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Determinants of vaccine hesitancy in Africa: a systematic review

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PREAMBLE

Declaration

I, Alexander Paone (PNXALE002), hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.
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Abstract

This MPH dissertation is a systematic review of the factors contributing to vaccine hesitancy in Africa. The dissertation comprises of the following three parts:

The research protocol (Part A) outlines the background and proposed methods of the research. The protocol outlines the search strategy used to identify research eligible for this review according to defined criteria. The objective of this research was to identify determinants of vaccine hesitancy in Africa. The protocol describes data collection methods and the analysis plan of this research in order to address the objective.

The literature review (Part B) provides a summary and interpretation of the current literature on barriers to vaccination, specifically vaccine hesitancy and its impacts on immunisation programs. The literature review identifies discord among literature in defining vaccine hesitancy and evaluating its presence and impact on varying populations, and reviews the attempts for standardisation by the Strategic Advisory Group of Experts Working Group on Vaccine Hesitancy. Lastly, the literature review identifies gaps in the literature, and suggests filling them ideally with a standardised metric.

The manuscript (Part C) is presented in a format suitable for Vaccine journal submission. The manuscript includes a background, a description of the methods used, and a presentation and discussion of the results of the systematic review.

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PROTOCOL

Determinants of vaccine hesitancy in Africa: a systematic review

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Abstract
BACKGROUND: Vaccine hesitancy is defined by the World Health Organization (WHO) as a complex and context specific delay in acceptance or refusal of vaccines despite availability of vaccination services. The reasons why individuals hesitate or choose not to vaccinate are variable and not well described, and the factors contributing to vaccine hesitancy are unclear. Vaccine hesitancy influences vaccine coverage. In order to achieve high vaccination coverage and develop strategies to target vaccine hesitancy and to improve vaccination uptake, factors contributing to vaccine hesitancy must be better understood. The factors associated with vaccine hesitancy in low and middle-income countries (LMICs), specifically on the African continent, should be examined within their own context in order to develop context-specific strategies to address hesitancy. **AIM**: The aim of this review is to describe the determinants contributing to vaccine hesitancy in Africa. **METHODS**: A systematic review protocol for the study was developed and registered in the PROSPERO International Prospective Register of systematic reviews (registration number CRD42016051699). The systematic review study will search seven online databases for peer-reviewed papers that have conducted studies in any African country. Studies investigating the reasons why participants hesitate to vaccinate, or choose to delay or refuse vaccination of themselves or their dependents will be included. Studies to be included in the review will be on vaccine hesitancy against any WHO licensed vaccines as of 2016. Risk of bias for the included studies will be assessed using the CASP tool. Findings will be reported according to the WHO's Strategic Advisory Group of Experts (SAGE) on Vaccine Hesitancy which categorises three broad groups of factors contributing to vaccine hesitancy. The findings can be used as a foundation to characterise vaccine hesitancy as well as to develop Africa-specific strategies to mitigate the impact of vaccine hesitancy on vaccine coverage.
Keywords: vaccine hesitancy, determinants, immunisation, vaccine, SAGE, Africa, immunization

Background
In the last four decades, African countries have achieved steady progress in reducing vaccine preventable diseases (VPDs) (1). The success is built on the expanded programme on immunisation (EPI), a platform used to administer vaccines mainly to children since its establishment in 1974 (1).

Recently, there are reports suggesting that vaccination coverage in many African countries has plateaued at suboptimal levels (2, 3). Many factors are thought to contribute to the observed plateau, among them: limited access to vaccination services, inadequate resources as well as vaccine hesitancy (1, 4). Vaccine hesitancy is a complex and context specific delay in acceptance or refusal of vaccines despite the availability of vaccine services (5). Not only does vaccine hesitancy impact those making the decision for themselves, but also those dependent on others to make the decision for them, such as children. Therefore, vaccine hesitancy has been associated with low compliance with vaccination schedules in some settings (4). Reports from developed countries show that vaccine hesitancy is increasing and could reverse some gains achieved through (6). Vaccine hesitancy is an under studied field, particularly so among African countries. It is possible that vaccine hesitancy contributes to suboptimal vaccination coverage observed among many African countries.

There have been many factors and reasons (broadly herein referred to as determinants) described to be associated with vaccine hesitancy (7). However, vaccine hesitancy is poorly understood in Africa. Our systematic review study describes the determinants associated with vaccine hesitancy in Africa.

The WHO, through the Strategic *Advisory Group of Experts* (SAGE) on Vaccine Hesitancy has categorised determinants associated with vaccine hesitancy into three groups of influences: contextual influences, individual and group influences, and vaccine/vaccination specific issues (7). Each of these categories has a number of subcategories that point to more specific, individual- and community-level influences of

vaccine hesitancy. We will use the SAGE categories of hesitancy to describe the determinants associated with vaccine hesitancy in Africa.

The aim of this review is to describe the determinants of vaccine hesitancy in Africa.

While few existing strategies have been designed to address vaccine hesitancy, even fewer have been evaluated for impact (8). Understanding the determinants of vaccine hesitancy is an important step towards the development of comprehensive strategies needed to improve vaccination uptake in African countries (9).

Study objectives

1. Primary objective

To identify and describe the determinants of vaccine hesitancy in Africa.

Study eligibility criteria

We will use participants, intervention, comparator, and outcome (PICO) to structure our study eligibility criteria.

1. Participants

Persons living in Africa and choosing not to be vaccinated with WHO-licensed vaccines as at December 2016. Persons may include patients, parents, guardians, caretakers, children, and adolescents. The SAGE Working Group on Vaccine Hesitancy defines a vaccine-hesitant individuals as "a heterogeneous group in the middle of a continuum ranging from total acceptance to complete refusal; these individuals may refuse some vaccines, but agree to others; delay vaccines or accept vaccines but are unsure of doing so" (7).

2. Study settings

Studies conducted in any country on the African continent, with no date restriction.

3. Intervention

Provision of any WHO-licensed vaccines/immunisation services as of December 2016, excluding seasonal or outbreak vaccines (10). Specific vaccines and vaccine preventable diseases (VPDs) to be included in this study will be all WHO-licensed vaccines. See **Appendix 1** for a complete list.

4. Comparator

Not applicable.

5. Outcome

Determinants of vaccine hesitancy among study participants as defined by the SAGE Working Group on Vaccine Hesitancy Model of Determinants.

6. Study designs

Quantitative studies (randomised controlled trials, controlled before-and-after studies, interrupted time series designs, cohort studies, case-control studies, cross-sectional studies) and qualitative studies (focus group discussions, in-depth interviews, direct observation, case studies, ethnography, and action research) will be included in the searches. Only randomised control studies that specifically aim to address vaccine hesitancy will be included. Interventional studies such as clinical trials or studies testing vaccine efficacy or effectiveness and not designed to measure the determinants of vaccine hesitancy for

example will be excluded. Non peer-reviewed papers including grey literature will be excluded. Systematic reviews and narrative reviews will be excluded.

Methods

This is a systematic review study. A systematic review protocol for the study has been developed and published in the PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42016051699.

1. Search strategy

The PICO elements will be used to build a search strategy. Databases to be searched include: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Web of Science, World Health Organization Library Information System (WHOLIS), Africa Wide, and CINAHL. Papers of any publication date will be included. See **Appendix 2** for full search strategy.

2. Study selection

Prior study selection, search strategy will be optimised in PubMed database. PubMed has the most extensive and comprehensive search engine with the ability to also search for medical subject headings (MeSH). Search strategy optimisation will include the first author applying the search query to get outputs, and screening titles and abstracts to identify ten relevant studies. From the relevant studies, the first author will read full articles to identify any key terminologies that may not have been included in the first search and these new terms will be added. Additional optimisation will include testing sensitivity and specificity by systematically adding or omitting synonymous search terms, followed by the assessment of the outputs.

Following optimissation of the search query, the first author will search all identified databases and import the results into EndNote citation manager. Duplicates will be removed and recorded for a PRISMA diagram. The PRISMA flow chart will be used to summarise each step of the selection of studies for the review, including the reasons for exclusion of studies.

The results will then be imported into a MS Excel file where titles and abstracts will be screened by the first author. Results will be excluded based on the inclusion and exclusion criteria, recorded for the PRISMA diagram, and the process will also be completed and verified by the second author. Full text articles of the remaining papers will be identified by the first author and shared with the second author to begin the data extraction process. Reference lists from the included studies will be screened for possible relevant studies.

3. Data extraction

Once eligible studies have been selected, the data will be extracted using a data extraction form. The data extraction form will be piloted, and revised if necessary, prior to extracting data from the full text of all selected studies. The final data extraction form will be completed in Excel and use a standardised code-frame. The first author and two supervisors will compare their data extraction forms after reading full text articles in order to compare and discuss any discrepancies.

4. Dealing with missing data

If a selected study is found to have missing data, the study correspondent author will be contacted and requested for the missing data. Any missing data will be described for each included study and discussed to identify the extent to which the results of this review may be altered.

5. Assessment of the risk of bias

Risk of bias for the selected studies will be assessed using a critical appraisal tool (CASP). CASP appraisal tools are the optimal tool for appraising the variety of study designs that will make up this review situated within the field of public health. Critically appraising the studies used in this review will ensure high quality, trustworthy and relevant research (11).

Data analysis

1. Quantitative data analysis and synthesis

Quantitative data will include the number of participants per study, the number of studies per country and region (as determined by MeSH geographical terms), among other variables which will be piloted during the data extraction process.

2. Qualitative data analysis and synthesis

The qualitative data will be extracted using qualitative thematic coding within the data extraction form by the first author and a study team with experience in qualitative data analysis. The outcomes of the studies will be coded and distributed into three groups of determinants based on the SAGE Determinants model (contextual factors, individual/group factors, and vaccine-related factors) (9). Distributing factors using the SAGE Determinants model will compliment research on interventions targeting vaccine hesitancy.

Discussion

This review will identify determinants of vaccine hesitancy in various countries and study settings within Africa. The identified determinants will be discussed with reference to broader challenges for vaccine uptake, such as misinformation, cultural values, inequality, economic development, political stability, and literacy levels. Here, synthesis of qualitative research is valuable as it will bring to the forefront the critical issues affecting the reasons why individuals choose not to vaccinate, which can help to target future research on interventions into vaccine hesitancy and increase vaccine uptake within an African context.

Study strengths and limitations

This review will use unbiased study methods to describe vaccine hesitancy in Africa. A research limitation and potential source of bias may be the decision to exclude non-peer reviewed studies. However, due to the evolving nature of the vaccine hesitancy field, it was determined that unpublished studies are likely to show higher levels of non-standardisation in defining vaccine hesitancy, hence their exclusion. A potential limitation of this study will be its generalisability, due to the unlikelihood that every African country will be represented.

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LITERATURE REVIEW

Introduction

Vaccine hesitancy is complex and varies by context. Until recently, vaccine hesitancy did not have a standardised definition that could be used by a range of stakeholders. While there is abundant literature describing factors or predictors of low uptake, there is limited research specifically aimed at identifying factors of vaccine hesitancy, even less so in African countries. The Strategic Advisory Group of Experts (SAGE) Working Group (WG) on Vaccine Hesitancy has attempted to define vaccine hesitancy and develop a metric to guide future research, which can be targeted to fill some of the gaps in the current research. The aim of this literature review is to describe vaccine hesitancy, the impact of vaccine hesitancy on vaccination, the current literature including gaps that exist to date, and the progress of and potential for standardisation within the topic of vaccine hesitancy.

Search strategy

The search strategy for this literature review was adapted from the search strategy utilised for the accompanying systematic review on factors associated with vaccine hesitancy in Africa (**Appendix 2**). The search strategy conducted for this literature review did not exclude review articles, and was not limited to countries within Africa.

Summary and interpretation of literature

Success of vaccination

Immunisation is one of the most successful and cost-effective public health interventions (4). Administration of vaccines is a preventative measure against vaccine preventable diseases (VPDs), and immunisation is effective at both individual and community levels. There is overwhelming evidence demonstrating the benefits of immunisation, the best example of which is the eradication of smallpox following a global immunisation campaign led by the World Health Organization (WHO) (1). There have also been significant achievements in the decline of diseases such as tetanus, diphtheria, and polio (4). Maximum benefits from immunisation are achievable when individuals are receptive of vaccines. To reach such targets, many obstacles, including vaccine hesitancy must be overcome.

The significant reduction of VPDs can be attributed to efforts of a number of global health organisations (2). The WHO launched the Expanded Programme on Immunisation (EPI) in 1974, which aims to make safe and effective vaccines accessible to all children globally (3). There have been successful efforts by a number of initiatives to increase EPI coverage, such as: Universal Childhood Immunisation, the Global Alliance for Vaccines and Immunisation (GAVI), the Millennium Development Goals, and most recently, the Global Vaccine Action Plan (GVAP) (4) which has set a target to utilise national vaccination programmes to reach 90% national vaccination coverage by 2020 (5).

Barriers to vaccination

Despite these international efforts, coverage estimates have plateaued in recent years (6). In sub-Saharan Africa, despite WHO Africa Region's EPI strategic plans of action during the 2000's, only 77% DTP3 (an indicator of EPI performance) coverage was achieved (4). Overall vaccination coverage in sub-Saharan Africa has remained constantly below that of other regions, and countries within Africa show large disparities in coverage (7).

To prevent and optimise control of VPDs, uptake rates must be improved in Africa. There have been significant reductions in VPDs where high vaccine coverage has been achieved (2). High uptake is crucial because, unlike medicines, vaccines work at both the individual and community level (8). In order to

achieve community-level immunity, there must be high uptake among individuals. Vaccine hesitancy contributes to low rates of uptake, and is an important challenge to overcome, as there are a number of determinants which can vary among diverse populations.

While the impact of vaccine hesitancy on vaccine coverage is observed in both developed and developing countries alike, the factors vary according to context. In developed countries there has been a paradigm shift from increasing access to increasing acceptance (9). Given the long history of vaccines in developed countries such as the United States, there has been significant increase in availability and the number of mandated vaccines, which has led to the absence of VPDs in the environment and in the memories of various stakeholders (10). Saad Omer reports on this in the United States, where a major reason for vaccine refusal is a low level of concern about the risk of many VPDs (24). Developed countries, such as the United Kingdom, also have the funding available to monitor vaccine acceptance and thus anticipate how to address hesitancy (25). Where uptake is low in developed countries, factors in play are understood to involve education, advocacy and acceptance (11). Developed countries are also challenged by a loss of public trust in vaccines (12). Misinformation and anti-vaccine movements, as well as the communication and media environment which have promulgated and dramatised such movements, are also prominent factors of low vaccine uptake that are found to a much lesser degree in developing countries (10, 13, 14).

Considering the differences between developing and developed countries, context-specific strategies must be developed to improve vaccine uptake rates in Africa. Developing countries, such as those in Africa, experience different factors contributing to the observed low vaccination coverage. Challenges such as competing health demands, poverty, inadequate knowledge on vaccination, religion, culture, weak health systems and underfunding, political will and competition for scarce resources (11) are prevalent in sub-Saharan African. Education of stakeholders, effective communication, and training of health workers have been identified as strategies that can have a positive impact on vaccine uptake in sub-Saharan Africa (11). An increase in uptake would reduce the risk of morbidity and mortality caused by VPDs and their complications among individuals as well as their communities by improving herd immunity. The increase in human capital that could be achieved improving vaccine coverage is also a cost-effective strategy to strengthening the long-term economic prospects of these developing countries (15). While most factors contributing to vaccine hesitancy differ between developed and developing countries, some countries in Africa, such as South Africa, are beginning to see an increase in factors more often reported in developed countries thanks to advancements in communication which have led to anti-vaccine movements (3).

Addressing vaccine hesitancy

Vaccine hesitancy has been an under researched topic without standardised terminologies or themes. There is much variation in the way vaccine hesitancy is defined, as well as the aims and objectives of literature which describes factors of vaccine hesitancy.

The literature search has identified numerous, sometimes competing, definitions of vaccine hesitancy. Peretti-Watel et al note the different attitudes within the field, such as those who consider vaccine hesitancy a long-standing phenomenon and attribute it to anti-vaccination attitudes, ignorance, misinformation or irrationality, versus those who describe it as a more recent attitude, distinct from anti-vaccination trends but correlated with knowledge and information (16). There was also some disjunction in defining vaccine-hesitancy as an empirical concept, as a general mental representation derived from the perception of objects or interventions, versus the current definition which covers a wide range of heterogeneous elements (16).

There is a gap in the literature that explicitly aims to describe factors contributing to vaccine hesitancy. Among literature which has reported factors of vaccine hesitancy, doing so is not often the primary research objective, and there is variation in the ways the factors are reported. The literature yields a variety of synonymous terms that may or may not be considered vaccine hesitancy, including terminology such as "factors", "reasons", "determinants" or "motivations" for "rejection", "non-acceptance", "refusal" or "hesitancy" of vaccinations. There is also much research aiming to determine predictors of vaccine uptake, refusal or hesitancy based on socio-economic determinants, rather than reasons as described by participants. While there may be overlap between studies in some of the reported factors, there is a lack of a standardised method to identify similar factors that could be targeted by interventions to address vaccine hesitancy.

Among research which has explicitly aimed to describe factors of vaccine hesitancy, there is a lack of standardisation in the way these factors are explained. A popular model utilised by some research focused on vaccine hesitancy is the Health Belief Model. The Health Belief Model "predicts that an individual's health behavior will depend on the value placed on achieving a goal and the belief that a certain behavior will achieve that goal" (17). The Health Belief Model takes into consideration the individual's perceived susceptibility and severity of a disease, as well as the perceived effectiveness and benefits of the intervention. While the Health Belief Model may be used to explain some factors of vaccine hesitancy at the individual level, it does not accurately take into account the influence of broader contextual factors (8). While other models, have been used in previous literature to explain vaccine hesitancy do share the common ground of viewing factors on a continuum, they do not adequately explain vaccine hesitancy at the population level, and cannot account for individuals who may accept a vaccine but remain doubtful and hesitant (18). To successfully mitigate vaccine hesitancy and ultimately increase acceptance and uptake, there is a need for a further development and standardisation within the field of vaccine hesitancy.

Standardising "vaccine hesitancy"

The SAGE Working Group on Vaccine hesitancy was conceived in 2012 with the aim to standardise the field of vaccine hesitancy, and to develop themes and tools to guide research and interventions. The SAGE has developed a definition for vaccine hesitancy, based upon experience in various settings and the use of the term in literature. The standardisation is expected to minimise subjectivity and ensure that clinicians, policy makers, researchers and other stakeholders would consistently use a standard term to cover the range of factors associated with vaccine hesitancy (19). According to SAGE, vaccine hesitancy refers to a "delay in acceptance or refusal of vaccines despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence" (8). While vaccine uptake is sometimes affected by vaccine hesitancy, hesitancy does not always result in vaccine refusal, as individuals who accept some vaccines can still be considered hesitant if they reject other vaccines or have some doubts.

In addition to defining vaccine hesitancy, SAGE has developed the Vaccine Hesitancy Determinants Matrix, which SAGE describes as "useful for guidance on development of vaccine hesitancy indicators, survey questions, diagnostic tools, and strategies for intervention, and research" (8), and which was used as a foundation for this systematic review on vaccine hesitancy in Africa (**Appendix 4**). The SAGE Determinants matrix includes determinants identified from research studies and experiences of WG members and other experts. The SAGE Determinants Matrix is comprised of three main groups of influences of vaccine hesitancy: contextual influences, individual and group influences, and vaccine

specific issues. Each of these groups includes a range of determinants of vaccine hesitancy. Some of these determinants are comparably broad, "costs" for example, or another determinant covering "religion/culture/gender/socioeconomic" factors of vaccine hesitancy.

An important point of the SAGE WG's definition, which accounts for some of this uncertainty within the topic, is that vaccine hesitancy is "present when vaccine acceptance in a specific setting is lower than would be expected, given the availability of vaccination services" (8), thus a behavioral phenomenon that is not only vaccine and context specific, but also measured within the context of services made available and specific vaccination goals (16). Furthermore, SAGE defines vaccine hesitancy as set on a continuum from total acceptance, to complete refusal, with vaccine hesitant individuals the heterogeneous group in the middle (8, 19).

While SAGE has the potential to be the driving force behind standardisation within the field of vaccine hesitancy, there is still a lack of clarity in some of SAGE materials developed to date. There is noted difficulty determining vaccine hesitancy at the population level for numerous reasons identified in the literature. One reason is that hesitancy is not directly related to uptake, as the definition includes those who have accepted vaccines despite having significant doubts about them (18). Furthermore, there can be variation in hesitancy according to the specific vaccine (18), such as concerns regarding the HPV vaccine as a new vaccine or as a vaccine associated with female reproduction (20, 21). An important feature of vaccine hesitancy at the individual level is the perceived risks versus benefits of vaccinations, which occurs at the individual level (22). For these reasons, Dubé et al caution drawing a general picture of vaccine-hesitant characteristics of individuals at the population level (18).

While there is difficulty determining characteristics of a vaccine hesitant population, some literature has emphasised the societal impact that vaccine hesitant attitudes of individuals can have on their communities. Aside from population-level health impacts of trends in non-vaccination, such as loss of herd immunity, Abeysinghe refers to growing literature within the social sciences that suggests the perception and management of risk occurs at both societal and individual levels (22). This work supports the argument that wider social representations of vaccination such as public discourse, not just individuals, make up an important factor underpinning vaccine hesitancy (22). This does not permit the generalisation of a populations' apparent hesitancy when uptake may be low across specific settings, vaccines or other contexts, but rather points to the potential impact that individuals' may have on their communities when others are presented with the choice to vaccinate.

There is emphasis within SAGE's definition of vaccine hesitancy regarding the issue of access. While vaccine hesitancy may be present in low-uptake situations, situations in which there are system failures such as stock-outs or limited availability of services, vaccine hesitancy cannot be explained as the main cause of low uptake (19). According to the SAGE WG, these situations of access or system failures fall outside of the scope of SAGE's definition of vaccine hesitancy when the individuals lack the opportunity to accept or refuse vaccines (8). This explains why estimates of coverage or uptake cannot be used as an indicator of vaccine hesitancy. Vaccine hesitancy is indicated by the choice to vaccinate or not, based on individuals' assessment of risks and benefits of vaccination, rather than a problem of lack of access to vaccination services or the greater health system (22).

Despite clarification on these issues of access and system failures by emphasising individual's choice in order to determine if vaccine hesitancy is the main factor of non-vaccination, SAGE has still incorporated all of the above (poor availability, far travel distances, poor communication, etc.) into their Determinants Matrix. The determinants within the Matrix related to access are, by SAGE's definition, not

determinants of vaccine hesitancy because in most cases they preempt the opportunity to hesitate. However, there is also need for further clarification on where issues of access fall within the vaccine hesitancy continuum, as participants who decide the vaccination is not worth the time or effort of traveling a far distance could be categorised as vaccine-hesitant, whereas participants who accept vaccines but cannot possibly access them would not be.

Gaps in the literature

In addition to the need to continue to develop and refine a standardised metric, there are several gaps in research specifically on vaccine hesitancy that may suggest strategies to move forward. In terms of research methods, there is a disconnection between quantitative and qualitative research, missing the opportunity to quantify the overall impact of vaccine hesitancy across different population strata in various settings (7). Especially in Africa where vaccine hesitancy is less associated with vaccine confidence, there is a need to determine the weight of other determinants and structural barriers as factors of hesitancy and overall uptake (23). Future research focusing on these gaps using a standardised toolset will help to mitigate vaccine hesitancy and increase overall uptake of vaccines, but there remains a need for research assessing interventions already in place to address concerns (7).

Conclusion

Vaccine hesitancy is a complex and context specific issue not adequately addressed by the majority of literature to date. Vaccine hesitancy has a negative impact on vaccination coverage globally, which is crucial to the success of vaccination owing to the nature of vaccines working at a community level to improve health. In order to increase vaccination coverage globally, there is the need for more context-specific research explicitly aiming to identify factors of vaccine hesitancy. This research is especially vital in African countries, where vaccination coverage rates have plateaued in recent years, and where factors of vaccine hesitancy differ from those experienced in other, more developed regions. Future research should utilise a standardised metric, and avoid some of the previously used terminology that may be considered synonymous with vaccine hesitancy. Increasing the amount of standardised research in the field will illuminate context-specific needs and support future interventions targeting vaccine hesitancy to ultimately improve vaccination coverage.

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MANUSCRIPT

Determinants of vaccine hesitancy in Africa: a systematic review

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Abstract

BACKGROUND: Vaccine hesitancy is defined as a complex and context specific delay in acceptance or refusal of vaccines despite availability of vaccination services. The reasons why individuals hesitate or choose not to vaccinate are variable and not well described, and the factors contributing to vaccine hesitancy are unclear. **AIM**: The aim of this review is to identify and describe determinants of vaccine hesitancy in Africa. **METHODS**: A systematic review protocol for the study was registered in the PROSPERO International Prospective Register of systematic reviews (registration number CRD42016051699). A search was conducted in seven online databases for studies set in African countries in which participants described factors of vaccine hesitancy against any World Health Organization licensed vaccines as of December 2016. Study and participant characteristics were extracted from the studies, and were extracted using the SAGE Determinants of Vaccine Hesitancy Matrix. The data was analysed to determine factors of vaccine hesitancy overall, and stratified by study and participant characteristics. **RESULTS:** This systematic review study included 28 peer-reviewed papers set in 13 African countries, which were assessed for risk of bias using the CASP tool. Most factors of hesitancy were individual and group influences, namely health system trust and personal experience. Costs and a variety of contextual factors were also prominent factors of vaccine hesitancy among participants. The results were also stratified by subgroups, showing differences between urban and rural settings, programme designs, and vaccines. **CONCLUSION:** Vaccine hesitancy is one factor that impacts vaccine coverage. In order to achieve high vaccination coverage and develop strategies to target vaccine hesitancy and to improve vaccination uptake, factors contributing to vaccine hesitancy must be better understood. The results suggest that determinants of vaccine hesitancy in African countries are primarily associated with access, and availability of resources and information. The results underscore the need to develop context-specific strategies to reduce vaccine hesitancy.

Keywords: vaccine hesitancy, determinants, immunisation, vaccine, SAGE, Africa, immunization

Introduction

Immunisation is one of the most successful and cost-effective interventions that improve public health. Vaccines are preventative measures effective at both individual and community levels to protect from infectious diseases. The best example of the vaccine success may be the eradication of smallpox following a global immunisation campaign led by the World Health Organization (WHO) (1). In the last four decades, African countries have achieved steady progress in reducing vaccine preventable diseases (VPDs). The success is built on expanded programme on immunisation (EPI), a platform used to administer vaccines mainly to children since its establishment in 1974 (2).

Overall vaccination coverage in sub-Saharan Africa has remained constantly below that of other regions, and countries within Africa show large disparities in coverage (3). Recently, there are reports suggesting that vaccination coverage in many African countries has plateaued at suboptimal levels (4, 5). Many factors are thought to contribute to the observed plateau, among them: limited access to vaccination services, inadequate resources, and vaccine hesitancy (2, 3).

Vaccine hesitancy is a complex and context specific delay in acceptance or refusal of vaccines despite the availability of vaccination services (6). Not only does vaccine hesitancy impact those making the decision for themselves, but also those who are dependent on others to make the decision for them, such as children, a group for which low compliance with vaccination schedules has been associated with vaccine hesitancy (3). Reports from developed countries show that vaccine hesitancy is increasing and could reverse some gains achieved through vaccination (7), but factors of vaccine hesitancy vary from those observed in developing countries, especially those in Africa. While there has been a paradigm shift away from increasing access and towards increasing acceptance in developing countries (8), developing countries face additional factors of hesitancy not limited to acceptance or access, such as competing health demands, poverty, and political, religious and cultural factors (9). In order to target vaccine hesitancy, more research must be undertaken to increase understanding what it is and how it manifests, particularly so among African countries. This systematic review study describes the factors associated with vaccine hesitancy in Africa.

In an effort to standardise the field, the *Strategic Advisory Group of Experts* (SAGE) Working Group (WG) on Vaccine Hesitancy has categorised a number of factors associated with vaccine hesitancy (identified via literature, experiences and experts) into a Determinants of Vaccine Hesitancy Matrix (10, 11). This systematic review defines vaccine hesitancy in concordance with SAGE, and uses the SAGE Determinants of Vaccine Hesitancy Matrix to report the factors associated with vaccine hesitancy in Africa.

Research on vaccine hesitancy using a standardised metric, such as that defined by SAGE, has the potential to advance the field and design more effective interventions. While few existing strategies have been designed to address vaccine hesitancy, even fewer have been evaluated for impact (12). Understanding the factors contributing to vaccine hesitancy is an important step towards the development of comprehensive strategies needed to improve vaccination uptake in African countries (13).

Methods

A systematic review protocol for the study was registered in the PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42016051699. The PICO format (participants, intervention, comparator, and outcome) was used to structure this review.

1. Types of studies selected

Both quantitative studies (randomised controlled trials, controlled before-and-after studies, interrupted time series designs, cohort studies, case-control studies, cross-sectional studies) and qualitative studies (focus group discussions, in-depth interviews, direct observation, case studies, ethnography, and action research) were eligible for inclusion. Interventional studies such as clinical trials or studies testing vaccine efficacy or effectiveness and not designed to measure the outcomes associated with vaccine hesitancy were excluded. Reviews (including systematic and narrative) editorials, and non-peer-reviewed papers, including grey literature, were excluded.

Studies needed to have investigated any WHO-licensed vaccines as of December 2016, excluding seasonal or outbreak vaccines (14) (see **Appendix 1** for inclusion/exclusion criteria) were eligible for inclusion. The vaccine was required to be available at the time of study, and participants must have been presented with the vaccine for the study to have met inclusion criteria.

2. Study Participants

Persons living in Africa who were vaccine hesitant, choosing not to be vaccinated with any WHO-licensed vaccines as of December 2016. Participants included patients, parents, guardians, caretakers, children, and adolescents. The SAGE Working Group on Vaccine Hesitancy defines vaccine-hesitant individuals as "a heterogeneous group in the middle of a continuum ranging from total acceptance to complete refusal; these individuals may refuse some vaccines, but agree to others; delay vaccines or accept vaccines but are unsure of doing so" (10).

3. Study outcomes

3.1 Primary outcomes

The primary study outcomes were determinants of vaccine hesitancy. The determinants were obtained from the reported participants' reasons for hesitating to vaccinate themselves or their children/dependents were identified as the primary outcome of this study.

4. Study settings

Studies conducted in any country on the African continent, with no date restriction, were eligible for inclusion in this review.

5. Search strategy

Databases searched were: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, Web of Science, World Health Organization Library Information System (WHOLIS), Africa Wide, and CINAHL. Papers of any publication date were included. The search strategy was optimised in PubMed database, which has the most extensive and comprehensive search engine with the ability to also search for medical subject headings (MeSH). Search strategy optimisation involved the first author applying the search query for outputs, and screening titles and abstracts to identify ten relevant studies. From the relevant studies, the first author read full articles to identify any key terminologies that may not have been included in the first search and these new terms will be added. Additional optimisation included testing sensitivity and specificity by systematically adding or omitting synonyms from search terms, followed by the assessment of the outputs. Once the search strategy was optimised, the first author

searched all identified databases and imported the results into EndNote. The final search strategy is presented in **Appendix 2**.

6. Study selection

All search results were imported into EndNote and duplicates were removed. The results were then imported into an MS Excel file where titles and abstracts were screened by the first author to determine whether they met the study inclusion criteria. This step was duplicated by the last author (supervisor), and any disagreements were resolved by discussion. A search for full-texts of the included studies based on the screening of titles and abstracts was conducted by the first author. Studies that could not be found were requested from the UCT Health Sciences Library, and any studies that could not be found by the library or that required additional payment were flagged as studies for which the full text could not be found. Full texts were read by both the first and last authors to finalise eligibility and inclusion, and any disagreements were resolved by discussion or further clarification by contacting the study authors. The reference lists from the included studies were screened for potentially eligible studies by the first author, first by titles and abstracts, then by full texts if they could be found. The PRISMA flow chart (**Figure 1)** summarises each step of the selection of studies for the review.

7. Data extraction

Full texts of the eligible studies were read by the first author, and data was extracted using a data extraction form. The data extraction form was developed in MS Excel, and was piloted by the first author with the first ten studies and any necessary adjustments were made. The data extraction form was consistent with outcomes in order to extract all relevant data from the full texts (the specific variables are discussed below in the analysis section). Codeframes were developed by the first author to extract both quantitative and qualitative data from the texts into the extraction form.

8. Assessment of the risk of bias

Risk of bias of the selected studies was assessed using a critical appraisal tool (CASP) during the data extraction step. CASP appraisal tools are robust for a variety of study designs, and was used to score the quality of the studies included in this review (15). The results of the CASP scoring are presented in **Table 2** in the appendix.

9. Quantitative and qualitative data analysis

9.1 Quantitative data analysis

The quantitative data extracted from each of the studies included the journal, year of publication, primary objective or aim of the study, the sample size, the study design and data collection methods, the country and study setting, the vaccine of focus, whether the vaccine was delivered routinely or via a campaign or other activity, where the vaccine was administered, the participants' genders and ages, and the decision-maker status of the participants (i.e. whether they were making the decision for themselves or for a dependent). Code frames were developed for each of these outcomes (**Appendix 3**).

Analysis of the quantitative data was conducted by the first author, and results were presented with a map illustrating the number of studies per country and the corresponding vaccines per each study.

9.2 Qualitative

Qualitative data was consistent with the primary outcome of this review, which were the determinants contributing to participants' vaccine hesitancy. The data included reasons that were explicitly identified by the studies, or that were mentioned in the results as factors of non-vaccination. Reasons for vaccine hesitancy were extracted verbatim as short quotes into an MS Excel data extraction form, and coded

using thematic coding. A single study could be assigned multiple codes. If more than one reason was stated in one line, the line was duplicated so that one code could be assigned to each reason.

The SAGE Determinants of Vaccine Hesitancy Matrix was the guideline for the codeframe developed and used to extract, analyse and report the findings. The codeframe was further adapted from code frames used in review articles by SAGE (13) and Larson et al (16) to create sub-codes (or sub-determinants) where the qualitative data was too specific to fit into some broader determinants of the SAGE Matrix. The utilised codeframe is included in **Appendix 4**.

Analysis of the qualitative data was conducted by the first author, and involved quantifying the number of responses corresponding to each sub-code (i.e. sub-determinant). The frequency of reported sub-determinants was then analysed within the hierarchy of the SAGE Determinants Matrix, including their corresponding SAGE Determinants, as well as SAGE's three groups of determinants, to determine the most frequently reported factors of vaccine hesitancy among the selected studies. The qualitative sub-determinants were then linked to the quantitative data of their corresponding studies, allowing for analysis across subgroups.

Results

Characteristics of included studies

1. Search of relevant records

The search yielded 2497 records from the seven identified databases. After removing duplicates, the titles and abstracts of 2007 records were screened; 1773 were excluded based on eligibility criteria. After retrieving the full text of 234 potentially eligible records (21 of which could not be found), 23 studies met the inclusion criteria. After screening the reference lists of the 23 included studies, 5 studies from the references list met the inclusion criteria, resulting in the 28 total studies included in this review. The search of relevant records is represented as a PRISMA diagram in **Figure 1**. **Table 1** provides a summary of the included studies.

2. Study designs and methods

The majority (19/28 i.e. 67.9%) of studies were of cross-sectional design (17-35). Seven (25%) of the studies described themselves as having qualitative study designs (36-40), two of which were ethnographies (41, 42). The remaining two (7.1%) studies were case-control studies (43, 44). All included studies used a combination of surveys, interviews, and focus groups. The majority (22/28 i.e. 78.6%) of studies were published between 2005 and 2015. Combined, a total of 32646 participants (median 385.5, range 40-1255) were represented in the included records. **Table 1** provides a summary of included studies.

2.1 Assessment of the risk of bias

CASP (critical appraisal skills programme) critical appraisal tools were utilised to score the risk of bias for each of the studies included in this review. CASP appraisal tools are robust for diverse types of study designs (15). CASP tools designed to assess cross-sectional study designs, case-control studies, and qualitative studies were utilised. Using the CASP tool, none of the studies indicated a significant methodological flaw as the average percentage score was 72%, with the lowest percentage score 55% (**Table 2**).

3. Study settings

Out of 54 African countries in the continent, the included studies were from 13 countries (**Figure 2**). The majority (12/28 i.e. 42.9%) of studies were conducted in Nigeria. Uganda contributed three studies, Ethiopia and Tanzania each contributed two studies, and the remaining countries (Benin, Burkina Faso, Egypt, Gabon, Guinea, Mozambique, South Africa, Sudan and Togo) had one study each.

Whether the studies were conducted in urban or rural settings was also assessed, as this could influence the reasons for vaccine refusal. Three (10.7%) studies were conducted in urban settings, two (7.1%) in semi-urban/rural settings, and eight (28.6%) in rural settings. Eight (28.6%) studies were conducted in both urban and rural settings within their countries, and the remaining seven (25%) did not specify the study setting (**Table 1**).

4. Study vaccines, participants, and delivery

4.1 Vaccines

The vaccines of the included studies, as well as the study participants' roles in vaccine decision-making were assessed. The included studies covered six vaccines: routine childhood (RC) vaccines (that varied by study based on the country-specific EPI), oral polio vaccine (OPV), human papilloma virus (HPV) vaccine, oral cholera vaccine (OCV), Hepatitis-B vaccine (HepB), and Measles-Rubella (MR) (**Table 1**). The

majority (17/28, 60.7%) of studies focused on routine childhood immunisation (RC). HPV and OCV each contributed two studies (7.1%), and there was one study each (3.6%) focusing on HepB and on MR.

4.2 Participants decision-making position

Caregivers providing data on the hesitancy to vaccinate their children were the most represented participants (21/28, 75%). Among OPV studies, three sampled caregivers, and two sampled both caregivers and independent decision-makers. One study focused on HPV vaccination sampled caregivers, while the other sampled both caregivers and independent decision-makers. One study focused on OCV sampled independent decision-makers, while the other sampled both caregivers and independent decision-makers. The two studies on HepB and on MR both sampled independent decision-makers as participants providing data on their vaccine-hesitancy.

4.3 Delivery methods and sites

Vaccine delivery methods, as well as the location where vaccines are administered, may influence the reasons for vaccine refusal (13). Therefore, the vaccine delivery strategies covered in the included studies were assessed. Vaccine delivery methods of the included studies were recorded either as part of a vaccination campaign, or as part of routine immunisation activities. Campaigns included SIAs (supplemental immunisation activities), IPDs (immunisation plus days), and demonstration projects. 12 studies (42.9%) reported hesitancy towards vaccines delivered routinely (as opposed to via campaigns or SIAs), half of which indicated that the vaccines were delivered at health centres. Among the ten studies on vaccine campaigns (35.7%), four reported vaccine delivery at home, three reported delivery of vaccines in a school or university setting, and two reported on campaigns that set up vaccination posts to deliver vaccines. The remaining six studies (21.4) did not specify the delivery sites and/or delivery methods.

Reported determinants of vaccine hesitancy

5. Reported determinants overall

The reported reasons for non-vaccination are reported in this review in congruence with the SAGE Determinants Matrix (13). The codeframe used for analysis was adapted from the matrix and includes additional, more specific "sub-determinants" of those in the SAGE model (16). See **Appendix 5** for definitions of SAGE determinants, and **Appendix 4** for the adapted SAGE determinants matrix with the added “sub-determinants”. **Figure 3** illustrates the frequencies of each reported SAGE determinant of vaccine hesitancy. **Figure 4** depicts the frequencies of all (305) reported sub-determinants of non-vaccination that were extracted from all the included studies, as well as the vaccine types.

5.1 Individual and group influences

Overall, individual and group influences made up the majority (169/305, 55.4%) of reasons for vaccine hesitancy. A more detailed analysis of the individual and group influences showed the most frequently reported determinants were "health system and providers-trust and personal experience" (61/169, 36.1%) (**Figure 3**). Within this determinant, fear of side effects, and dissatisfaction with health system (most commonly including long lines and difficult personal interactions, but also a lack of resources in some instances) each contributed 26.2%. Other significant determinants within individual and group influences were knowledge and awareness (43/169, 25.4%), and beliefs/attitudes about health prevention (24/169, 14.2%) (**Figure 4**).

5.2 Vaccine specific issues

Vaccine specific issues made up 23.6% (72/305) of factors for vaccine hesitancy overall. Within vaccine specific issues, the most frequently reported determinants were costs (35/72, 48.6%), the design of

vaccination programme or mode of delivery (17/72, 23.6%), and unavailable vaccines due to supply (12/72, 16.7%) (**Figure 3**). Within costs, the interruption of time normally spent on other activities (17/35, 48.6%%) and the inability to access the vaccine site due to the handicap or illness of recipient or caregiver (10/35, 28.6%) were the most prominent sub-determinants. Within the design of the vaccination programme or mode of delivery, procedural issues (including issues with vaccination cards or difficult multi-stage processes) were most frequently reported (7/17, 41.1%) (**Figure 4**).

5.3 Contextual influences

Contextual influences made up 12.8% (39/305) of all reported reasons for vaccine hesitancy, of which religion/culture/gender/socioeconomic (15/39, 38.5%), geographic barriers (14/39, 35.9%), and political issues (10/39, 25.6%) were the most frequently reported determinants (**Figure 3**). Husband or head-of-household refusal (8/15, 53.3%) and religion (5/15, 33.3%) made up the majority of the religion/culture/gender/socioeconomic determinant (**Figure 4**).

5.4 Other reported determinants of vaccine hesitancy

The remaining 8.2% (25/305) of reasons reported in the studies were categorised as "other" (**Figure 3**). The determinants in this category included reasons that did not fit the SAGE determinants model, participants who reported already having the vaccine, non-specified issues of access or lack of opportunity, and reasons categorised by the studies as "other".

6 Vaccine hesitancy, stratified by vaccines

6.1 Routine childhood immunisations (RC)

The majority (17/28 i.e. 60.7%) of studies focused on routine childhood immunisation (RC), all of which sampled caregivers as participants providing data on their hesitancy to vaccinate their children. A closer investigation of participants' hesitancy towards routine immunisations found that the most frequently reported determinants fell within individual and group influences (116/211, 55%) (**Figure 3**), of which dissatisfaction with the health system (13/116, 11.2%), motivation (forgetfulness, disinterest, laziness) (12/116, 10.3%), and knowledge/awareness (32/116, 27.5%) made up the majority of responses. Costs were a major factor within vaccine specific issues (57/211, 27.0%), especially the interruption of time normally spent on other activities (14/57, 24.5%), and the vaccine being unavailable at the delivery site (11/57, 19.2%) (**Figure 3**). Geographic barriers made up 57.1% (12/21) of contextual influences inhibiting RI uptake among participants.

6.2 Oral polio vaccine (OPV)

Among studies looking at OPV, vaccine safety (4/22, 18.2%), and the belief that the vaccine was not necessary (4/22, 18.2%) were the most frequent sub-determinants of individual and group influences (**Figure 4**). General disapproval of vaccines was reported more among OPV than any other vaccine included in this review. Prominent contextual influences (12/35, 34.3%) of OPV refusal included politics/policies/mandates (6/12, 50%) and religion/culture/gender/socioeconomic (5/12, 41.7%) (**Figure 3**). Head of household refusal, a sub-determinant of religion/culture/gender/socioeconomic, was reported more among OPV refusal than refusal of other vaccines included in this review.

6.3 Oral cholera vaccine (OCV)

The most frequently reported determinants of vaccine hesitancy among OCV study participants were dissatisfaction with health system (7/29, 24.1%) (**Figure 3**), of which, the belief or fear that the child was too young to receive the vaccine (2/7, 28.5%) was reported more among OCV than any other vaccine. Lack of information on the time or place of the vaccine made up 60.0% of the knowledge/awareness

determinant, and was reported more among OCV than any other vaccine. The interruption of time normally spent on other activities was the most frequent vaccine-specific issue, making up 50% of the costs determinant (**Figure 4**).

6.4 Measles-rubella vaccine (MR)

The most frequently reported factor of vaccine hesitancy of the MR vaccine was the fear of side effects or infection (2/10, 20%), a sub-determinant of SAGE's "health system and provider's trust and personal experience" determinant, within individual/group influences (**Figure 4**).

6.5 Human papillomavirus vaccine (HPV)

Among participants who refused the HPV vaccine, the fear of side effects and the distrust or fear of the vaccine's effect on fertility (3/13, 23.0%) were the most prominent reasons for their decision (**Figure 4**). The latter determinant was reported more with HPV than with any other vaccine, along with concerns with the vaccine being newly introduced (1/13, 7.7%).

6.6 Hepatitis B vaccine (HepB)

For HepB, reasons categorised as "other" aside, all reported factors fell within individual and group influences. Lack of knowledge of eligibility or when to receive (1/7, 14.3%), the belief that the vaccine was not necessary (1/7, 14.3%), and fear of side effects (1/7, 14.3%) were each mentioned as determinants of HepB vaccine hesitancy (**Figure 4**).

7. Vaccine hesitancy by study settings

A closer investigation into the settings in which the included studies were conducted revealed some differences between urban and rural settings. Factors of vaccine hesitancy stratified by study settings are presented in **Figure 5**.

7.1 Rural settings

Within individual and group influences in rural areas (44/90, 48.9%), "health system and provider's trust and personal experience" (16/44, 36.4%), knowledge/awareness (14/44, 31.8%) were the most frequently reported determinants, with a range of sub-determinants reported within each respectively. Beliefs/attitudes about health and prevention (6/44, 13.6%) also had a significant impact on the participant's vaccine hesitancy. Vaccine-specific issues (29/90, 32.2%) that were reported more in rural settings than in other settings were the reliability and/or source of vaccine supply (6/29, 20.7%), and the inability to access the vaccine site due to the handicap or illness of recipient or caregiver (7/29, 24.1%). Within contextual influences (10/90, 11.1%), geographic barriers (6/10, 60%) was more frequently reported in rural areas than in any other setting.

7.2 Urban settings

Not unlike rural settings, "health system and provider's trust and personal experience" was the most prominent determinant among urban settings, making up the approximately one quarter (5/21 23.8%) of reported reasons for vaccine hesitancy. Within this determinant, fear of side effects (2/5, 40%) and the belief that too many vaccines are harmful (1/5, 20%), were reported more in urban areas than in any other setting. Other determinants that were reported more within urban settings than other settings included the belief that vaccines could not be received when recipient sick (2/21, 9.5%), mode of delivery (2/21, 9.5%) (specifically procedural issues and limited opening times of vaccination sites, general disapproval of vaccines (1/21, 4.8%) and head of household refusal (1/21, 4.8%).

8. Vaccine Hesitancy by delivery method and site

Factors of vaccine hesitancy stratified by delivery methods and delivery sites are presented in **Figure 6**.

8.1 Vaccination campaigns

Factors of vaccine hesitancy varied depending on whether the delivery method was a campaign or routine immunisation activities. Among studies which reported on vaccination campaigns, the most frequently reported determinants fell within individual and group influences, including "health system and provider's trust and personal experience" (24/94, 25.5%). Within this determinant, fear of side effects (7/24, 29.2%) was reported more among campaigns than among any other delivery method. Vaccine specific issues (20/94, 21.3%) were costs (8/20, 40%) and the design of the programme or delivery (7/20, 35%), including limited open hours and being absent from the delivery site during the campaign. Contextual issues among campaigns (16/94, 17%) were religious/cultural/gender/socioeconomic (6/16, 37.5%) and political (8/16, 50%). Political determinants were reported more among vaccination campaigns than the other delivery methods.

8.2 Routine immunisation activities

A closer investigation of studies reporting on routine immunisation activities found that individual and group influences made up most of the reasons for participants' vaccine hesitancy (64/113, 56.6%). Within this group, dissatisfaction with the health system (9/113, 8%), and motivation (8/113, 7.1%) were most frequently reported. Among vaccine specific issues (27/113, 24%), costs (15/113, 13.3%) (specifically inability to access the vaccine site due to the handicap or illness of recipient or caregiver (7/113, 6.2%)), and the vaccine not being available (7/113, 6.2%) were the most frequently reported factors of vaccine hesitancy. Geographic barriers also made up 7.1% (8/113) of vaccine hesitancy factors among studies on routine vaccinations, more than any other vaccination delivery method.

8.3 Vaccination delivery sites

Determinants of vaccine hesitancy also varied by vaccination site. When vaccinations were offered at health facilities, the greatest determinant was "health system and provider's trust and personal experience" (19/91, 20.9%), notably dissatisfaction with the public health system (10/91, 11%). Vaccine specific issues were greater when vaccines were delivered at health centers (26/91, 28.6%). Costs (14/91, 15.4%) (specifically interruption of time (6/91, 6.6%)), the design of the vaccination programme (6/91, 6.6%) (notably procedural issues (5/91, 5.5%)), and reliability (6/91, 6.6%) were most frequently reported.

Contextual influences were more frequently reported (10/27, 37%) when vaccinations were delivered at homes compared to other vaccination sites. Political concerns (5/27, 18.5%), religion (2/27, 7.4%) and head of household refusal (2/27, 7.4%) were most frequently reported with home-delivery, while costs were of least concern (except when the recipient was not at home during delivery (1/27, 3.7%)).

When vaccinations were delivered at vaccination posts, in or close to villages or markets for example, insufficient information on the time and place of the vaccine delivery (3/29, 10.3%) and the belief or fear that the child was too young to receive the vaccine (2/29, 7%) were more frequently reported than at other delivery sites. Costs (4/29, 13.8%) were also frequently reported as determinants of vaccine hesitancy among vaccine delivery at vaccination posts.

When vaccinations were delivered at schools or universities, fear of side effects (4/23, 17.4%) was more frequently reported than at other vaccination sites. The mode of administration, frequently reported as

fear of injections (2/23, 8.7%) was a concern that was unique to vaccines delivered at school compared to other vaccination sites.

9. Vaccine hesitancy by participants' decision-making position

The role of the participant in decision making, whether they were independently making the decision to vaccination themselves, or making the decision as a caregiver for their child or a dependent, was expected to yield different factors of vaccine hesitancy. Factors of vaccine hesitancy stratified by participants decision-making roles are presented in **Figure 5**.

9.1 Independent decision-makers

Among participants who were making the independent decision to vaccinate themselves, the most frequently reported reasons for vaccine refusal were fear of side effects (4/31, 12.9%), the interruption of time normally spent on other activities (2/31, 6.5%), limited open hours (2/31, 6.5%), and distrust in something offered for free (2/31, 6.5%).

9.2 Caregivers

Among participants who were caregivers making the decision to vaccinate their child or dependents, the most frequently reported reasons for vaccine hesitancy were "health system and provider's trust and personal experience" (45/238, 18.9%) (specifically dissatisfaction with the public health system (14/238, 5.9%)), knowledge and awareness (35/238, 14.7%), costs (30/238, 12.6%) (specifically interruption of time (14/238, 5.9%), and inability to access due to illness or injury (9/238, 3.8%)), [11] beliefs and attitudes about health and prevention (predominantly (12/238, 5%)) and geographic barriers (13/238, 5.5%).

9.3 Both independent decision-makers and caregivers

Among studies in which both caregivers and the recipient were vaccine hesitant, factors were largely associated with "health system and provider's trust and personal experience" (10/36, 27.8%), specifically fear of side effects (3/36, 8.3%) and fear the vaccine would affect fertility (3/36, 8.3%). Other concerns were of vaccine efficacy and safety (4/36, 11.1%), and knowledge and awareness (4/36, 11.1%).

Discussion

While this review could not include studies representing each African country due to non-availability of the published relevant literature, it is significant that all of the African regions (as defined by MeSH) have been represented by at least one country. Nearly half of all studies (12/28, 43%) were conducted in Nigeria. A closer investigation into the frequency of determinants reported by the participants included in this review revealed no mentions of historical factors overall. Political determinants were not more frequently mentioned in Nigeria than in any other country, aside from two mentions of the belief that the government should allocate resources to other funds rather than to vaccination services. This may be explained by Nigeria continuing to demonstrate one of the lowest rates of childhood immunisation in the world, as well as the history of vaccination in Nigeria, including the 2003 boycott of polio vaccination, and the subsequent extensive research in the country (19).

Over half of all reasons for non-vaccination reported in the included studies fell into the individual and group influences group defined by SAGE. This reflects the number of determinants and sub-determinants being greater within this group than in the other two groups. The same can be said for the most frequently reported determinant within this group, "health system and providers-trust and personal experience", which included a number of sub-determinants that fit best within this determinant. One of the more frequently reported sub-determinants of "health system and providers-trust and personal experience" was dissatisfaction with the health system, which included difficult personal interactions and a lack of resources or necessities at health centres. The wide range of sub-determinants identified within the determinants of the individual and group influences group sheds light on the need to further define determinants in order to cover the diverse factors of vaccine hesitancy that were found by this review.

Despite considerable support by GAVI to make vaccines more accessible within LMICs, costs were a major factor across all studies. As expected, geographic barriers and the inability to access vaccine sites were determinants of vaccine hesitancy that were reported more frequently in rural than in urban settings. Not all costs were explicitly financial in terms of the actual cost of the vaccine, or even the cost of accessing the vaccine. Costs such as the inability to access due to inability or illness (of the recipient or caregiver), or the interruption of time normally spent on other activities or responsibilities, might be explained by what McKnight describes as the notion that vaccines are a low-involvement good, especially in subsistence-household economies, where vaccination requires a concerted effort and interruption of daily demands (42).

Interventions to reduce vaccine hesitancy and increase uptake of vaccines must be context specific. Within the contextual influences group, SAGE has included the communication and media environment, religion, culture, gender, politics, and geography. While contextual factors will always be of great importance when addressing vaccine hesitancy, this group of determinants did not contribute a significant number of determinants of vaccine hesitancy among the reviewed studies. A few conclusions can be drawn from the findings on contextual factors. First, whether or not contextual influences are a major factor of vaccine hesitancy, the results seem to indicate that the current interventions are appropriately context specific. Alternatively, it is possible that participants may not recognise these contextual barriers as the primary reason for their hesitancy. Second, it is clear that more emphasis must be placed on individual and group influences, such as beliefs and attitudes about health and prevention, and trust in the health system, as well as on vaccine-specific issues such as the design of the programme or mode of delivery and costs.

The results suggest that addressing vaccine hesitancy in Africa should be prioritised among caregivers. This is likely due to the fact that nearly all populations are presented with the option to receive routine childhood immunisations at some point during the early years of their, or their children's, lives. This is in contrast to the other vaccines included in the study, which are not routinely administered to the general public, either because they are often presented as part of RC immunisations (such as OPV and MR), or are only presented to or considered necessary for certain populations, such as OCV in certain settings, HepB for health workers, and HPV, which is not only considered an adolescent vaccine but is also relatively new compared to the others.

Nearly one-fifth of included studies focused on oral polio vaccine (OPV), all of which were conducted in Nigeria, which can be attributed to the extensiveness of research, as well as a consequence of the historical issues in the country being specific to polio vaccinations. That the main determinants of vaccine hesitancy were vaccine safety, general disapproval of vaccines, and politics, may also point to the history of polio vaccination in the country. Despite these results being significant within this review, further interpretation is not merited considering global plan to switch from OPV to IPV.

While only two of the included studies focused on oral cholera vaccine (OCV), it is significant that both were conducted on campaigns where the vaccine was delivered at vaccination posts. This may explain why the determinants of vaccine hesitancy among OCV included a lack of information on the time or place of the vaccine (reported more among OCV than any other vaccine), and the interruption of time spent on other activities. Schaetti's studies of perceptions of cholera (45, 46), which sampled the same population as his study included in this review, may explain why the belief that the child was too young to receive the vaccine was such a prominent determinant of vaccine hesitancy in the presence of other, perhaps more familiar and less invasive, curative and preventative methods for children affected by or at risk of cholera.

HPV is a unique vaccine not only because it is a newly introduced vaccine, but also because of some stigma surrounding it due to its relevance to adolescent sexual health and reproduction (47). The determinants of hesitancy surrounding HPV reflected these unique characteristics of the vaccine, as fear of the vaccine's effect on fertility and concerns with the vaccine being newly introduced were reported more among HPV studies than any other vaccine. These results are especially valid in the African context, in which only girls are currently being targeted for HPV vaccination.

Determinants of vaccine hesitancy varied between vaccination campaigns and routine immunisation activities, as well as between different delivery sites. While issues of communication and access were reported at health facilities, contextual issues were more apparent when vaccines were delivered at home. The results suggest that advocacy and communication of vaccination campaigns should be optimised to reduce some of the factors associated with vaccine hesitancy reported among the campaigns included in this review. For routine immunisation activities, cost reduction and interventions to build trust between health care workers and vaccine recipients should be considered.

Study strengths and limitations

A strength of this review was the use of the SAGE Determinants of Vaccine Hesitancy Matrix, to characterise the reported reasons for vaccine hesitancy among the participants in the included studies (**Appendix 5**). The codeframe (**Appendix 4**) was adapted from other studies (16) in order to expand on some of the broader determinants in the SAGE matrix.

The outcomes of the included studies were broad, ranging from identifying reasons for non-vaccination, to assessing coverage, to evaluating immunisation programmes. This range among the outcomes of the included studies can be attributed to the lack of a standard research approach to identify factors contributing to vaccine hesitancy. Therefore, most studies became eligible for inclusion when investigators identified reasons participants chose not to vaccinate (or complete vaccination), which was not always explicitly stated as a study objective despite presenting the data. Another research limitation and potential source of bias may be the decision to exclude non-peer reviewed studies. However, due to the evolving nature of the vaccine hesitancy field, it was determined that unpublished studies are likely to show higher levels of non-standardisation on defining vaccine hesitancy, hence the exclusion.

A potential limitation of this study is the coding and analysis of secondary data. Because it is not known what surveys, questionnaires or interview guides were used to collect data within the original studies, there is the potential of reduced accuracy when coding and reanalysing the reported results. SAGE has suggested that the Determinants Matrix be used as a guide for data collection in future studies on vaccine-hesitancy, which would likely minimise this limitation within this, and future, reviews.

Another limitation of this study is related to the SAGE Determinants Matrix due to contradictions with the definition of vaccine hesitancy. Despite SAGE's clarification that issues of access fall outside of the scope of vaccine hesitancy when participants have not been presented with the choice to vaccinate or not, these access issues are included in SAGE's Determinants Matrix, and were therefore included in the codeframe used by this review. The decision to include issues of access in this review, despite the contradiction in the SAGE materials, was made due to the context of vaccine delivery in Africa and to emphasise the necessary improvement of access to vaccines. There is a need for further clarification on where issues of access fall within the vaccine hesitancy continuum, as participants who decide the vaccination is not worth the time or effort of traveling a far distance could be categorised as vaccine-hesitant, whereas participants who accept vaccines but cannot possibly access them would not.

There is also a need for further clarification of other determinants that may not meet the definition of vaccine hesitancy, such as the availability or supply of vaccines at delivery sites. For example, if a person accepts a vaccine, they may still be considered vaccine-hesitant if they do not have confidence in the health system's ability to reliably keep stock, but they should not be considered hesitant if that was actually the reason for their non-vaccination.

Conclusion

Vaccine hesitancy in Africa is broad and has a range of determinants. Materials produced by SAGE, including their definition of vaccine hesitancy and their matrix of determinants, were used to analyse the quality studies which were included in this review. Despite strict inclusion criteria, the results are likely to be different if there were more studies that were primarily aimed at investigating vaccine hesitancy, especially if they also used the SAGE model. Well conducted future studies on vaccine hesitancy in Africa are likely to shed more light on the topic, and if a model such as SAGE's becomes the standardised tool for such studies, future reviews on vaccine hesitancy will be more accurate.

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Table 1: Summary of Included Studies

First Author	Year	Title	Vaccine	Delivery Strategy	Delivery Site	Decision-maker	Country	Setting	Income	Study Design	Methods	Sample
Abd Elaziz	2010	A measles and rubella (MR) catch-up vaccination campaign in an Egyptian University: Vaccine uptake and knowledge and attitudes of students	MR	campaign	school (university)	independent	Egypt	urban	LMIC	cross-sectional	survey	240
Abdulraheem	2011	Reasons for incomplete vaccination and factors for missed opportunities among rural Nigerian children	routine childhood	routine	not specified	caregiver	Nigeria	rural	LMIC	cross-sectional	survey, interview	685
Babalola	2011	Maternal reasons for non-immunisation and partial immunisation in northern Nigeria	routine childhood	not specified	not specified	caregiver	Nigeria	rural and urban	LMIC	cross-sectional	survey, interview	4442
Dugas	2009	Portrait of a lengthy vaccination trajectory in Burkina Faso: from cultural acceptance of vaccines to actual immunization	routine childhood	not specified	not specified	caregiver	Burkina Faso	rural	LIC	ethnography	interview, focus group	64
Ekunwe	1994	How disease prevention fails without good communication	routine childhood	not specified	health facility	caregiver	Nigeria	not specified	LMIC	qualitative	interview, focus group	225
Eng	1991	The acceptability of childhood immunization to Togolese mothers: a sociobehavioral perspective	routine childhood	not specified	not specified	caregiver	Togo	not specified	LIC	qualitative	focus group	110
Fatiregun	2013	Assessing full immunisation coverage using lot quality assurance sampling in urban and rural districts of southwest Nigeria	routine childhood	not specified	not specified	caregiver	Nigeria	rural and urban	LMIC	cross-sectional	survey, interview	1178
Gammino	2014	An Evaluation of Polio Supplemental Immunization Activities in Kano, Katsina, and Zamfara States, Nigeria: Lessons in Progress	OPV	campaign	home	caregiver	Nigeria	not specified	LMIC	cross-sectional	survey, interview	884
Helman	2004	Perceptions of childhood immunisations in rural Transkei - a qualitative study: original article	routine childhood	routine	health facility	caregiver	South Africa	rural	UMIC	qualitative	survey, interview, focus group	60
Ibekwe	2006	Hepatitis B vaccination status among health workers in Enugu, Nigeria	HepB	routine	not specified	independent	Nigeria	semi	LMIC	cross-sectional	survey	246
Itimi	2012	Community participation and childhood immunization coverage: a comparative study of rural and urban communities of Bayelsa State, south-south Nigeria	routine childhood	routine	not specified	caregiver	Nigeria	rural and urban	LMIC	cross-sectional	survey	558
Jani	2008	Risk factors for incomplete vaccination and missed opportunity for immunization in rural Mozambique	routine childhood	routine	health facility	caregiver	Mozambique	rural	LIC	cross-sectional	interview	668
LaMontagne	2011	Human papillomavirus vaccine delivery strategies that achieved high coverage in low- and middle-income countries	HPV	campaign	school	caregiver	Uganda	not specified	LIC	cross-sectional	interview	1489
Larson	2015	Measuring Vaccine Confidence: Introducing a Global Vaccine Confidence Index	routine childhood	not specified	not specified	caregiver	Nigeria	not specified	LMIC	cross-sectional	survey, interview	12554
Loevinsohn	1989	Missed opportunities for immunization during visits for curative care: practical reasons for their occurrence	routine childhood	routine	not specified	caregiver	Sudan	urban	LMIC	cross-sectional	interview	236
Luquero	2013	First Outbreak Response Using an Oral Cholera Vaccine in Africa: Vaccine Coverage, Acceptability and Surveillance of Adverse Events, Guinea, 2012	OCV	campaign	vaccination post	both	Guinea	rural	LIC	cross-sectional	survey, interview	5248
Makoutode	2009	Impact of parental attitudes on infant vaccinal coverage in Benin	routine childhood	routine	not specified	caregiver	Benin	rural	LIC	cross-sectional	survey	438
McKnight	2014	Designing the Expanded Programme on Immunisation (EPI) as a service: Prioritising patients over administrative logic	routine childhood	not specified	not specified	caregiver	Ethiopia	rural and urban	LIC	ethnography	interview	83
Michael	2014	An Evaluation of Community Perspectives and Contributing Factors to Missed Children During an Oral Polio Vaccination Campaign – Katsina State, Nigeria	OPV	campaign	home	caregiver	Nigeria	rural and urban	LMIC	cross-sectional	survey, focus group	96
Michael	2014	An Assessment of the Reasons for Oral Poliovirus Vaccine Refusals in Northern Nigeria	OPV	campaign	not specified	both	Nigeria	not specified	LMIC	cross-sectional	survey	148
Mohammed	2014	Characteristics of persons refusing oral polio vaccine during the immunization plus days – Sokoto, Nigeria 2011	OPV	campaign	home	caregiver	Nigeria	urban	LMIC	case-control	survey, interview	121
Mohamud	2014	Immunization coverage of 12–23 months old children and associated factors in Jigjiga District, Somali National Regional State, Ethiopia	routine childhood	routine	not specified	caregiver	Ethiopia	rural and urban	LIC	cross-sectional	survey, interview	582
Murele	2014	Vaccine perception among acceptors and non-acceptors in Sokoto State, Nigeria	OPV	routine	not specified	both	Nigeria	rural and urban	LMIC	qualitative	interview	72
Schaetti	2012	Improving Community Coverage of Oral Cholera Mass Vaccination Campaigns: Lessons Learned in Zanzibar	OCV	campaign	vaccination post	independent	Tanzania	semi	LIC	cross-sectional	interview	367
Schwarz	2009	Reasons for non-adherence to vaccination at mother and child care clinics (MCCs) in Lambaréné, Gabon	routine childhood	routine	health facility	caregiver	Gabon	not specified	UMIC	qualitative	survey, interview	40
Tugumisirize	2002	Missed opportunities and caregiver constraints to childhood vaccination in a rural area in Uganda	routine childhood	not specified	health facility	caregiver	Uganda	rural	LIC	cross-sectional	survey	408
Vonasek	2016	Do Maternal Knowledge and Attitudes towards Childhood Immunizations in Rural Uganda Correlate with Complete Childhood Vaccination?	routine childhood	routine	not specified	caregiver	Uganda	rural	LIC	cross-sectional	survey, interview	1000
Watson-Jones	2012	Reasons for Receiving or Not Receiving HPV Vaccination in Primary Schoolgirls in Tanzania: A Case Control Study	HPV	campaign	school	both	Tanzania	rural and urban	LIC	case-control	interview	404

Table 2: CASP Scores

Study Details				CASP Results			
Author	**Year**	**Title**	**Study design**	**Yes**	**Unsure/ Unclear**	**No**	**Score (% Yes)**
Abd Elaziz, K. M.	2010	A measles and rubella (MR) catch-up vaccination campaign in an Egyptian University: Vaccine uptake and knowledge and attitudes of students	cross-sectional	8	3	0	73%
Abdulraheem	2011	Reasons for incomplete vaccination and factors for missed opportunities among rural Nigerian children	cross-sectional	11	0	0	100%
Babalola	2011	Maternal reasons for non-immunisation and partial immunisation in northern Nigeria	cross-sectional	7	4	0	64%
Dugas	2009	Portrait of a lengthy vaccination trajectory in Burkina Faso: from cultural acceptance of vaccines to actual immunization	qualitative	9	1	0	90%
Ekunwe	1994	How disease prevention fails without good communication	qualitative	6	4	0	60%
Eng	1991	The acceptability of childhood immunization to Togolese mothers: a sociobehavioral perspective	qualitative	8	2	0	80%
Fatiregun	2013	Assessing full immunisation coverage using lot quality assurance sampling in urban and rural districts of southwest Nigeria	cross-sectional	9	2	0	82%
Gammino	2014	An Evaluation of Polio Supplemental Immunization Activities in Kano, Katsina, and Zamfara States, Nigeria: Lessons in Progress	cross-sectional	8	3	0	73%
Helman	2004	Perceptions of childhood immunisations in rural Transkei - a qualitative study: original article	qualitative	8	2	0	80%
Ibekwe	2006	Hepatitis B vaccination status among health workers in Enugu, Nigeria	cross-sectional	7	4	0	64%
Itimi	2012	Community participation and childhood immunization coverage: a comparative study of rural and urban communities of Bayelsa State, south-south Nigeria	cross-sectional	9	2	0	82%
Jani	2008	Risk factors for incomplete vaccination and missed opportunity for immunization in rural Mozambique	cross-sectional	8	3	0	73%
LaMontagne	2011	Human papillomavirus vaccine delivery strategies that achieved high coverage in low- and middle-income countries	cross-sectional	7	4	0	64%
Larson	2015	Measuring Vaccine Confidence: Introducing a Global Vaccine Confidence Index	cross-sectional	7	4	0	64%
Loevinsohn	1989	Missed opportunities for immunization during visits for curative care: practical reasons for their occurrence	cross-sectional	8	3	0	73%
Luquero	2013	First Outbreak Response Using an Oral Cholera Vaccine in Africa: Vaccine Coverage, Acceptability and Surveillance of Adverse Events, Guinea, 2012	cross-sectional	8	3	0	73%
Makoutode	2009	Impact of parental attitudes on infant vaccinal coverage in Benin	cross-sectional	8	3	0	73%
McKnight	2014	Designing the Expanded Programme on Immunisation (EPI) as a service: Prioritising patients over administrative logic	qualitative	8	2	0	80%
Michael	2014	An Evaluation of Community Perspectives and Contributing Factors to Missed Children During an Oral Polio Vaccination Campaign – Katsina State, Nigeria	cross-sectional	6	5	0	55%
Michael	2014	An Assessment of the Reasons for Oral Poliovirus Vaccine Refusals in Northern Nigeria	cross-sectional	8	3	0	73%
Mohammed	2014	Characteristics of persons refusing oral polio vaccine during the immunization plus days – Sokoto, Nigeria 2011	case-control	7	3	2	58%
Mohamud	2014	Immunization coverage of 12–23 months old children and associated factors in Jigjiga District, Somali National Regional State, Ethiopia	cross-sectional	10	1	0	91%
Murele	2014	Vaccine perception among acceptors and non-acceptors in Sokoto State, Nigeria	qualitative	6	4	0	60%
Schaetti	2012	Improving Community Coverage of Oral Cholera Mass Vaccination Campaigns: Lessons Learned in Zanzibar	cross-sectional	7	4	0	64%
Schwarz	2009	Reasons for non-adherence to vaccination at mother and child care clinics (MCCs) in Lambaréné, Gabon	qualitative	9	1	0	90%
Tugumisirize	2002	Missed opportunities and caretaker constraints to childhood vaccination in a rural area in Uganda	cross-sectional	7	4	0	64%
Vonasek	2016	Do Maternal Knowledge and Attitudes towards Childhood Immunizations in Rural Uganda Correlate with Complete Childhood Vaccination?	cross-sectional	9	2	0	82%
Watson-Jones	2012	Reasons for Receiving or Not Receiving HPV Vaccination in Primary Schoolgirls in Tanzania: A Case Control Study	case-control	7	5	0	58%
				Average Score			**72%**

Figure 1: PRISMA Diagram

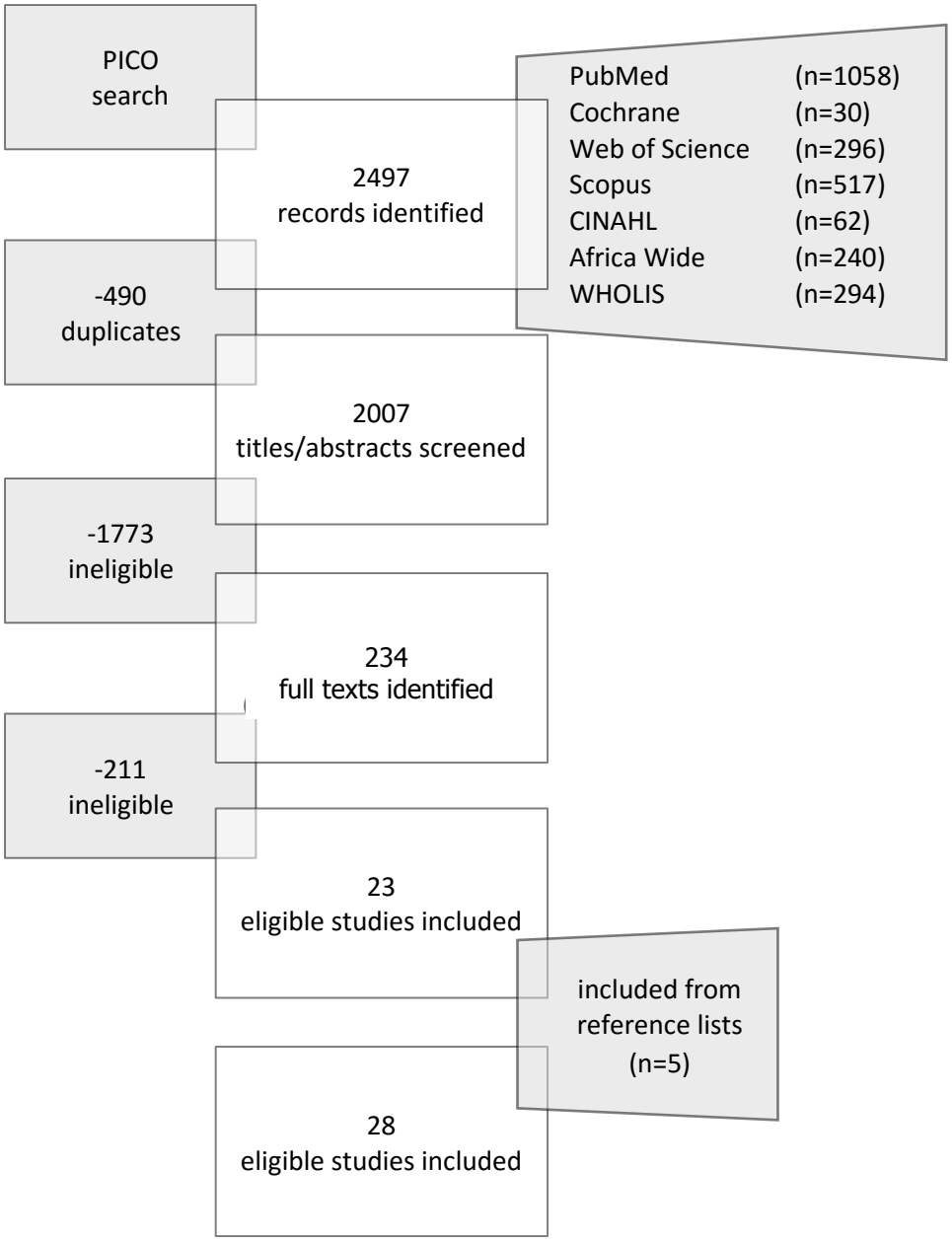


Figure 2: Map of included studies and vaccines

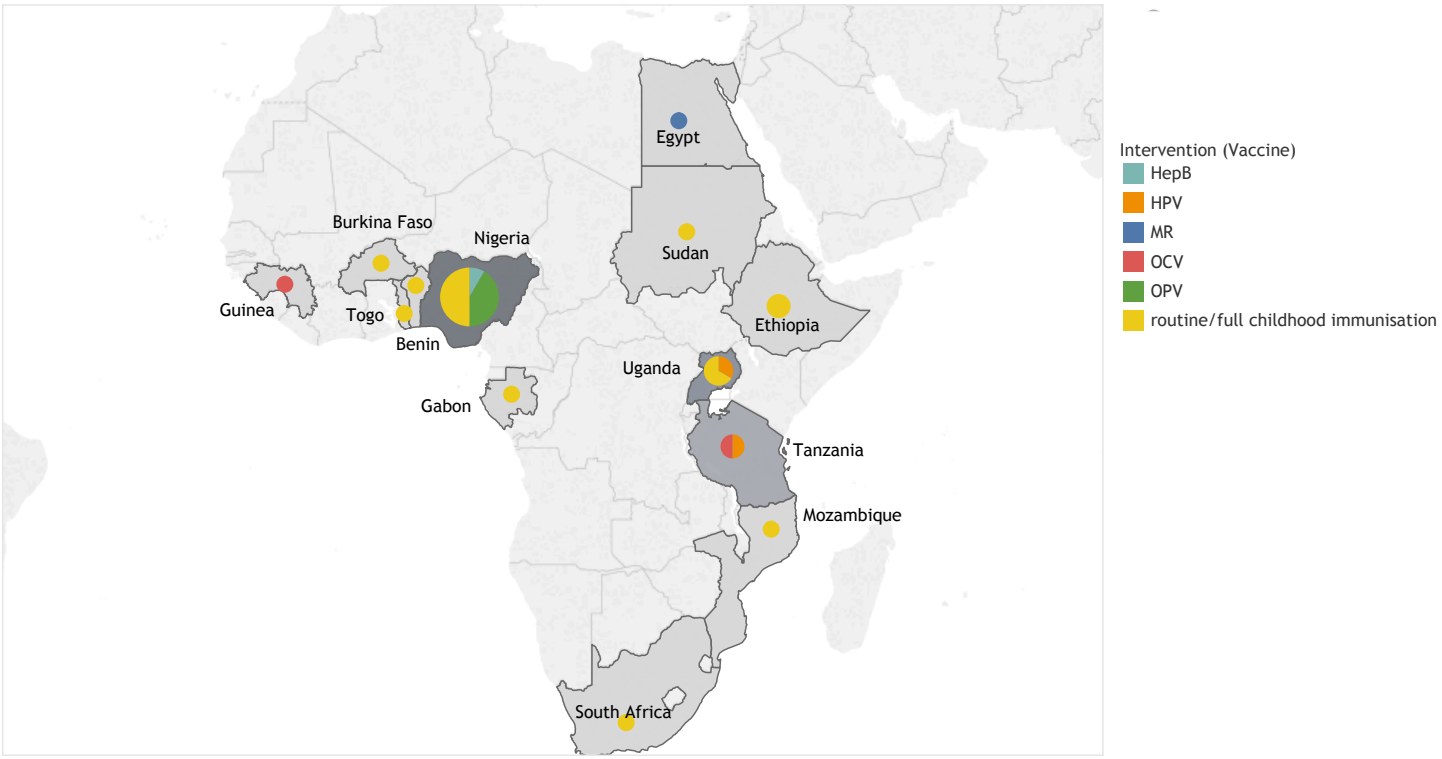


Figure 3: Reported determinants of vaccine hesitancy

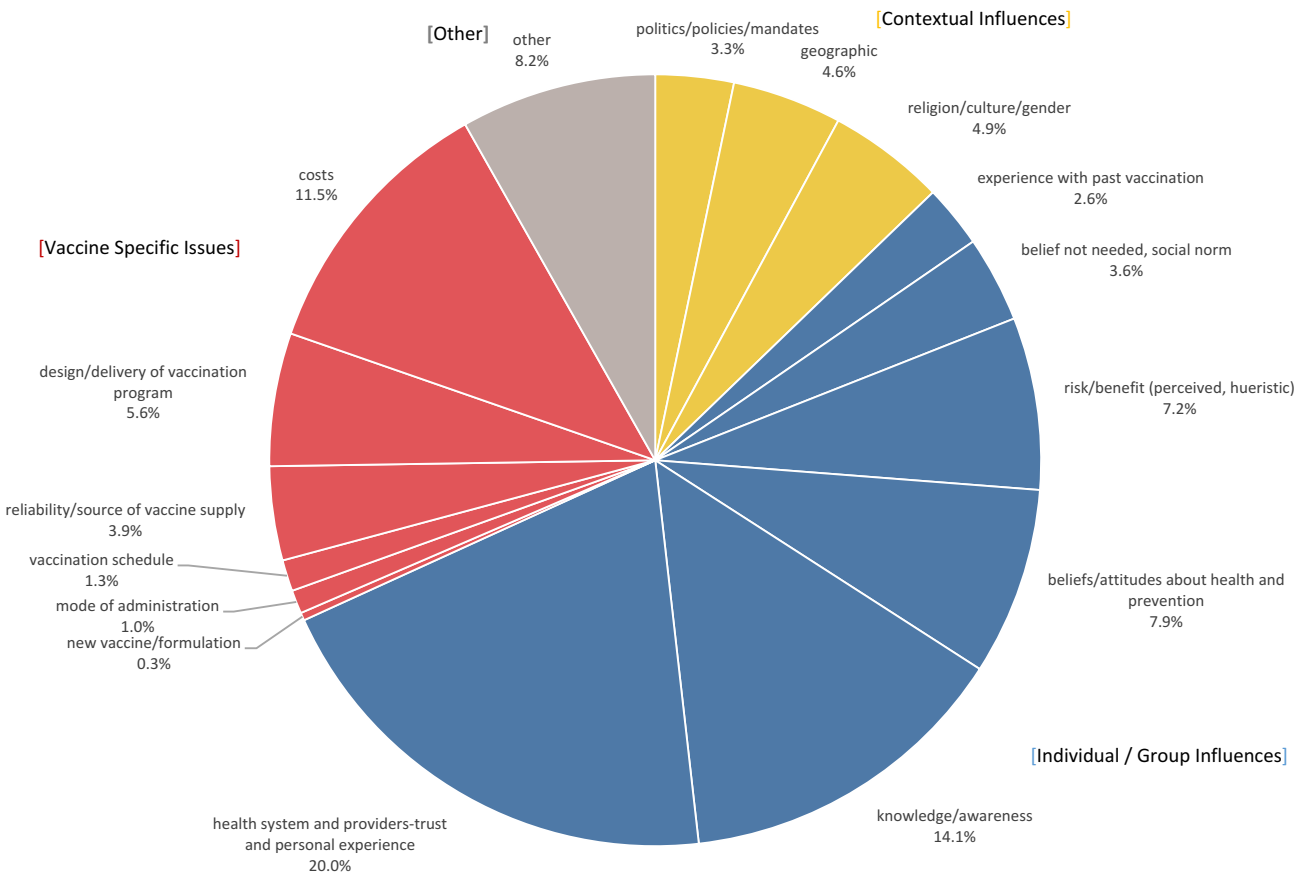
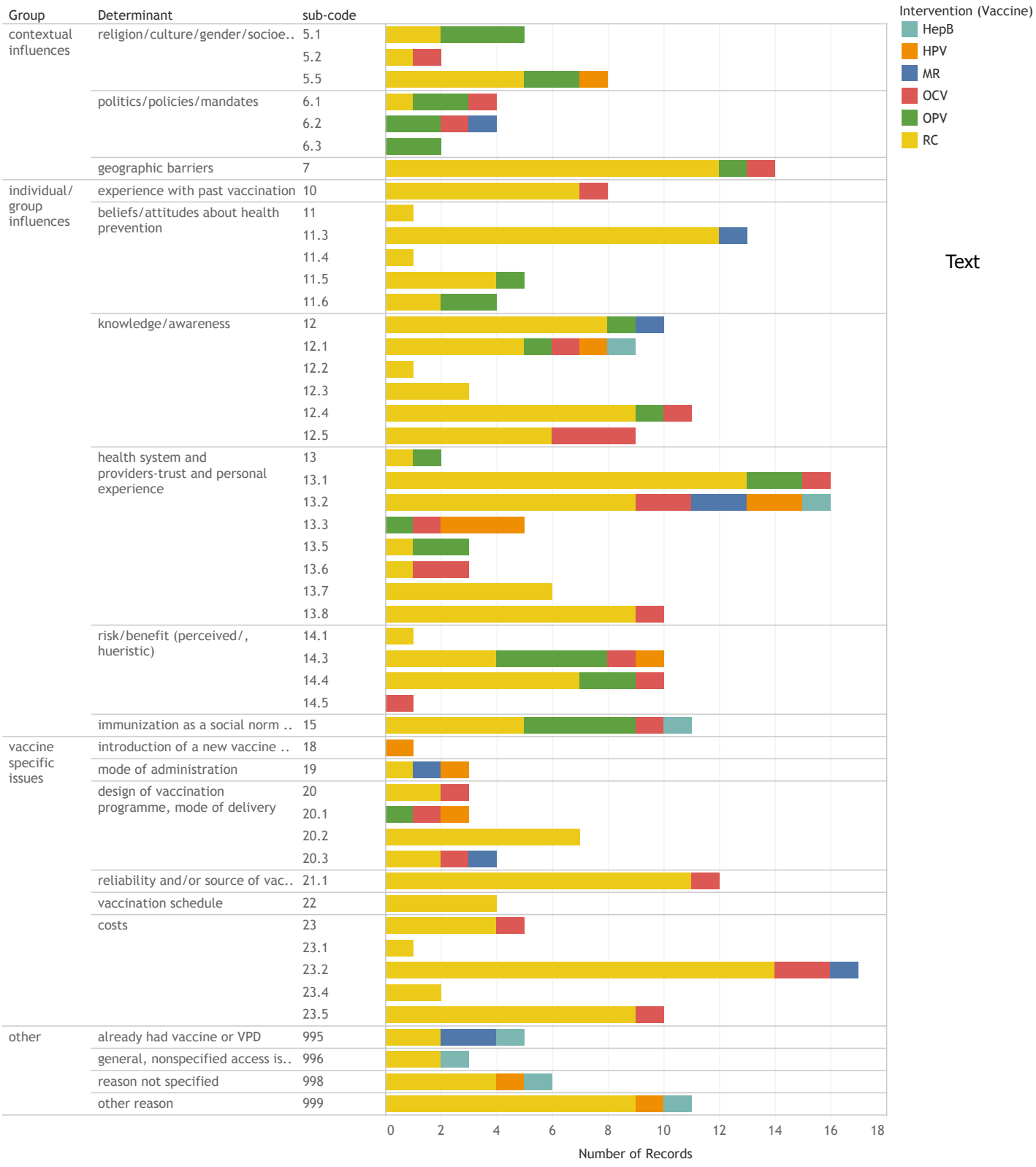


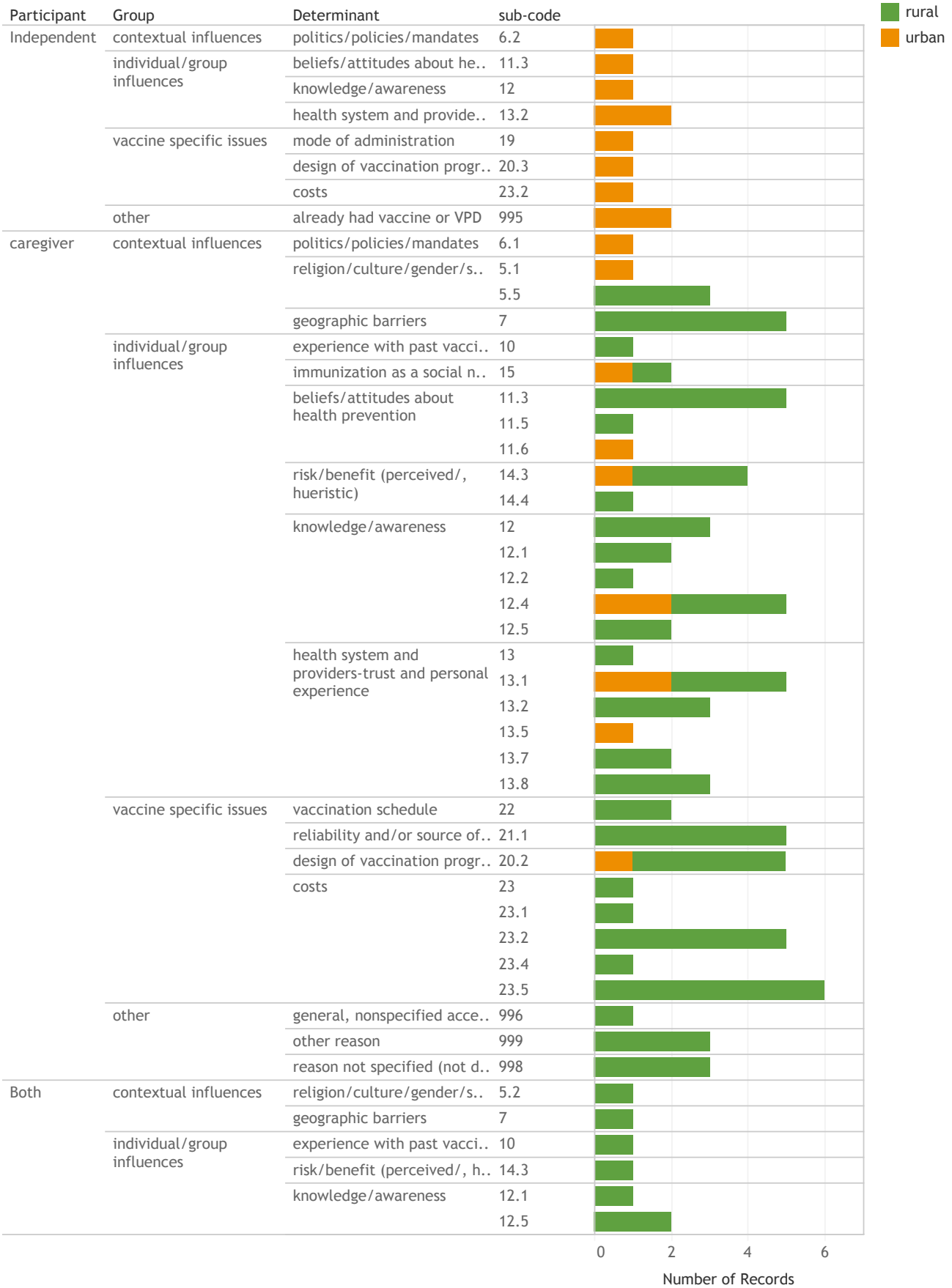
Figure 4: Reported sub-determinants of vaccine hesitancy, by vaccine



Text

Sum of Number of Records for each sub-code broken down by Group and Determinant. Color shows details about Intervention (Vaccine). Please refer to the Codeframe (Appendix 2) for the corresponding sub-determinants of the depicted sub-codes

Figure 5: Reported sub-determinants of vaccine hesitancy, by participant and setting



Participant	Group	Determinant	sub-code
Both	individual/group influences	health system and providers-trust and personal experience	13.2
			13.6
			13.8
	vaccine specific issues	reliability and/or source of..	21.1
		design of vaccination progr..	20.1
		costs	23.2
			23.5

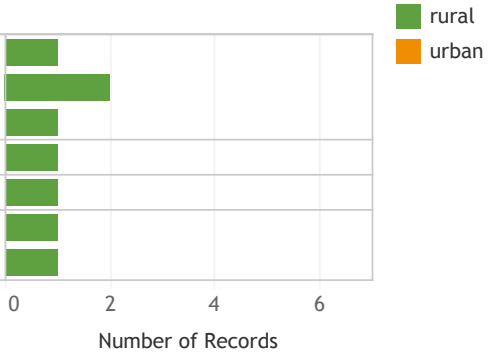
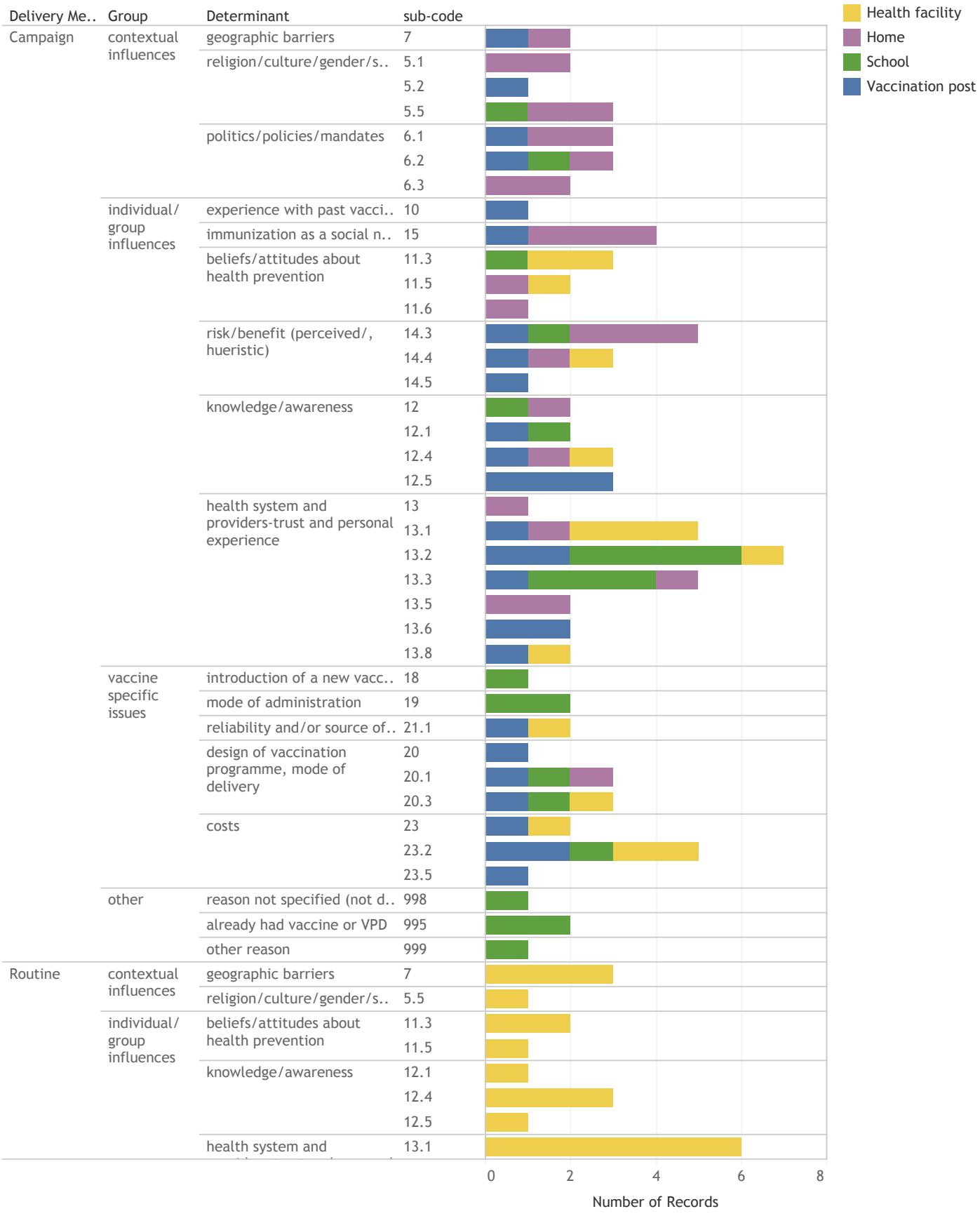
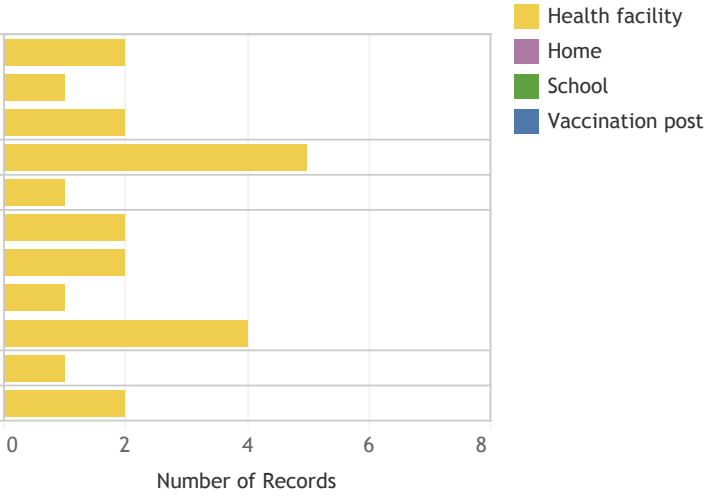


Figure 6: Reported sub-determinants of vaccine hesitancy, by delivery method and site



Delivery Me..	Group	Determinant	sub-code
Routine	individual/ group influences	health system and providers-trust and personal experience	13.2
			13.7
			13.8
	vaccine specific issues	reliability and/or source of..	21.1
		design of vaccination progr..	20.2
		costs	23
			23.2
			23.4
			23.5
	other	general, nonspecified acce..	996
		other reason	999



Appendix 1: Inclusion/exclusion criteria

<table>
<tr><td>Participants</td><td colspan="3">patients, parents, guardians, teachers/educators, elders, or adolescents, living in an African country, who are presented with the opportunity to make a decision to receive a WHO-qualified vaccine (either as an independent decision-maker for themselves or as a caregiver or their child or dependent)</td></tr>
<tr><td>Interventions</td><td colspan="3">vaccines, immunisations, or inoculations, including maternal vaccines/immunisations, vaccine/immunisation programmes or campaigns</td></tr>
<tr><td rowspan="14">Included WHO-qualified Vaccines and VPDs (WHO, 2017)</td><td>BCG</td><td>HPV</td><td>Polio Vaccine - Oral (OPV) Bivalent Types 1 and 3</td></tr>
<tr><td>cholera: inactivated oral</td><td>Japanese Encephalitis Vaccine (Inactivated)</td><td>Polio Vaccine - Oral (OPV) Monovalent Type 1</td></tr>
<tr><td>Diphtheria-Tetanus</td><td>Japanese Encephalitis Vaccine (live, attenuated)</td><td>Polio Vaccine - Oral (OPV) Monovalent Type 2</td></tr>
<tr><td>Diphtheria-Tetanus (reduced antigen content)</td><td>Measles</td><td>Polio Vaccine - Oral (OPV) Monovalent Type 3</td></tr>
<tr><td>Diphtheria-Tetanus-Pertussis (acellular)</td><td>Measles and Rubella</td><td>Polio Vaccine - Oral (OPV) Trivalent</td></tr>
<tr><td>Diphtheria-Tetanus-Pertussis (acellular)-Hepatitis B-Haemophilus influenzae type b-Polio (Inactivated)</td><td>Measles, Mumps and Rubella</td><td>Rabies</td></tr>
<tr><td>Diphtheria-Tetanus-Pertussis (whole cell)</td><td>Meningococcal A Conjugate</td><td>Rotavirus</td></tr>
<tr><td>Diphtheria-Tetanus-Pertussis (whole cell)-Haemophilus influenzae type b</td><td>Meningococcal A Conjugate (paediatric)</td><td>Rubella</td></tr>
<tr><td>Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B</td><td>Meningococcal A+C</td><td>Tetanus Toxoid</td></tr>
<tr><td>Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae type b</td><td>Meningococcal ACYW-135 (conjugate vaccine)</td><td>Typhoid (Polysaccharide)</td></tr>
<tr><td>Haemophilus influenzae type b</td><td>Meningococcal ACYW-135 (polysaccharide)</td><td>Yellow Fever</td></tr>
<tr><td>Hepatitis A (inactivated)</td><td>Pneumococcal (conjugate)</td><td></td></tr>
<tr><td>Hepatitis B</td><td>Polio Vaccine - Inactivated (IPV)</td><td></td></tr>
<tr><td>Comparison / Outcome</td><td colspan="3">reasons or factors of: acceptance, refusal, hesitancy, or anti-vaccination (as defined by participant who refused)</td></tr>
</table>

Appendix 2: Search terms and strategy

"PICO"		Terms	MeSH Terms
P	**Participants**	patient* OR parent* OR guardian* OR teacher OR educator OR adolescen* OR elder*	"Patients"[Mesh] OR "Parents"[Mesh] OR "Legal Guardians"[Mesh] OR "School Teachers"[Mesh] OR "Adolescent"[Mesh]
	Setting	Africa* OR "South* AND Africa*" OR "West* AND Africa*" OR "East* AND Africa*" OR "North* AND Africa*" OR "Central AND Africa*" OR "Sub Saharan" OR Sub-Saharan OR Subsaharan OR Algeria OR Angola OR Benin OR Botswana OR "Burkina Faso" OR Burundi OR Cameroon OR "Cape Verde" OR "Central African Republic" OR CAR OR Chad OR Comoros OR Congo OR "Democratic Republic Of Congo" OR "Republic Congo" OR Zaire OR DRC OR Djibouti OR Egypt OR "Equatorial Guinea" OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR "Guinea Bissau" OR "Ivory Coast" OR "Cote D'ivoire" OR Kenya OR Lesotho OR Liberia OR Libya OR OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Morocco OR Mozambique OR Moçambique OR Mocambique OR Namibia OR Niger OR Nigeria OR Reunion OR Réunion OR Rwanda OR "Sao Tome" OR "São Tomé" OR "São Tomé AND Príncipe" OR Senegal OR Seychelles OR "Sierra Leone" OR Somalia OR "South Africa" OR "South Sudan" OR Sudan OR Swaziland OR Tanzania OR Tanganyika OR Togo OR Tunisia OR Uganda OR "Western Sahara" OR Zambia OR Zimbabwe	"Africa" [Mesh] OR "Africa South of the Sahara"[Mesh] OR "Africa, Central"[Mesh] OR "Cameroon"[Mesh] OR "Central African Republic"[Mesh] OR "Chad" [Mesh] OR "Congo"[Mesh] OR "Democratic Republic of the Congo" [Mesh] OR "Equatorial Guinea"[Mesh] OR "Gabon"[Mesh] OR "Africa, Eastern"[Mesh] OR "Burundi"[Mesh] OR "Djibouti"[Mesh] OR "Eritrea" [Mesh] OR "Ethiopia"[Mesh] OR "Kenya"[Mesh] OR "Rwanda"[Mesh] OR "Somalia"[Mesh] OR "South Sudan"[Mesh] OR "Sudan"[Mesh] OR "Tanzania"[Mesh] OR "Uganda"[Mesh] OR "Africa, Southern"[Mesh] OR "Angola"[Mesh] OR "Botswana"[Mesh] OR "Lesotho"[Mesh] OR "Malawi" [Mesh] OR "Mozambique"[Mesh] OR "Namibia"[Mesh] OR "South Africa" [Mesh] OR "Swaziland"[Mesh] OR "Zambia"[Mesh] OR "Zimbabwe" [Mesh] OR "Africa, Western"[Mesh] OR "Benin"[Mesh] OR "Burkina Faso" [Mesh] OR "Cape Verde"[Mesh] OR "Cote d'Ivoire"[Mesh] OR "Gambia" [Mesh] OR "Ghana"[Mesh] OR "Guinea"[Mesh] OR "Guinea-Bissau" [Mesh] OR "Liberia"[Mesh] OR "Mali"[Mesh] OR "Mauritania"[Mesh] OR "Niger"[Mesh] OR "Nigeria"[Mesh] OR "Senegal"[Mesh] OR "Sierra Leone"[Mesh] OR "Togo"[Mesh] OR "Africa, Northern"[Mesh] OR "Algeria"[Mesh] OR "Egypt"[Mesh] OR "Libya"[Mesh] OR "Morocco" [Mesh] OR "Tunisia"[Mesh]
Intervention	**General**	vaccin* OR immuni* OR innoculat* OR "maternal vaccin*"	"Vaccination"[Mesh]) OR "Immunization"[Mesh] OR "Vaccines"[Mesh] OR "Immunization Programs"[Mesh] OR "Organization and Administration"[Mesh]
Comparison / Outcome		accept* OR hesit* OR uptake OR refus*	"Vaccination Refusal"[Mesh] OR "Anti-Vaccination Movement"[Mesh]
Filters		Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Comparative Study, Clinical Trial, Phase IV, Controlled Clinical Trial, Interview, Journal Article, Multicenter Study, Observational Study, Randomized Controlled Trial, Humans	

Search Strategy:
Search #1 = [Participants: Terms]
Search #2 = [Participants: MeSH Terms]
Search #3 = #1 OR #2
Search #4 = [Setting: Terms]
Search #5 = [Setting: MeSH Terms]
Search #6 = #4 OR #5
Search #7 = [Intervention: Terms]
Search #8 = [Intervention: MeSH Terms]
Search #9 = #7 OR #8
Search #10 = [C/O: Terms]
Search #11 = [C/O: MeSH Terms]
Search #12 = #10 OR #11
Final Search (#13) = #3 AND #6 AND #9 AND #12, apply filters

Databases:

PubMed	- Searched 19 Jan 2017
Cochrane (CENTRAL)	- Searched 19 Jan 2017
Scopus	- Searched 20 Jan 2017
Web of Science	- Searched 20 Jan 2017
CINAHL	- Searched 20 Jan 2017
Africa Wide	- Searched 20 Jan 2017
WHOLIS	- Searched 26 Jan 2017

Appendix 3: Quantitative codeframe

Intervention (Vaccine)	
Code	**Description**
1	routine childhood
2	measles rubella (MR)
3	HPV
4	polio (OPV)
5	cholera (OCV)
6	Hepatitis B

Delivery Site	
Code	**Description**
1	not specified
2	home, door-to-door
3	health facility
4	school/university
5	vax post/site

Delivery Method	
Code	**Description**
1	not specified
2	campaign
3	routine
4	RCT
5	SIA (supplemental)

Urban/Rural	
Code	**Description**
1	not specified
2	Rural
3	Semi
4	Urban
5	both rural and urban

Gender	
Code	**Description**
1	both/not specified
2	male
3	female

Age	
Code	**Description**
1	not specified
2	maternal
3	infant
4	child
5	adolescent
6	adult

Study Design/Methods	
Code	**Description**
1	randomised controlled trials
2	controlled before and after
4	cohort
5	case-control
6	cross-sectional
7	focus group
8	interview (in-depth)
10	case study
11	ethnography
13	qualitative

Literacy / Education	
Code	**Description**
1	not specified / multiple/various
2	primary/basic education
3	secondary education
4	tertiary/university education
5	high levels of illiteracy in population
6	medium levels of literacy
7	low levels of illiteracy

Participant's decision role	
Code	**Description**
1	Independent decision-maker
2	caregiver (decision-making for child/dependent)
3	Both (caregiver and child)
5	not specified
6	both as independent decision-makers, and as caregivers

Appendix 4: Qualitative codeframe

Code	Sub-determinant	SAGE Determinant	SAGE Group
1	contextual influences (general/other)	contextual influences (general/other)	contextual influences
2	communication & media environment	communication & media environment	
2.1	access to information		
2.2	mass media (use and influence)		
3	influential leaders, gatekeepers and anti-/pro-vaccination lobbies	influential leaders, gatekeepers and anti-/pro-vaccination lobbies	
4	historical influences	historical influences	
5	religion/culture/gender/socioeconomic	religion/culture/gender/socioeconomic	
5.1	Religion		
5.2	Culture		
5.3	Gender (of dependent)		
5.4	Gender (of independent)		
5.5	Husband or head-of-household refusal		
6	politics/policies/mandates	politics/policies/mandates	
6.1	government involvement, interference		
6.2	distrust in something offered for free		
6.3	belief govt should allocate resources to other areas (not vax)		
7	geographic barriers	geographic barriers	
8	pharmaceutical industry	pharmaceutical industry	
9	individual/group influences (general/other)	individual/group influences (general/other)	individual/group influences
10	experience with past vaccination	experience with past vaccination	
11	beliefs/attitudes about health and prevention	beliefs/attitudes about health and prevention	
11.1	attitude		
11.2	beliefs		
11.3	motivation (forgetfulness, disinterest, laziness)		
11.4	practice (general non-use of health services)		
11.5	practice (use of traditional/alternative practices)		
11.6	practice (general disapproval of vaccines, no detailed reasons)		
12	knowledge/awareness	knowledge/awareness	
12.1	vaccination knowledge (whether additional doses are required, eligibility/age/when to receive)		
12.2	general health knowledge		
12.3	myths/rumours		
12.4	belief that vax cannot be received when recipient is sick		
12.5	insufficient informaiton on time/place of vax/campaign		
13	health system and providers-trust and personal experience	health system and providers-trust and personal experience	
13.1	satisfaction with public health system, difficult personal inteactions, symbolic violence, lack of resources/necesities (i.e. water) at facilities		
13.2	distrust/fear vaccine due to: side effects (fear)		
13.3	distrust/fear vaccine due to: infertility (fear)		
13.4	distrust/fear vaccine due to: belief it will encourage promiscuity		
13.5	distrust/fear vaccine due to: beliefs too many injections are harmful		
13.6	distrust/fear vaccine due to: belief child too young to receive		
13.7	vaccinators absent		
13.8	long wait, delays, crowds at delivery site		
14	risk/benefit (perceived, hueristic)	risk/benefit (perceived, hueristic)	
14.1	susceptibility to disease		
14.2	disease severity		
14.3	vaccine safety		
14.4	vaccine efficacy		
14.5	vaccine efficacy of something that is free		
15	immunization as a social norm vs. not needed / harmful (need for vaccine, necessary)	immunization as a social norm vs. not needed / harmful (need for vaccine, necessary)	
16	vaccine specific issues (general/other)	vaccine specific issues (general/other)	vaccine specific issues
17	risk/benefit (scientific evidence)	risk/benefit (scientific evidence)	
17.1	use of evidence		
17.2	trust in evidence		
18	introduction of a new vaccine or new formulation	introduction of a new vaccine or new formulation	
19	mode of administration	mode of administration	
20	design of vaccination program, mode of delivery	design of vaccination program, mode of delivery	
20.1	absent from vax site (absent from school, not at home during delivery)		
20.2	procedural issues (multi-stage, problems with vax booklet/card		
20.3	limited open hours/days		
21	reliability and/or source of vaccine supply	reliability and/or source of vaccine supply	
21.1	vaccine not available		
22	vaccination schedule	vaccination schedule	
23	costs	costs	
23.1	financial (cost of vaccine itself)		
23.2	time (interruption of time normally spent on other activities/responsibilities)		
23.3	administrative		
23.4	access (cost of transportation)		
23.5	inability to access to due to ability, or illness (of recipient or caregiver)		
24	role of healtcare professionals	role of healtcare professionals	
24.1	patient communication		
24.2	vaccination expectations		
24.3	organizational culture		
24.4	place of work		
995	already had the vaccine/vpd	other	other
996	general, nonspecified access issues, no opportunity		
997	unclear relevance		
998	reason not specified (*not data?*)		
999	other reason		

Appendix 5: SAGE WG Determinants of Vaccine Hesitancy (definitions)

SAGE Determinant	Description
contextual influences	Influences arising due to historic, socio- cultural, environmental, health system/institutional, economic or political factors
communication & media environment	Media and social media can create a negative or positive vaccine sentiment and can provide a platform for lobbies and key opinion leaders to influence others; social media allows users to freely voice opinions and experiences and it can facilitate the organization of social networks for or against vaccines .
influential leaders, gatekeepers and anti-/pro- vaccination lobbies	Community leaders and influencers, including religious leaders in some settings, celebrities in others, can all have a significant influence on vaccine acceptance or hesitancy.
historical influences	Historic influences (such as the negative experience of the Trovan trial in Nigeria) can undermine public trust and influence vaccine acceptance, as it did for polio, especially when combined with pressures of influential leaders and media. A community's experience isn't necessarily limited to vaccination but may affect it.
religion/culture/gender/socioeconomic	A few examples of the interplay of religious/cultural influences include: Some religious leaders prohibit vaccines; Some cultures do not want men vaccinating children; Some cultures value boys over girls and fathers don't allow children to be vaccinated),
politics/policies/mandates	Vaccine mandates can provoke vaccine hesitancy not necessarily because of safety or other concerns, but due to resistance to the notion of forced vaccination
geographic barriers	A population can have general confidence in a vaccine and health service, and be motivated to receive a vaccine but hesitate as the health center is too far away or access is difficult.
pharmaceutical industry	Industry may be distrusted and influence vaccine hesitancy when perceived as driven only by financial motives and not in public health interest; This can extend to distrust in government when perceived that they are also being pushed by industry and not transparent.
individual/group influences	Influences arising from personal perception of the vaccine or influences of the social/peer environment
experience with past vaccination	Past negative or positive experience with a particular vaccination can influence hesitancy or willingness to vaccinate. Knowledge of someone who suffered from a VPD due to non-vaccination may enhance vaccine acceptance. Personal experience or knowledge of someone who experienced an AEFI can also influence hesitancy.
beliefs/attitudes about health and prevention	Vaccine hesitancy can result from 1) beliefs that vaccine preventable diseases (VPD) are needed to build immunity (and that vaccines destroy important natural immunity) or 2) beliefs that other behaviors (breastfeeding, traditional/alternativ e medicine or naturopathy) are as or more important than vaccination to maintain health and prevent VPDs.
knowledge/awareness	Decisions to vaccinate or not are influenced by a number of the factors addressed here, including level of knowledge and awareness. Vaccine acceptance or hesitancy can be affected by whether an individual or group has accurate knowledge, a lack of awareness due to no information, or misperceptions due to misinformation. Accurate knowledge alone is not enough to ensure vaccine acceptance, and misperceptions may cause hesitancy, but still result in vaccine acceptance.
health system and providers-trust and personal experience	Trust or distrust in government or authorities in general, can affect trust in vaccines and vaccination programmes delivered or mandated by the government. Past experiences that influence hesitancy can includes system procedures that were too long or complex, or personal interactions were difficult.
risk/benefit (perceived, heuristic)	Perceptions of risk as well as perceptions of lack of risk can affect vaccine acceptance. Complacency sets in when the perception of disease risk is low and little felt need for vaccination. E.g. Patient's or caregiver's perceptions of their own or their children's risk of the natural disease or caregivers' perceptions of how serious or life threatening the VPD is.
immunization as a social norm vs. not needed / harmful	Vaccine acceptance or hesitancy is influenced by peer group and social norms
vaccine specific issues	Directly related to vaccine or vaccination
risk/benefit (scientific evidence)	Scientific evidence of risk/benefit and history of safety issues can prompt individuals to hesitate, even when safety issues have been clarified and/or addressed. e.g. suspension of rotavirus vaccine due to intussusception; Guillain-Barre syndrome following swine flu vaccine (1976) or narcolepsy (2011) following (A)H1N1 vaccination; milder, local adverse events can also provoke hesitancy.
introduction of a new vaccine or new formulation	Individuals may hesitate to accept a new vaccine when they feel it has not been used/tested for long enough or feel that the new vaccine is not needed, or do not see the direct impact of the vaccine (e.g. HPV vaccine preventing cervical cancer). Individuals may be more willing (i.e. not complacent) to accept a new vaccine if perception of the VPD risk is high.

mode of administration	Mode of administration n can influence vaccine hesitancy for different reasons. E.g. oral or nasal administration ns are more convenient and may be accepted by those who find injections fearful or they do not have confidence in the health workers skills or devices used.
design of vaccination program, mode of delivery	Delivery mode can affect vaccine hesitancy in multiple ways. Some parents may not have confidence in a vaccinator coming house-to- house; or a campaign approach driven by the government. Alternatively if a health centre is too far or the hours are inconvenient
reliability and/or source of vaccine supply	Individuals may hesitate if they do not have confidence in the system's ability to provide vaccine(s) or might not have confidence in the source of the supply (e.g. if produced in a country/culture the individual is suspicious of) ; health workers may also be hesitant to administer a vaccine (especially a new one) if they do not have confidence that the supply will continue as it affects their clients trust in them. Caregivers may not have confidence that a needed vaccine and or health staff will be at the health facility if they go there.
vaccination schedule	Although there may be an appreciation for the importance of preventing individual vaccine preventable diseases, there may be reluctance to comply with the recommended schedule (e.g. multiple vaccines or age of vaccination). Vaccination schedules have some flexibility that may allow for slight adjustment to meet individual needs and preferences. While this may alleviate hesitancy issues, accommodating individual demands are not feasible at a population level.
costs	An individual may have confidence in a vaccine's safety and the system that delivers it, be motivated to vaccinate, but not be able to afford the vaccine or the costs associated with getting themselves and their child(ren) to the immunization point. Alternatively, the value of the vaccine might be diminished if provided for free.
role of healthcare professionals	Health care professionals (HCP)are important role models for their patients; if HCPs hesitate for any reason (e.g. due to lack of confidence in a vaccine's safety or need) it can influence their clients' willingness to vaccinate

VACCINE

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AUTHOR INFORMATION PACK

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