



SYSTEMATIC REVIEW

Determinants of human papillomavirus (HPV) vaccine hesitancy in sub-Saharan Africa: A systematic review

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Abstract

Background: Vaccine hesitancy is a major public health issue that has negatively impacted vaccine uptake in sub-Saharan Africa (SSA). The reasons why individuals hesitate or refuse to vaccinate are variable and factors contributing to vaccine hesitancy are not well outlined. This review, therefore, aims to identify and describe the determinants of HPV vaccine hesitancy in SSA.

Methods: A systematic search was conducted across four electronic databases (PubMed, Scopus, CINAHL and Web of Science) from 2007 until October 2021 and updated in January 2022. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, 13 studies were eligible and were

included in the analysis. Data extraction and synthesis were guided by the Health Belief Model. Quality assessment was performed using the NIH and CASP quality assessment tools.

Results: *The most frequently reported factors influencing HPV vaccine hesitancy included concerns about side effects and infertility; limited knowledge of HPV vaccine, HPV infection, and cervical cancer; lack of awareness of vaccination opportunities; mistrust of health workers, health authorities, and new vaccines; influence by caregivers, peers, community members or respected members of the society and religious and cultural factors. Other factors included accessibility issues (roads in poor condition, transport costs), adolescent absenteeism on vaccination day and dropping out of school.*

Conclusion: *To reduce hesitancy and improve HPV vaccination coverage, vaccination programs need to develop and implement inclusive and context-specific strategies to enhance vaccine confidence, alleviate concerns, engage, and provide appropriate information to stakeholders involved in HPV vaccination, and dispel rumours and misinformation. The capacity of teachers and healthcare providers must be reinforced to equip them with knowledge about HPV vaccines, improve their interpersonal communication skills so that they can be better advocates for the vaccine within their communities.*

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Introduction

Vaccine hesitancy is defined by the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization as a complex, context-specific phenomenon that varies across time, place and vaccines and involves a delay in acceptance or refusal to vaccinate despite the availability of vaccines (1). Moreover, vaccine hesitancy has grown to be a huge public health concern that prompted the WHO to rank it as one of the ten greatest threats to global health (2). Studies have previously shown that vaccine hesitancy is a widespread phenomenon worldwide, with some variation in the reasons given for refusing to accept a single or multiple vaccines (1,3).

Human papillomavirus (HPV) vaccine hesitancy is unique due to its association with social stigma (4), the involvement of a different target population than is typical for national immunization programs, and the special consideration given to the approach to vaccine delivery (5). Hesitancy to HPV vaccine is influenced by many factors including sociocultural factors such as stigma associated with HPV being a sexually transmitted infection and lack of knowledge about HPV and the associated risks, especially among adolescents who are the main target population for vaccination (5–7). Rapid social media dissemination of misinformation such as supposed vaccine “controversies”, long-term anti-fertility rumors and misconceptions following the vaccination of young girls increases the risk of the erosion of trust and confidence in HPV vaccine that can result in lost opportunities to protect health (8).

The COVID-19 pandemic intensified barriers due to misinformation about COVID-19 vaccines and disrupted national immunization programs. For instance, HPV vaccine introduction in Cameroon had to be delayed because there was suspicion that the HPV vaccine was a COVID-19 vaccine (9). Hesitancy toward the HPV vaccine poses a serious threat to HPV vaccination programs and can impact vaccine uptake and coverage in SSA (10). Unless such reluctance is overcome, HPV vaccine coverage

may remain below the 80% target (6,11), perpetuating the already high burden of cervical cancer in the region (12). According to the global analysis of the burden of cervical cancer, the highest incidences (ASIR age-standardized incidence rate >40 per 100,000) and mortality rates (>20 per 100,000) are observed in eastern, southern and western Africa (12).

Countries in SSA with support from international partners such as GAVI and UNICEF are progressively introducing or scaling up HPV vaccination to reverse the cervical cancer curve (6). There are efforts to demonstrate governments' commitment to the 'WHO Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem by 2030'. As a result, there is hope for more women to have access to effective vaccines against HPV, which causes more than 70% of all cervical cancer (13). Therefore, to realize the full benefit of HPV vaccination and reduce the burden of cervical cancer in SSA, the issue of growing reluctance to vaccinate against HPV must be well-understood to inform the development and implementation of context-specific interventions.

This review was developed to (1) describe the determinants of HPV vaccine hesitancy, (2) suggest interventions based on the identified determinants, (3) identify knowledge and research gaps, and (4) discuss the differences and similarities between the reasons for vaccine hesitancy to HPV vaccine in sub-Saharan Africa and other regions. To the authors' knowledge this is the first review to comprehensively document the factors contributing to vaccine hesitancy to HPV vaccine, making it an

important resource for policy makers and countries wishing to introduce or scale up HPV vaccination, thus reducing the burden of cervical cancer in SSA.

Methods

Search strategy

This review was developed in line with the PRISMA guidelines (14) as displayed in Figure 1 and adopted the Population, Intervention, Comparator, Outcome (PICO) approach, to search for studies exploring reasons for HPV vaccine hesitancy in SSA. The population under review was any stakeholder involved in HPV vaccination decision-making in the SSA. In place of the intervention, the factors or determinants influencing the outcome were assessed. There was no comparator, and the determined outcome was HPV vaccine hesitancy. Keywords and terms were drawn from previous review studies on vaccine hesitancy (15). These were used to develop a broad search string that was adapted to four databases including PubMed, Scopus, CINAHL (EbscoHOST) and Web of Science.

The complete list of keywords and terms is presented in Appendix A and the PubMed search strategy in Appendix B. The searches were limited to items published from 2007 to October 2021 and were updated in January 2022. Database search results were downloaded and combined in Mendeley reference management software. The initial step involved removing all duplicates. The remaining articles were then screened by reading article titles and abstracts to determine if they were relevant to the review. For potentially eligible articles, full-text papers were obtained and scrutinized for relevance. The reference lists and bibliographies of all included articles were hand-searched to look for additional eligible studies not retrieved by the electronic search.

Inclusion/exclusion criteria

The review includes studies:

- i. Conducted in sub-Saharan Africa since 2007,
- ii. in which the vaccine was publicly available through demonstration project or national vaccination program and the population presented with the vaccine;
- iii. published in English;
- iv. which investigated any WHO-licensed HPV vaccine;
- v. that were quantitative and qualitative;
- vi. which investigated reasons why participants hesitated to vaccinate or choose to delay or refuse HPV vaccination for themselves or their dependents;

vii. which compared different vaccines or in which countries from inside and outside SSA were included solely if data for HPV vaccination and/or SSA countries were included.

Studies were excluded if they:

- i. Did not include original data (commentaries or editorials)
- ii. were in a language other than English.
- iii. focused on evidence from non-SSA countries.
- iv. were done before HPV vaccine became publicly available
- v. did not include reasons for refusal, concern, mistrust/confidence in the vaccine or vaccination.
- vi. were articles that focused only on reasons for accepting HPV vaccination, uptake or intentions to vaccinate, or knowledge or awareness.
- vii. were interventional studies such as clinical trials or studies aimed to test vaccine efficacy or effectiveness and not designed to measure the determinants of vaccine hesitancy.
- viii. were systematic and narrative reviews and editorials.

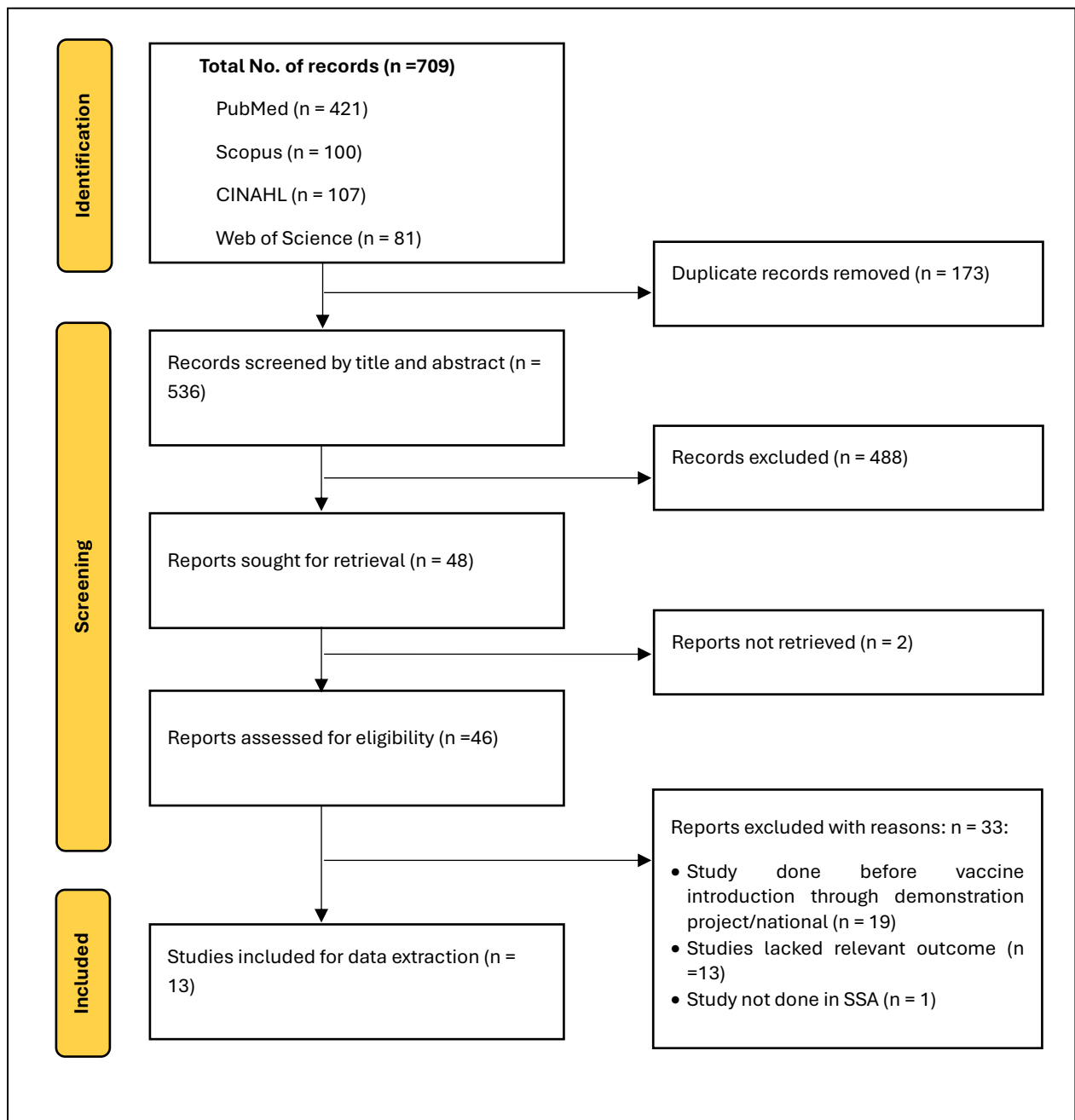


Figure 1. PRISMA flow diagram – study selection process

Data extraction and synthesis

Thirteen studies met the inclusion criteria (Figure 1).

For each selected study, data was extracted using a standardized form adapted from a previous hesitancy review (16) and developed in MS Excel. The extraction form was piloted and necessary adjustments were made. Extracted information included: first author name, year study was conducted, country, study design, study instrument (self-administered questionnaire, interview, online, FGD), study settings (school-based or facility-based), study population and their age, sample size, the type of program: demonstration project or National program (Appendix C). Key outcomes were tabulated and thematically organized into groups based on the six Health Belief Model (HBM) constructs with the following headings: perceived susceptibility to HPV infection or cervical cancer, perceived benefits of and perceived barriers to getting HPV vaccine, cues to action and modifying factors (see tables 1a & 1b).

Assessment of the risk of bias

Two tools were utilized to appraise the included studies. The “Critical Appraisal Skills Program qualitative checklist” was used to appraise qualitative studies (17) as shown in Appendix D. For the longitudinal cohort, cross-sectional, and case-control studies risk of bias was assessed using appropriate checklists published by the US National Heart, Lung and Blood Institute for observational cohort and cross-sectional and case-control respectively (18) as described in Appendix E.

Table 1a. Determinant factors of vaccine hesitancy: perceived barriers

First Author	Country	Perceived barriers					
		Issues of trust	Sexual health aspects of the vaccine	Concerns about vaccine safety	Logistical barriers	Influencers	Fear of injections
Adeyanju, G.C	Malawi	<ul style="list-style-type: none"> • Trust in healthcare workers • Low confidence in the system delivering it 	<ul style="list-style-type: none"> • HPV vaccine ruins girls' fertility • Vaccines are a means to reduce the population 	<ul style="list-style-type: none"> • Low confidence in the safety of the vaccine 			
Vermandere H	Kenya		<ul style="list-style-type: none"> • Fear of interference with fertility • It might encourage unsafe sex 	<ul style="list-style-type: none"> • Fear of side effects • Afraid of unsafe administration (i.e. using unclean needles) 	<ul style="list-style-type: none"> • Lack of time • Transport cost 	<ul style="list-style-type: none"> • Family/friends opposed • Daughter opposed • Partner opposed 	<ul style="list-style-type: none"> • Perceiving three doses as inconvenient
Turiho	Uganda	<ul style="list-style-type: none"> • A disguised population control measure by government • Rumoured connivance of local politicians with scientists to inject children with a vaccine to retard their intellectual development and render them politically subservient. 	<ul style="list-style-type: none"> • Could become barren or would face a greater risk of life-threatening childbirth complications • She would give birth to only twins. • A disguised plot to enhance infertility • Would affect their menstruation making it heavy and painful 	<ul style="list-style-type: none"> • Pain and swelling at the injection site and heard friends complaining about it for some time after the injections • Misconceptions about the safety of the HPV vaccination: • HPV vaccine causes cervical cancer, which would ultimately kill the vaccinated person • Fear of long-term physical damage 		<ul style="list-style-type: none"> • Discouraged or barred from HPV vaccination due to misinformation by parents 	
Masika	Kenya		<ul style="list-style-type: none"> • Induces early sexual activity 	<ul style="list-style-type: none"> • Vaccine not safe • Fear of side effects 	<ul style="list-style-type: none"> • Pupil absenteeism • Poor accessibility of the region 	<ul style="list-style-type: none"> • Negative attitude towards the vaccine by some parents or teachers 	
Milondzo	South Africa			<ul style="list-style-type: none"> • Negative attitude toward HPV vaccination: due to concerned about the rumours of HPV vaccine side effects/ misinformation was the main driver of negative attitudes 	<ul style="list-style-type: none"> • Inconvenience of using health facility-based services) • Cost of vaccination 		

First Author	Country	Perceived barriers					
		Issues of trust	Sexual health aspects of the vaccine	Concerns about vaccine safety	Logistical barriers	Influencers	Fear of injections
Turiho (qualitative)	Uganda	<ul style="list-style-type: none"> Vaccination was a trick by government to prevent over-population by injecting girls with medicine that would prevent them from giving birth in future 	<ul style="list-style-type: none"> Fear that HPV vaccination could have adverse effects on reproductive health of the vaccinated girls 	<ul style="list-style-type: none"> HPV vaccination was still experimental Long term physical damage to the vaccinated arms since some girls got swollen arms after the injection. The vaccine had been deliberately made to cause death 		<ul style="list-style-type: none"> locally prominent radical traditionalist and Pan Africanist campaigned against all vaccinations via his FM radio 	
Watson-Jones	Tanzania		<ul style="list-style-type: none"> Concern over infertility 	<ul style="list-style-type: none"> Concern over other side effects 		<ul style="list-style-type: none"> Pupil absenteeism because parent refused Girl refused 	<ul style="list-style-type: none"> Were afraid of injections
A.B. Wiyeh	South Africa		<ul style="list-style-type: none"> Fertility related concerns 	<p><u>Concerns around vaccine safety</u></p> <ul style="list-style-type: none"> Knowing/ hearing stories about someone affected by HPV vaccination Previous negative experience with HPV vaccination Inadequate handling of concerns around vaccine safety. Lack of transparency on safety data, accountability and support following the occurrence of HPV vaccine side effects Fear of vaccine side effects. <p>Consent:</p> <ul style="list-style-type: none"> Some respondents felt parental consent should be mandatory and respected. Others considered the request for parental consent as being suspicious considering the importance of vaccines and that consent was not required for other childhood vaccines Belief that the vaccination campaign is an ongoing vaccine trial 	<ul style="list-style-type: none"> Concerns around the use of the school-based strategy for HPV vaccination. 		
Mabeya	Kenya				<ul style="list-style-type: none"> distance to the clinic / health facility 		
Rujumba	Uganda	<ul style="list-style-type: none"> Unfriendly healthcare workers 		<ul style="list-style-type: none"> Rumours and misconceptions about the vaccine and vaccination 	<ul style="list-style-type: none"> Absenteeism or dropout from school Change of 	<ul style="list-style-type: none"> Discouraged by their peers particularly for the 	<ul style="list-style-type: none"> Fear of injection pain

First Author	Country	Perceived barriers						
		Issues of trust	Sexual health aspects of the vaccine	Concerns about vaccine safety	Logistical barriers	Influencers	Fear of injections	
		<ul style="list-style-type: none"> Mistrust of government intention of introducing new vaccines 				residential location or school within or outside the district between doses <ul style="list-style-type: none"> Busy schedules and gendered nature of domestic work 	second dose <ul style="list-style-type: none"> Girls refused to be vaccinated Girls discouraged by their parents 	
Msyamboza	Malawi			<ul style="list-style-type: none"> Vaccination venue was unclean and unsafe 	<ul style="list-style-type: none"> Girl ill/absent from school on vaccination day Transferring out of the district dropping out of school Inconvenient location/time Unacceptable waiting time 	<ul style="list-style-type: none"> Someone else said vaccine not good idea Others in community or school were also refusing Girl didn't want to be vaccinated Parent refused 	<ul style="list-style-type: none"> Too much pain after 1st or 2nd dose 	
LaMontagne	Uganda		<ul style="list-style-type: none"> Impact on fertility 	<ul style="list-style-type: none"> Concerns about safety Vaccine is new Vaccine is experimental 	<ul style="list-style-type: none"> Difficulty in determining the girl's eligibility School absenteeism 			
		<ul style="list-style-type: none"> Mistrust of the government to maliciously infect them with the coronavirus vaccine was being used as a cover by pharmaceutical industries to infect them with the coronavirus and as a means to make money 		<ul style="list-style-type: none"> Information surrounding the emergence, spread and management of COVID-19 was the main reason parents and guardians refused to have their children vaccinated. Influence of Social Media Believed all the fake news and rumours about the HPV vaccine going around on social media and were not willing to accept the right information not enough evidence from manufacturers to show that the vaccine was safe 				

Table 1b. Determinant factors of vaccine hesitancy: perceived susceptibility, benefits, constructs and the modifying factors

First Author	Country	Perceived susceptibility	Perceived benefits	Cues to action	cultural/religious moderators	Socio-demographic		
						Education level	Age	Unemployment
Adeyanju, G.C	Malawi		<ul style="list-style-type: none"> • Believed children’s immune systems protected against diseases 			<ul style="list-style-type: none"> • secondary or tertiary education showed lower intentions than those with no formal or primary education 	<ul style="list-style-type: none"> • young adult (25–34 years) old indicated a higher belief in rumours 	<ul style="list-style-type: none"> • Unemployed had a negative effect on safety perception. (being young adults, unemployed, or having low trust in healthcare workers' increased belief in rumours). • Belief in rumours having low trust in healthcare workers increased those beliefs). • Confidence in vaccine effectiveness decreased if the participants were unemployed or thought that the HPV vaccine reduces fertility.
Vermandere H	Kenya	<ul style="list-style-type: none"> • Daughter is too young for vaccine against an STI 	<ul style="list-style-type: none"> • Doubted the efficacy of the vaccine 	<ul style="list-style-type: none"> • Not knowing about the vaccination opportunity • Lack of vaccine information 				
Masika	Kenya		<ul style="list-style-type: none"> • Vaccine not necessary (teachers' Questionnaire) 	<ul style="list-style-type: none"> • Lack of enough information 	<ul style="list-style-type: none"> • cultural and religious beliefs that were against vaccinations <p><i>'We have some religions that don't allow modern medicine, so the government should come in and decide what to do with the parent.'</i></p>			
Milondzo	South Africa			<ul style="list-style-type: none"> • Low levels of knowledge about the link between HPV 				

First Author	Country	Perceived susceptibility	Perceived benefits	Cues to action	cultural/religious moderators	Socio-demographic		
						Education level	Age	Unemployment
				infection and cervical cancer				
Turiho (qualitative)	Uganda				<ul style="list-style-type: none"> religious and cultural transgressions. Parents implicated two cult-like groups (names withheld) in that region of the country for notoriously discouraging their members to vaccinate their children. 			
Watson-Jones	Tanzania		<ul style="list-style-type: none"> Had not understood the value of the vaccine 	Adults: <ul style="list-style-type: none"> Insufficient knowledge about the vaccine 				
A.B. Wiyeh	South Africa	Complacency: Risk of cervical cancer perceived as being low	Calculation: <ul style="list-style-type: none"> People who felt that the risk of vaccinating children with the vaccine far outweighed the benefits of receiving the vaccine were more likely to express hesitant comments. 					
Mabeya	Kenya			<ul style="list-style-type: none"> low HPV knowledge among caregivers 				

First Author	Country	Perceived susceptibility	Perceived benefits	Cues to action	cultural/religious moderators	Socio-demographic		
						Education level	Age	Unemployment
Rujumba	Uganda		<ul style="list-style-type: none"> Girls did not consider vaccination to be useful 	<ul style="list-style-type: none"> Limited healthcare workers', VHTs' and teachers' knowledge about HPV vaccine and national HPV vaccination policy Lack of strategies targeting out-of-school girls Lack of reminder/recall strategies for 2nd vaccine dose Inadequate knowledge about the HPV vaccine inadequate knowledge about the benefits of completing the vaccine series. Caregivers' lack of awareness of vaccine and vaccination activities 	<ul style="list-style-type: none"> VHTs and healthcare workers reported that some traditional practices and religious beliefs were against vaccination in general 			
Msyamboza	Malawi	<ul style="list-style-type: none"> Girl not at risk for cervical cancer Girls are too young for HPV vaccine 	<ul style="list-style-type: none"> Does not believe vaccination is good for child 	<ul style="list-style-type: none"> Was not aware of HPV vaccine program 				
LaMontagne	Uganda			<ul style="list-style-type: none"> Lack of awareness of the program 				
Haddison E	Cameroon	<ul style="list-style-type: none"> prevalence of cervical cancer in Cameroon was too low to warrant introduction of the HPV vaccine into the immunisation schedule 	<ul style="list-style-type: none"> Vaccine was not necessary for Cameroonians 	<ul style="list-style-type: none"> Inadequate sensitisation of the community before introduction of the vaccine hence the confusion with COVID 19 	<ul style="list-style-type: none"> socio-cultural beliefs and saw the vaccine as a threat to procreation 			

VHT, village health team

Results

A total of 709 articles were retrieved from the four databases, of which 173 were duplicates. After removing duplicates, the remaining 536 records were screened by title and abstract. Of these, 488 records were excluded for not meeting the inclusion criteria, while the full texts of 48 articles were retrieved for the assessment of final eligibility. Of the 48 articles, 13 met the eligibility criteria and were included in the literature review (Figure 1).

Characteristics of included studies

Study designs and methods: The majority (8/13; 61.5%) of studies were of cross-sectional design (19–26) of which two used mixed methods. Three studies used qualitative study design (8,27,28). The remaining two studies were cohort and case-control studies respectively (7,29). All included studies used a combination of interviews, focus groups, social media responses, and analysis of reports and minutes.

Assessment of the risk of bias: None of the qualitative studies indicated a significant methodological shortcoming. The average percentage score was 73%, with the lowest percentage score of 50% (Appendix D). Overall, longitudinal cohort, cross-sectional, and case-control studies were well conducted. Eight out of ten studies were found to be of moderate quality and 2/10 studies were of strong quality. (Appendix E). The two mixed methods studies (23,26) were assessed as “moderate” for their quantitative sections and “good” for their qualitative part. (See Appendix D and E).

Study setting: Included studies were conducted in 6 countries. Most of the studies were conducted in Eastern Africa (Uganda 4, Kenya 3 and Tanzania 1) (7,21–23,26–29), followed by Southern Africa which contributed 4 studies (South Africa 2 and Malawi 2) (8,19,24,25) and finally one study from Cameroon in Central Africa (20). 10 of 13 (77%) studies were conducted between 2007 and 2018 (7,21–29). Three studies were published in 2011, two studies each from 2013 and 2018, and a single study each from 2008, 2012, 2016, 2019, 2020 and 2021.

Study participants: A total of 36207 participants (median 404, range 24 -3,000) were represented in the included studies. Participants ranged from adolescent girls, caregivers, schoolteachers, health care providers (HCPs) to community leaders. Caregivers were the most represented participants (9 of 13 studies) (7,19,21,22,24,25,27–29). Five studies sampled multiple decision-makers (7,8,22,27,28) while the other three sampled independent decision-makers that included HCPs (20), teachers (23) and adolescents (26).

Type of programme and delivery strategy: In SSA, countries publicly provide HPV vaccine mainly through demonstration projects and national programs. The two are assumed to have a similar effect on public knowledge and awareness of HPV vaccine because campaigns are conducted prior to vaccine introduction. In more than half (62%) of the studies, vaccines were available through demonstration projects (19,21–23,25,26,28,29) while 4 of them (31%) (8,20,24,27) were after the introduction of HPV vaccine into the national immunization program. The study from Tanzania was performed during phase 4 clinical trial (7). Among the thirteen studies, nine reported vaccine delivery using both the facilities and schools (7,19–21,25–29) while one (23) used school-based only and two studies reported using facility-based (22,24) strategies only. One study did not specify the delivery strategy as it was an analysis of social media responses (8).

Determinants of vaccine hesitancy

Perceived susceptibility: Four of the thirteen included studies (31%) reported on complacent and hesitant participants who perceived a low susceptibility to cervical cancer (8,20,25,29). Participants who were mainly mothers or caregivers of adolescents perceived their daughters as less susceptible to the disease hence reducing the uptake of the vaccine. Refusers often justified their decision by stating their adolescent girls were not at risk for cervical cancer and therefore did not need vaccination against HPV (8,25).

Other caregivers who perceived cervical cancer as a sexually transmitted infection (STI) stated their daughters were too young to contract the disease (29). This perception was sometimes driven by misinformation, as participants reported the disease to be hereditary and did not affect their family line (8). Haddison E et al. observed that vaccinators were also sceptical of the HPV vaccine and felt that it was not necessary to introduce it into the vaccination schedule since the prevalence of cervical cancer in the country was considered to be too low (20).

Perceived benefits: More than half of the included studies (62%) presented results of participants with low perceptions of the benefits of HPV vaccination. Low perceived vaccine effectiveness was prevalent among hesitant participants, namely caregivers, adolescents, health workers and teachers across all the represented countries (7,8,19,20,23,25,27,29). In Cameroon and Kenya, health workers and teachers felt HPV vaccines were unnecessary for adolescent girls (20,23). Caregivers in a study in South Africa considered the risk of vaccinating their children to outweigh the benefits (8). Their counterparts in Malawi believed their children's immune systems offered better protection against disease than the vaccine (19). Moreover, 22% of Tanzanian parents doubted the long-term protection of the vaccine while in Uganda adolescents refused to be vaccinated because they viewed vaccines as having no additional benefit (27).

Perceived barriers

Concerns about trust: Trust is an essential component in effective HPV vaccine delivery. Trust issues were expressed in 5 of the 13 articles (19,20,26–28). Participants from Malawi and Uganda studies had concerns associated with the trust of healthcare workers (19,27). Participants in the Ugandan study reported that this mistrust was spawned by the unfriendly nature of the health workers (27). In the same study, the population was found not to trust the government's intention to introduce new vaccines, particularly HPV vaccine. In two other Ugandan studies, some participants believed the government was using vaccines as a measure to control the population by injecting girls with vaccines that would render them barren (26,28).

Additionally, participants had the perception that their local politicians had colluded with scientists to inject their children with a vaccine that would retard their intellectual development and render them politically subservient (26). Lastly, Cameroonian vaccinators expressed trust issues with the government and pharmaceutical companies (20). Considering that the HPV vaccine was introduced during the COVID-19 pandemic, vaccinators had little trust in the government and stated that it had malicious intentions of infecting them with the coronavirus (20). They were also suspicious of pharmaceutical companies that were seen as using the HPV vaccine as a cover for infecting them with coronavirus and a money-making scheme.

Concerns about vaccine safety/side effects: All included studies except one (22) described concerns about potential side effects of HPV vaccination (7,8,19–21,23–29). This was often expressed as fear of long-term side effects that were mainly triggered by either misconceptions or rumours and misinformation on HPV vaccine side effects (7,8,19–21,23–27,29). In Uganda, misconceptions that HPV vaccine could cause cervical cancer, lead to long-term physical damage and cause death to the vaccinated were largely based on previous experiences with polio vaccination that killed several children in the community (28). Two of the included studies (25,29) reported fear of unclean or unsafe administration of the vaccine.

In addition, Wiyeh et al found the requirement for parental consent before vaccination raised doubts about the safety of the vaccine (8). Participants reported a lack of transparency of safety data, unresolved concerns about vaccine safety, and a lack of accountability and support for adverse events in the same study. In Cameroon, HPV vaccine was introduced to the national program during the COVID-19 pandemic (20). Safety concerns due to information surrounding COVID-19 disease and vaccines were the main drivers of vaccine hesitancy (20).

Concerns about sexual health aspects of the vaccine: This category of concern was raised in all countries represented in this review (7,8,19,23,26–29). Participants commonly reported fear that HPV vaccine would interfere with the fertility of vaccinated girls (7,19,21,26,28,29) and induce early sexual activity (23,29). This was articulated by participants in various ways, including those who perceived HPV vaccine could ruin girls' fertility, vaccines were a way to reduce the population, and this was a disguised plot to increase infertility. In Kenya, participants were afraid HPV vaccination could encourage unsafe sex and induce early sexual activity respectively (23,29). Fears and concerns of adolescent girls who were interviewed in a study conducted in Uganda included that the HPV vaccine would affect their menstrual periods, resulting in heavy and painful periods, they would be at increased risk of life-threatening obstetric complications and that they would deliver twin babies: the main factors behind the adolescents' hesitation were rumours and misinformation from peers and/or their mothers (26).

Fear of injections/pain: Fear of the needle and the pain due to the injection were mentioned as reasons for vaccine refusal by adolescents in studies from Uganda, Tanzania, Kenya and Malawi (7,25,27,29). Of the four studies, two identified injection pain after the 1st or 2nd dose of HPV vaccine as the discouraging factor to the uptake of the subsequent dose (25,29).

Logistical barriers: School absenteeism associated with parents' refusal to have their children vaccinated was frequently mentioned as a reason for non-uptake in studies that used the school-based strategy to vaccinate adolescents (7,21,25,27).

For the facility-based approach, reasons for non-uptake included distance to the clinic/health facility, inconvenient location and or time, long distance to the facility, long waiting time, transport cost and challenges in determining the girl's eligibility (21,22,24,25,29).

Cues to action

HPV-related knowledge and awareness: Four studies found levels of knowledge of HPV vaccine, and/or HPV and cervical cancer were consistently low among specific demographic groups that included adolescents, parents and caregivers (7,22,24,27). In fact, in some cases, the adolescents who had been vaccinated did not understand why they had been vaccinated or the disease/ infection which the vaccine was intended to prevent, or even the name of the vaccine they had received (27). HCWs, village health team members (VHTs) and teachers who are the frontline workers for vaccination programs had little to moderate knowledge (27).

Besides, three of the included studies (23,27,29) revealed sometimes the population lacked important information regarding the opportunities to vaccinate that could motivate them to be vaccinated. In

Uganda, caregivers of school-going girls claimed their daughters were not vaccinated as they were not aware of the vaccination program activities. Some caregivers got to learn about the vaccination from their daughters after vaccination at school. In the same study, it was noted that those girls who were absent from school on the vaccination day were not aware of alternative vaccination points (27). Others reported they were not aware that their daughters were eligible for vaccination (27). In the study by Masika et al, a third of the total respondents mentioned lack of information to have been the greatest barrier to HPV vaccine uptake (23).

Influencers: In this review, six studies done in Kenya, Tanzania, Uganda, and Malawi demonstrated that adolescents' decision-making was influenced by key actors ranging from their caregivers who were against vaccination (7,23,25,26,29), their peers or friends who discouraged them from vaccination (26,27,29), some community members who had refused vaccination (25), to prominent members of the society that advised the community against vaccination (28). In Kenya, some women refused the vaccine for their daughters because they believed their partner would not approve of HPV vaccination (26,27,29).

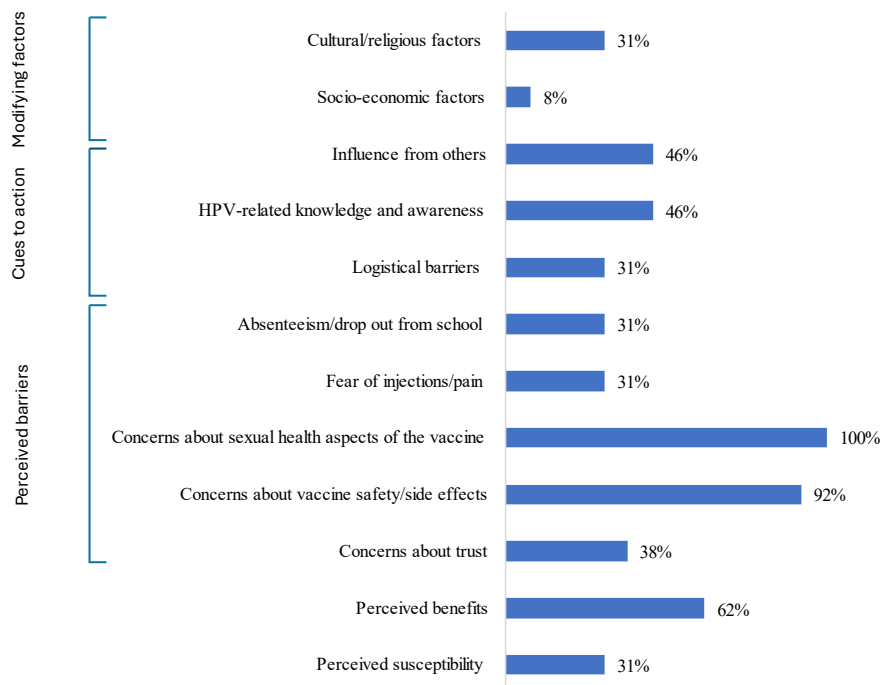


Figure 2. Proportion of articles reporting on the determinant factors of vaccine hesitancy

Socioeconomic factors: One study reported the sociodemographic variable as a determinant of vaccine hesitancy (19). Of all the demographic variables studied including participant education, employment and gender, only education directly influenced vaccination decision-making. Respondents who had secondary or tertiary education exhibited lower intentions to take up vaccines than those with no formal or primary education. Being unemployed seemed to be associated with poor vaccination confidence and uptake. Furthermore, those unemployed had low trust in healthcare workers, increased belief in rumours and thought HPV vaccine reduced fertility. Among the caregivers whose age range was between 18 – 60 years, those between 25 and 34 years were found to have a higher belief in rumours (19).

Cultural / religious factors: Four studies revealed HPV vaccine perceptions and decisions regarding uptake are shaped by cultural and religious factors among study participants (20,23,27,30). Participants in the study done by Masika et al reported some cultural and religious beliefs that were

anti-vaccination as they opposed modern medicine that includes vaccines (23). In Malawi, participants who believed in traditions or religions reported being uncomfortable with visits to the doctor (19). In another study, parents pointed to some religious groups they termed ‘cult-like groups’ that discouraged their congregation from vaccination (28). Additionally, VHTs and HCWs reported that certain traditional practices and religious beliefs opposed vaccination (27) while HCWs in Cameroon described HPV vaccine as a threat to procreation, which went against their cultural beliefs (20).

Discussion

The number of HPV vaccine hesitancy studies done in SSA remains low despite the increasing vaccine hesitance and interest in the topic as a whole. Furthermore, countries in SSA have steadily integrated HPV vaccine into their national immunization programs over the past 11 years (31,32); continued and extensive research is needed to monitor the rapid evolution of this field, shaped by complex, multi psychological behaviour changing with time and context (1).

Across SSA studies, the most prevalent factors were around: concerns about potential side effects including infertility caused by the vaccine; issues surrounding sexual health aspects of the vaccine; knowledge gaps on HPV vaccine and/or HPV and cervical cancer among parents/caregivers, adolescents, teachers, and health care providers; lack of awareness of the vaccination opportunities; school absenteeism or drop out from school; issues around trust of health authorities, health workers, and new vaccines; and perceived low susceptibility to HPV infection or cervical cancer and vaccine effectiveness (Figure 2).

Overall, stakeholders' reasons for hesitating or refusing HPV vaccine for themselves or their dependents, or not recommending it to others, are quite similar across all included studies. These similarities may be explained by the fact that SSA countries share a common culture and practices that tend to shape their beliefs and behaviours (33).

Concerns about vaccine safety

Concerns about the safety of the HPV vaccine were the most common reason for HPV vaccine hesitancy. Participants expressed concern about long-term side effects interfering with fertility in young girls. A systematic review of determinants of HPV vaccine hesitancy in Europe found a similar picture, with almost all included studies citing infertility concerns (34). Rumours and misinformation were the main drivers of negative attitudes among the stakeholders (24).

In 2020, for example, the efforts to introduce HPV vaccine in the national program in Cameroon was challenged by the infodemic that came with COVID-19, particularly the misconceptions about the COVID-19 vaccine's accelerated development. The population was suspicious claiming what was fronted as HPV vaccine introduction was a trial for COVID-19 vaccines (9).

These concerns are critical elements calling for targeted communication strategies to address public concerns, dispel rumours and misconceptions, thus counteract anti-vaxxers practices in SSA countries.

Trust concerning HPV vaccination

Public mistrust was noted to be a common aspect of HPV vaccine hesitancy; mistrust of the overall health system that provides the health services, the government that makes pertinent decisions for the population and lack of trust in health workers. This resonates with the findings SAGE documented (1) and a systematic review of qualitative studies in low- and middle-income countries that explored and reported the negative effect mistrust of the health system, the government, and health workers have on vaccine uptake (35). One explanation for the lower levels of trust relates to past experiences with the health system or in most cases health workers. The quantitative study from the Democratic Republic of

Congo during the Ebola disease epidemic also reported on associations between mistrust in the government and Ebola vaccine acceptance (36). Mistrust can be spread by health workers when they are seen to be unreliable, and unfriendly to the public or when they portray incompetence. Thus, immunization programs that assist healthcare workers to improve their vaccine communication skills, and educate them about evidence-based approaches to the most frequent concerns coupled with constant vaccine promotion activities in the communities are necessary.

Stakeholders influence

This review, as has been shown by other studies found that the decision not to vaccinate is strongly influenced by what those in the surrounding recommend or practice (37,38). This includes stakeholders such as peers, parents/caregivers, community leaders, and other community members. The role of various stakeholders in HPV vaccine uptake has also been captured in other studies (39–41). The review further shows the vital role fathers play that could influence HPV vaccine coverage. There were instances when girls were not vaccinated because their fathers had opposed, and women could not override or contradict their husband's decision. This is likely due to the fact that culturally, adolescents need approval from their fathers to be vaccinated or women need approval from their husbands before their daughters are vaccinated against HPV. This is also a proven practice in Ivory Coast, Mali, Ghana and Nigeria where men are identified as the primary vaccine decision-makers in their families (42,43). It is therefore essential that HPV vaccine promotion activities are inclusive, educating stakeholders, including fathers, about HPV and the benefits of vaccination, to help them make informed vaccination decisions and provide necessary support to their families (44).

Other barriers

This review also identified other barriers that significantly influenced hesitancy including pupil absenteeism and those related to access (due to poor road access, and cost). HPV vaccine cost was the least frequently reported because in all the included studies vaccines were available to the public at no cost. In cases where health facilities were solely utilized to deliver vaccines to the target population, travel costs, as well as time constraints, were the main barriers to vaccine uptake. The introduction of HPV vaccine in the national programs, and free of charge to the public, reduces this challenge (30).

Further financial constraints such as travel costs can be reduced when a mixture of approaches that include school and facility-based as well as community outreach are implemented to accommodate both school and non-school-going adolescents. The integration of the three approaches is key to improving and sustaining public demand for vaccination. The absenteeism noted in the review draws us to the importance of good record-keeping and tracking to ensure adolescents are fully vaccinated.

Knowledge and awareness HPV vaccine and vaccine program

Knowledge and awareness among the beneficiaries: The knowledge gap observed among caregivers and adolescents due to non-exposure to information about HPV, HPV vaccine, or cervical cancer is not unique to SSA (45), as it has been reported in other parts of the world (46,47). Furthermore, the same has been echoed by 25 other studies in a review that revealed limited knowledge of HPV vaccine among unsensitized parents that could not make informed decisions about vaccination (48). Conversely, other studies have shown high acceptance of vaccines despite low knowledge level (49). Despite these conflicting perspectives, knowledge of cervical cancer, HPV infection, and HPV vaccine, is recognized as an important cue for HPV vaccine acceptance (49,50).

For this study, we defined awareness as having heard of the HPV program, a definition guided by the kind of awareness measured by the included studies. This review demonstrates that participants were hesitant to be vaccinated or have their dependants vaccinated as they were not aware of the HPV program. These findings can be explained by the limited community sensitization activities to raise awareness about the vaccine and vaccination activities.

The impact of early initiation of social mobilization coupled with sustainable continuous communication campaigns to promote knowledge and awareness is a proven strategy to ensure vaccine uptake that should always be realized (51).

Knowledge and awareness among the providers: As for the teachers and health workers, they were found to have mixed levels of knowledge that ranged between low and high. The teachers with little knowledge were likely to be those that did not receive pre-HPV vaccine introduction training and were the same that were less likely to recommend it to their daughters or adolescents. Additionally, female teachers were noted to have more knowledge of HPV vaccine and cervical cancer than their male counterparts. This finding is consistent with a study done in Malaysia among secondary school teachers which showed that awareness of HPV vaccine was higher in female teachers (54%) than in males (33%) (52). This emphasizes the importance of the training aspect to empower teachers and healthcare workers with HPV vaccine-related knowledge, improve their skills to handle complex conversations and, if coupled with the right support, their hesitant behavior towards vaccines is likely to improve (5).

Perceived low benefit

This review reveals the negative effect on HPV vaccine acceptance when the population has a low perception of its benefit and effectiveness in protecting against cervical cancer. Participants commonly reported HPV vaccine to be non-beneficial and considered the natural immune system as better protection or perceived the risk of acquiring HPV infection and or cancer to be low. Although studies did not explore the reasons for this behaviour, it was often linked to a low understanding or little information about the vaccine. This reemphasizes the need to improve the knowledge among all the stakeholders who are involved in adolescent girls' vaccination so that they are able to make informed decisions regarding lifesaving HPV vaccines (44,49).

Socio-cultural and religious modifiers

Cultural and religious beliefs that prohibited vaccination were repeatedly mentioned in studies across SSA. Previous research has also demonstrated low vaccination coverage among certain ethnic groups that was associated with strong cultural and religious beliefs (53–55).

The importance of involving local and religious leaders in the efforts to effectively address religious and cultural barriers and promote immunization cannot be overemphasized. There are proven successful experiences from interventions in SSA countries that involved religious leaders to promote child survival that other countries can explore (62).

Limitations

Some limitations of this systematic review have been outlined below and should be considered when interpreting results:

Only articles published in English were included in the analysis, which might have led to an underrepresentation of findings from certain countries in SSA.

Based on the geographical restriction to SSA, the findings of this review may not be generalizable to parts of the world with different contexts or settings as countries in SSA.

The inclusion of studies with broad primary outcomes ranged from reasons for non-vaccination, and assessment of HPV vaccination coverage to evaluation of the vaccination program or demonstration project. This meant that studies were considered eligible for inclusion as long as they reported reasons participants did not vaccinate or complete vaccination as a primary or secondary outcome. The range of outcomes seen in the included studies may be associated with the lack of standardization of research approach to VH and its contributing factors in SSA context.

While the search was expanded to include studies that were conducted between 2007 to 2022 to capture all the emerging reasons for hesitancy and their trend, most eligible studies were done during implementation of demonstration projects or at the initial stage of HPV vaccine introduction to the national program. Given the evolving nature of hesitancy, the generalizability of the findings of this review may thus necessitate further investigation.

Conclusion

The purpose of this review was to describe the determinants contributing to HPV vaccine hesitancy in Sub-Saharan Africa. Perceptions around safety concerns and potential side effects were the most common, the impact of which is indicated by the persistent low HPV vaccination coverage. Public trust on HPV vaccination is shaken across SSA and knowledge and awareness gaps exist among all key stakeholders with a significant effect on vaccine uptake. As countries in SSA consider introducing or scaling up HPV immunization programs nationwide, it is fundamental that strategies are developed with the goal to mitigate vaccine hesitancy, improve HPV vaccination coverage and reduce the burden of cervical cancer.

These strategies should focus on providing information regarding the safety and effectiveness of HPV vaccine; aim to rebuild and maintain public trust in health care providers, health authorities and the government and implement tailored and culturally acceptable health promotion campaigns, vaccine communication and educational interventions to increase key stakeholders' knowledge and awareness about HPV vaccine and all aspects surrounding it.

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Appendices

Appendix A. MeSH terms and keywords

"PICO"		Keywords	MeSH Terms
P	Participants	parent* OR guardian* OR teacher OR educator OR adolescent*	"Adolescent"[Mesh] OR "Female"[Mesh] OR "Parents"[Mesh] OR "Young Adult"[Mesh] OR "Adult"[Mesh]
	Setting	“Sub-Saharan Africa*” OR Angola OR Benin OR Botswana OR “Burkina Faso” OR Burundi OR Cameroon OR “Cape Verde” OR “Central African Republic” OR Chad OR Comoros OR Congo OR “Cote d'Ivoire” OR Djibouti OR “Equatorial Guinea” OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR “Guinea-Bissau” OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR “Sao Tome and Principe” OR Senegal OR Seychelles OR “Sierra Leone” OR Somalia OR “South Africa” OR Sudan OR Swaziland OR Tanzania OR Togo OR Uganda OR Zaire OR Zambia OR Zimbabwe	"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 "Eswatini"[Mesh] OR "Lesotho"[Mesh] OR "Malawi"[Mesh] OR "Mozambique"[Mesh] OR "Namibia"[Mesh] OR "South Africa"[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]
	Intervention	“Human papillomavirus vaccine” OR “HPV vaccine”	"Papillomavirus Vaccines"[Mesh] OR "School Health Services"[Mesh]
	Outcome	accept* OR hesit* OR uptake OR refus* OR doubt* OR dilemma* OR attitude* OR distrust OR mistrust OR objector* OR awareness OR dropout* OR perception* OR misconception* OR uptake or behavi* OR refus* OR misinformation OR barrier* OR belief* OR rejection OR opposition OR choice* OR hesitan* OR rumo* OR delay OR constraint OR obstacle OR incomplete OR "decision making" OR confidence OR knowledge OR concern* OR denial OR antivaccin* OR controvers* OR anxiety OR fear*	"Vaccination Refusal"[Mesh] OR "Patient Acceptance of Health Care"[Mesh] OR "Health Knowledge, Attitudes, Practice"[Mesh] OR "Trust"[Mesh] OR "Uncertainty"[Mesh]

Appendix B. PubMed search strategy

Search #1 = [Participants: Terms]

Search #2 = [Participants: MeSH Terms]

Search #3 = #1 OR #2

Search #4 = [Setting: Terms]

Search #5 = [Setting: MeSH Terms]

Search #6 = #4 OR #5

Search #7 = [Intervention: Terms]

Search #8 = [Intervention: MeSH Terms]

Search #9 = #7 OR #8

Search #10 = [Outcome: Terms]

Search #11 = [Outcome: MeSH Terms]

Search #12 = #10 OR #11

Search#13 = #3 AND #6 AND #9 AND #12, apply filters (2011- to date)

Appendix C. Summary of characteristics of included studies

First Author	Year of study	Country	Study design	Study instrument	Sample size	Study population	Age	Type of program	Delivery strategy
Caregivers									
Adeyanju, G.C	2020	Malawi	Cross-sectional	self-administered questionnaire, backward elimination regression analysis	n = 600 for all caregivers n = 133 (caregivers of adolescent girls)	Caregivers of adolescent girls	18–24 years: 18%; 25–34 years: 40%; 35–45 years: 33%; 45–60 years: 8%; 60 years and older: 1%);	Demonstration project	School-based & Facility-based
LaMontagne	2008 - 2009	Uganda	cross-sectional	interviews-open-ended questionnaire	• 680 school based (400-2008, 280- 2009) • 809 CDP: 361 2008, 448- 2009	Caregivers of 9 and 14 year girls	Not mentioned	Demonstration project	School-based & Facility-based
Milondzo	2018	South Africa	Cross-sectional	• self-administered questionnaire (school parents) • online	615 respondents	Caregivers of girls aged ≥9 years in private schools	Facebook users aged ≥25 years	National vaccination programme	Facility-based
Msyamboza	2016	Malawi	cross-sectional	Analysis of programme data, supportive supervision reports and minutes of National HPV Task Force meetings	26,766	caregivers of partially or unvaccinated eligible girls	1. >9 years, 2051(7.7%) 2. >9 years, 884 (3.3%) 3. 9–13 years 23,831 (89.0%)	Demonstration project	School-based & Facility-based
Vermandere H	2013 (At the end of the program)	Kenya	Longitudinal, cohort study	Interview	256	Mother to adolescents	Not mentioned	Demonstration project	School-based & Facility-based
HCWs/Teachers									
Haddison E,	2021	Cameroon	cross-sectional	self-administered questionnaire with both open-ended and closed questions	24	HCWs (Vaccinators)	28 to 58 years	National vaccination programme	School-based & Facility-based

First Author	Year of study	Country	Study design	Study instrument	Sample size	Study population	Age	Type of program	Delivery strategy
Masika	2013	Kenya	cross-sectional, mixed-methods	self-administered questionnaire, FGD	339/13FGD	Primary school teachers	average 40 years	Demonstration project	School-based
Adolescents									
Turiho	2011	Uganda	cross-sectional, mixed methods	self-administered questionnaire, FGD	777	Adolescent girls	9–19 years	Demonstration project	School-based & Facility-based
Mixed population									
A.B. Wiyeh	2019	South Africa	Qualitative	social media responses	157 comments	Social media users (Unknown adults)		National vaccination programme	N/A
Mabeya	2012 - 2013	Kenya	Cross-sectional	Interviews	3000 girls	School girls and parents	9 to 14 years	Demonstration project	Facility-based
Watson-Jones	2011	Tanzania	Case control	Interviews	<ul style="list-style-type: none"> • 159 pupil/adult case pairs • 245 pupil/adult controls 	<ol style="list-style-type: none"> 1. Adolescent girls (unvaccinated) 2. Their caregivers 	< 30 years, 30–39, 40–49, 50+, and unknown	Vaccination project: Phase IV cluster-randomised trial	School-based & Facility-based
Rujumba	2018	Uganda	Qualitative	In-depth interviews (IDIs) and Key informant interviews (KIIs)	8 IDIs and 32 KIIs	Primary school girls; Caregivers; HCWs; Village Health Team members (VHTs); teachers or school administrators	<ol style="list-style-type: none"> 1. 12.0 (10–15) 2. 39.3 (25–56) 3. 39.3 (26–57) 4. 40.4 (32–47) 5. 36.0 (26–45) 	National vaccination programme	School-based & Facility-based
Turiho	2011	Uganda (Ibanda district)	Qualitative	FGDs and KIIs	<p>FGDs: School girls, parents and guardians</p> <p>KIIs: School teachers, HCWs and community leaders.</p>	<ol style="list-style-type: none"> 1. School girls, 2. Caregivers 3. School teachers 4. Health workers 5. Community leaders 		Demonstration project	School-based & Facility-based

Appendix D. Risk of bias assessment of the included studies according to the Quality Assessment Tool for Qualitative Studies by Critical Appraisal Skills Program (CASP)

Criteria		CASP Results for qualitative studies				
		A.B. Wiyeh(CS)	Turiho (CS)	Rujumba (CS)	Masika (M)	Turiho (M)
1	Was there a clear statement of the aims of the research?	Yes	Yes	Yes	Yes	Yes
2	Is a qualitative methodology appropriate?	Yes	Yes	No	Yes	Yes
3	Was the research design appropriate to address the aims of the research?	N/A	Yes	Yes	Yes	Yes
4	Was the recruitment strategy appropriate to the aims of the research?	N/A	Yes	Yes	Yes	Yes
5	Was the data collected in a way that addressed the research issue?	No	Yes	Yes	Yes	Yes
6	Has the relationship between researcher and participants been adequately considered?	No	Yes	CT	CT	CT
7	Have ethical issues been taken into consideration?	No	CT	Yes	Yes	Yes
8	Was the data analysis sufficiently rigorous?	Yes	Yes	Yes	Yes	Yes
9	Is there a clear statement of findings?	Yes	Yes	Yes	Yes	Yes
10	Is there a clear statement of findings?	Yes	Yes	Yes	Yes	Yes
CASP Results		50%	90%	80%	90%	90%

Each question is given a score based on a response of yes, no, can't tell (CT). Every yes response merits a score of 1. CS for Cross-sectional studies, mixed studies (M)

Appendix E. Risk of bias assessment of the included studies according to the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies by the National Heart, Lung, and Blood Institute

NIH Results for observational cohort and cross sectional studies										
Criteria	Adeyanju, G.C	Turiho	Masika	LaMontagne	Haddison E,	Mabeya	Milondzo	Msyambaza	Watson-Jones	Vermandere H
Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Were all the subjects selected or recruited from the same or similar populations (including the same time period)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was a sample size justification, power description, or variance and effect estimates provided?	No	Yes	Yes	Yes	No	Yes	N/A	No	Yes	No
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	No	Yes	No	No	No	Yes	No	No	Yes	Yes
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	N/A	N/A	N/A	N/A	N/A	Yes	No	No	No	Yes
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Was the exposure(s) assessed more than once over time?	No	No	No	No	No	No	No	No	No	No
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Were the outcome assessors blinded to the exposure status of participants?	No	No	No	No	No	No	N/A	No	No	No
Was loss to follow-up after baseline 20% or less?	No	No	No	Yes	No	No	No	No	No	NA
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Quality rating	Fair (8)	Fair (9)	Fair (9)	Good (11)	Fair (6)	Good (10)	Fair (6)	Fair (5)	Fair (8)	Fair (9)

Quality was rated as poor (0–4 out of 14 questions), fair (5–10 out of 14 questions), or good (11–14 out of 14 questions); NA: not applicable, NR: not reported