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IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

Stakeholder Understandings of the Human Papillomavirus (HPV) vaccine in Sub-Saharan Africa: A Qualitative Systematic Review

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Abstract

Cervical cancer rates in Sub-Saharan Africa (SSA) are amongst the highest in the world. The World Health Organization currently estimates that worldwide, cervical cancer will kill more than 443,000 women per year by 2030, of which 90% of deaths are predicted to occur in SSA. The Human Papillomavirus (HPV) vaccine provides primary protection against the most common cancer-causing strains of HPV that are responsible for cervical cancer. Over the last five years, there has been a slow increase in the number of African countries that have introduced the HPV vaccine via demonstration and pilot projects, and a minority of African countries that have incorporated the HPV vaccine into their National Immunisation Programmes. As part of this systematic review, a literature review was conducted and revealed that research has been conducted on top-down barriers and facilitators to HPV vaccine uptake and have found that poor health system capabilities, inaccessibility to medical care, low cervical cancer screening levels, inadequate infrastructure, finances, and health worker training are significant systemic barriers to HPV vaccination success in SSA. Little research has been conducted on demand-side or end-user perspectives of, and decisions around, the HPV vaccine. In order to complement existing research, and inform current and future implementation approaches, this qualitative systematic review explored stakeholder understandings of the HPV vaccine in SSA. This review searched the following databases: Embase (via Scopus), Scopus, MEDLINE (via PubMed), PubMed, EBSCOhost, Academic Search Premier, Africa-Wide Information, CINAHL, PsycARTICLES, PsycINFO, SocINDEX, Web of Science, and the Cochrane Controlled Register of Trials (CENTRAL) and found a total of 259 articles. Of these, 31 articles met the inclusion and exclusion criteria and were included in the review. Braun and Clarke's six step process for conducting a thematic analysis was used for analysis and studies were assessed for quality using the Critical Appraisal Skills Programme (CASP) checklist. Three major themes emerged from the thematic analysis: knowledge is intertwined with misinformation; fear shapes contradictory perceptions about the HPV vaccine; and social norms and gender dynamics are relevant factors in how stakeholders understand the HPV vaccine in SSA. This review iterates the importance of first working with communities to gauge understandings of the HPV vaccine, before trying to implement change through education, sensitization and behavior change.

Keywords: Human Papillomavirus (HPV); Human papillomavirus vaccine (HPV vaccine); Sub-Saharan Africa (SSA); thematic analysis; systematic review; qualitative research

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Part A: Protocol

Background to Protocol

The human papillomavirus (HPV) is the most common sexually transmitted infection (STI) among men and women world-wide (CDC, 2016a; WHO, 2018). HPV is predominately transmitted through vaginal and anal sex, though it can also be transmitted through oral sex (WHO, 2018). The most common agents of transmission include direct contact with infected genital skin, mucous membranes, and bodily fluid, likely after the onset of first sexual activity (CDC, 2016a; WHO, 2017). Most sexually active men and women are infected or repeatedly infected with HPV throughout the life course, likely unknowingly, since 70-90% of HPV cases are asymptomatic and spontaneously resolve within one to two years (WHO, 2018). HPV types are designated as ‘high’, ‘intermediate’ or ‘low-risk’ types depending on their oncogenicity or cancer-causing strength (WHO, 2017, 2018). Although the majority of HPV cases are asymptomatic and do not cause health issues, roughly 10% of HPV infections with intermediate to high risk types of HPV infection do not naturally regress, and instead, remain undetected in the reproductive tract initiating persistent infection (WHO, 2018). Depending on the type of HPV, persistent infection can cause a spectrum of health outcomes that range in severity from genital warts, to cases of respiratory papillomatosis, and to more severe cases of HPV-related cancer in men and women alike (WHO, 2017, 2018). This analysis will specifically focus on cervical cancer, the most common clinical consequence of persistent HPV infection (WHO, 2017, 2018).

HPV is comprised of over two hundred strains of ‘papillomavirus isolates’ commonly known as HPV ‘types’ that derive from the papovaviridae family (Sanclimente & Gill, 2002; WHO, 2017). A precancerous lesion, coupled with persistent infection with high risk types of HPV (most commonly type 16 and 18) will likely initiate the formation of invasive carcinomas that over time progress to cancers of the cervix, vulva, vagina, anus, penis, oropharynx, head, and neck that affect both men and women respectively (CDC, 2016b; WHO, 2018). Oncogenic or high risk types (16, 18, 31, 33, 35, 39, 45, 51, 52, and 58) are associated with cervical, vulvar, vaginal, and anal cancers, and non-oncogenic or low-risk types (6, 11, 40, 42, 43, 44, and 54) are associated with genital warts (Lacombe-Duncan et al., 2018; Munoz et al., 2003; Sanclimente & Gill, 2002). The most common strains associated with genital warts are HPV types 6 and 11, which are responsible for approximately 90% of these lesions (Braaten &

Laufer, 2008). The most common and oncogenic of all HPV types is type 16, accounting for almost half of all cervical cancers alone, and together with HPV 18, account for approximately 70% of cervical cancers (Clifford et al., 2003; Kidd et al., 2017).

HPV-related cancers are preventable due to the licensure of prophylactic HPV vaccines, first approved in 2006 by the Federal Drug Administration (FDA) in the United States (Kidd et al., 2017). There are currently three vaccines that target the most common types of HPV, all of which are considered to be equally effective (WHO, 2018). Current recommendations for administration of the HPV vaccine is prior to the onset of sexual activity for both adolescent males and females, ideally between the ages of 9-14 years old, and in theory, prior to initial exposure to HPV (WHO, 2018).

National programs maintaining at least a 50% coverage or 2 or 3 dose schedules “have demonstrated a dramatic impact on population level HPV prevalence, persistent HPV infection, genital warts, and cervical intraepithelial neoplasia” (Gallagher et al., 2018). Since the HPV vaccines have been introduced, over 80 countries in the world have initiated HPV vaccination programs, the majority of which are high income countries (HIC) or upper-middle income countries (UMIC) (Gallagher et al., 2018). Low-income countries (LIC) and low-middle income countries (LMIC) have faced historical, programmatic, and residual barriers to HPV vaccination delivery, accessibility and coverage when compared to middle-income and high-income counterparts (Gallagher et al., 2018). Gavi, the Global Alliance for Vaccines and Immunizations, has been integral in scaling up HPV vaccine support and accessibility in LIC/LMICs through provision of demonstration projects and national project initiatives for eligible countries (Gallagher et al., 2018). Although there has been a lag in HPV vaccine introductions in LIC/LMIC since licensure, “the pace since the HPV vaccine became accessible in these countries, given the barriers to introduction, is encouraging” (Gallagher et al., 2018; WHO, 2018). Africa, and more specifically Sub-Saharan Africa (SSA), bears the highest burden of cervical cancer world-wide, and requires high rates of HPV vaccine uptake in order to curb the cervical cancer epidemic through primary prevention (L. Bruni et al., 2019 ; WHO, 2017).

Introduction

The global burden of HPV disproportionately affects Africa, evident in rates of penile and cervical cancers being amongst the highest in the world (Olesen et al., 2014; WHO, 2017). Cervical cancer accounts for 22% of all newly diagnosed cancers on the continent of Africa and the age-standardized mortality rates are 7 to 10 times higher in Africa than in North America, Australia, New Zealand, and Western Asia (Saudi Arabia and Iraq) (Bray et al., 2018). Globally, Africa has the highest regional incidence and mortality rates from cervical cancer and was the leading cause of death in women in Africa in 2018 (Bray et al., 2018). The Report on Human Papillomavirus and Related Diseases in Africa estimated that in 2018 there were 81,687 deaths and 119,284 incident cases of cervical cancer, the vast majority of which (111,632 incident cases) occurred in Sub-Saharan Africa (L. Bruni et al., 2019). In 2018, the most elevated rates of cervical cancer incidence and mortality were seen in Southern Africa (e.g., Swaziland), Eastern Africa (Malawi and Zimbabwe) and Western Africa (Guinea, Burkina Faso, and Mali) (Bray et al., 2018). Stark differences between cervical cancer morbidity and mortality between HICs and LMICs are attributable to a variety of factors, including but not limited to, differences in population-based screening, HPV vaccine coverage at the population level, health care system efficiencies and epidemiological differences (Abdullahi et al., 2014; Black & Richmond, 2018; WHO, 2018).

The introduction of prophylactic HPV vaccines have made primary prevention of cervical cancer possible in places that bear even the greatest burden of the epidemic (Black & Richmond, 2018). In 2006, the first licensed HPV vaccination was the quadrivalent vaccine, followed by the addition of the bivalent vaccine and nonavalent vaccine in 2007 and 2014 respectively (WHO, 2017). The vaccines are intended to be administered before the recipients onset of sexual activity and therefore prior to exposure to HPV (WHO, 2018). Although all three of the HPV vaccines have become available for adolescent males and females, the uptake of the HPV vaccine in Africa and SSA has been specifically targeted at adolescent females in order to most cost-effectively curb the cervical cancer epidemic in countries heavily impacted by HPV, yet often under resource constraint countries (L. Bruni et al., 2019 ; WHO, 2017, 2017 2019). As of June 2018, the HPV vaccine has been licensed in National immunisation programmes in over 100 countries world-wide, nine of which are in SSA: Botswana (2015), Lesotho (2012), Rwanda (2011), Sao Tome and Principe (2016),

Senegal (2016), Seychelles (2014), South Africa (2014), Uganda (2012), and Mauritius (2016) (Black & Richmond, 2018; L. Bruni et al., 2019 ; Chido-Amajuoyi et al., 2019; Gallagher et al., 2018). Over twice as many Sub-Saharan African countries are recently or currently undergoing pilot programmes for HPV vaccination (Black & Richmond, 2018).

Despite HPV vaccination programs being introduced and steadily implemented in Sub-Saharan African countries since 2011, cervical cancer incidence in women in SSA remains abnormally high when compared to the rest of the world (Black & Richmond, 2018).

Previous mixed methods and qualitative systematic reviews in Africa have more generally examined knowledge and awareness of the HPV vaccine, as well as HPV vaccine willingness and acceptability. Such reviews concluded that although there are generally low to moderate levels of knowledge and awareness of the HPV vaccine, there is a notable understanding of the importance of the HPV vaccine. This has led to high levels of willingness and acceptability, as well as positive attitudes and practices towards HPV vaccination, however the disconnect behind historically low HPV vaccination uptake rates in Africa persists (Abdullahi et al., 2014; Melissa S. Cunningham et al., 2014; Perlman et al., 2014). Research into ‘supply-side’ barriers and facilitators of HPV vaccination in SSA has shown that top-down factors have slowed the HPV vaccines’ success including poor service access, inadequate infrastructure and finances, limited health worker training, competing morbidities, vaccine cost, inaccessibility to medical care, and cold chain capacity constraints (Black & Richmond, 2018; Perlman et al., 2014).

Adolescents, parents and care givers, teachers and health care workers and political, community and religious leaders have been identified as key populations of stakeholders that are not only relevant to HPV vaccination, but also vital to its success, as they create a required ‘demand’ for the HPV vaccine (Abdullahi et al., 2014; Marshall et al., 2018; Newman et al., 2018; Perlman et al., 2014; Radisic et al., 2017). In this review, relevant demand-side stakeholders will therefore be considered end-users or beneficiaries of the HPV vaccine, thus including adolescent recipients, as well as stakeholders who contribute to and shape decision-making around the HPV vaccine at the interpersonal and communal level. The literature may present other demand-side stakeholders who are influential on the demand side of the HPV vaccine and the review will recognize and incorporate such stakeholders with justification for inclusion, using a reflexive process for transparency. Data on HPV vaccine coverage in Sub-Saharan African countries is limited, but from available data, there is a lack

of qualitative exploration of how demand-side stakeholders understand the HPV vaccine in SSA.

Review Questions

Main Research Question:

This systematic review aims to utilize relevant literature to provide a contextual understanding of how demand-side stakeholders understand and perceive of the HPV vaccine in SSA. The main research question is therefore “How do relevant demand-side stakeholders in SSA understand the HPV vaccine?”

Subsidiary research questions

- How are understandings of the HPV vaccine shaped by experiences, perceptions, knowledge, attitudes, and beliefs in SSA?
- What specific contextual factors in SSA contribute to understandings around the HPV vaccine?

Objectives of the review questions

The objective of this systematic review is to identify, organize, and analyse qualitative data on ‘demand-side’ perceptions, understandings and experiences of the HPV vaccine in SSA using a thematic analysis approach. If the qualitative data proves to be sufficiently available and viable in quality and quantity, this review will conduct a thematic analysis to highlight emerging themes around the HPV vaccine in SSA that can potentially contribute to the pool of HPV vaccination knowledge in terms of what works, for whom, in what contexts, and why (Booth et al., 2013).

The key objectives are:

1. To identify, appraise and synthesize qualitative research evidence on how stakeholders understand, experience and perceive the HPV vaccine in SSA.
2. To identify and generate themes of relevant factors of influence on stakeholder understandings of HPV.
3. To identify hypotheses for subsequent consideration and assessment of current and future HPV vaccination roll out strategies in SSA.

Identifying, appraising and synthesising the qualitative evidence of stakeholders understandings, experiences, and perceptions of the HPV vaccine in SSA will compliment reviews on HPV vaccine effectiveness and help improve understandings of the barriers and facilitators of successful implementation of HPV vaccination strategies in SSA (Odendaal et al., 2015).

Methodology

This qualitative systematic review is in fulfilment of the mini-dissertation component of the Master of Public Health at the University of Cape Town. This review will therefore be led by one lead author and reviewer (CD) with oversight guidance from two supervisors (AS & SC). The APA style of referencing will be used.

Literature search strategy

This systematic review will utilize qualitative literature to assess understandings of the HPV vaccine from identified key populations of adolescents, care givers, teachers, health care providers, political, community and religious leaders, along with any other relevant stakeholder (on the demand-side of the HPV vaccine) that the literature may speak to. Exploring the understandings, perspectives, and experiences stakeholders will provide a consensus of the status of the HPV vaccine in SSA, contributing to the greater understanding of the HPV-related disease epidemic in SSA.

Optimal searches for comprehensive systematic reviews should include searches from Embase, MEDLINE, Web of Science, and Google Scholar as a minimum requirement for a systematic review (Bramer et al., 2017). This review will search the following relevant databases: Embase (via Scopus), Scopus, MEDLINE (via PubMed), PubMed, EBSCOhost, Academic Search Premier, Africa-Wide Information, CINAHL, PsycARTICLES, PsycINFO, SocINDEX, Web of Science, and the Cochrane Controlled Register of Trials (CENTRAL). After abstract screening is complete, the reference lists of included articles will also be searched to see if additional articles meet the outlined inclusion criteria. Due to time, resource and language constraints, grey literature and non-English articles will not be included in this review. Background information on eligible studies will be maintained

(Appendix B).

Initial key words have been selected based off a preliminary search of the literature, the aims of the systematic review, synonyms in the area of a study and the development of a comprehensive search strategy with oversight from a senior librarian. Search terms from other reviews will be scrutinized and should additional relevant search terminology arise, a justification for inclusion will be made and an audit trail will be maintained. MeSH terms will be sought. In order to capture all countries in SSA, the PubMed list of Sub-Saharan African countries will be used. From initial scoping, qualitative data on the HPV vaccine in SSA appears to be relatively scarce, justifying the use of a broad range of search terms to increase sensitivity of the search, to maintain a broad scope and to encompass all relevant studies and search terminology (Barnett-Page & Thomas, 2009; Bramer et al., 2017; Harris et al., 2018). The table below includes initial MeSH terminology and key words that will be used in the search, as well as the PubMed filter for Sub-Saharan African countries. Since this is a qualitative analysis, the search strategy will be iterative in nature, and a thorough audit trail will be maintained for transparency and replicability.

Table 1: Search terms

Population	("Papillomavirus Vaccines"[Mesh] OR "Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18"[Mesh] OR "human papillomavirus vaccine" OR "HPV vaccine" OR "human papillomavirus vaccination" OR "HPV vaccination")
Interest	AND "Health Knowledge, Attitudes, Practice"[Mesh] OR Knowledge OR attitude OR attitudes OR belief OR beliefs OR perceptions OR perception OR comprehend OR comprehension OR experience OR experiences OR understand OR understandings OR feel OR feelings OR opinion OR opinions OR point of view OR view OR views

Context

AND

("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 "Sao Tome and Principe"[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 "Cabo 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" OR "Sub Saharan Africa" OR " Central Africa " OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Congo" OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR "Gabon" OR "Sao Tome and Principe" OR " Eastern Africa " OR "East Africa" OR "Burundi" OR "Djibouti" OR "Eritrea" OR "Ethiopia" OR "Kenya" OR "Rwanda" OR "Somalia" OR "South Sudan" OR "Sudan" OR "Tanzania" OR "Uganda" OR " Southern Africa " OR "Angola" OR "Botswana" OR "Lesotho" OR "Malawi" OR "Mozambique" OR "Namibia" OR "South Africa" OR "Swaziland" OR "Zambia" OR "Zimbabwe" OR " Western Africa " OR "West Africa" OR "Benin" OR "Burkina Faso" OR "Cabo Verde" OR "Cote d'Ivoire" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Liberia" OR "Mali" OR "Mauritania" OR "Niger" OR "Nigeria" OR "Senegal" OR "Sierra Leone" OR "Togo"

Article inclusion and exclusion criteria

In order for articles to be considered relevant for this review, the following inclusion criteria must be met:

- i.)* **Included article publication dates must range between 2006 to the date of search.** This date range is intended to capture stakeholder experiences, understandings and perspectives of the HPV vaccine since the introduction of the HPV vaccine in 2006.
- ii.)* **Included articles must take place in a country in SSA.**
- iii.)* **Included articles must be methodologically qualitative in both data collection and data analysis.** The search strategy will not be limited to qualitative study designs alone in order to identify and utilize qualitative components of mixed methods studies, as to which such components must also be methodologically qualitative in nature (both for data collection and analysis procedures).
- iv.)* **Articles must examine one or more relevant themes that contribute to how stakeholders understand the HPV vaccine in SSA.** Such themes could include HPV vaccine experiences, perceptions, knowledge, beliefs, attitudes etc.
- v.)* **Articles must be published in English.** Although this introduces bias, this review will acknowledge such limitations.
- vi.)* **Articles must include perspectives from stakeholders who contribute to the ‘demand’ for the HPV vaccine** including adolescents, caregivers, teachers, health care providers, and political, community and religious leaders etc. Any other relevant demand-side stakeholders that the literature may bring forth will be documented through an audit trial and will be justified for inclusion based on the aims of the review.

Articles examining HPV-related health outcomes (such as cervical cancer) that do not include relevant data on the HPV vaccine and HPV vaccination in SSA will not be included. For the purpose of this review, articles must have qualitative data specifically relating to HPV vaccine or HPV vaccination services in SSA. Studies on vaccination in general, but do not explicitly include the HPV vaccine will also be excluded.

Article selection

Due to the nature of the mini dissertation stipulations, there will be one lead reviewer (CD) with input from two overseeing supervisors (AS & SC). After the search strategy has been run in the named databases, the results will be assessed for titles and abstract eligibility. Relevant articles will be uploaded into Endnote where duplicates will be identified and removed. Following this, full text review of eligible studies will assess adherence to inclusion criteria. The two overseeing supervisors (AS & SC) will randomly identify 20% of title/abstracts and 20% of full text articles and will individually review them (10% per supervisor) against the inclusion and exclusion criteria as a method of increasing rigour. Any disagreements on article selection will be resolved via discussion between CD and one or both of the supervisors (AS & SC). A list of eligible studies will then be collated and basic background information will be maintained in a study log including first author, year of study, study location, study population, data collection and analysis methods and authors aims (Appendix C). Based on the Cochrane Qualitative Research Methods Group for searching qualitative evidence (Harris et al., 2018), a search strategy will be developed and adapted for each database (Appendix A). A PRISMA flow diagram will be created to show search results and the process of screening and selecting studies for inclusion.

Data extraction

Once studies are coded and initial themes are solidified, the data extraction table will group collated data by potential themes and will maintain the source of data (original transcripts, participant quotes from analysis or secondary author interpretations). The form will be used to extract primary themes or first-order constructs (original participant quotes) and secondary themes or second-order constructs (author's analysis or interpretations) from individual studies (Appendix C).

Appraisal of evidence

Included qualitative studies (methodological and analytical) and the qualitative components of mixed methods studies will be critically appraised using the Critical Appraisal Skills Programme (CASP) checklist (Appendix E). Through the use of the CASP quality assessment tool, this review will systematically assess each article's validity and applicability

of results which will ultimately provide a level of confidence in the relevance, richness and depth of the qualitative data that the study contributes to answering the review question (CASP, 2018). Studies will not be excluded based off the CASP assessment alone, but will speak to the level of confidence in the findings of each study and therefore how much each study is utilized in the thematic analysis (CASP, 2018).

Data synthesis

This review will utilize a thematic analysis approach to interpret and synthesize results across various studies in order to contribute to the knowledge around stakeholder understandings of the HPV vaccine across SSA (Cahill et al., 2018; Tong et al., 2007). This review will follow Braun and Clarke's 6-step framework for summarizing, organizing, and analysing data into an interpretive thematic analysis (Braun & Clarke, 2006). Since this systematic review aims to answer a specific research question, semantic themes will be developed based off of the explicit evidence from the qualitative data (Braun & Clarke, 2006). The 6-step framework is outlined below:

- Become familiar with the data
- Generate initial codes
- Search for themes
- Review themes
- Define themes
- Write up and analyse

(Braun & Clarke, 2006).

A thematic analysis of the available data will be conducted in order to consider a framework for factors that may contribute to demand-side stakeholder understandings of the HPV vaccine and how such factors may influence HPV vaccination services in SSA, potentially producing useful insight for amending current HPV vaccination efforts, as well as shaping HPV vaccination campaigns in SSA in the future.

Timeline

The initial scoping for this review began in September 2018. The data extraction process is will be completed by April 2019 to which a completed systematic review is expected by June 2019.

Table 1: Timeline

Part A: Protocol	
First draft (all components)	Due January 31, 2019
Edits	Due February 10, 2019
Final Protocol	Due February 15, 2019
Part B: Literature Review	
Refined search strategy	Due February 20, 2019
Title and abstract screening	Due March 5, 2019
Full text screening	Due March 10, 2019
Literature review draft	Due March 15, 2019
Edits	Due April 25, 2019
Final Literature review	Due April 1, 2019
Part C: Manuscript	
Data extraction	Due April 10, 2019
Appraisal	Due April 15, 2019
Synthesis	Due April 15, 2019
Manuscript draft	Due April 25, 2019
Edits	Due May 10, 2019
Intention to Submit	Due May 20, 2019
Final edits (Parts A, B and C)	Due May 31, 2019
Mini-dissertation submission	Due June 30, 2019
Dissemination	Once the mini dissertation has been graded and final corrections have been made, the manuscript will be submitted to the relevant journal for consideration of publication.

Study limitations

As per mini-dissertation stipulations (University of Cape Town) there can only be one lead author and reviewer (CD) which introduces selection bias. This proposal acknowledges the risk for study limitation and publication bias due to the selection of English language only studies, unavoidable due to language capacity and time and resource constraints. Selection and publication bias will be mitigated as much as possible through triangulation with two overseeing supervisors who are well versed in the field, the creation of a thorough audit trail, detailed procedures outlining the process of the thematic analysis for replicability purposes, and random sampling of title/abstracts and full texts for agreement between lead author and overseeing supervisors.

Ethical Considerations

This qualitative systematic review will utilize existing research on HPV vaccination in SSA and therefore does not need ethical review or considerations as it does not conduct primary research.

Dissemination

This mini-dissertation will be available on the University of Cape Town's thesis library. The manuscript portion of the outlined mini-dissertation will adhere to a pre-selected journal and will be written according to that journal's formatting requirements. The manuscript portion of the mini-dissertation will be submitted to that journal for review for publication and dissemination to the larger academic community will be contingent on journal acceptance of the manuscript.

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Part B: Literature Review

Introduction

The Human papillomavirus (HPV) is comprised of more than 150 related viruses that derive from the Papillomaviridae family (WHO, 2018). The variety of HPV viruses are commonly known as HPV ‘types’, which are grouped into low and high risk types depending on the health outcomes caused (CDC, 2016a; Feller et al., 2009; Sanclemente & Gill, 2002; WHO, 2018). There are 40 types of HPV that affect the genital tract and are transmitted sexually through anal, oral, and vaginal sex, as well as skin-to-skin genital contact (CDC, 2016b; WHO, 2018). HPV is highly transmissible, is the most common viral infection of the reproductive tract and the most frequent sexually transmitted disease in the world (WHO, 2018). HPV will likely infect or repeatedly infect most sexually active men and women throughout the life course, likely unknowingly, as 70-90% of HPV cases are asymptomatic and spontaneously resolve within one to two years (WHO, 2017, 2018).

A small proportion of persistent infections with specific HPV genotypes do not naturally regress on their own and instead initiate productive infection that can cause a range of distinct clinical manifestations including “latent infection of basal cells that is insufficient for infection transmission, subclinical infection that is active but asymptomatic, or clinical infection that initiates benign, potentially malignant, or malignant lesions” depending on the HPV type (Feller et al., 2009; Sanclemente & Gill, 2002; WHO, 2018). The spectrum of health outcomes resulting from HPV infection is dependent on dual factors; the type of HPV infection and the stage of maturation (WHO, 2018). Low-risk types of HPV (HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81) are associated with benign oral lesions and genital warts and high-risk types (predominately HPV 16, 18 and less frequently HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) are associated in the development of malignant epithelial neoplasms or cancer of the cervix, anus, penis, vulva, vagina, and oropharynx (Burd, 2003; Feller et al., 2009; WHO, 2018). HPV type 16 and 18 account for the largest numbers of HPV-related cancers globally, and together are the most common types of HPV identifiable in cervical cancers (Olesen et al., 2014).

HPV is most often a latent infection that is unintentionally passed from person-to-person (WHO, 2018). Since the majority of HPV cases naturally regress on their own, testing for

HPV is not a commonality (WHO, 2018). HPV is most often detected in women through abnormal Papanicolaou test which indicates precancerous or cancerous lesions in the cervix, that have been reliably attributed to certain types of HPV infection (WHO, 2018). Cervical cancer is the most common clinical consequence of persistent HPV infection, and therefore, is the focus of the majority of the literature around HPV (WHO, 2019). Although HPV is most commonly associated with female cervical cancer, it is notable that there is considerable non-cervical HPV-associated cancers such as anogenital cancers of the penis and anus in men, along with oral, head, neck, and anal cancers amongst men and women alike (Moscicki & Palefsky, 2011; Olesen et al., 2014). Although HPV is a gender-neutral infection, the duration of this literature review will focus on female HPV-infection and cervical cancer outcomes.

Biology of Human Papillomavirus

HPV types are initially designated as cutaneous (associated with the skin) or mucosal (associated with mucus membranes that line the surface of internal organs (Sanclemente & Gill, 2002). Cutaneous HPV infection causes common warts and planters warts, whereas mucosal HPV causes more serious outcomes such as genital warts and cancer depending on acquisition of a low or high risk mucosal type of HPV (Sanclemente & Gill, 2002; WHO, 2018). HPV gains entry through micro-abrasions in the basal cells to which the virus directly binds to the cell surface ligands and then adapts to the natural host of skin or mucosae epithelial cells, infecting and exploiting the cellular machinery (Muñoz et al., 2006; Sanclemente & Gill, 2002). HPV infection is instigated when single or multiple viruses exploit the epithelial basal cells, replicate the infected cells, and produce mature virions that express the viral genes (Feller et al., 2009).

Although HPV is a necessary cause of cervical cancer, it is usually not considered to be sufficient on its own, as the spectrum of health outcomes is governed by complex interactions between multiple factors including the specific HPV genotype causing the infection, the genetic components and host immune response of the infected individual, the phenotype of the infected epithelial cells, and the differing environments and lifestyles in which one lives (Feller et al., 2009; WHO, 2018). Chronic smoking, multiparity, long-term use of hormonal contraceptives, and human immunodeficiency virus (HIV) co-infection have been shown to play a significant role in cervical cancer risk (de Sanjosé et al., 2018). Immunosuppression, a

symptom of HIV infection, significantly increases the risk of not only developing HPV, but also catalysing a more aggressive type of infection (Feller et al., 2009). HIV and HPV acquisition have a fluid and synergistic relationship where risk of acquisition of each disease is positively correlated, becoming hugely problematic in endemic areas, especially Sub-Saharan Africa (SSA) where 70% of the global burden of HIV infection is found and where the rates of cervical cancer are amongst the highest in the world (Mahon, 2018; Olesen et al., 2014; WHO, 2017).

Cervical Cancer

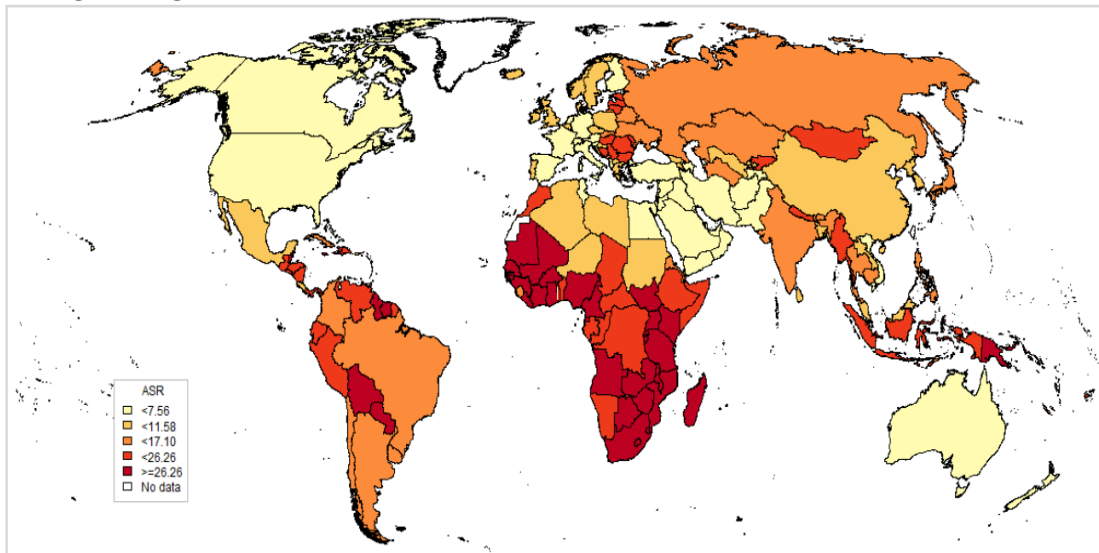
Female cervical cells are highly susceptible to HPV infection (WHO, 2018). Once persistent infection occurs in the cervix and remains untreated, precancerous lesions then develop and over time, mature into cervical cancer (WHO, 2017). Initial HPV infection typically occurs in young women in the first decade of sexual activity (Schiffman et al., 2007). Persistent HPV infection is rare and only occurs in less than 10% of new infections (WHO, 2017). Persistent infection establishes as a precancer within 5-10 years and progresses into invasive cancer over many years, sometimes even decades (Schiffman et al., 2007). Cervical cancer is a slow progressing disease by nature and has multi-tiered prevention strategies that make it avertable through primary prevention via the HPV vaccine, secondary prevention via screening and tertiary prevention via surgical removal (WHO, 2018, 2019).

It has been established that the prevalence of cervical cancer in women is closely related to the corresponding risk or incidence (Clifford et al., 2005). Although cervical cancer is indeed preventable, it was the fourth most common cancer in all women in 2018, representing 6.6% of female cancers world-wide (WHO, 2018). There are significant geographical discrepancies of cervical cancer prevalence and incidence rates; 85% of global incident cases and 90% of global cervical cancer mortality occurred in low-and middle-income countries in 2018 (WHO, 2018).

Africa bears the highest burden of cervical cancer world-wide, with age-standardized mortality rates more than doubling the rates of any other continent (L. Bruni et al., 2019). In SSA specifically, the age-standardised incidence rates of cervical cancer are among the highest in the world, reflected in the map (below) by Bruni and colleagues (L. Bruni et al., 2019). Of the 81,687 annual cervical cancer deaths in Africa in 2018, 76,444 occurred in

SSA, where cervical cancer is the second most common cancer in women (L. Bruni et al., 2019). The highest incidence rates of cervical cancer in SSA are in Eastern, Middle, and Southern Africa with standardized mortality rates of 30, 21.1, and 20 per 100,000 women respectively (L. Bruni et al., 2019).

Figure 4: Age-standardised incidence rates of cervical cancer in the World (estimates for 2018)



Data accessed on 05 Oct 2018.

Rates per 100,000 women per year.

For more detailed methods of estimation please refer to <http://gco.iarc.fr/today/data-sources-methods>

Data sources: Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2018). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: <https://gco.iarc.fr/today>, accessed [05 October 2018].

Source: (L. Bruni et al., 2019)

The HPV vaccine

The introduction and widespread use of vaccines has curbed and eradicated the occurrence of several infectious diseases and has been called one of the greatest public health achievements in the twentieth century, as increased immunization rates have resulted in significantly decreased risk of the disease at the population level (Malone & Hinman, 2003). The HPV vaccine is no exception to this, affording direct protection against the most common cancer causing types of HPV, if ideally administered before the onset of sexual activity (WHO, 2018). The HPV vaccine increases the human bodies level of immunogenicity, producing 50 times more titres of neutralising antibodies than what would be produced by natural infection, which should future infection occur, pre-emptively prepares the antibodies to attach to the human papillomavirus and prevent it from infecting the cells of the body (NCI, 2018 ; Schiffman et al., 2007).

In 2006, Gardasil, a quadrivalent vaccine that targets HPV types 6, 11, 16, and 18, was released as the first prophylactic HPV vaccine approved by the United States Food and Drug Administration (FDA) (WHO, 2017). In 2009, a bivalent HPV vaccine, Ceravix, followed and was aimed at targeting the most common types of HPV (types 16 and 18) (WHO, 2017). In 2014, the nonavalent vaccine, Gardasil9 was then approved and targeted HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (WHO, 2017). If given to individuals before the onset of sexual activity, all three of the HPV vaccines are nearly perfect in terms of efficacy for protecting against the types of HPV that are targeted (NCI, 2018 ; Schiffman et al., 2007; WHO, 2017).

Although the HPV vaccines are now currently available for males and females alike, it wasn't until 2014 that the US Advisory Committee on Immunisation Practices approved the initial routine use of the quadrivalent vaccine, Gardasil, for males (NCI, 2018 ; Olesen et al., 2014; WHO, 2017). The gender-based time lag of HPV vaccine approval is of notable importance as it inherently created significant global disparities between sexes in the prevention of HPV-related cancers which has contributed to an unrelenting perception that HPV is a feminized disease and health problem (Chido-Amajuoyi et al., 2019). Globally, the HPV vaccine and the “initial licensure and marketing aimed strictly at adolescent girls and not boys, [caused] confusion about HPV infection, the HPV vaccine and sexual activity, and outrage over early industry efforts to promote legislation requiring the vaccine” (Brewer et al., 2017). In turn, these energies have been transformed into a global unease towards the HPV vaccine among stakeholders, which has slowed the adoption of the HPV vaccine to this day, regardless of abundant data showing high effectiveness and safety of the HPV vaccine (Brewer et al., 2017; Chido-Amajuoyi et al., 2019; WHO, 2018).

The HPV vaccine in Sub-Saharan Africa

Although Africa bears the highest burden of cervical cancer world-wide, as of June 2018, only ten African countries (including Libya), and nine Sub-Saharan African countries have included the HPV vaccine into National Immunisation Programmes: Botswana (2015), Lesotho (2012), Rwanda (2011), Sao Tome and Principe (2016), Senegal (2016), Seychelles (2014), South Africa (2014), Uganda (2012), and Mauritius (2016) (Black & Richmond, 2018; L. Bruni et al., 2019 ; Chido-Amajuoyi et al., 2019; Gallagher et al., 2018). Twenty-two Sub-Saharan African countries currently have or have previously had HPV vaccine demonstration projects in place: Benin, Burundi, Burkina Faso, Cameroon, Cote d'Ivoire,

Ethiopia, Gambia, Ghana, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Nigeria, Sierra Leone, Tanzania, Togo, Zambia, and Zimbabwe (L. Bruni et al., 2019 ; Dochez et al., 2017), largely through the support the Global Alliance for Vaccines and Immunizations (GAVI), an international public-private health partnership committed to increasing access to immunizations in developing countries, along with additional donors of the World Health Organization, UNICEF, and PATH (Dochez et al., 2017).

Rollout of the HPV vaccine in SSA has not been without its unique challenges. According to Dochez and colleagues, the HPV vaccine inherently produces unique public health considerations including the involvement of “an older target age group (9–14 year-olds instead of infants and young children), preferred delivery platforms of a school-based programme (instead of primary health care facilities) and therefore the involvement of multiple authorities at country level (Ministry of Health and Ministry of Education), socio-behavioural and gender issues as girls are being targeted, the stigma of HPV being a sexually transmitted infection and delayed tangible health benefits of the HPV vaccine as there is a long delay in demonstrating the vaccines control and impact” (Dochez et al., 2017). Additionally, very few African countries have strong adolescent health programs which may be essential for effective delivery (Dochez et al., 2017).

Research has been conducted on ‘supply-side’ barriers and facilitators of HPV vaccination in SSA and have found that a variety of top-down factors including poor service access, inadequate infrastructure and sustainable financing, limited health worker training, competing morbidities, vaccine cost, inaccessibility to medical care, and cold chain capacity constraints, have played a role in slow HPV vaccine uptake, (Abdullahi et al., 2014; Black & Richmond, 2018; Perlman et al., 2014; WHO, 2019). Health inequities, gender disparities, and socioeconomic and cultural factors also play significant roles in cervical cancer screening and early detection in Africa where cervical cancer is not typically not identified or treated until advanced stages (WHO, 2018, 2019). The World Health Organization predicts that at least one third of all HPV-related cancers in Africa could be prevented with comprehensive vaccination implementation (WHO, 2019).

Vaccination facilitators and barriers

A key factor in vaccination uptake in low-and middle-income countries is whether relevant stakeholders actively seek a vaccine, and therefore create a vaccination ‘demand’ (Brewer et al., 2017). In this review, demand-side stakeholders will be considered to be adolescents, caregivers, health care providers, teachers, and political, religious and community leaders. There are multi-faceted factors that contribute to where relevant stakeholders fall on the spectrum of attitudes and beliefs towards the HPV vaccine. It is hypothesized that attitudes towards the HPV vaccine sit on a spectrum that mirrors the continuum of attitudes towards vaccines more generally with active HPV vaccination support and active HPV vaccination refusal on either end of the spectrum, and HPV vaccination hesitancy somewhere in the middle of the continuum (Cooper et al., 2019).

To date, meta-analyses have shown that risk appraisals are the most significantly correlated factor to vaccination behaviour, with perceived likelihood of disease, perceived severity of disease, and anticipatory regret directly contributing to an individual’s behaviour towards a given vaccine (Brewer et al., 2017). Research has found that peoples thoughts and feelings inform their motivations or non-motivations to get vaccinated (Brewer et al., 2017). In a report that draws on hundreds of psychological and behavioural science studies of vaccinations, Brewer and colleagues found that “thoughts and feelings can motivate getting vaccinated- with risk beliefs and anticipated regret about the infectious disease established as reliably correlated with getting vaccinated and low confidence in vaccine effectiveness and concern about safety reliably correlated with not getting vaccinated” (Brewer et al., 2017). This sentiment is reinforced by previous experience in countries such as Cameroon and Uganda in regards to the tetanus toxoid campaigns and in Nigeria in regards to the oral polio vaccine where resistance to immunization became wide-spread when public figures expressed concerns about the safety of the vaccines in turn creating a rhetoric that had monumental influence on the public’s perceptions of the vaccines (Leach & Fairhead, 2008; Yahya, 2007).

Sub-Saharan African literature around HPV and the HPV vaccine has assessed attitudes in a plethora of different ways, ultimately creating a wide range of interchangeable terminologies such as HPV and HPV vaccine : ‘facilitators’, ‘knowledge’, ‘awareness’, ‘acceptability’,

‘attitudes’, ‘beliefs’, ‘intention’, ‘efficacy’, ‘perceptions’, ‘uptake’, and ‘perspectives’ and inversely, antonyms such as HPV and HPV vaccine: ‘barriers’, ‘hesitancy’, ‘refusal’, ‘scepticism’, ‘denial’, ‘concerns’ and ‘fear’ (Abdullahi et al., 2014; Melissa S. Cunningham et al., 2014; Lacombe-Duncan et al., 2018; Newman et al., 2018; Perlman et al., 2014; Radisic et al., 2017; Santhanes et al., 2018; Trim et al., 2012). Although the fore mentioned factors are, in theory, distinct and separate constructs, literature around HPV and the HPV vaccine has often used them as similar and overlapping terminologies, which has made theory around HPV and the HPV vaccine in SSA challenging to tease apart (Brewer et al., 2017).

The Gap in Research

Research in Africa has included exploration of knowledge, attitudes and practices of general adolescent vaccination and findings included sub-optimal knowledge about vaccine preventable diseases among adolescents, parents, and teachers (Abdullahi et al., 2014). Two systematic reviews supported this notion about HPV and the HPV vaccine specifically, concluding that although there was low to moderate levels of knowledge and awareness of cervical cancer, HPV, and the HPV vaccine among parents, teachers, and adolescents in SSA, that there was a willingness and understanding of the importance of being knowledgeable on the HPV vaccine, though the disconnect for this was unclear (Abdullahi et al., 2014; Perlman et al., 2014). High levels of willingness and acceptability towards the HPV vaccine in SSA among parents, adolescents and teachers has been attributed to the notion that the HPV vaccine provides direct protection against cervical cancer acquisition (Abdullahi et al., 2014; Perlman et al., 2014). Contrary to Brewer and colleagues’ assumption that risk appraisals are the most significantly correlated factor to actual vaccine initiation, Santhanes and colleagues found that the perception of the risk of HPV was high in Africa (ranging from 41-78%), yet the relationship between risk appraisal and intention to vaccinate was mixed (Santhanes et al., 2018). Given the incredible impact and value that vaccination has had, “its underuse in countries where it is available and affordable is an avoidable tragedy that is an ongoing crisis that has motivated further research into understanding why people get vaccinated and why they do not” (Brewer et al., 2017). Thus far, both quantitative and qualitative data on HPV vaccination coverage in Sub-Saharan African countries is limited compared to countries in Europe and North America (WHO, 2017). There is a lack of qualitative exploration of how relevant demand-side stakeholders understand the HPV vaccine in SSA. Undertaking such

research will not only be useful in improving current HPV vaccination rollout strategies, but will also contribute to future strategies where demand-side stakeholder opinions and understandings are not only likely to be acknowledged, but also utilized in shaping effective HPV vaccination programmes that can potentially curb the cervical cancer epidemic in SSA.

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Part C: Journal “ready” Manuscript

This article has been prepared for submission to *Qualitative Health Research*. Author instructions are available online and in Appendix E (<https://uk.sagepub.com/en-gb/afr/journal/qualitative-health-research#submission-guidelines>).

Front sheet (per Journal requirements):

Stakeholder Understandings of the Human Papillomavirus (HPV) vaccine in Sub-Saharan Africa: A Qualitative Systematic Review

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Abstract

Cervical cancer rates in Sub-Saharan Africa (SSA) are amongst the highest worldwide. The Human Papillomavirus (HPV) vaccine provides primary protection against the most common cancer-causing strains of HPV, including those that cause cervical cancer. There has been an increase in Sub-Saharan African countries that have introduced the HPV vaccine. Research has been conducted on supply-side barriers and facilitators to HPV vaccine uptake in SSA. In order to compliment such research and to inform current and future implementation approaches, this qualitative systematic review explored stakeholder understandings, perspectives, and experiences of the HPV vaccine in SSA. Thirty-one studies were found eligible for inclusion and were analysed thematically using Braun and Clarke's methods for conducting a thematic analysis. The quality of included studies was assessed using the Critical Appraisal Skills Programme (CASP) checklist. The review found that HPV vaccine knowledge is intertwined with misinformation, that fear shapes contradictory perceptions about the HPV vaccine and that social norms and gender dynamics are relevant factors in how stakeholders understand the HPV vaccine in SSA.

Keywords: Human Papillomavirus (HPV); Human papillomavirus vaccine (HPV vaccine); Sub-Saharan Africa (SSA); thematic analysis; systematic review; qualitative

Introduction

Human papillomavirus (HPV) is the established causative agent of cervical cancer which is the most common clinical consequence of HPV infection (WHO, 2018). Cervical cancer is the second most common cancer among women in Africa, which as a continent, has an estimated population of 372.2 million women aged 15 years and older who are at risk of developing cervical cancer (L. Bruni et al., 2019). Roughly 119,284 new cases of cervical cancer are diagnosed annually in Africa, the vast majority of which occur in Sub-Saharan Africa (SSA) (L. Bruni et al., 2019). There is growing evidence that HPV is also a relevant factor in other anogenital and head and neck cancers in both men and women (L. Bruni et al., 2019). There are 40 types of HPV that affect the genital tract and are transmitted sexually through anal, oral, and vaginal sex, as well as skin-to-skin genital contact (CDC, 2016b; WHO, 2017, 2017). HPV is highly transmissible, with estimations that two thirds of those who have had sexual contact with HPV-infected persons will become infected themselves (CDC, 2016b; WHO, 2018). HPV is the most common viral infection of the reproductive tract and the most common sexually transmitted disease in the world (CDC, 2016b; Feller et al., 2009; WHO, 2018).

The HPV vaccine was first introduced in 2006 and offers primary protection against the most common cancer-causing strains of HPV (types 16, 18, 6, 11, 31, 33, 45, 52 and 58) (WHO, 2017). In SSA, late presentation to care (only after symptoms present) is an established and common health trend (WHO, 2017, 2018). Late stages of disease detection, along with health inequities, gender disparities, socioeconomic and cultural factors have been key drivers in high rates of cervical cancer mortality in SSA (WHO, 2017). The World Health Organization (WHO) estimates that at least one third of all HPV-related cancers in Africa could be prevented with comprehensive vaccination implementation (WHO, 2017).

As of June 2018, ten African countries (including Libya (2013)), and nine Sub-Saharan African countries have included HPV vaccination in their National Immunisation Programs: Botswana (2015), Lesotho (2012), Rwanda (2011), Sao Tome and Principe (2016), Senegal (2016), Seychelles (2014), South Africa (2014), Uganda (2012), and Mauritius (2016) (Black & Richmond, 2018; L. Bruni et al., 2019 ; Chido-Amajuoyi et al., 2019; Gallagher et al., 2018). Twenty-two SSA countries have HPV vaccine demonstration projects in place: Benin, Burundi, Burkina Faso, Cameroon, Cote d'Ivoire, Ethiopia, Gambia, Ghana, Kenya, Liberia,

Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Nigeria, Sierra Leone, Tanzania, Togo, Zambia, and Zimbabwe (L. Bruni et al., 2019 ; Dochez et al., 2017). Recent momentum around the HPV vaccine in SSA over the last 5 years is largely through the support of the Global Alliance for Vaccines and Immunization (GAVI), an international public-private health partnership committed to increasing access to immunizations in developing countries, along with additional donors including the World Health Organization, PATH and UNICEF (Dochez et al., 2017).

In order for any type of vaccination to be successful, high levels of uptake are required in order to promote herd immunity, a notion where enough people in the population are vaccinated so the pathogen cannot reproduce (Brewer et al., 2018). In 2014, the estimated coverage of the HPV vaccine in African women age 10-20 years old was 1-2% (Bruni et al., 2016; Chido-Amajuoyi et al., 2019). From 2013-2015, Gavi implemented roughly 20 HPV vaccine demonstration projects, the majority of which were in SSA, and were anticipated to reach a total of about 400,000 women (Bruni et al., 2016). Since implementation expansion in 2015, recent and accurate data on HPV vaccination coverage is limited or unavailable for most countries that have introduced the HPV vaccine into national immunisation programmes or through demonstration projects (Black & Richmond, 2018). Based on available data from South Africa, Seychelles, Senegal, and Rwanda, Black and Richmond estimate that National immunisation programmes HPV coverage rates range from 72% in South Africa to 98.7% in Rwanda (Black & Richmond, 2018), yet comprehensive HPV vaccination coverage rates for the whole of SSA remain unclear due to a lack of available health informatics post-implementation. According to Gavi, all five of the countries with the highest numbers of deaths from cervical cancer remain in SSA, highlighting the major public health concern of the continued prevalence and incidence of cervical cancer and the need for increased uptake of the HPV vaccine in SSA (GAVI, 2018).

Factors that contribute to coverage rates of the HPV vaccine in SSA are multifactorial (WHO, 2017). Previous research in SSA has largely focused on supply-side barriers to HPV vaccination which threaten the success of HPV vaccine implementation. Such research has found, for example, that poor health system capabilities, inaccessibility to medical care, low cervical cancer screening levels, inadequate infrastructure, finances, and health worker training are significant systemic barriers to HPV vaccination success (Bingham et al., 2009; Black & Richmond, 2018; Francis et al., 2011; Harries et al., 2009; Perlman et al., 2014).

Despite a steady rise in the number of African countries introducing the HPV vaccine into national immunisation programmes and demonstration/pilot projects, along with extensive data showing the safety and effectiveness of the HPV vaccine, there is clear controversy when it comes to actual HPV vaccination behavior in SSA (Brewer et al., 2018; CDC, 2016b; WHO, 2019). Persistent skepticism around the HPV vaccine has contributed to stakeholder uncertainty in vaccination behaviour and actual decision making around the HPV vaccine. This has motivated further research into understanding why people get vaccinated and why they do not, especially given “the incredible impact and value that vaccination has had” and the continued lack of clarity around low levels of HPV vaccination uptake in countries where it has become available and affordable (Brewer et al., 2017).

Rather than further contribute to knowledge of the HPV vaccine from a health systems perspective, this review aimed to explore perspectives and understandings of relevant stakeholders who are decision-makers and end-users of the HPV vaccine in SSA. Such stakeholders would be considered individuals who are invested in creating a ‘demand’ for the HPV vaccine, including adolescents, parents and caregivers, teachers and health care providers, and political, community and religious leaders. By exploring an ‘end-user’ or ‘demand-side’ point of view, understandings of the HPV vaccine may further highlight and add perspective to factors that promote or inhibit HPV vaccination efforts in SSA, that are identified and validated by demand-side stakeholders themselves. Much of the previous research has been around health-system and supply-side exploration of the HPV vaccine from a quantitative point of view (Bardaji et al., 2018; Compaore et al., 2016; Dairo et al., 2018; Dreyer et al., 2015; Newman et al., 2018). In contrast, this review aims to utilize qualitative research to gain a variety of demand-side stakeholders and users understandings of the HPV vaccine in the Sub-Saharan African context, where health informatics and research around the HPV vaccine are scarce compared to high-income country counterparts (Du et al., 2015; Durham et al., 2016; Markowitz et al., 2018). Utilizing empirical qualitative evidence from a variety of stakeholder point of views provides the opportunity to highlight factors that influence HPV vaccination behaviour and decision-making processes from stakeholders who hold various levels of status on the spectrum of ‘demand’ for the HPV vaccine in SSA. This includes recipients of the HPV vaccine (such as adolescents themselves) amongst stakeholder perspectives, whose views are often marginalized compared to higher-level stakeholders (such as politicians), thus giving a comprehensive spectrum of understandings of the HPV

vaccine from demand-side stakeholders in SSA.

Methods

Overview

Qualitative systematic review methods were utilized with the aim of capturing the complexity of stakeholder understandings and thought processes of the HPV vaccine in SSA. Qualitative research is well-placed for exploring complex beliefs and behaviours, and for understanding how different factors influence these (Braun & Clarke, 2006). This approach is thus appropriate for gaining insight into demand side stakeholder understandings, perceptions, and experiences of the HPV vaccine in SSA, a research question that cannot be answered utilizing quantitative methods alone. In the construction of this review, systematic methods were utilized for searching the qualitative research using strict inclusion and exclusion criteria, appraising the evidence using a critical appraisal tool, and synthesizing evidence using Braun and Clarke's thematic analysis approach (Braun & Clarke, 2006; Brewer et al., 2018; Carlsen & Glenton, 2016).

Aims and objectives of review question:

This systematic review aims to provide contextual understanding of how demand-side stakeholders understand and perceive of the HPV vaccine in SSA. The main research question is therefore: "How do demand-side stakeholders in SSA understand the HPV vaccine?" This review aims to highlight emerging themes around the HPV vaccine in SSA that can potentially contribute to the pool of HPV vaccination knowledge in terms of what works, for whom, in what contexts, and why (Booth et al., 2013).

The key objectives are:

1. To identify, appraise and synthesize qualitative research evidence on how stakeholders understand, experience and perceive the HPV vaccine in SSA.
2. To identify and generate themes of relevant factors of influence on stakeholder understandings of HPV.
3. To identify hypotheses for subsequent consideration and assessment of current and future HPV vaccination roll out strategies in SSA.

Identifying, appraising and synthesising the qualitative evidence of stakeholders understandings, experiences, and perceptions of the HPV vaccine in SSA will compliment reviews on HPV vaccine effectiveness and contribute to understandings of the barriers and facilitators of successful implementation of HPV vaccination strategies in SSA (Odendaal et al., 2015).

Search strategy

As a minimum requirement, optimal searches for comprehensive systematic reviews should include searches from Embase, MEDLINE, Web of Science, and Google Scholar (Bramer et al., 2017). This review conducted systematic and comprehensive searches from March-April 2019 using the following relevant databases: Embase (via Scopus), Scopus, MEDLINE (via PubMed), PubMed, EBSCOhost, Academic Search Premier, Africa-Wide Information, CINAHL, PsycARTICLES, PsycINFO, SocINDEX, Web of Science, and the Cochrane Controlled Register of Trials (CENTRAL). The search strategy was prepared with support from an experienced librarian based at the University of Cape Town and consisted of terms related to HPV and the HPV vaccine, terms related to comprehension and understandings, terms related to SSA, and terms related to qualitative research (Appendix A).

Inclusion and exclusion criteria

This review sought studies on stakeholder understandings of the HPV vaccine in SSA, therefore including studies on understandings, experiences, perceptions, attitudes, beliefs, knowledge, comprehensions, feelings, and opinions of the HPV vaccine in SSA. The population of interest included relevant stakeholders who create a ‘demand’ for the vaccine including adolescents, parents and caregivers of adolescents, teachers, health care providers, and political, religious, and community leaders.

Only English articles were included in this review due to language capabilities of the lead author and review team. Eligible studies were published from 2006-June 2019 in order to capture all relevant data since the introduction of the HPV vaccine in 2006 (WHO, 2017, 2018). Eligible studies had to use a qualitative study design and qualitative methods for both data collection and data analysis. Qualitative data collection methods included: focus group discussions (FGDs), in-depth interviews (IDIs), semi-structured interviews (SSIs), key

informant interviews (KIIs), and observation. Qualitative data analysis methods included: thematic analysis, ethnographies, meta-ethnographies, content analysis, phenomenological analysis, discourse analysis, narrative analysis, case-study analysis, and grounded theory. Mixed-methods study designs that had a qualitative component were included if the component utilized qualitative methods for both data collection and analysis.

Studies outside of SSA were excluded. Studies examining HPV-related health outcomes (such as cervical cancer) that did not include relevant data on the HPV vaccine and HPV vaccination in SSA were excluded. Other studies that focused on vaccination more generally, but did not explicitly include the HPV vaccine, were also excluded. Studies that did not make use of qualitative methods for data collection and/or analysis were excluded. Systematic reviews that met inclusion criteria were excluded based on the nature of secondary rather than primary analysis. However, the reference lists of each systematic review were evaluated in order to identify additional relevant papers that may have been missed by the search strategy. Grey literature and non-English studies were excluded.

Study Selection

Studies were selected through a 4-stage process:

1. Specified electronic databases were searched using the search strategy and results were collated into Endnote X9 where duplicates were removed.
2. Title and abstracts were then screened for eligibility. To maintain rigor, 20% of eligible title and abstracts were screened by two independent reviewers (10% of total eligible title/abstracts per supervisor).
3. Eligible title and abstracts were then reviewed for full text eligibility. In order to maintain rigor, 20% of all eligible full texts were screened by two independent reviewers (10% of total eligible full texts per supervisor).
4. A final list of eligible studies was collated and uploaded into Covidence software for quality assessment and data extraction. The search process is outlined in the PRISMA diagram (figure 1 below) and the included studies were mapped in figure 2.

Once eligible studies were finalized, data from each study was extracted in Microsoft Excel. Background information from each study was also extracted and included first author name,

year of study, year of publication, the country where the study took place, the study participants, the qualitative data collection and analysis methods, and the aim of the study (Carlsen & Glenton, 2016) (See Appendix D).

Study quality assessment

The 31 studies were assessed by the lead author (CD) using the Critical Appraisal Skills Programme (CASP) appraisal tool for quality assessment purposes. Each study was assessed against the CASP checklist criteria which included assessment of the following study features: aims of the research question, the qualitative methodology, the research design, the recruitment strategy, data collection, reflexivity, ethical issues being considered, data analysis and findings being of substantial value and evidence (Appendix E). Studies were not excluded based on the CASP appraisal tool assessment alone, but this assessment informed the analyses and overarching findings of the review.

Data extraction and analysis

According to Braun and Clarke (2006), thematic analysis is a “method for identifying, analysing, and reporting patterns (themes) within data” (Braun & Clarke, 2006). Braun and Clarke’s thematic analysis methods were used to systematically report experiences, meanings and the reality of participants across the dataset (Braun & Clarke, 2006). This review’s thematic analysis was conducted by the lead author (CD) and utilized an inductive approach, whereby theme creation was data driven and at the semantic (i.e. explicit) level to capture rich description of the entirety of the data set. The data extraction process was shared with and checked by advisors (AS and SC) . The ultimate objective was to develop an in-depth picture of stakeholders’ understandings of the HPV vaccine in the Sub-Saharan African context (Braun & Clarke, 2006).

The thematic analysis was initiated by thoroughly engaging with the depth and breadth of content through repeated re-reading and initial identification of patterns of meaning across the dataset of eligible studies (Braun & Clarke, 2006). Following Braun and Clarke’s guidelines for thematic analysis, each individual study in the dataset was coded and systematically examined, with full and equal attention given to each data item in order to identify interesting aspects that could form the basis of repeated themes across the dataset

(Braun & Clarke, 2006). Upon re-review, initial re-occurring themes across studies were derived and copied into an excel sheet and collated together, maintaining the original source of data (original transcripts, direct quotes, and secondary authors analysis) for transparency and reflexivity. Initially, as many potential themes/patterns were coded as possible, while still maintaining record of surrounding data for contextual purposes (Braun & Clarke, 2006). Individual extracts of data were coded into all relevant and applicable themes in order to maintain proper conceptualization, and to also realize potential tensions within the coded data and to retain accounts which depart from the dominant analysis (Braun & Clarke, 2006).

After all the data was initially coded and collated, codes were then sorted into potential broader-level themes and a mind-map approach was used to group the most substantial codes together and identify the overarching theme that was represented by lead author (CD) in collaboration with advisors (AS and SC) (Braun & Clarke, 2006). Codes were then shifted and loosely grouped into sub-themes in a way that supported and provided evidence for the overarching identified theme (Braun & Clarke, 2006). Internal homogeneity of data was assessed by re-reading through coded data extracts to see if they coherently supported the overarching theme. In several instances, initial sub-themes were collapsed into each other to form a more articulate sub-theme that better supported the overarching theme (for example, in theme 3: 'gender dynamics in SSA', the sub-theme 'gender expectations' was collapsed into sub-theme 'gender influence on health seeking behavior' in order to more concisely and better support the overarching theme).

Distinctions between themes were then assessed in order to maintain external heterogeneity of themes, ensure codes worked in relation to the dataset, and also provide the opportunity to code additional data that may have been originally missed within themes (Braun & Clarke, 2006). Finally, the overall themes and the components of each individual theme (made up of sub-themes) were confirmed and named. This was done by revisiting the coded collated data extractions and organizing the extracts in a logical way with potential accompanying narrative that clearly articulated why the sub-theme had emerged and how it contributes to the overarching theme. This, in turn, contributed to the greater narrative of stakeholder understandings, experiences and perceptions of the HPV vaccine in SSA (Braun & Clarke, 2006).

Results

After deduplication, abstract and title screening and full text screening, thirty-one eligible studies were used in this review. The initial database searched the following databases Embase (via Scopus), Scopus, MEDLINE (via PubMed), PubMed, EBSCOhost, Academic Search Premier, Africa-Wide Information, CINAHL, PsycARTICLES, PsycINFO, SocINDEX, Web of Science, and the Cochrane Controlled Register of Trials (CENTRAL) and produced 259 articles, of which 174 were then removed due to duplicate status. The remaining 85 articles were then screened and 18 articles were excluded based off of title/abstract screening. From there, 67 articles were screened for full text eligibility to which 36 total articles were excluded for various reasons including the wrong study design, the wrong outcome being studied, the wrong study setting and the wrong patient population. Thus, 31 studies in total were eligible for the systematic review.

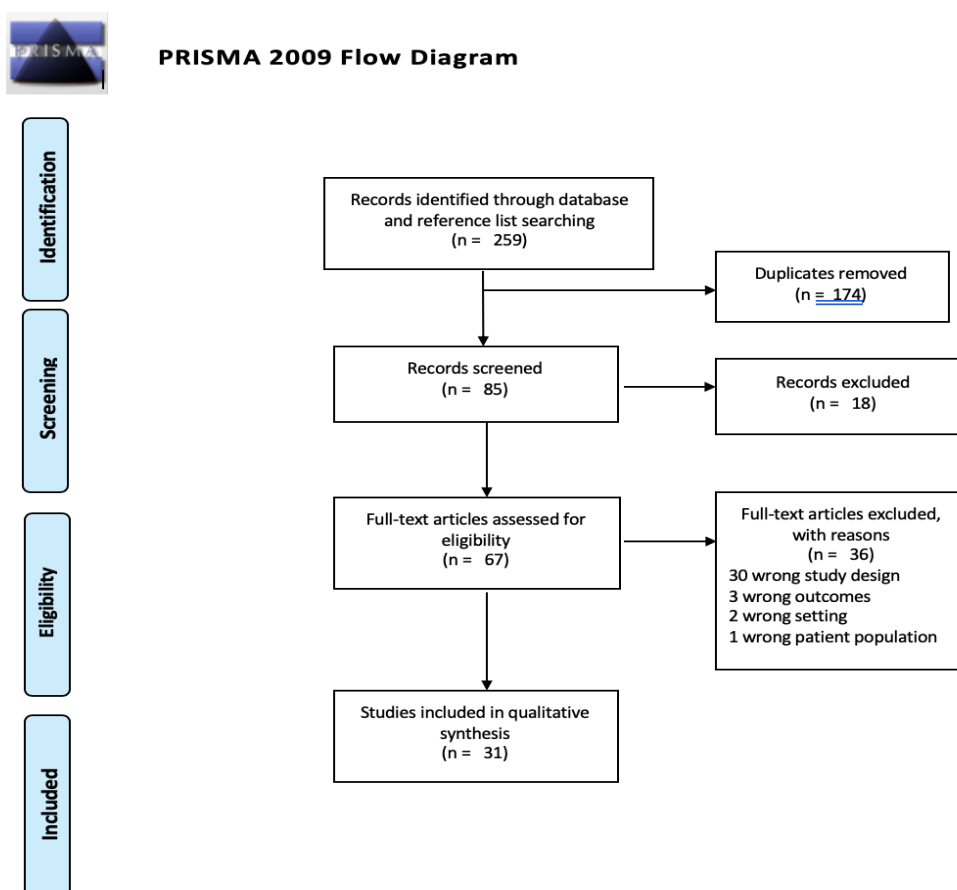


Figure 1: PRISMA diagram of search strategy and results (Moher et al., 2009)

Study characteristics

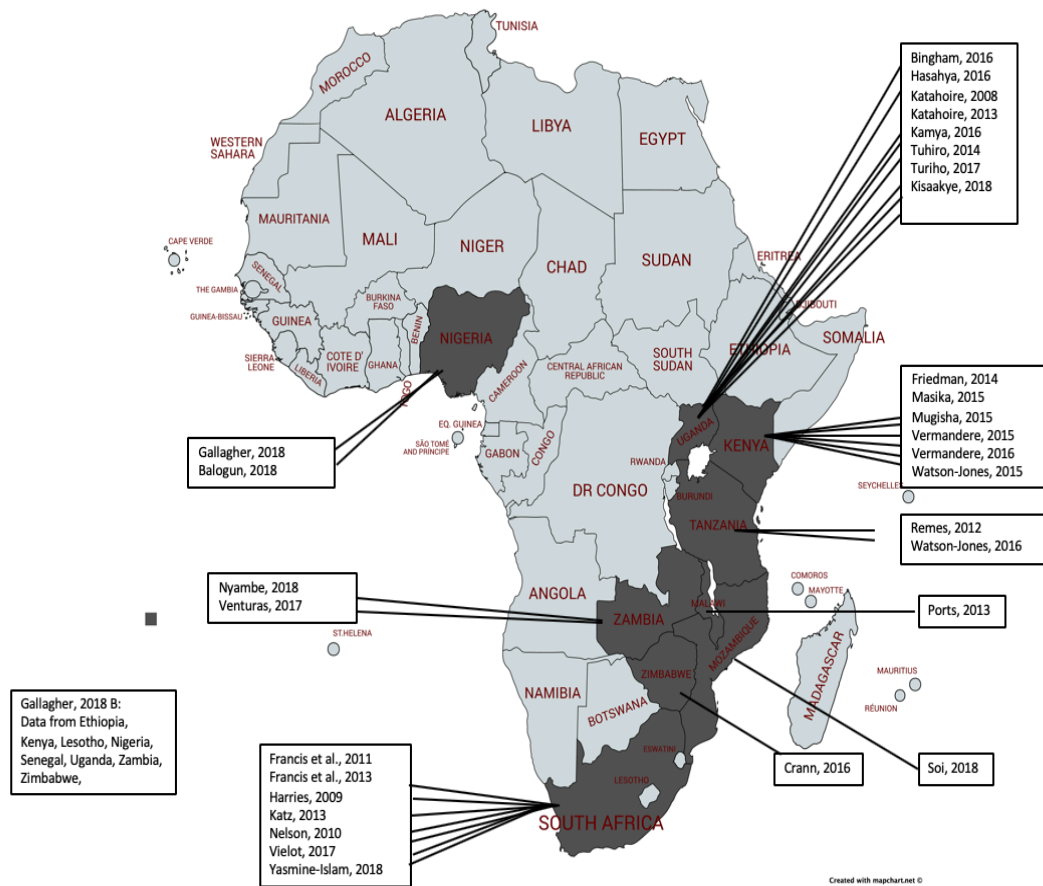


Figure 2: Included studies in thematic analysis mapped by country of origin (first author, year).

As shown in figure 2, the majority of included studies came from Eastern and Southern Africa, predominately from Uganda, Kenya, and South Africa. All of the studies utilized focus group discussions or interviews (or both) for data collection methods. Thematic, comparative analysis, narrative synthesis, grounded theory and content analysis were the four methods of data analysis across studies. Included studies took place between 2006-2018. See Appendix D for more information about the studies.

Themes

Three major themes emerged from the analysis: 1) that knowledge about the HPV vaccine is intertwined with misinformation, 2) that fear creates contradictory perceptions of the HPV vaccine, 3) and that social norms and gender dynamics play a role in stakeholder understandings of the HPV vaccine in SSA.

Theme 1: Knowledge intertwined with misinformation

This theme initially explores stakeholder knowledge around cervical cancer, HPV, and the HPV vaccine, followed by perceived causes and risk perceptions of cervical cancer, how language and symptomology play a role in understandings of HPV and cervical cancer and finally, how misinformation is present in stakeholder perceptions and understandings of the HPV vaccine.

This review found that there was generally low levels of technical knowledge about cervical cancer, HPV and the HPV vaccine in SSA (Balogun & Omotade, 2018; Francis et al., 2011; Remes et al., 2012; Turiho et al., 2014; Vermandere et al., 2015; Watson-Jones et al., 2015). This was evident in the ways that people spoke about cervical cancer, HPV, and the HPV vaccine; asking questions that displayed confusion and uncertainty about the physiology of female reproductive tract affected by cervical cancer, confusion about the fact that HPV is the causative agent of cervical cancer, and a lack of awareness that a HPV vaccine exists (Balogun & Omotade, 2018; Francis et al., 2011; Harries et al., 2009; Katahoire et al., 2013; Ports et al., 2013; Remes et al., 2012; Watson-Jones et al., 2012). These points are illustrated in the participant quote from a focus group discussion in Uganda, *“I have never heard about cancer of the cervix. What is the difference between the cervix and the uterus? We thought it was the same thing.”* (Katahoire et al., 2008). Further evidence in this regard can be found in Table 2 below:

Table 2: Confusion around cervical cancer and the HPV vaccine

(Ports et al., 2013)	"I've heard of it [cervical cancer], but I don't know what it is"- FGD-Female-Malawi
(Kisaakye et al., 2018)	"I am not aware of the HPV vaccine, and I don't know what it protects against"-Interview-Adolescent-Uganda
(Remes et al., 2012)	“That disease you are talking about, we are completely in the dark about it”-FGD-Tanzania-Parent
(Francis et al., 2011)	“...they are so anxious to know about this HPV because no one knows about it, and for most of them, this is the first time they have heard about it.”-FGD-Participant-South Africa

There were exceptions to a lack of technical knowledge about HPV and cervical cancer,

evident when some stakeholders, usually health care providers, clinicians, and educators, were well aware that HPV causes cervical cancer (Balogun & Omotade, 2018; Crann et al., 2016; Francis et al., 2013). Some stakeholders were also aware that HPV infection is a silent infection that affects men and women alike (Francis et al., 2011). Although this was not the norm across all studies, where minimal technical knowledge about cervical cancer, HPV, and the HPV vaccine was more prominent, it does highlight the varying degrees of knowledge of cervical cancer, HPV, and the HPV vaccine across SSA. It is notable that even with low-levels of baseline technical knowledge about cervical cancer, HPV, and the HPV vaccine, there was high levels of willingness to learn more about the HPV vaccine across several studies (Abdullahi et al., 2014; Francis et al., 2011; Katahoire et al., 2013; Moodley et al., 2009; Watson-Jones et al., 2015). This is best illustrated in the statement from a participant in a focus group discussion in Uganda: *"People say that cancer has no cure but the health worker told us that this cancer, which they were vaccinating against, could be prevented, so I was very happy because it meant that if I got vaccinated I would not die of cancer"* (Katahoire et al., 2013).

Perceived causes of cervical cancer

Contradictions arose where several stakeholders expressed that they were unaware of HPV, how it spreads, and its consequences, yet the same stakeholders often insinuated that promiscuity and poor hygiene were the cause of cervical cancer (Balogun & Omotade, 2018; Nyambe et al., 2018; Ports et al., 2013; Vermandere et al., 2015). These stakeholders often implicitly had some level of awareness that HPV is sexually transmitted, evident in the quote from a religious leader in a focus group discussion in Nigeria: *"If a woman has sex anyhow with different men, it can cause cancer... If you sleep with 5 men that is 5 different diseases, 8 men means 8 different diseases.... So, if a woman sleeps around she can have cervical cancer"* (Balogun & Omotade, 2018). Promiscuity as the cause of cervical cancer was supported by a father in the same focus group, quoted saying: *"When a woman is promiscuous...there is no way she will not have the cancer, so that is what I think can cause the cervical cancer"* (Balogun & Omotade, 2018). Others attributed sexual activity to the accumulation of sexually transmitted infections, that when left untreated, cause a block in a woman's reproductive tract and that produces cancer from a 'combination of several diseases' (Vermandere et al., 2015).

Some stakeholders had difficulty with the rationale of promiscuity as the etiology of cervical cancer, as they themselves currently knew or had known someone with cervical cancer who had led a conservative lifestyle (Balogun & Omotade, 2018; Vermandere et al., 2015). There was cognitive dissonance around the fact that even among stakeholder acquaintances with cervical cancer, their partners with often healthy and seemed unaffected by HPV. This led to some skepticism around HPV being the true cause of cervical cancer and further displayed a lack of knowledge about HPV and the possibility of being an asymptomatic carrier of the disease (Balogun & Omotade, 2018; Vermandere et al., 2015).

Other perceived causes attributed to cervical cancer across the study settings were a modern lifestyle of processed food and reliance on medication (Balogun & Omotade, 2018; Katahoire et al., 2008; Vermandere et al., 2015), genetics (Balogun & Omotade, 2018; Masika et al., 2015; Vermandere et al., 2015), witchcraft (Nyambe et al., 2018), vaginal insertion of drugs (Nyambe et al., 2018; Remes et al., 2012), males as carriers (Turiho et al., 2014), existing STDs progressing to cervical cancer (Vermandere et al., 2015), poor sexual habits (Nyambe et al., 2018) and frequent childbirth or frequent abortion (Remes et al., 2012). Although several studies used focus group discussions and interviews to assess preliminary perceptions of cervical cancer, HPV, and the HPV vaccine, there was often an educational component at the completion of the study to address misinformation (Francis et al., 2011; Remes et al., 2012).

Risk perception of HPV and cervical cancer

In general, cancer was widely feared by participants across studies (Balogun & Omotade, 2018; Francis et al., 2011; Remes et al., 2012; Turiho et al., 2017). One opinion leader in Kenya explained that cancer diagnosis in Africa is comparable to the stigma and isolation of HIV/AIDs (Friedman et al., 2014). These connotations were also associated with cervical cancer, which stakeholders across studies described as ‘painful’, ‘dangerous’, ‘horrible’, ‘incurable’, ‘deadly’, and a ‘death sentence’ (Hasahya et al., 2016; Katahoire et al., 2013; Ports et al., 2013). Such perceptions about cervical cancer were consistent across studies and were often based on stakeholder experience from knowing someone with cervical cancer and having watched them suffer from the disease (Balogun & Omotade, 2018; Francis et al., 2011; Hasahya et al., 2016; Katahoire et al., 2013; Ports et al., 2013; Vermandere et al., 2015).

Across the majority of all studies, it was clear that female stakeholders perceived a high risk of cervical cancer for both themselves and their female counterparts (Hasahya et al., 2016; Katahoire et al., 2008; Nelson et al., 2010; Ports et al., 2013). Often, the perceived risk of cervical cancer was reinforced by high rates of cervical cancer mortality from the Sub-Saharan African country in which the stakeholder lived. The high perceived risk of a feared disease (cervical cancer) sparked the desire to prevent it from occurring, with this review finding that the perception of the HPV vaccine as a means of protection against cervical cancer was a key influence on stakeholders' understandings of and willingness to learn about the HPV vaccine (Katahoire et al., 2013; Turiho et al., 2017).

The fear of cervical cancer, the pain associated with it, and the desire to avoid it were frequently mentioned across studies, which often led stakeholders to conduct a risk assessment of short term pain (of the HPV vaccine injection) weighed up with long term pain (of potential cervical cancer diagnosis), normally reaching the conclusion that "prevention is better than cure" when discussing the HPV vaccine across studies (Balogun & Omotade, 2018; Francis et al., 2011; Harries et al., 2009; Katahoire et al., 2013; Ports et al., 2013; Remes et al., 2012). This is further evident in two quotes from female stakeholders who participated in a focus group discussion in Uganda; *"I have had injections before and I know the pain lasts a short time but I feared that the pain from cancer can last forever"* and *"I normally fear injections but when I thought about the pain that I could suffer if I got cancer I decided to be vaccinated no matter what"* (Turiho et al., 2017).

Language and symptomology

How people speak about a health topic is often a good indication of what they understand about it (Graham & Brookey, 2008). Stakeholders spoke about cervical cancer in varying ways across SSA. This review supports Katahoire's & colleagues' findings that stakeholders do not often make distinctions between the cervix, uterus, and womb when discussing cervical cancer and that there are local language nuances that are vital to understanding how people themselves understand both disease and prevention of disease (Katahoire et al., 2008).

Cervical cancer was most often referred to as 'cancer of the womb' in South Africa, Kenya, and Uganda (Francis et al., 2011; Friedman et al., 2014; Harries et al., 2009; Katahoire et al.,

2008; Nelson et al., 2010; Vermandere et al., 2015). The HPV vaccine was referred to as the ‘cancer of the womb vaccination’ in South Africa (Francis et al., 2011). Across studies, ‘cancer of the uterus’ was the second most common reference to cervical cancer, supporting the previous finding that there was explicit confusion about the difference between the cervix and the uterus across some studies (Bingham et al., 2009; Katahoire et al., 2008; Katahoire et al., 2013; Venturas & Umeh, 2017; Vermandere et al., 2015)

Cervical cancer was most commonly spoken about through explanation of its symptoms rather than its technical name, and the reliance on symptomology rather than terminology was evident across stakeholder interviews and focus groups when expressing understandings and perceptions of cervical cancer as a health topic (Francis & Katz, 2013; Friedman et al., 2014; Katahoire et al., 2008; Nelson et al., 2010; Nyambe et al., 2018; Remes et al., 2012). When stakeholders were asked what they knew about cervical cancer, responses consistently included explanation or recognition of the disease through perceived symptoms (accurate or inaccurate), usually including vaginal bleeding, foul odor, vaginal discharge, and pain during intercourse (Crann et al., 2016; Hasahya et al., 2016; Nyambe et al., 2018; Remes et al., 2012). Stakeholder reliance on symptomology is notable in understandings of HPV and cervical cancer in the Sub-Saharan African context.

There was obvious reliance on symptomology for disease recognition, but notably, symptomology was also a driver in health seeking behavior (Crann et al., 2016; Hasahya et al., 2016; Nyambe et al., 2018). Most stakeholders expressed that symptoms of disease were the driver of seeking care and that getting a vaccine for something when symptoms are not present may inhibit action towards HPV vaccine uptake, best illustrated by a policy maker in Zambia expressing: “*Health seeking behavior in Zambia is not the best... [A woman] will not go to the clinic unless she is sick...So expecting healthy people to voluntarily come for vaccination is difficult*” (Nyambe et al., 2018). Interpreting symptomology as necessary for vaccination was also evident in one participant from a focus group in Kenya asking: “*What are you vaccinating us against, yet we are not sick?*” (Watson-Jones et al., 2012). Developing symptoms as a tangible indicator of having a disease and only then seeking care is of noteworthy importance as late presentation to care in advanced stages of disease is extremely common and has driven extreme rates of cervical cancer mortality in SSA (Crann et al., 2016; Hasahya et al., 2016; Nyambe et al., 2018; Ports et al., 2013). As further explored in the following theme, fear is a large part of late presentation and is especially relevant when

exploring understandings of the HPV vaccine in SSA.

Misinformation

Across studies, the most powerful and prevalent piece of misinformation revealed by stakeholders was a two-sided and polarized argument around infertility; some stakeholders believed (and feared) that cervical cancer itself causes infertility, while other stakeholders believed (and feared) that the HPV vaccine causes infertility. Misinformation was prevalent on both sides of the argument and it was clear that across studies, stakeholder knowledge about cervical cancer, HPV, and the HPV vaccine was intertwined with misinformation. Misinformation was perpetuated in communities in different ways; Nyambe and colleagues attributed persistent misinformation in Zambia to low levels of social mobilization around the HPV vaccine, where Masika and colleagues attributed misinformation around the HPV vaccine in Kenya to a lack of uniform and top-down training of relevant stakeholders ranging from policy makers, to health care providers, to teachers assisting with administering the HPV vaccine (Masika et al., 2015; Nyambe et al., 2018). Insufficient comprehensive training on the HPV vaccine further contributed to the gaps in rollout procedures and was considered to substantially damage school-based HPV vaccination programmes success in Zambia, Kenya, Mozambique, and Zimbabwe, where teachers (assisting health care providers administer the HPV vaccine to adolescent girls) expressed how they did not receive sufficient information on the HPV vaccine (Crann et al., 2016; Masika et al., 2015; Nyambe et al., 2018; Soi et al., 2018; Venturas & Umeh, 2017). This is illustrated in the quotes of a teacher in Kenya saying, “*They [the health care providers] met just some of the teachers... because us, we didn’t hear*” (Vermandere et al., 2015), with another teacher from a different study in Kenya suggesting “*all teachers should be given the same information...For instance, in our district, only the headteacher and two other teachers were called*” (Masika et al., 2015).

Studies also pointed to the ways that improper training around the HPV vaccine led to poor communication, which in turn, perpetuated existing misconceptions about the HPV vaccine, while inevitably also introducing skepticism, fear and uncertainty around the HPV vaccine within communities and even in the minds of key stakeholders such as health care providers and teachers (Venturas & Umeh, 2017; Vermandere et al., 2015). A prominent sentiment echoed in several studies was that a lack of comprehensive information given to communities at the onset of introduction of the HPV vaccine, almost always initiated and even expedited,

Theme 2: Fear shaping contradictory perceptions of the HPV vaccine

When discussing both cervical cancer diagnosis and making decisions around the HPV vaccine, stakeholders mentioned fear as a predominate emotion (Balogun & Omotade, 2018; Francis et al., 2011; Remes et al., 2012; Turiho et al., 2017). The fear of cervical cancer itself was so great that some females expressed that they were reluctant to seek care and would prefer not to know their status or diagnosis, often due to the common perception that cervical cancer leads to an inevitable death (Francis & Katz, 2013; Hasahya et al., 2016). This is evident in the quote by a female stakeholder in a focus group discussion in Uganda saying: *"I fear going for a check-up since after getting the diagnosis of cervical cancer, I will then know that I am dying"* (Hasahya et al., 2016). This was also supported in South Africa where women expressed that they do not "want to face" the possibility of cervical cancer diagnosis (Francis & Katz, 2013).

Fear of death, suffering, pain, or reduced quality of life, and most commonly, fear of infertility, were mentioned as contributing to hesitance that stakeholders had when it came to discussing both cervical cancer and the decision (or indecision) to get the HPV vaccine, ironically, the very thing that protects against the cervical cancer diagnosis (Balogun & Omotade, 2018; Francis et al., 2011; Remes et al., 2012; Turiho et al., 2017). Fear of infertility as a result of cervical cancer and fear of infertility as a result of the HPV vaccine created a polarized debate, with stakeholders often firmly believing in one or the other as the etiology of infertility. This debate was emotionally fueled as male and female stakeholders alike placed significant value on a woman's ability to bear children, therefore making infertility widely feared, highly stigmatized, shameful, and indicative of a female's worth (Friedman et al., 2014; Greenfield et al., 2015; Hasahya et al., 2016; Masika et al., 2015; Remes et al., 2012)

Although stakeholders feared cervical cancer due to perceived physical pain and suffering that it causes, a much more prevalent fear was the emotionally charged notion that cervical cancer causes infertility amongst women (Francis & Katz, 2013; Harries et al., 2009; Katahoire et al., 2013; Turiho et al., 2017). Depending on the timing of presentation, type of HPV strain, severity of symptoms, and progression of disease, infertility as a result of cervical cancer is indeed a possibility, but is not always a given (WHO, 2017, 2018). Amongst stakeholders who harbored the belief that cervical cancer diagnosis caused

infertility, infertility was perceived as inevitable and was by far the most detrimental perceived outcome of cervical cancer (Friedman et al., 2014; Hasahya et al., 2016; Katahoire et al., 2013; Nyambe et al., 2018; Remes et al., 2012; Soi et al., 2018; Venturas & Umeh, 2017; Watson-Jones et al., 2015). Stakeholders who firmly believed cervical cancer diagnosis inherently produced infertility, clearly supported the HPV vaccine, largely to protect women from cervical cancer and in turn, their future fertility, illustrated from stakeholder statements in table 4 below:

Table 4: Fears that cervical cancer would cause infertility

Study	Quote
(Katahoire et al., 2013)	"I know that if a woman gets that cancer she cannot bear children and that is very sad"- FGD-Participant-Uganda
(Francis et al., 2013)	"Cervical cancer is where cells in your womb grow out of control and they need treatment...Uncontrollable growth of bad cells in your womb."-FGD-Participant-South Africa
(Katahoire et al., 2013)	"I was fully vaccinated because I want to have children without any problems."- FGD- Adolescent girl- Uganda
(Katahoire et al., 2013)	"The cancer destroys your uterus and you can never have children. I do not want to die childless so I had to make sure that I got all three doses."- FGD-Adolescent girl-Uganda
(Turiho et al., 2017)	"I was well taught by my teachers and the health workers who came to our school that the HPV vaccination would protect me from cervical cancer, which can lead to failure to produce children... With HPV vaccination, we shall have healthy lives in future and be able to give birth to children..."-FGD-Adolescent girl-Uganda
(Turiho et al., 2017)	"We would let our daughters to get vaccinated because we want them to be healthy in future... and have children..." -FGD-Parent-Uganda
(Harries et al., 2009)	"If it [HPV vaccine] can improve the future for all our daughters then it is a good thing. In the past we never knew about things like this and a lot of women's reproductive organs were removed because they contracted cancer. So I think it is a good thing"- FGD-Participant- South Africa

Ironically, other stakeholders on the opposite side of the debate expressed contrary beliefs that the HPV vaccine, which provides primary protection against the most common cancer-causing strains of HPV, was in and of itself, the cause of infertility amongst women (Friedman et al., 2014; Katahoire et al., 2013; Remes et al., 2012; Venturas & Umeh, 2017; Watson-Jones et al., 2012). The origin of this sentiment could not be identified, but had a significant influence on some stakeholders' perceptions of the HPV vaccine across the studies. The fear that the vaccine inevitably would cause infertility was the most prevalent reason for stakeholder hesitancy around the HPV vaccine, as evident below in table 5 of stakeholder statements:

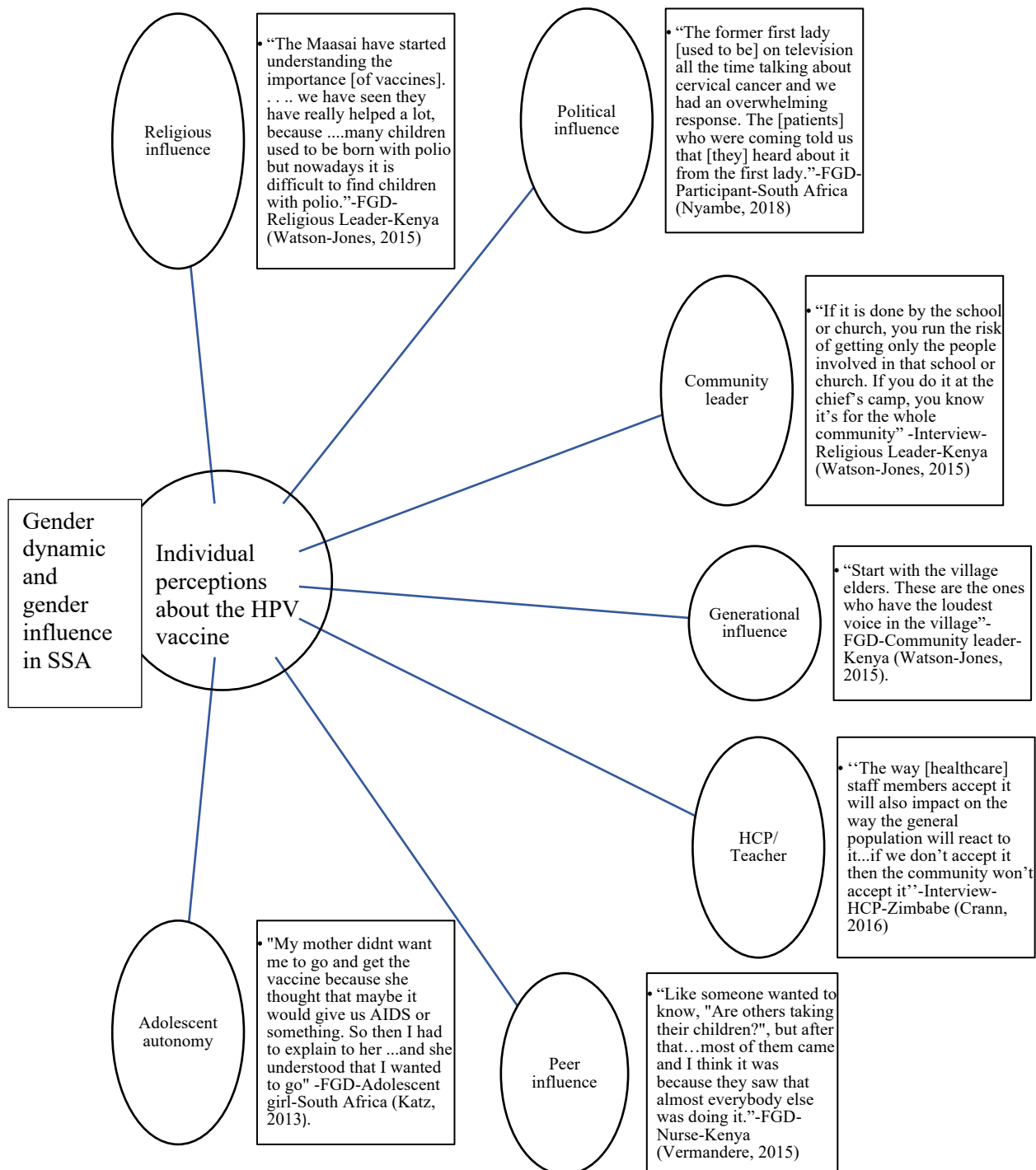
Table 5: Fears that the HPV vaccine would inevitably cause infertility

Study	Quote
(Katahoire et al., 2013)	"I heard women in the village saying that girls that were vaccinated may not have babies in the future. At the time I had already received the first dose so I decided not to receive the other two"-FGD-Female participant-Uganda
(Katahoire et al., 2013)	"At first I agreed to be vaccinated but when I heard that the vaccinations could prevent me from having children I decided not to receive the other doses."-FGD-Female participant-Uganda
(Remes et al., 2012)	"The vaccine could disorder and destroy the eggs that a girl has, and reproducing would be a problem."- FGD-Male teacher-Tanzania
(Turiho et al., 2017)	"I know some girls who did not get vaccinated because they thought that the vaccine against HPV would prevent them from producing children or getting pregnant in future... They said it destroys a woman's egg (ovaries) so that she does not produce children" -FGD-Adolescent participant-Uganda
(Hasahya et al., 2016)	"Girls vaccinated during their reproductive age will only get two children" FGD-Participant-Uganda
(Soi et al., 2018)	"There was a misbelief that we were vaccinating girls to make them sterile, to not be able to have children. It even reached a point when the girls were no longer going to school" -Interview-District Health Directorate-Mozambique
(Katahoire et al., 2013)	"I could not lie about my age to the teacher because she already knew that I was 10, so when they sent us out to be vaccinated I quickly went towards the toilets and hid. I thought that perhaps they wanted to kill us or prevent us from having children" -FGD-Participant- Uganda
(Turiho et al., 2017)	"Some girls think that HPV vaccination can protect them from getting pregnant and that is why they go around having sex with men...The girls say that since they received the HPV vaccine, they cannot get pregnant when they sleep with men"- FGD- Female adolescent- Uganda
(Turiho et al., 2017)	"They said it kills a woman's eggs and she does not produce children... Some people got scared after being told in the villages that people who get vaccinated against HPV will not produce children in future... Some believed that the vaccine was meant to reduce fertility of women in future by destroying their ovaries..." -FGD-Parent-Uganda
(Venturas & Umeh, 2017)	"What I have heard about the vaccine, some say that it has been developed to reduce the population, to reduce the fertility in a woman, an African woman." FGD-Participant-Zambia
(Venturas & Umeh, 2017)	"They were saying if they give those vaccines to young girls, maybe those young girls they won't get pregnant in the future, it will prevent them from getting pregnant, so those are beliefs that they have"-FGD-Participant-Zambia
(Watson-Jones et al., 2012)	"...the boys will enquire why it is only the girls who are getting the vaccine. . .The boys will discourage the girls, telling them that the vaccine will damage their lives." -FGD-Community Leader, Kenya
(Remes et al., 2012)	"Vaccinations in this country that are linked to issues of reproduction have had very bad results later on" -FGD-male teacher- Tanzania

Therefore, this two-sided infertility argument was polarized, with some stakeholders believing that cervical cancer itself causes infertility and other stakeholders believing that HPV vaccine causes infertility. Both beliefs had great authority in stakeholder decisions around the HPV vaccine in SSA (Vermandere, 2016).

As evident from some of the stakeholder excerpts above, the debate around the cause of infertility was further polarized and fueled by pertinent distrust of both local health systems and governments, as well as international vaccine initiatives and high-income countries who were perceived to be providing HPV vaccines (Bingham et al., 2009; Friedman et al., 2014; Venturas & Umeh, 2017; Watson-Jones et al., 2012). Stakeholders in Zambia expressed that the lack of information given at implementation about the HPV programme implied that a lack of research had been done on the HPV vaccine, and other stakeholders took this sentiment one step further in saying that the government must be conducting research by using young girls as the guinea pigs for experimentation (Bingham et al., 2009). Other stakeholders expressed their concerns that the HPV vaccine was a government supported initiative for population control methods of Africans or that Africa was receiving ‘second-tier’ left over vaccines from first world countries (Friedman et al., 2014; Harries et al., 2009; Nyambe et al., 2018). These findings support previous research that have found there are wide-spread anti-fertility rumours and underlying suspicion of public health initiatives that play a role in vaccine uptake, especially the HPV vaccine (Remes et al., 2012). This highlights how widespread the double-sided argument around fertility and the HPV vaccine is - with some stakeholders seeing the HPV vaccine as a way to protect fertility, while others see the HPV vaccine as a danger to fertility. The lack of clarity around the issue is summarized in the following quote by an adolescent stakeholder from a focus group discussion in Uganda saying: *“People say that the HPV vaccine may make us fail to bear children in future; but we have also been told that it is not true that the injection can cause infertility. So we do not know the truth”* (Turiho et al., 2017).

Theme 3: Social norms and gender dynamics influence on understandings of the HPV vaccine in SSA



When examining external influences on stakeholder understandings and interpretations of the HPV vaccine in SSA, there was evidence across studies that layers of social influence play a role in how stakeholders perceive the HPV vaccine. This is in agreement with Tuiro and colleagues who found HPV vaccination behaviours, actions and attitudes are shaped by both exposure to information and interaction with fellow community members (Tuiro et al.,

2017). Stakeholders expressed that they sought information, opinions, and beliefs from various sources and influences in the community, including political leaders, religious figures, community leaders, elders, health care providers, teachers, and peers. Notably, adolescent autonomy was also a factor, evident in some adolescents expressing they would get the HPV vaccine regardless of parents and caregivers beliefs about it (Katahoire et al., 2013; Katz et al., 2013; Remes et al., 2012). These layers of social influence seemed to exist within a prominent gender dynamic in the Sub-Saharan African context, outlined in figure 3 above.

Many of the countries in which the studies included in this review were based, have rolled out HPV vaccination programmes that mainly target female adolescents in attempts to curb the extreme morbidity and mortality rates of cervical cancer, the most common clinical consequence of HPV infection in SSA (Friedman et al., 2014). Several stakeholders across the studies expressed confusion over HPV being a gender neutral virus and yet adolescent females being the only targeted population for HPV vaccination (Crann et al., 2016; Harries et al., 2009; Vermandere et al., 2015; Watson-Jones et al., 2012). This confusion is evident in a question asked by a public health nurse in Kenya; *“Why target women and not men? Why don’t you target the source? Why don’t you put out the fire from where it starts?”* (Watson-Jones et al., 2015).

Some male stakeholders expressed disinterest in the HPV vaccine since female only vaccination ultimately excluded males and warped perceptions that both HPV and cervical cancer are feminized diseases that don’t affect men (Crann et al., 2016; Harries et al., 2009; Vermandere et al., 2015). The necessity of having a cervix in order to be directly affected by cervical cancer, coupled with a traditional cultural focus of reproductive health being a part of a ‘woman’s job’, reinforced feminization of HPV and caused feelings of resentment, confusion, and distrust from stakeholders of both sexes (Harries et al., 2009; Watson-Jones et al., 2012). Some stakeholders called for gender neutral vaccination in the future and in the interim, gender neutral education since HPV affects both sexes and current generations of adolescents boys and girls would one day become parents and need to educate their sons and daughters alike (Francis & Katz, 2013; Vermandere et al., 2015). Other stakeholders expressed concern that just vaccinating girls was not only discriminatory, but also confusing for boys, especially when trying to close the unequal gendered power dynamic (Katahoire et al., 2013; Watson-Jones et al., 2012).

In some studies, stakeholders raised that the progressively early age of sexual debut of adolescents of both sexes was an enabling factor to support the HPV vaccine within communities (Harries et al., 2009; Katz et al., 2013; Turiho et al., 2017; Watson-Jones et al., 2012). Stakeholders from such studies explained that children in the communities are sexually active at the early age of 10 or 11, and thus suggested that the HPV vaccine should be administered earlier than adolescence in order to provide maximum protection prior to exposure to the HPV (Harries et al., 2009). Earlier sexual debut was attributed to adolescents initiating sexual experimentation earlier on (Harries et al., 2009; Katz et al., 2013; Turiho et al., 2017; Watson-Jones et al., 2012), early and arranged marriages (Soi et al., 2018; Watson-Jones et al., 2012) and most concerningly, age-discordant relationships and gender-based violence and abuse of female children and adolescents, especially in South Africa (Francis et al., 2011; Katz et al., 2013; Nelson et al., 2010; Nyambe et al., 2018). The HPV vaccine was perceived to provide some protection in an environment where some perceived gendered based violence to be inevitable, especially in South Africa, illustrated by one South African mother saying *“I feel certain about [vaccinating my child] because there is AIDS and HIV out there and we all are aware of it...My child can be raped, and I will feel bad about it, but I am at peace [knowing] that she is participating in the Kganya Motsha [HPV vaccine trial] and will be protected against sexually transmitted diseases”* (Katz et al., 2013). The inevitability of rape in South Africa was also mentioned in an interview with a Sangoma (Nelson et al., 2010) and a father (Watson-Jones et al., 2012) and protecting females against such sexual abuse outcomes was seen as facilitator for the HPV vaccine.

In this manner, the HPV vaccine was seen as a harm reduction strategy against gender-based sexual violence, which to some stakeholders was unescapable for females (Francis et al., 2011; Francis & Katz, 2013; Katz et al., 2013; Nelson et al., 2010; Nyambe et al., 2018). The reality of rape and abuse was coupled with concern about the unintended consequences of pregnancy and HIV and other STD acquisition, which many stakeholders expressed would be the responsibility and burden of the female (and not the male perpetrator) due to the unequal power dynamic between men and women in SSA (Harries et al., 2009; Katz et al., 2013; Nelson et al., 2010; Turiho et al., 2017). Such outcomes also increased the likelihood of abandonment by male partners seen in the quote by a health care provider in Zambia: *“Most of the women who come [to the cancer ward] have already been left by their husbands before coming here....So three quarters of the [women] who are here were once married”* (Nyambe

et al., 2018).

A notable gender dynamic was also interwoven in health seeking behaviour where stakeholders in some studies (Zambia, Zimbabwe, Kenya and Tanzania) expressed that males have the ultimate say in health decisions, including vaccination (Crann et al., 2016; Nyambe et al., 2018; Remes et al., 2012; Venturas & Umeh, 2017; Vermandere et al., 2015). One female stakeholder from a focus group in Zambia explained this further: “*[that there is a] the cultural background that a woman should seek permission from her husband, whether she should take her daughter for the vaccine...so those are cultural issues that will always be there*” (Venturas & Umeh, 2017). Some teachers in Tanzania agreed, explaining that school meetings were not always successful when it came to educating parents and caregivers about the HPV vaccine for their adolescent daughters because even if the mother was convinced to get the daughter the HPV vaccine, that many fathers refused and had the final say in HPV vaccination behaviour (Remes et al., 2012).

This notion was contradicted by studies in South Africa and Malawi where stakeholders agreed that the responsibility for soliciting care for children lies with women, [seen in] mothers and other female family members taking the lead in the healthcare decisions, and fathers generally being absent from the process (Francis et al., 2011; Ports et al., 2013). Across studies, male and female stakeholders urged men to be more included in education around cervical cancer and HPV vaccination, as men are carriers of HPV and can also have cancer outcomes (Harries et al., 2009) and also because it would minimize the stigma around the HPV vaccine being siloed as a female responsibility and health issue (Katahoire et al., 2013). This is further evident in the quote by one focus group participant in Zambia saying: “*...but with education we should include the male folk because mostly we side line them, [but] they also play an important role*” (Venturas & Umeh, 2017).

Discussion

Three major findings emerged from this review. Firstly, this analysis found that low levels of technical knowledge about cervical cancer and HPV, along with minimal awareness of the existence of the HPV vaccine, contribute to misinformation amongst Sub-Saharan African communities and countries. This supports previous reviews in Africa and SSA more specifically (Abdullahi et al., 2014; M. S. Cunningham et al., 2015; Francis & Katz, 2013;

Perlman et al., 2014). Misinformation is fueled by both rumors and fear, both of which simultaneously contribute to a growing suspicion and distrust of vaccination programmes (in general and HPV vaccination specifically) in SSA. Distrust of HPV vaccination inevitably feeds back into the stream of misinformation and has left many stakeholders unable to disentangle the persisting parallel knowledge and misinformation around the HPV vaccine that perseveres in SSA.

Secondly, beliefs around infertility have created a significant divide in stakeholder understandings of the HPV vaccine in SSA. This review found that demand side stakeholders largely have two opposing perceptions about the causes of infertility; one side attributing infertility to cervical cancer diagnosis, in turn, making such stakeholders supportive of the HPV vaccine as it prevents the most common cancer-causing strains of HPV and the other side attributing infertility to the HPV vaccine itself, therefore igniting HPV vaccine hesitancy and outright refusal amongst stakeholders who harbor such beliefs. These divergent perspectives on infertility have been a major factor in stakeholder understandings of the HPV vaccine and will have to be addressed in order to get Sub-Saharan African countries to fully invest in uptake of the HPV vaccine.

Thirdly, social layers of influence not only affect where stakeholders get information on the HPV vaccine, but also how stakeholders perceive and process the information about the HPV vaccine in relation to the source from which it originated. This was evident in some stakeholders requesting validation or further information about the HPV vaccine from certain stakeholders, usually of greater social status, such as the government or religious leaders whom many stakeholders perceived to act in the best interest of the community. However, as mentioned previously, there were some stakeholders who distrusted the government and were skeptical that the intentions of the HPV vaccination programmes were actually a covert population control method. The disconnect in where and whom stakeholders choose to place their trust is of notable importance. Within social layers of influence, a notable gender dynamic emerged as a significant factor in how stakeholders perceive the HPV vaccine. Gendered dynamics included the perception that the HPV vaccine was a viable harm reduction strategy against gender-based violence, that there are significant differences in gendered decision-making about health seeking behaviors across countries in SSA, and finally, that female-only vaccination warps perceptions of HPV to be a female-only issue which perpetuates misinformation.

This review suggests that HPV vaccination programmes will have to sufficiently engage with local communities before rollout, learning understandings, conceptions and misconceptions, language nuances, and perceptions around HPV, the HPV vaccine, and cervical cancer prior to proceeding with education and social mobilization around the HPV vaccine. Utilizing local language nuances of disease terminology and recognized symptomology may be an important consideration for HPV vaccination roll out strategies across SSA, where stakeholders may be more likely to understand that the HPV vaccine can curb the perceived symptoms of cervical cancer, rather than preventing the disease (cervical cancer) itself (Francis & Katz, 2013; Friedman et al., 2014; Katahoire et al., 2008; Nelson et al., 2010; Nyambe et al., 2018; Remes et al., 2012). Engagement with and involvement of various social actors such as government leaders, religious leaders, HPV vaccination programme leaders, community liaisons and community members themselves may facilitate improvements in stakeholder perceptions of the HPV vaccine in SSA, especially when mitigating the belief that the HPV vaccine causes infertility, a prominent and wide-spread rumor across SSA. Finally, implementation of HPV vaccination programmes without thorough understanding of gender dynamics within the context of the specific country implementing the vaccine can potentially create roadblocks for HPV vaccination uptake, as well as perpetuate confusion, misinformation, distrust and stigma. This is notable as this review found that, depending on the country, health seeking behavior and decision making around the HPV vaccine was driven by either male or female head of households, insinuating that locally appropriate interventions need to speak to country specific gender dynamics in health seeking behavior.

Reflexivity

The lead researcher has a background in public health and acknowledges that this has shaped positive attitudes towards vaccination more generally. As cervical cancer is largely preventable, the lead researcher undertook this analysis in order to better understand extreme rates of morbidity and mortality from HPV and cervical cancer in SSA. Preceding the literature review, the lead researcher had no expertise in cervical cancer in SSA and upon conducting a literature review, had a base-line understanding of theory around cervical cancer, HPV, and the HPV vaccine in SSA (Braun & Clarke, 2006). From the protocol to the actual review, iterations of the research question (with collaboration with two supervisors) narrowed and refined the direction and scope of the research although the crux of the research

question remained the same (examining how stakeholders understand the HPV vaccine in SSA). The protocol initially stated that a framework will be considered to understand the results, but upon doing the actual review, the author decided that the themes in the analysis could stand alone (without a framework). Otherwise the protocol was closely adhered to when conducting the review. This analysis supports previous research about low levels of cervical cancer and HPV vaccine knowledge in SSA, but contributes new and relevant knowledge around how stakeholders interpret and understand the HPV vaccine in SSA, an under-researched area overall.

Strengths and limitations of the review

A strength of this review is the consideration and acknowledgement of discordant findings within the dataset and what such conflicts reveal about understandings of the HPV vaccine in SSA. As a systematic review that assesses understandings of the HPV vaccine from a variety of stakeholders point of views, all of whom in some way create a demand for the HPV vaccine in SSA, has never before been undertaken, the novelty of this review aims to provide a ‘big picture’ demand-side perspective to improve current and future HPV vaccination strategies in SSA.

Limitations include a single review author for all stages of the search strategy although this limitation was addressed through a 20% random sampling of title and abstracts and eligible full text studies, assessed by two independent reviewers. A ‘Confidence in Evidence from Reviews of Qualitative Research’ was not conducted. The date of studies ranges from 2006-2018, introducing the possibility that some of the previously published literature is out of date compared to present-day. Exclusion of grey literature is a limitation due to time and resource constraints, as well as exclusion of non-English studies due to the language capacities of the review team.

Conclusion

Stakeholders who create a demand for the HPV vaccine are arguably the most vital to its uptake and continued necessity, especially when the momentum of HPV vaccination on the continent of Africa has only recently been initiated. How stakeholders understand the HPV vaccine will be vital to the short- and long-term success of HPV vaccine programmes. This

review found that stakeholder understandings of the HPV vaccine are shaped by a dichotomous relationship between HPV vaccine knowledge co-existing with misinformation, a significant fear of infertility associated with both cervical cancer diagnosis and the HPV vaccine, and social and gender dynamics in SSA. This review iterates the importance of first working with communities to gauge local and context-specific understandings, before trying to implement change through one-size-fits all education, sensitization and behavior change strategies.

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Part D: Appendices

Appendix A: Search strategy

PubMed

("Papillomavirus Vaccines"[Mesh] OR "Human Papillomavirus Recombinant Vaccine Quadrivalent, Types 6, 11, 16, 18"[Mesh]

OR

“human papillomavirus vaccine” OR “HPV vaccine” OR “human papillomavirus vaccination” OR “HPV vaccination”

AND

"Health Knowledge, Attitudes, Practice"[Mesh]

OR

Knowledge OR attitude OR attitudes OR belief OR beliefs OR perceptions OR perception OR comprehend OR comprehension OR experience OR experiences OR understand OR understandings OR feel OR feelings OR opinion OR opinions OR point of view OR view OR views

AND

("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 "Sao Tome and Principe"[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 "Cabo 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" OR "Sub Saharan Africa" OR " Central Africa " OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Congo" OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR "Gabon" OR "Sao Tome and Principe" OR " Eastern Africa " OR “East Africa” OR "Burundi" OR "Djibouti" OR "Eritrea" OR "Ethiopia" OR "Kenya" OR "Rwanda" OR "Somalia" OR "South Sudan" OR "Sudan" OR "Tanzania" OR "Uganda" OR " Southern Africa" OR "Angola" OR "Botswana" OR "Lesotho" OR "Malawi" OR "Mozambique" OR "Namibia" OR "South Africa" OR "Swaziland" OR "Zambia" OR "Zimbabwe" OR " Western Africa" OR “West Africa” OR "Benin" OR "Burkina Faso" OR "Cabo Verde" OR "Cote d'Ivoire" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Liberia" OR "Mali" OR "Mauritania" OR "Niger" OR "Nigeria" OR "Senegal" OR "Sierra Leone" OR "Togo"

AND

“Qualitative Research” [Mesh] OR qualitative research OR "Empirical Research" [Mesh] OR "Focus Groups" [Mesh] OR "Interviews as Topic"[Mesh] OR "Observational Studies as

Topic"[Mesh] OR "Observational Study" [Publication Type]

OR

“empirical research” OR interviews OR “focus groups” OR “observational studies” OR “thematic analysis” OR Ethnography OR “meta-ethnography”

Other Databases

EbscoHost (Academic Search Premier, AfricaWide Information, CINAHL, PsychArticles, Psychinfo, SocIndex)

Scopus

Web of Science

“human papillomavirus vaccine” OR “HPV vaccine” OR “human papillomavirus vaccination” OR “HPV vaccination”

AND

Knowledge OR attitude OR attitudes OR belief OR beliefs OR perceptions OR perception OR comprehend OR comprehension OR experience OR experiences OR understand OR understandings OR feel OR feelings OR opinion OR opinions OR point of view OR view OR views OR decision OR decisions

AND

"Africa" OR "Sub Saharan Africa" OR " Central Africa " OR "Cameroon" OR "Central African Republic" OR "Chad" OR "Congo" OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR "Gabon" OR "Sao Tome and Principe" OR " Eastern Africa " OR “East Africa” OR "Burundi" OR "Djibouti" OR "Eritrea" OR "Ethiopia" OR "Kenya" OR "Rwanda" OR "Somalia" OR "South Sudan" OR "Sudan" OR "Tanzania" OR "Uganda" OR " Southern Africa" OR "Angola" OR "Botswana" OR "Lesotho" OR "Malawi" OR "Mozambique" OR "Namibia" OR "South Africa" OR "Swaziland" OR "Zambia" OR "Zimbabwe" OR " Western Africa" OR “West Africa” OR "Benin" OR "Burkina Faso" OR "Cabo Verde" OR "Cote d'Ivoire" OR "Gambia" OR "Ghana" OR "Guinea" OR "Guinea-Bissau" OR "Liberia" OR "Mali" OR "Mauritania" OR "Niger" OR "Nigeria" OR "Senegal" OR "Sierra Leone" OR "Togo"

AND

Qualitative research OR empirical research OR interviews OR focus groups OR observational studies OR thematic analysis OR Ethnography OR meta-ethnography

Appendix B: Study information log template

Research Question How do demand-side stakeholders understand the HPV vaccine in SSA?

Databases to search: Embase (via Scopus), Scopus, MEDLINE (via PubMed), PubMed, EBSCOhost, Academic Search Premier, Africa-Wide Information, CINAHL, PsycARTICLES, PsycINFO, SocINDEX, Web of Science, and the Cochrane Controlled Register of Trials (CENTRAL).

First author, year	Study Title	Study Location	Study population	Data type	Data analysis	Date of study	Authors aim
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Appendix C: Data extraction template

Overarching Theme #1:

Transcript Quote	Sub-theme	Direct participant quote from analysis	Sub-theme	Secondary author interpretation	Sub-theme	Reflexivity notes:
Study						
Study						

Overarching Theme #2

Transcript Quote	Sub-theme	Direct participant quote from analysis	Sub-theme	Secondary author interpretation	Sub-theme	Reflexivity notes:
Study						
Study						

Overarching Theme #3:

Transcript Quote	Sub-theme	Direct participant quote from analysis	Sub-theme	Secondary author interpretation	Sub-theme	Reflexivity notes:
Study						
Study						

Appendix D: Study information log completed

Key:

FGD- Focus group discussion
 KII- Key informant interview
 IDI- In depth interview
 SSI- semi-structured interview
 ID-SSI- In depth semi-structured interview

First author, year	Title	Where	Type of stakeholder	Data Collection	Data analysis	When
Balogun, 2018	"She must have been sleeping around...": Contextual interpretations of cervical cancer and views regarding HPV vaccination for adolescents in selected communities in Ibadan, Nigeria	Ibadan, Nigeria	Parents of adolescents, religious and traditional leaders, school teachers and adolescents, traditional healers	FGDs	Comparative case study approach to conduct narrative synthesis	2009
Bingham, 2009	Sociocultural Issues in the Introduction of Human Papillomavirus Vaccine in Low-Resource Settings	Uganda (India, Peru, Vietnam)	Children, parents, teachers/administrators, health workers/managers and community/religious leaders	FGDs and KIIs	Comparative analysis, table matrix technique, themes	2006-2008
Crann, 2016	Healthcare providers' perspectives on the acceptability and uptake of HPV vaccines in Zimbabwe	Zimbabwe	Health care providers	IDIs	Thematic analysis	2007
Francis, 2013	An Analysis of key stakeholders' attitudes and beliefs about barriers and facilitating factors in the development of a cervical cancer prevention program in South Africa	South Africa (Cape Town and Johannesburg)	Key stakeholders: e.g. clinicians, reproductive health professionals, educators, government officials, managers in non-governmental organizations, academics, infectious disease control experts	IDIs	Grounded theory and thematic analysis	2013
Francis, 2011	A qualitative analysis of South African women's knowledge, attitudes, and beliefs about HPV and cervical cancer prevention, vaccine awareness and acceptance, and maternal-child communication about sexual health	South Africa	Women	FGDs	Grounded theory and thematic analysis	Fall 2008
Friedman, 2014	Preparing for human papillomavirus vaccine introduction in Kenya: implications from focus-group and interview discussions with caregivers and opinion leaders in	Siaya County, Kenya	Caregivers and key informant opinion leaders	FGDs and KIIs	Grounded theory method through theme generation	July-August 2012

	Western Kenya					
Gallagher, 2018	The impact of human papillomavirus (HPV) vaccination campaign on routine primary health service provision and health workers in Tanzania: a controlled before and after study	Ibadan, Nigeria	Health workers	KIIs	Thematic analysis	2014
Gallagher, 2018b	Vaccine programme stakeholder perspectives on a hypothetical single-dose human papillomavirus (HPV) vaccine schedule in low and middle-income countries	Data from LMIC: Ethiopia, Kenya, Lesotho, Nigeria, Senegal, Uganda, Zambia, Zimbabwe, country 'z'	Immunisation managers and national immunisation technical advisory group members	SSIs	Thematic analysis	2017
Harries, 2009	Preparing for HPV Vaccination in South Africa: Key challenges and opinions	Western Cape Province, South Africa	National and provincial policy influential including policy makers and managers within non-governmental organizations, and academics/clinicians in the field of sexual and reproductive health, virology, infectious diseases and cervical cancer, public sector health care providers female community members.	IDIs and FGDs	Content analysis and thematic analysis	Feb-07
Hasahya, 2016	Beliefs, perceptions and health-seeking behaviours in relation to cervical cancer: a qualitative study among women in Uganda following completion of an HPV vaccination campaign	Nakasongola and Ibanda, found in central and western Uganda respectively	Women aged 25-29 with no previous cervical cancer symptoms	FGDs	Latent content and thematic analysis	Feb-March 2013
Yasmine-Isam, 2018	Acceptability of the two- versus three-dose human papillomavirus vaccination schedule among providers and mothers of adolescent girls: a mixed-methods study in five countries	5 LMIC- South Africa data	Mothers of vaccinated and unvaccinated adolescent girls	FGDs	Thematic analysis	Nov 2013- April 2014
Kamya, 2016	Evaluating Global Health Partnerships: A Case Study of a GAVI HPV Vaccine Application Process in Uganda	Kampala, Uganda	Key informants involved in the HPV vaccine application process	ID-SSIs	Thematic analysis	Aug-Oct 2017
Katahoire, 2013	Uganda: Acceptability of HPV Vaccine among young	Ibanda and Nakasongola, Uganda	Adolescent girls who have completed 3 doses of HPV, and partially or non-vaccinated girls	FGDs	Thematic analysis	2008-2009

	adolescent girls					
Katheoire, 2008	An Assessment of the Readiness for the Introduction of the HPV Vaccine in Uganda	Uganda-Gulu in the north, Soroti in the east, Mbarara in the west, and Masaka in the central region. Kampala, the capital city, was included because of its multi-ethnic and cosmopolitan nature, reflective of national diversity.	Children, parents/primary caregivers, head teachers/teachers, community and civic leaders, health professionals, district and national political and technical leaders	FGDs and KIIs	Thematic analysis	2007
Kisaakye, 2018	Level and factors associated with uptake of human papillomavirus infection vaccination among female adolescents in Lira District, Uganda	Lira District, Uganda	Adolescents and district health team members	IDIs and KIIs	Content analysis and thematic analysis	2016
Katz, 2013-	A Qualitative Analysis of Factors Influencing HPV Vaccination Uptake in Soweto South Africa among Adolescents and Their Caregivers	Soweto, South Africa	Adolescents and caregivers	ID-SSIs	Thematic analysis	2010
Masika, 2015	Knowledge on the HPV Vaccine and Cervical Cancer Facilitates Vaccine Acceptability among School Teachers in Kitui County, Kenya	Kitui County, Kenya	Primary school teachers	FGDs	Thematic analysis	2013
Mugisha, 2015	Feasibility of delivering HPV vaccine to girls aged 10 to 15 years in Uganda	Siaya County, Kenya	Health workers, district leaders, and EPI staff	IDIs and FGDs	Thematic analysis	2008-2009
Nelson, 2010	Adolescent girls who have completed 3 doses of vaccine, and partially or non-vaccinated girls	Johannesburg, South Africa	Traditional healers	FGDs	Grounded theory and thematic analysis	2010
Nyambe, 2018	The impact of the social environment on Zambian cervical cancer prevention practices	Zambia	HCPs, teachers, religious leaders, special interest groups (advocacy groups and non-governmental organizations), policy makers	IDIs	Thematic analysis	Feb-May 2016
Ports, 2013	Barriers and Facilitators to HPV Vaccination: Perspectives from Malawian Women	Chiradzulu, Malawi	Mothers	ID-SSI's	Thematic analysis	Aug-Nov 2011
Remes, 2012	A qualitative study of HPV vaccine acceptability among health workers, teachers, parents, female pupils, and religious leaders in northwestern	Mwanza Region, Tanzania	Parents, female pupils, teachers, health workers and religious leaders	SSIs and FGDs	Thematic analysis	March-August 2010

	Tanzania					
Soi, 2018	Human papillomavirus vaccine delivery in Mozambique: identification of implementation performance drivers using the Consolidated Framework for Implementation Research (CFIR)	Mozambique	District health facility immunization staff, Ministry of Education managers, teachers across the three demonstration districts, central level informants from MOH, research institutes, and immunization program partners.	KIIs	Thematic analysis	2018
Turiho, 2017	Perceptions of human papillomavirus vaccination of adolescent schoolgirls in western Uganda and their implications for acceptability of the HPV vaccination: a qualitative study	Western Uganda, Ibanda District	School girls, parents/guardians, school teachers, health workers, community leaders	FGDs	Thematic analysis	November-December 2011
Turiho, 2014	Effect of School-based Human Papillomavirus (HPV) Vaccination of Adolescent Girls' Knowledge and Acceptability of the HPV Vaccine in Ibanda District in Uganda	Ibanda District Uganda	Adolescent girls	FGDS	Thematic analysis	November-December 2012
Venturas, 2017	Health professional feedback on HPV vaccination roll-out in a developing country	Zambia	Health professionals	SSIs	Thematic analysis	2017
Vermandere, 2016	Introduction of HPV vaccination in Kenya	Kenya	Fathers, adolescents, teachers and vaccinators, school teachers, health workers and community leaders.	FGDs and KIIs	Thematic analysis	May 2012-March 2013
Vermandere, 2015	Implementation of an HPV vaccination program in Eldoret, Kenya: results from a qualitative assessment by key stakeholders	Eldoret, Kenya	Teachers, fathers, vaccinators	FGDs	Thematic analysis	May 2012-March 2013
Vielot, 2017	Acceptability of multipurpose human papillomavirus vaccines among providers and adolescent girls: A mixed-methods study in five countries	5 geographically diverse countries-South Africa data	Mothers	FGDs	Thematic analysis	Nov 2013-April 2014
Watson-Jones, 2015	Access and Attitudes to HPV Vaccination amongst Hard-To-Reach Populations in Kenya	Nairobi, Kenya	Ministry of health and education personnel, community and religious leaders, teachers, parents, girls and boys	FGDs	Thematic analysis	Nov 2012-Feb 2013
Watson-Jones, 2016	Feasibility and acceptability of delivering adolescent health	Tanzania	Health and education policy makers and district officials	KIIs	Thematic analysis	2013

	interventions alongside HPV vaccination in Tanzania					
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Appendix E: Critical Appraisal Skills Programme Checklist



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Summertown Pavilion, Middle
Way Oxford OX2 7LG

CASP Checklist: 10 questions to help you make sense of a **Qualitative** research

How to use this appraisal tool: Three broad issues need to be considered when appraising a qualitative study:

- ▶ Are the results of the study valid? (Section A)
- ▶ What are the results? (Section B)
- ▶ Will the results help locally? (Section C)

The 10 questions on the following pages are designed to help you think about these issues systematically. The first two questions are screening questions and can be answered quickly. If the answer to both is "yes", it is worth proceeding with the remaining questions. There is some degree of overlap between the questions, you are asked to record a "yes", "no" or "can't tell" to most of the questions. A number of italicised prompts are given after each question. These are designed to remind you why the question is important. Record your reasons for your answers in the spaces provided.

About: These checklists were designed to be used as educational pedagogic tools, as part of a workshop setting, therefore we do not suggest a scoring system. The core CASP checklists (randomised controlled trial & systematic review) were based on JAMA 'Users' guides to the medical literature 1994 (adapted from Guyatt GH, Sackett DL, and Cook DJ), and piloted with health care practitioners.

For each new checklist, a group of experts were assembled to develop and pilot the checklist and the workshop format with which it would be used. Over the years overall adjustments have been made to the format, but a recent survey of checklist users reiterated that the basic format continues to be useful and appropriate.

Referencing: we recommend using the Harvard style citation, i.e.: *Critical Appraisal Skills Programme (2018). CASP (insert name of checklist i.e. Qualitative) Checklist. [online] Available at: URL. Accessed: Date Accessed.*

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Paper for appraisal and reference: _____

Section A: Are the results valid?

1. Was there a clear statement of the aims of the research?

Yes

Can't Tell

No

HINT: Consider

- what was the goal of the research
- why it was thought important
- its relevance

Comments: _____

2. Is a qualitative methodology appropriate?

Yes

Can't Tell

No

HINT: Consider

- if the research seeks to interpret or illuminate the actions and/or subjective experiences of research participants
- Is qualitative research the right methodology for addressing the research goal

Comments: _____

Is it worth continuing?

3. Was the research design appropriate to address the aims of the research?

Yes

Can't Tell

No

HINT: Consider

- if the researcher has justified the research design (e.g. have they discussed how they decided which method to use)

Comments: _____

4. Was the recruitment strategy appropriate to the aims of the research?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- If the researcher has explained how the participants were selected
 - If they explained why the participants they selected were the most appropriate to provide access to the type of knowledge sought by the study
 - If there are any discussions around recruitment (e.g. why some people chose not to take part)

Comments:

5. Was the data collected in a way that addressed the research issue?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

- HINT: Consider
- If the setting for the data collection was justified
 - If it is clear how data were collected (e.g. focus group, semi-structured interview etc.)
 - If the researcher has justified the methods chosen
 - If the researcher has made the methods explicit (e.g. for interview method, is there an indication of how interviews are conducted, or did they use a topic guide)
 - If methods were modified during the study. If so, has the researcher explained how and why
 - If the form of data is clear (e.g. tape recordings, video material, notes etc.)
 - If the researcher has discussed saturation of data

Comments:



6. Has the relationship between researcher and participants been adequately considered?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If the researcher critically examined their own role, potential bias and influence during (a) formulation of the research questions (b) data collection, including sample recruitment and choice of location
- How the researcher responded to events during the study and whether they considered the implications of any changes in the research design

Comments:

Section B: What are the results?

7. Have ethical issues been taken into consideration?

Yes	<input type="checkbox"/>
Can't Tell	<input type="checkbox"/>
No	<input type="checkbox"/>

HINT: Consider

- If there are sufficient details of how the research was explained to participants for the reader to assess whether ethical standards were maintained
- If the researcher has discussed issues raised by the study (e.g. issues around informed consent or confidentiality or how they have handled the effects of the study on the participants during and after the study)
- If approval has been sought from the ethics committee

Comments:

8. Was the data analysis sufficiently rigorous?

Yes

Can't Tell

No

HINT: Consider

- If there is an in-depth description of the analysis process
- If thematic analysis is used. If so, is it clear how the categories/themes were derived from the data
- Whether the researcher explains how the data presented were selected from the original sample to demonstrate the analysis process
- If sufficient data are presented to support the findings
 - To what extent contradictory data are taken into account
- Whether the researcher critically examined their own role, potential bias and influence during analysis and selection of data for presentation

Comments:

9. Is there a clear statement of findings?

Yes

Can't Tell

No

HINT: Consider whether

- If the findings are explicit
- If there is adequate discussion of the evidence both for and against the researcher's arguments
- If the researcher has discussed the credibility of their findings (e.g. triangulation, respondent validation, more than one analyst)
- If the findings are discussed in relation to the original research question

Comments:

Section C: Will the results help locally?

10. How valuable is the research?

HINT: Consider

- If the researcher discusses the contribution the study makes to existing knowledge or understanding (e.g. do they consider the findings in relation to current practice or policy, or relevant research-based literature)
- If they identify new areas where research is necessary
- If the researchers have discussed whether or how the findings can be transferred to other populations or considered other ways the research may be used

Comments:

Appendix F: CASP appraisal outcomes by study

	Section A: Are results valid?						Section B: What are the results?		Section C: Will the results help locally?	
Author, year	Was there a clear statement of the aims of the research?	Is a qualitative methodology appropriate?	Was the research design appropriate to address the aims of the research?	Was the recruitment statement appropriate to the aims of the research?	Was the data collected in a way that addressed the research issue?	Has the relationship between researcher and participants been adequately considered?	Have ethical issues been taken into consideration?	Was the data analysis sufficiently rigorous?	Is there a clear statement of findings?	How valuable is the research?
Balogun, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Can't tell	Yes	Yes
Bingham, 2009	Yes	Yes	Yes	Yes	Yes	No	Yes	Can't tell	Yes	Can't tell
Crann, 2016	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Francis, 2011	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Can't tell
Francis, 2013	Yes	Yes	Yes	Yes	Yes	No	Can't tell	No	Can't tell	Yes
Friedman, 2014	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Can't tell	No	Yes
Gallagher, 2018	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Can't tell	Yes	Yes
Gallagher, 2018b	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes
Harries, 2009	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Can't tell	Yes
Hasahya, 2016	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Can't tell	Can't tell	Can't tell
Kamya, 2017	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Katahoire, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes
Katahoire, 2013	Yes	Yes	Yes	Yes	Yes	No	Yes	Can't tell	Yes	Yes
Katz, 2013	Yes	Yes	Yes	Yes	Yes	No	Yes	Can't tell	No	Yes
Kisaakye, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Can't tell	Yes	Yes
Masika, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mugisha, 2015	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Nelson 2010	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	No	Yes	Yes
Nambe 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes
Ports, 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Remes, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Can't tell
Soi, 2018	Yes	Yes	Yes	Yes	Yes	Can't tell	No	Yes	Yes	Yes
Tuhiro, 2014	Yes	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Yes	Yes
Tuhiro, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes
Venturas, 2017	Yes	Yes	Yes	Yes	Yes	Can't tell	Can't tell	Yes	Yes	Yes
Vermandere, 2015	Yes	Yes	Yes	Yes	Yes	Can't tell	Can't tell	Yes	Yes	Yes
Vermandere, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Can't tell	Yes	Yes
Vielot, 2017	Yes	Yes	Yes	Yes	Yes	No	Yes	Can't tell	Yes	Yes
Watson-Jones, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes
Watson-Jones, 2015	Yes	Yes	Yes	Yes	Yes	Can't tell	Yes	Yes	Yes	Yes
Yasmine Islam, 2018	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

Appendix G: Evidence for themes by study

Major themes	Theme 1: Knowledge about HPV vaccine intertwined with misinformation						Theme 2: Fear Shaping contradictory perceptions of the HPV Vaccine				Theme 3: Social norms and gender dynamics influence on understandings of the HPV vaccine in SSA	
	Sub-themes	Levels of Technical knowledge	Willingness to learn about HPV vaccine	Different perceptions of causes of cervical cancer	Risk perception of HPV and cervical cancer	Language and symptomology in HPV/cervical cancer understandings	Misinformation	Fear of cervical cancer	Fear that cervical cancer causes infertility	Fear that the HPV vaccine causes infertility	Distrust of HPV vaccine initiatives	Social influence on perceptions of HPV vaccine
Balogun, 2018	✓		✓	✓		✓	✓		✓			
Bingham, 2009					✓					✓		
Crann, 2016	✓				✓	✓			✓		✓	✓
Francis, 2011	✓	✓	✓	✓	✓		✓					✓
Francis, 2013				✓	✓		✓	✓	✓			✓
Friedman, 2014					✓	✓	✓	✓		✓		✓
Gallagher, 2018												
Gallagher, 2018b												
Harries, 2009	✓			✓	✓	✓		✓		✓		✓
Hasahya, 2016				✓	✓	✓	✓	✓	✓			
Kamya, 2017												
Katahoire, 2008				✓	✓							✓
Katahoire, 2013	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓
Katz, 2013											✓	✓
Kisaakye, 2018	✓					✓						
Masika, 2015			✓			✓						

Mugisha, 2015												
Nelson 2010				✓	✓							✓
Nyambe 2018			✓		✓	✓		✓		✓	✓	✓
Ports, 2013	✓		✓	✓	✓							✓
Remes, 2012	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Soi, 2018						✓		✓	✓			✓
Tuhiro, 2014	✓			✓				✓	✓			
Tuhiro, 2017			✓			✓	✓		✓	✓	✓	✓
Venturas, 2017					✓	✓		✓	✓	✓		✓
Vermandere, 2015			✓	✓	✓							✓
Vermandere, 2016	✓		✓			✓			✓		✓	
Vielot, 2017		✓					✓					
Watson-Jones, 2016									✓			✓
Watson-Jones, 2015	✓							✓		✓	✓	
Islam, 2018						✓						

Appendix H: Manuscript submission guidelines

4. Preparing your manuscript

4.1 Article Format (see previously published articles in QHR for style):

- Title page: Title should be succinct; list all authors and their affiliation; keywords. Please upload the title page separately from the main document.
- Blinding: Do not include any author identifying information in your manuscript, including author's own citations. Do not include acknowledgements until your article is accepted and unblinded.
- Abstract: Unstructured, 150 words. This should be the first page of the main manuscript, and it should be on its own page.
- Length: QHR does not have a word or page count limit. Manuscripts should be as tight as possible, preferably less than 30 pages including references. Longer manuscripts, if exceptional, will be considered.
- Methods: QHR readership is sophisticated; excessive details not required.
- Ethics: Include a statement of IRB approval and participant consent. Present demographics as a group, not listed as individuals. Do not link quotations to particular individuals unless essential (as in case studies) as this threatens anonymity.
- Results: Rich and descriptive; theoretical; linked to practice if possible.
- Discussion: Link your findings with research and theory in literature, including other geographical areas and quantitative research.
- References: APA format. Use pertinent references only. References should be on a separate page.

Additional Editor's Preferences:

- Please do not refer to your manuscript as a "paper;" you are submitting an "article."
- The word "data" is plural.

4.2 Word processing formats

Preferred formats for the text and tables of your manuscript are Word DOC or PDF. The text should be double-spaced throughout with standard 1 inch margins (APA formatting). Text should be standard font (i.e., Times New Roman) 12 point.

- Include figures, charts, and tables created in MS Word in the main text rather than at the end of the document.
- Figures, tables, and other files created outside of Word should be submitted separately. Indicate where table should be inserted within manuscript (i.e. INSERT TABLE 1 HERE).
- Photographs: Should have permission to reprint and faces should be concealed using mosaic patches – unless permission has been given by the individual to use their identity. This permission must be forwarded to QHR's Managing Editor.
 - TIFF, JPED, or common picture formats accepted. The preferred format for graphs and line art is EPS.
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