disagreements that would arise between the three independent reviewers will be settled in discussion with SD. In instances where the inputs of SD are not appreciated by KR, DT, and SM, FO would be consulted to settle the disagreement.

Full-text screening

Studies that would pass the titles and abstracts screening will be subjected to the full-text screening by three reviewers (NB, NM, and TS) who would function independently. The full-text screening will aim at ensuring that the eligibility criteria are firmly applied to the studies to reduce the risk of errors in this evidence synthesis [25]. In addressing disagreements as part of the quality assurance processes, the approach employed during the titles and abstracts screening would be relied on.

Quality assessment and final inclusion of studies

The quality appraisal tool used by Bangura and colleagues (2020) [26] when they studied the obstacles to childhood vaccination, see Appendix B, will be employed to assess the quality of studies that will pass the full-test screening. This quality appraisal tool has been modified and the assessment criteria have been increased from 14 to 15. The modification was aimed at ensuring the ease of scoring and the interpretation of scores as indicated on the attachment: Appendix B. The quality appraisal of studies will be done independently by KBM and EW. The settlement of disagreements, however, will be settled by FO without the involvement of SD because of the extensive experience of FO. None of the research papers will be excluded based on the methodological quality evaluation outcome.

Data extraction and results

The extraction of data from included studies will be done by six reviewers (second to seventh authors) and the eighth will recheck for the completion and accuracy of data. The issues of data inconsistency due to disagreements between the six reviewers will be addressed by FO. Two data extraction tools have been designed, with guidance from other systematic reviews [26, 27], for this review. Namely; Table 1: Characteristics of Included Studies, and Table 2: Summarized Study Findings.

Table 1
Characteristics of Included Studies

Author, year	Study Country (and World Bank Income Level)	Research Question(s) or Objective(s)	Research Methodology	Sociodemographic Features of Participants	Duration of Study (Years)	Methodological Quality Score (and Interpretation)	Sample Size (and Study Population)

Table 2
Summarized Study Findings

Study Title	Response Rate (%)	Determinants of Vaccine Hesitancy			Conclusions	Limitations
		Causes of Vaccine Hesitancy	**Reasons for Vaccine Hesitancy**	**Successful Control Measures of Vaccine Hesitancy**		

The first table of results will have the following details about the included studies: the author and year, the study country (and world bank income level), the research question(s) or objective(s), the research methodology, the sociodemographic features of participants, the duration of the study (years), the methodological quality score (and interpretation) and the sample size (and study population). To obtain data, which is lacking, SD will contact the corresponding authors of the included studies through their electronic mails. Upon the lack of response, after a month's wait, such need for data will be regarded as "missing".

The summarized study findings' table will highlight details of included studies such as; the study title, the response rate, and the determinants of vaccine hesitancy which has three facets (the causes of vaccine hesitancy, the reasons for vaccine hesitancy, and the successful control measures of vaccine hesitancy). The concluding remarks of the authors of the included studies and the limitations of these studies will be documented as part of the study findings.

A PRISMA flowchart diagram will be presented, as a figure, as part of the results of the review. The flowchart will highlight the reasons behind the exclusion of studies, and a numerical presentation of records at each stage of the review will be presented. The reference list of included studies will be screened by SD for extra studies. These studies will be included after passing the laid out quality assurance processes and duly documented in the table of results and PRISMA flowchart diagram.

Analytic considerations

The analytic stage of the review will commence from the various quality assurance stages concerning the resolution of disagreements between the reviewers. An assessment for agreement or otherwise between reviewers, performing the same task, will be done to ensure that various outcomes are reliable and devoid of bias [28]. The kappa coefficient, a robust statistic, will be utilized in this assessment and a kappa coefficient of at least 0.6 will reflect an agreement between the independent reviewers.

A meta-analysis will not be performed because the review is not an interventional study and does not seek to assess the effectiveness of measures that addressed vaccine hesitancy. This is evident as a similar study by Bangura et al., (2020) did not lead to the conduct of a meta-analysis [26]. However, a subgroup description of results will be done. The studies will be grouped according to their quality assessment outcomes (weak, moderate, and strong), the age groups of study participants (below 18 years, and 18 years and above), and the World Bank financial classifications of the study sites (low-income countries, lower-middle-income countries, and upper-middle-income countries).

The Quan-qual data obtained from the included studies will be analyzed independently [29]. The evidence obtained from the independent synthesis of the quantitative and qualitative data will be integrated via configuration [30]. This process will permit the comparison of the quantitative evidence to the qualitative evidence, and attempt to address the various aspects of the outcomes of interest [30]. The outcomes of the review will be presented as a narrative [31].

Discussion And Conclusions

This protocol is designed to serve as a teaching tool, and as a framework to be followed during the conduct of this systemic review. Although Wiafe et al., (2020, 2021) have previously developed and successfully applied a review protocol [23, 27], the current protocol seeks to improve the quality of the former. The protocol could also be applied to gather evidence of vaccine hesitancy relating to the COVID-19 pandemic. It is without a doubt that the stepwise approach towards the conduct of a systematic review has been duly explained and we recommend this protocol to the research and academic community.

The successful application of this protocol to the study of vaccine hesitancy will provide evidence of the potential benefits the protocol presents to science. The knowledge from the study that will be conducted, using this protocol, will contribute to the fight against vaccine hesitancy in low-middle-income countries. The evidence will further advocate for the need to educate people on the importance of getting vaccination services to achieve herd immunity.

Limitations of the review

The review is prone to selection bias due to the following:

1. The restriction of the literature quest to studies conducted in low-and middle-income countries.
2. The consideration of three (3) databases for primary studies identification.
3. The inclusion of studies that have only been conducted in the English language.

Abbreviations

BREC: Biomedical Research Ethics Committee

COVID-19: Coronavirus disease

PRISMA: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis

Quan-qual: Quantitative-qualitative

UKZN: University of KwaZulu-Natal.

Declarations

Ethics approval and consent to participate

None was required for the review because no primary data was collected. However, an ethics exemption was applied and granted by BREC of UKZN.

Consent for publication

None.

Availability of data and materials

None.

Competing interests

None.

Funding

None.

Authors' contributions

EW: The development of the search strategy, the testing of the search strategy, the methodological quality assessment of studies for final inclusion, the integration and interpretation of the extracted data, the co-supervision of the review, and the assessment of the manuscript for the quality of scientific content.

KR, DT, SM: The study conception, the database search, the titles and abstracts screening, the extraction of data, and the drafting of the manuscript.

NB, NM, TS: The study conception, the database search, the full-text screening, the extraction of data, and the drafting of the manuscript.

SD: The study conception, the building of the reference library, the extraction of data, and the drafting of the manuscript.

KBM: The assessment of the search strategy, the co-supervision of the review, the methodological quality assessment of studies for final inclusion, and the assessment of the manuscript for the quality of scientific content.

FO: The co-supervision of the review, the settlement of disagreement between reviewers, and the assessment of the manuscript for the quality of scientific content.

VB: The primary supervision of the review, the coordination of the review, and the assessment of the manuscript for the quality of scientific content.

All the authors have read the manuscript for scientific content and have approved the manuscript for publication.

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- APPENDIXBAPPRAISALOFMETHODOLOGICALQUALITYOFSTUDIES.docx
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