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## Emerging research and publication concerns

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Honesty, transparency, and adherence to high ethical standards are essential to guide the development and execution of research projects.<sup>1</sup> Breaches in research integrity as well as scientific misconduct are periodically reported. In one recent incident, evidence of apparent image tampering was identified in a research paper by Lesné, *et al.* that had been published in *Nature* in 2006. This paper described findings that addressed the relationship between amyloid beta-protein and memory loss in Alzheimer's disease. Therefore, this paper provided support for the amyloid hypothesis of Alzheimer's disease.<sup>2</sup> Extended investigation of this incident revealed possible data tampering concerns in more than 20 papers authored by Lesné.<sup>3</sup> This incident remains under investigation.

Plagiarism is an important cause of scientific misconduct. While text similarity may in part be tolerated in the introduction and methods sections of a research manuscript, it is not acceptable in the results section where the findings of the current study are described. Furthermore, the discussion section of a manuscript should focus on the interpretation of the research results as well as the strengths and limitations of the study, thus avoiding or limiting text similarity with manuscripts that are already in existence.<sup>4</sup> The introduction of artificial intelligence (AI) tools such as ChatGPT has the potential to improve writing efficiency and the quality, organisation and comprehensiveness of a scientific manuscript.<sup>5,6</sup> However, utilisation of AI tools in scientific publications has ignited ethical concerns and debate regarding whether authorship should in part be attributed to these tools.<sup>6</sup> Furthermore, the output of these tools should be carefully reviewed and edited to ensure that the resultant manuscript is original and avoids plagiarism. Interestingly, over-and-above the use of traditional software to conduct plagiarism checks such as iThenticate, AI tools such as ChatGPT can also be used to detect plagiarism.<sup>5</sup>

A recently identified trend is the huge increase in the number of extremely productive authors who publish more than 60 papers per annum or at least one paper every five days. In a yet to be peer-reviewed preprint that evaluated extremely productive authors during a recent 22-year period, when authors in the physics disciplines were excluded, the highest concentration of extremely published authors worked in clinical medicine. Furthermore, between 2016 and 2022, the largest increase in non-physics based

extremely published authors occurred in Thailand, Saudi Arabia, Spain, and India. Although the researchers did not explore whether these extremely published authors complied with acceptable authorship criteria, they questioned whether unethical behaviour such as paying for authorship may in part be contributing to this trend.<sup>7</sup>

The review by Zhaksylyk *et al.* provided practical guidance for avoiding or preventing scientific misconduct, including comment on appropriate education and the role of ethics committees and peer review.<sup>1</sup> Authors, reviewers and editors collectively have a stake in maintaining the integrity of academic journals. As we continue to develop the *Journal of the African Society for Infectious Diseases (JAfSPID)*, let us adhere to acceptable ethical and publication standards so that our journal prospers and becomes a reliable and trustworthy resource for paediatric infectious diseases in Africa.

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## Knowledge, practices, and influencers of antibiotic prescriptions of Nigerian doctors

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### Abstract

**Background:** There is a dire need to preserve antibiotics currently in use to avert resistance. Appropriate use of antibiotics would ensure antimicrobial stewardship. Doctors are in the forefront of prescriptions. Their knowledge of and proper prescription practice as well as what influences their antibiotic prescriptions go a long way in mitigating antimicrobial resistance.

**Aim:** To ascertain the knowledge, practices and influencers of antibiotic prescriptions of doctors in Nigeria.

**Methods:** An online self-administered questionnaire on aspects of knowledge of when to prescribe antibiotics, actual prescription practice, and factors that influence prescription, was employed. Questionnaires were sent out in doctors' social media groups as google forms soliciting for responses. Responses were automatically entered into google spreadsheets and data analysed using SPSS version 21.

**Results:** A total of 258 doctors responded. The overall mean (SD) knowledge score (%) was 66.0±9.3 with a range of 40.0-93.3. Family physicians and paediatricians had higher mean knowledge scores than those in other specialities ( $p<0.001$ ). The overall mean appropriate practice score was 66.8±8.4 with a range of 40.0-85.7. The mean proper practice scores were highest among the family physicians, paediatricians and public health physicians ( $p=0.002$ ). The greater the years of medical practice the more the mean knowledge score ( $p=0.007$ ) and likewise doctors in tertiary care knew more than those in secondary and primary care ( $p=0.002$ ). Possession of prior information on antibiotic stewardship resulted in higher knowledge ( $p<0.001$ ) and practice ( $p=0.015$ ) scores, while having facility antibiotic protocols/ antibiotic stewardship committees was akin to better knowledge ( $p=0.032$ ) and prescription practice ( $p=0.012$ ). There was a weak though statistically significant positive linear relationship between knowledge and practice scores ( $r_s=0.291$ ,  $p<0.001$ . Knowledge accounted for only 9.2% ( $R^2=0.092$ ) of

variability in practice scores. A 1% increase in knowledge score increased practice score by 0.3%. Major influencers of prescribing practice were history of prior use of antibiotics by the patient (97.3%), cost of antibiotics intended to be prescribed (95.3%), age of patient (93.1%), request for antibiotics by the patient (89.6%), and patients presenting with high fevers (70.5%).

**Conclusion:** Demographic characteristics of respondents influenced knowledge but not necessarily practice. Knowledge of appropriate antibiotic prescription had little effect on actual prescribing practice. The factors that affected prescribing practice were previous training on AMS and availability of institutional protocols and treatment guidelines. It is recommended that all medical practitioners receive training on AMS and adhere to institutional treatment protocols.

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## Introduction

Antibiotics are among the most frequently prescribed medications. Since the discovery of penicillin, the first antibiotic, scores of antibiotics of varied classes have been added to the physician's armamentarium against microbial infections. An innate feature of every biological species is to self-propagate and prevent extinction. This invariably applies to microbes which ensure survival by mutation of genetic material in a bid to avert extermination by antimicrobial agents. Herein lies the principle of antimicrobial resistance.

Although antimicrobial resistance (AMR) is a natural phenomenon, the process has been much enhanced because of the overuse, underuse, and misuse of antimicrobials.<sup>1</sup> Infections caused by antibiotic-resistant microbes are difficult and sometimes impossible to treat. They pose a severe public health threat.<sup>2</sup> The world is currently running out of effective antibiotics and reports show that common bacterial infections, including urinary tract infections, sepsis, sexually transmitted infections, and some forms of diarrhoea, now manifest high rates of resistance against antibiotics previously used to treat these infections.<sup>2</sup> Antibiotic-resistant infections necessitate extended hospital stays, additional follow-up doctor visits and costly toxic alternatives.<sup>3</sup> Antibiotic resistance is a global phenomenon and multiple factors have been found to contribute to its increasing prevalence. These factors hinge on inadequate human behaviour such as patient self-medication, noncompliance with recommended treatments, and over-prescription of antimicrobials by physicians in the absence of appropriate indications.<sup>4</sup> Hospital practices, especially in large facilities, also provide a fertile ground for breeding and transmitting antibiotic resistant microbes.<sup>4</sup> Other determinants of antibiotic resistance are traits inherent in and factors associated with the microorganism.<sup>5</sup>

Nigeria has a high burden of AMR and the reasons for this are multifactorial.<sup>6</sup> Prescription monitoring is virtually non-existent and prescription-only medicines, including antimicrobials, are routinely available over the counter in pharmacies and patent medicine outlets. Even though there is legislation on control of use of antimicrobials, this is not enforced and drugs are sold in open markets by untrained persons many times under unfavourable storage conditions, without need for formal prescriptions.

To combat antibiotic resistance, the concept of antimicrobial stewardship (AMS) was enunciated. AMS is the effort to measure and improve how antibiotics are prescribed by clinicians and used by patients.<sup>7</sup> Clinicians ought to be primarily responsible for the decision to use antibiotics. Protocols and guidelines are put in place for healthcare personnel to avert antibiotic abuse. To ensure that options exist for treating infections, it is imperative to make the best use of currently available antimicrobials based on local antibiotic sensitivity patterns. This is the main thrust of AMS programmes which hitherto have been focussing on ensuring the proper use of antimicrobials to provide the best patient outcomes, lessen the risk of adverse effects, promote cost-effectiveness, and reduce or stabilize levels of resistance.<sup>8</sup>

In Nigeria, most hospitals do not implement AMS strategies; prescriptions are based on clinical acumen and affordability, with minimal laboratory support.<sup>9, 10</sup> It has also been reported that among health workers (physicians and others), antibiotics are prescribed for infections considered to be viral.<sup>11</sup>

Continued research on the knowledge, attitudes, prescribing habits and factors that underlie the prescribing habits of clinicians is vital. This study was therefore carried out to ascertain the knowledge gaps, prescribing practices, and factors that influence antibiotic prescription among Nigerian doctors. This will contribute to raising awareness on the severity and magnitude of the problem of improper and over-prescription of antibiotics which is a prerequisite for improving prescription practices. Information generated would be helpful in initiating and designing simple interventions geared towards improving clinicians' antibiotic prescription, and in the long run, safeguarding the few available potent antimicrobials.

## Methods

An online descriptive, cross-sectional, questionnaire-based survey was conducted on medical doctors in private and public health facilities in Nigeria from September to November, 2021. A link to the questionnaire was sent to medical doctors' social media groups on WhatsApp and Telegram, requesting them to fill Google forms (self-administered questionnaires) anonymously and voluntarily. The link was sent out once every week for the three-month survey. The questionnaire (attached as a supplementary file) consisted of 39 questions designed to collect sociodemographic data, evaluate the knowledge the medical doctors had of judicious use of antibiotics, their antibiotic prescribing practices, their attitudes towards, in addition to influencers of, antibiotic prescription. The questionnaire entered data automatically into Excel spreadsheets.

Demographic information included age, gender, duration of medical practice, level of practice, place of practice, type of practice and field of medicine practiced. Knowledge addressed appropriate indications and use of antibiotics for common ailments. The practice section looked out for the use of antibiotics in common clinical situations, adjudging whether they were judiciously employed or not. There were also queries on knowledge of antimicrobial stewardship, bacterial resistance and facility-based policies on antibiotic use. There were 15 queries testing knowledge of appropriate antibiotic prescription and 7 on aspects of prescription practice. For Knowledge and Practice, using a 5-point Likert scale (1-5) the best answer got 5, and this could either be 'Always' or 'Never' (for Practice) and 'Strongly agree' or 'Strongly disagree' (for Knowledge). If 'Always' (or 'Strongly agree') scored 5, then 'Often' (or 'Agree') scored 4, 'Sometimes' 3 (or 'Neutral'), 'Rarely' (or 'Disagree') 2 and 'Never' (or 'Strongly disagree') 1. If 'Never' was the best answer, it scored 5, and in the same vein scores decreased till 'Always' scored 1. The total available score for Knowledge was 75 (15 questions multiplied by 5). For Practice, it was 35 (7 questions multiplied by 5). For each respondent the Knowledge score was calculated as totalled scores out of 75, and percentages of the proportions generated by multiplying by 100. Likewise, the Practice score for each respondent was calculated as totalled scores out of 35, and percentages of the proportions generated by multiplying by 100.

Nine questions were posed on factors that may have an influence on antibiotic prescription. As regards 'influencers of prescriptions' responses were recorded on a 5-point scale, where 'always' was 5, 'often' 4, 'sometimes' 3, 'rarely' 2 and 'never' 1, for each subject. Percentages of proportions were calculated for each response. The internal consistency of the study instrument was quite reliable for the knowledge and influencer domains as indicated by Cronbach's alpha ( $\alpha$ ) scores<sup>12</sup> of 0.7 and 0.6 respectively, but not for the practice domain ( $\alpha = 0.4$ ).

## Statistical Analysis

Data were analysed using SPSS Version 21 software. The normality of the knowledge and practice scores were tested using Kolmogorov-Smirnov test. The result showed that the data for both knowledge ( $p=0.014$ ) and practice ( $p<0.001$ ) scores were not normally distributed. Therefore, Mann-Whitney U Test was used to compare the mean knowledge and practice scores between two independent groups of a categorical variable, while Kruskal-Wallis H Test was used when the categorical variable had three or more independent groups. The relationship between knowledge and practice scores was examined using Spearman's rank-order correlation while Log-Log Linear regression analysis was used to predict

the effect of a change in knowledge score on practice score. P-value  $\leq 0.05$  was considered statistically significant.

## Results

A total of 258 doctors responded to the online questionnaire. Their characteristics are outlined in table 1.

**Table 1.** Characteristics of respondents

Characteristic	Frequency [N=258]	Percentage
<b>Age in years</b>		
20 – 30	32	12.4
31 – 40	97	37.6
41 – 50	89	34.5
51 – 60	27	10.5
61 – 70	11	4.3
>70	2	0.7
<b>Gender</b>		
Female	116	45.0
Male	142	55.0
<b>Number of years in practice</b>		
$\leq 10$	84	32.6
11 – 20	127	49.2
21 – 30	20	7.8
31 – 40	24	9.3
>40	3	1.1
<b>Level of practice</b>		
Primary care [general practice]	65	25.2
Secondary care [specialist practice]	25	9.7
Tertiary care [teaching hospital practice]	168	65.1
<b>Place of practice</b>		
Public [government-owned] facility	212	82.2
Faith-based [mission-owned] facility	13	5.0
Private facility	33	12.8
<b>Specialty</b>		
Internal medicine	19	7.4
Obstetrics & gynaecology	27	10.5
Paediatrics	78	30.2
Surgery	29	11.2
Family medicine	17	6.6
Public health	18	7.0
General duty medical officer	70	27.1

The overall mean knowledge score was  $66.0 \pm 9.3$  with a range of 40.0-93.3. Using Kruskal-Wallis H Test, the comparison between the means of knowledge scores between doctors of various specialties is shown in table 2. Family physicians and paediatricians had higher mean knowledge scores than those in other specialities ( $p < 0.001$ ).

**Table 2.** Comparison of knowledge of appropriate antibiotic prescriptions of doctors from various specialties

Specialty	N	Mean Score	95% CI	Standard deviation	Minimum score	Maximum score	p Value
Internal medicine	19	65.1	61.4-68.7	7.6	53.3	80.0	p<0.001
Obstetrics & gynaecology	27	63.0	59.9-66.0	7.8	44.0	74.7	
Paediatrics	78	70.9	68.9-72.8	8.6	42.7	93.3	
Surgery	29	63.5	60.4-66.7	8.3	42.7	77.3	
Family medicine	17	71.0	66.0-76.0	9.7	50.7	89.3	
Public health	18	63.1	59.6-66.7	7.2	48.0	74.7	
General duty medical officer	70	62.4	60.2-64.6	9.1	40.0	85.3	
Total	258	66.0	64.8-67.1	9.3	40.0	93.3	

The overall mean appropriate practice score was  $66.8 \pm 8.4$  with a range of 40-85.7. Using Kruskal-Wallis H Test, the comparison between the means of practice scores between doctors of various specialties is shown in table 3. It is also noteworthy that the mean proper practice scores were highest among the family physicians, followed by paediatricians and public health physicians ( $p=0.002$ ).

**Table 3.** Comparison of practice of appropriate antibiotic prescriptions of doctors from various specialties

Specialty	N	Mean Score	Standard deviation	95% CI	Minimum score	Maximum score	p Value
Internal medicine	19	67.2	11.0	61.9-72.5	40.0	85.7	p=0.002
Obstetrics & gynaecology	27	61.8	7.7	58.7-64.8	45.7	77.1	
Paediatrics	78	68.5	8.4	66.6-70.4	40.0	82.9	
Surgery	29	66.1	7.5	63.3-69.0	54.3	80.0	
Family medicine	17	70.1	8.2	65.9-74.3	48.6	80.0	
Public health	18	68.3	8.8	63.9-72.6	45.7	80.0	
General duty medical officer	70	65.8	7.5	64.0-67.6	48.6	80.0	
Total	258	66.8	8.4	65.8-67.8	40.0	85.7	

The greater the years of medical practice, the more the mean knowledge score ( $p=0.007$ ) and likewise doctors in tertiary care scored higher than those in secondary and primary care ( $p=0.002$ ). Possession of prior information on antibiotic stewardship resulted in higher knowledge ( $p<0.001$ ) and practice ( $p=0.015$ ) scores, while having facility antibiotic protocols/ antibiotic stewardship committees was akin to better knowledge ( $p=0.032$ ) and prescription practice ( $p=0.012$ ). These are shown in table 4.



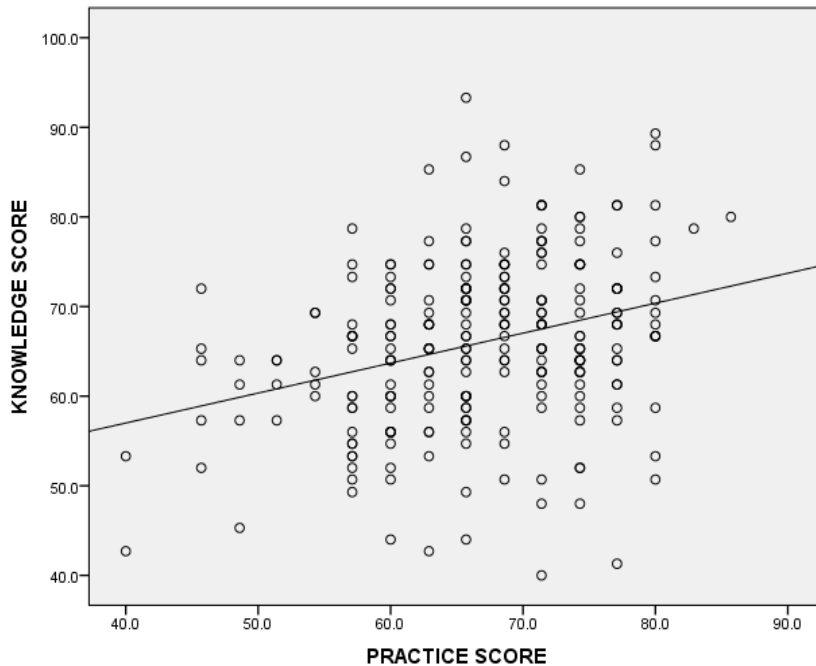
**Table 4.** Sociodemographic characteristics and associated knowledge and practice scores

Characteristics	Knowledge score		Practice Score		Total (%)
	Mean ± SD	p-value	Mean ± SD	p- value	
<b>Gender</b> Female Male	66.1±9.4 65.8±9.2	0.791	67.4±8.8 66.3±8.2	0.185	116 (45.0) 142 (55.0)
<b>Years of practice</b> ≤ 10 years 11-20 years 21-30years >30 years	62.8±9.7 67.1±8.7 69.6±8.1 67.8±9.0	0.007	65.8±7.7 67.2±8.7 67.9±9.5 67.2±8.7	0.380	84(32.6) 127 (49.2) 20 (7.8) 27 (10.4)
<b>Level of practice</b> Primary care Secondary care Tertiary care	62.6±9.0 64.4±10.2 67.5±8.9	0.002	65.8±8.3 67.9±10.7 67.0±8.1	0.374	65 (25.2) 25 (9.7) 168 (65.1)
<b>Type of facility</b> Public Faith-based Private	66.6±9.4 62.8±6.7 63.4±8.9	0.052	66.9±8.3 64.4±7.2 67.4±9.5	0.369	212 (82.2) 13 (5.0) 33 (12.8)
<b>Possession of previous information on antibiotic stewardship</b> Yes No	68.6±8.3 62.2±9.2	<0.001	67.9±8.3 65.23±8.4	0.015	151 (58.5) 107 (41.5)
<b>Availability of hospital protocols guiding antibiotic prescription and/or antibiotic stewardship committee</b> Yes No Not sure	68.2±9.7 64.6±8.6 65.8±9.4	0.032	69.3±9.3 65.7±8.5 66.2±7.5	0.012	63 (24.4) 94 (36.4) 101(39.2)

About half of the doctors (151, 58.5%) had received some information (formally or informally) on antibiotic stewardship.

About a third (101,39.1%) had no idea if their hospitals had antibiotic protocols, a quarter (63, 24.4%) replied that their facilities did have guidance, while the rest (94, 36.4%) said their hospitals had no protocols guiding antibiotic prescriptions and/or antibiotic stewardship committee .

Spearman’s rank correlation was run to determine the relationship between knowledge about antibiotic prescription and proper prescription practice. There was a weak, though statistically significant, positive linear relationship between knowledge and practice scores ( $r_s=0.291$ ,  $p<0.001$ ) as shown in Figure 1.



**Figure 1.** Relationship between knowledge about antibiotic prescription and appropriate prescription practice

Log-Log linear regression analysis was used to predict the effect of an increase in knowledge score on practice score. The result showed that the knowledge accounts for only 9.2% ( $R^2=0.092$ ) of variability in practice scores. A 1% increase in knowledge score increases practice score by 0.3%.

Influencers of antibiotic prescription were rated on a 5-point Likert scale ranging from ‘Always’ through ‘Often’, ‘Sometimes’, ‘Rarely’ to ‘Never’. The influencers included the following: patients’ request for antibiotics, doctor being unsure of diagnosis, very high fever in the patient, wanting to finish off available near-expiry drugs, advertisement by pharmaceutical representatives, prescribing to keep patient clientele, prior antibiotic use by the patient, cost of particular antibiotics, and age of the patient. Details are shown in figure 2.

Summing up the proportions of ‘always’, ‘often’ and ‘sometimes’ for each factor, the total affirmative responses were generated as follows: history of prior use of antibiotics by the patient (97.3%), cost of antibiotics intended to be prescribed (95.3%), age of patient (93.1%), request for antibiotics by the patient (89.6%), and patients presenting with high fevers (70.5).

## Discussion

Key to the preservation of available antibiotics is their rational use by informed and dedicated healthcare workers. Doctors are the major prescribers of these drugs in the milieu of healthcare delivery. As such, it behoves the doctor to acquire relevant knowledge and have his practice tailored accordingly towards achieving desired results without endangering the efficacy of antibiotics. The overall mean score of doctors’ knowledge about antibiotic prescriptions was 66%. This is similar to scores from studies done in China, India, the USA, and the Carribean where responses to questionnaires were also anonymous and online.<sup>13-16</sup> However, the knowledge of when to prescribe antibiotics varied appreciably among the cadres of physicians. Those in family medicine and paediatrics, as well as more experienced doctors, and those employed in tertiary care facilities, exhibited better knowledge than their peers. The finding among family physicians and paediatricians may be explained by the fact that these doctors were mostly from tertiary care facilities.

Multidisciplinary clinicians in Jeddah, Saudi Arabia<sup>17</sup> from university, public and private hospitals, did not exhibit such disparity in knowledge.

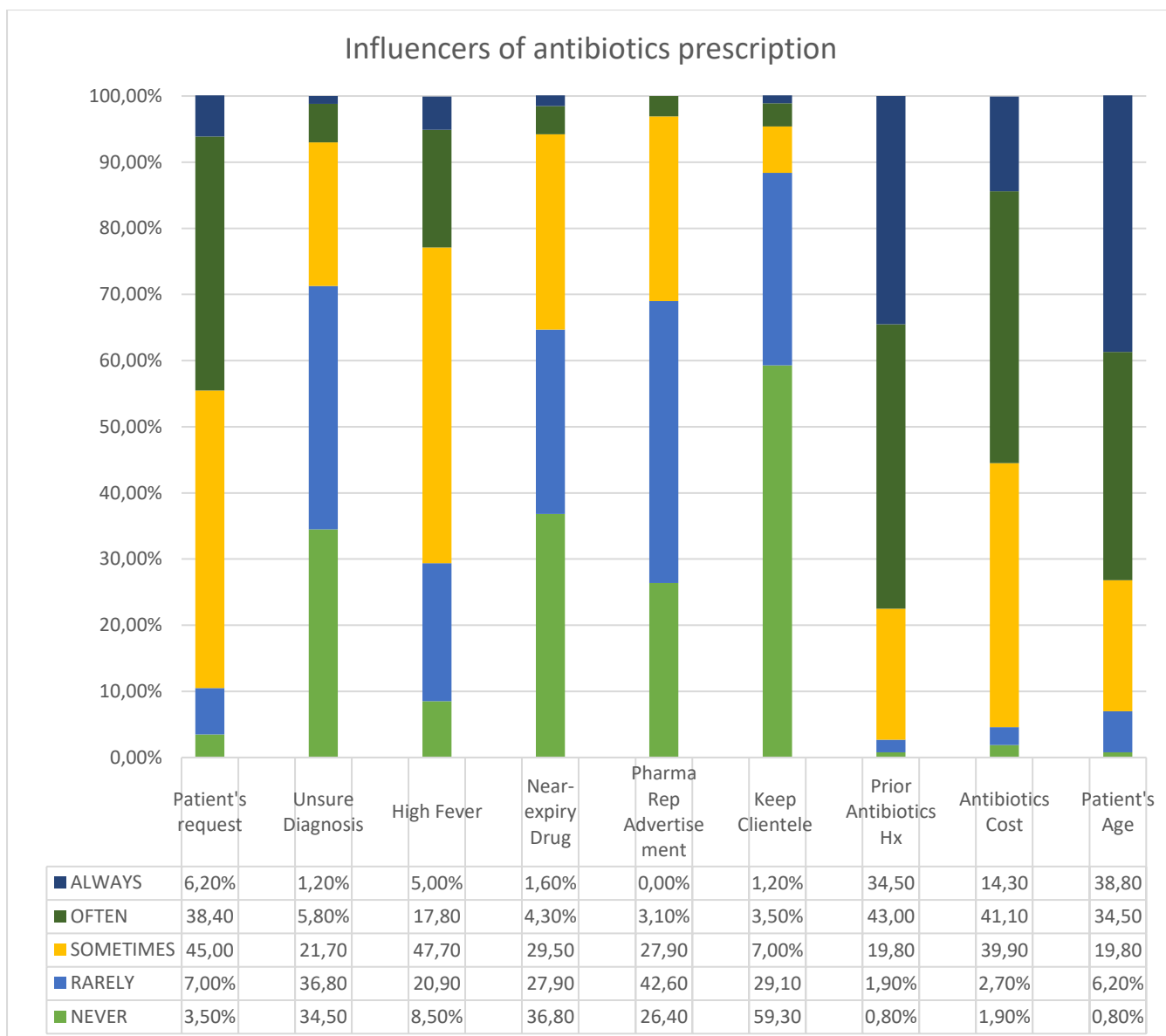
From this study the major factors influencing antibiotic prescription practice were history of prior use of antibiotics by the patient, cost of the antibiotic intended to be prescribed, age of the patient, request for antibiotics by the patient, and patients presenting with high fevers. The presentation with high fever is usually a common reason for empirical antibiotic prescription by clinicians.<sup>18, 19</sup> Having knowledge of a patient's prior exposure to antibiotics either following self-treatment or from prescriptions of other health care providers, goes a long way to ensure success of antimicrobial therapy.<sup>20</sup> The antimicrobials the patient has been exposed to, their dosages, dosing frequency and duration of therapy would give a clue to possible antimicrobial resistance, and hence guide further prescriptions. Drug cost is essential vis-à-vis affordability by the patient, averting incomplete or erratic dosing of drugs in an environment where out of pocket payment is the norm.<sup>20</sup> Pertaining to age, certain drugs are restricted for very young infants and the elderly, hence consideration of age is appropriate.

Many of the Nigerian medical practitioners agreed to patients' demands for antibiotics. This naturally leads to antibiotic prescriptions that may not be strictly indicated. This factor was highlighted by other studies as contributing to antibiotic overuse among physicians.<sup>21, 22, 23</sup> In one study it resulted in an increased likelihood of subsequent future requests for unnecessary antibiotics.<sup>24</sup> More frequent antibiotic prescriptions for young children have been noted to be a common practice being given as accompaniment to virtually all prescriptions.<sup>18, 19</sup> Presence of a high fever prompts the use of antibiotics empirically. This is common practice and was even thought to speed up recovery from malaria when given along with antimalarial drugs.<sup>19</sup>

Clinicians' use of antibiotics in situations where diagnosis was uncertain has been reported.<sup>25, 26, 27</sup> It was however, not observed in this study probably due to the subset of doctors that completed the survey. Pharmaceutical representatives who advertised their drugs and offered gifts and sponsorships do regularly influence prescribers.<sup>28, 29, 30</sup> This was however played down among this group of doctors.

It has been observed that doctors tend to have individual propensities for antibiotic prescriptions and may not easily be influenced to make changes.<sup>31</sup> Findings observed among some groups of Nigerian doctors had not altered appreciably even after a period of twenty-four years.<sup>32</sup> The locus of decision-making in antibiotic prescribing is thought to reside in the individual physician.<sup>20, 33</sup> This physician's mindset must necessarily be attuned towards antimicrobial stewardship so as to preserve the few available antimicrobials. To aid this an eight-step modification of the World Health Organization's six-step approach, to help minimize poor quality and erroneous prescribing, has been proposed by Pollock et al.<sup>34</sup> These include (1) evaluating and clearly defining the patient's problem; (2) specifying the therapeutic objective; (3) selecting the appropriate drug therapy; (4) initiating therapy with appropriate details and considering non-pharmacologic therapies; (5) providing patient information, instructions and warnings; (6) evaluating therapy regularly; (7) considering drug cost when prescribing; and (8) using computers and other tools to reduce prescribing errors.

Using guidelines for common outpatient infections and ensuring strict adherence to them by audit and feedback, tracking individual prescribing behaviour, and giving feedback on their performance relative to peers or established benchmarks, have been advocated.<sup>27</sup> This however will not be applicable to the numerous prescriptions made in privately-owned clinics not in the purview of large, structured institutions.



**Figure 2.** Influencers of antibiotic prescription

## Conclusion

We conclude that just having the knowledge of proper use of antibiotics does not necessarily translate to appropriate prescription practice. Deciding whether or not to prescribe an antibiotic can be a complex process, during which physicians are influenced not only by medical information, but also by their interactions with patients and other stakeholders in the healthcare industry. It is noteworthy that previous training on AMS and availability of institutional antibiotic stewardship committees and treatment protocols/guidelines for antibiotic therapy of common illnesses were the factors associated with appropriate antibiotic prescription practice. By understanding the factors that affect physicians' antibiotic prescribing decisions and applying concepts from the social and behavioural sciences, inappropriate prescribing can be reduced, which in turn can reduce the threat of resistance.

It is recommended that all practising doctors receive trainings on AMS, and that all healthcare institutions, public and private, have well constituted antibiotic stewardship committees, while

physicians should be encouraged to adhere to well-articulated guidelines/protocols for antibiotic use, which are revised periodically.

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## RESEARCH

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

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Human papillomavirus, HPV vaccination, vaccine hesitancy, decision-making process, sub-Saharan Africa

### 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.

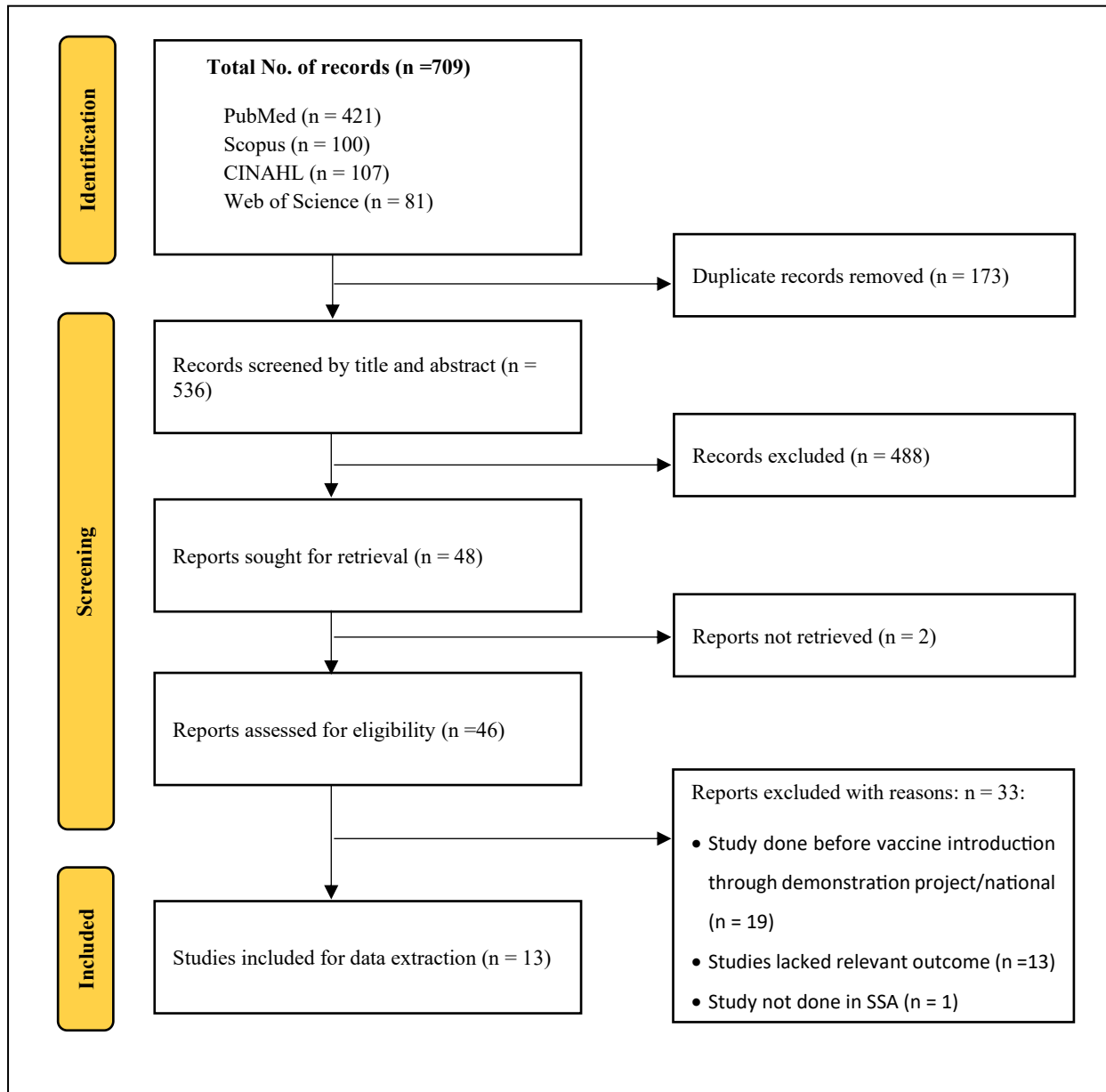
Studies were excluded if they:

- 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.

### **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).



**Figure 1.** PRISMA flow diagram – study selection process

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

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"> <li>Vaccination was a trick by government to prevent over-population by injecting girls with medicine that would prevent them from giving birth in future</li> </ul>	<ul style="list-style-type: none"> <li>Fear that HPV vaccination could have adverse effects on reproductive health of the vaccinated girls</li> </ul>	<ul style="list-style-type: none"> <li>HPV vaccination was still experimental</li> <li>Long term physical damage to the vaccinated arms since some girls got swollen arms after the injection.</li> <li>The vaccine had been deliberately made to cause death</li> </ul>		<ul style="list-style-type: none"> <li>Locally prominent radical traditionalist and Pan Africanist campaigned against all vaccinations via his FM radio</li> </ul>	
Watson-Jones	Tanzania		<ul style="list-style-type: none"> <li>Concern over infertility</li> </ul>	<ul style="list-style-type: none"> <li>Concern over other side effects</li> </ul>		<ul style="list-style-type: none"> <li>Pupil absenteeism because parent refused</li> <li>Girl refused</li> </ul>	<ul style="list-style-type: none"> <li>Were afraid of injections</li> </ul>
A.B. Wiyeh	South Africa		<ul style="list-style-type: none"> <li>Fertility related concerns</li> </ul>	<p><u>Concerns around vaccine safety</u></p> <ul style="list-style-type: none"> <li>Knowing/ hearing stories about someone affected by HPV vaccination</li> <li>Previous negative experience with HPV vaccination</li> <li>Inadequate handling of concerns around vaccine safety.</li> <li>Lack of transparency on safety data, accountability and support following the occurrence of HPV vaccine side effects</li> <li>Fear of vaccine side effects.</li> </ul> <p><b>Consent:</b></p> <ul style="list-style-type: none"> <li>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</li> <li>Belief that the vaccination campaign is an ongoing vaccine trial</li> </ul>	<ul style="list-style-type: none"> <li>Concerns around the use of the school-based strategy for HPV vaccination.</li> </ul>		
Mabeya	Kenya				<ul style="list-style-type: none"> <li>distance to the clinic / health facility</li> </ul>		
Rujumba	Uganda	<ul style="list-style-type: none"> <li>Unfriendly healthcare workers</li> </ul>		<ul style="list-style-type: none"> <li>Rumours and misconceptions about the vaccine and vaccination</li> </ul>	<ul style="list-style-type: none"> <li>Absenteeism or dropout from school</li> <li>Change of</li> </ul>	<ul style="list-style-type: none"> <li>Discouraged by their peers particularly for the</li> </ul>	<ul style="list-style-type: none"> <li>Fear of injection pain</li> </ul>

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

**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"> <li>• Believed children’s immune systems protected against diseases</li> </ul>			<ul style="list-style-type: none"> <li>• secondary or tertiary education showed lower intentions than those with no formal or primary education</li> </ul>	<ul style="list-style-type: none"> <li>• young adult (25–34 years) old indicated a higher belief in rumours</li> </ul>	<ul style="list-style-type: none"> <li>• Unemployed had a negative effect on safety perception. (being young adults, unemployed, or having low trust in healthcare workers' increased belief in rumours).</li> <li>• Belief in rumours having low trust in healthcare workers increased those beliefs).</li> <li>• Confidence in vaccine effectiveness decreased if the participants were unemployed or thought that the HPV vaccine reduces fertility.</li> </ul>
Vermandere H	Kenya	<ul style="list-style-type: none"> <li>• Daughter is too young for vaccine against an STI</li> </ul>	<ul style="list-style-type: none"> <li>• Doubted the efficacy of the vaccine</li> </ul>	<ul style="list-style-type: none"> <li>• Not knowing about the vaccination opportunity</li> <li>• Lack of vaccine information</li> </ul>				
Masika	Kenya		<ul style="list-style-type: none"> <li>• Vaccine not necessary (teachers' Questionnaire)</li> </ul>	<ul style="list-style-type: none"> <li>• Lack of enough information</li> </ul>	<ul style="list-style-type: none"> <li>• cultural and religious beliefs that were against vaccinations <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></li> </ul>			
Milondzo	South Africa			<ul style="list-style-type: none"> <li>• Low levels of knowledge about the link between HPV</li> </ul>				

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"> <li>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.</li> </ul>			
Watson-Jones	Tanzania		<ul style="list-style-type: none"> <li>Had not understood the value of the vaccine</li> </ul>	<b>Adults:</b> <ul style="list-style-type: none"> <li>Insufficient knowledge about the vaccine</li> </ul>				
A.B. Wiyeh	South Africa	<b>Complacency:</b> Risk of cervical cancer perceived as being low	<b>Calculation:</b> <ul style="list-style-type: none"> <li>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.</li> </ul>					
Mabeya	Kenya			<ul style="list-style-type: none"> <li>low HPV knowledge among caregivers</li> </ul>				

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

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, school teachers, 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 program 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 1<sup>st</sup> or 2<sup>nd</sup> 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*

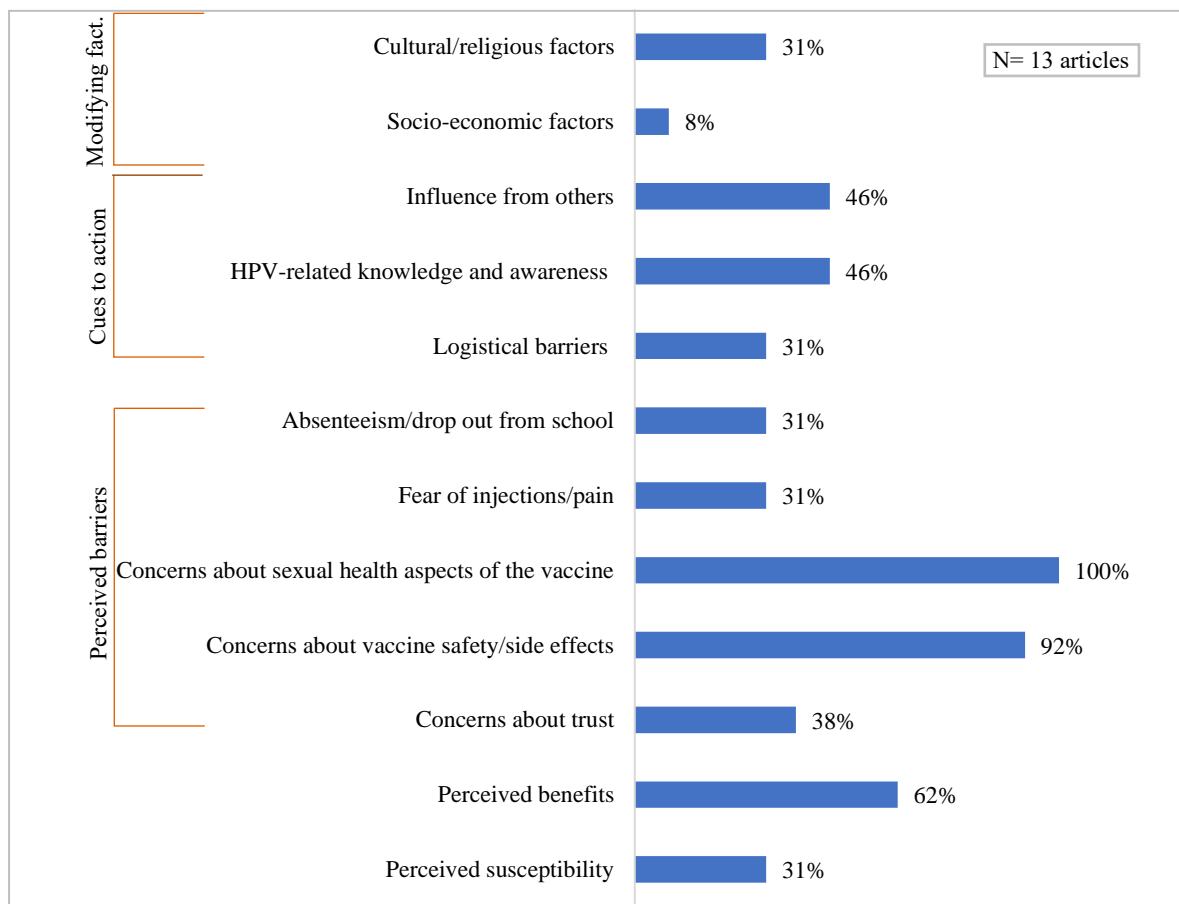
In this review, six studies done in Kenya, Tanzania, Uganda, and Malawi demonstrated that adolescents' decision-making was influenced by key actors ranging from their caregivers who were against vaccination (7,23,25,26,29), their peers or friends who discouraged them from vaccination (26,27,29), some 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).

### *Socio-economic factors*

One study reported the sociodemographic variable as a determinant of HPV vaccine hesitancy (19). Of all the demographic variables studied including participants' age, 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).



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

## 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.

**Author contributions:** All authors (LNO, OOM, AH, AMM, and VA) developed the review concept and wrote the initial draft of the manuscript. All authors contributed to the overall review process, including the literature search, screening, data extraction, and analysis. All authors approved the final version of the manuscript.

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## Appendices

### Appendix A. MeSH terms and keywords

"PICO"		Keywords	MeSH Terms
<b>P</b>	<b>Participants</b>	parent* OR guardian* OR teacher OR educator OR adolescen*	"Adolescent"[Mesh] OR "Female"[Mesh] OR "Parents"[Mesh] OR "Young Adult"[Mesh] OR "Adult"[Mesh]
	<b>Setting</b>	“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 Zimbabw	"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]
	<b>Intervention</b>	“Human papillomavirus vaccine” OR “HPV vaccine”	"Papillomavirus Vaccines"[Mesh] OR "School Health Services"[Mesh]
	<b>Outcome</b>	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
<b>Caregivers</b>									
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
<b>HCWs/Teachers</b>									
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
<b>Adolescents</b>									
Turiho	2011	Uganda	cross-sectional, mixed methods	self-administered questionnaire, FGD	777	Adolescent girls	9–19 years	Demonstration project	School-based & Facility-based
<b>Mixed population</b>									
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"> <li>• 159 pupil/adult case pairs</li> <li>• 245 pupil/adult controls</li> </ul>	<ol style="list-style-type: none"> <li>1. Adolescent girls (unvaccinated)</li> <li>2. Their caregivers</li> </ol>	< 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"> <li>1. 12.0 (10–15)</li> <li>2. 39.3 (25–56)</li> <li>3. 39.3 (26–57)</li> <li>4. 40.4 (32–47)</li> <li>5. 36.0 (26–45)</li> </ol>	National vaccination programme	School-based & Facility-based
Turiho	2011	Uganda (Ibanda district)	Qualitative	FGDs and KIIs	<p><b>FGDs:</b> School girls, parents and guardians</p> <p><b>KIIs:</b> School teachers, HCWs and community leaders.</p>	<ol style="list-style-type: none"> <li>1. School girls,</li> <li>2. Caregivers</li> <li>3. School teachers</li> <li>4. Health workers</li> <li>5. Community leaders</li> </ol>		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
<b>CASP Results</b>		<b>50%</b>	<b>90%</b>	<b>80%</b>	<b>90%</b>	<b>90%</b>

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

<b>NIH Results for observational cohort and cross sectional studies</b>										
<b>Criteria</b>	<b>Adeyanju, G.C</b>	<b>Turiho</b>	<b>Masika</b>	<b>LaMontagne</b>	<b>Haddison E,</b>	<b>Mabeya</b>	<b>Milondzo</b>	<b>Msyambaza</b>	<b>Watson-Jones</b>	<b>Vermandere H</b>
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
<b>Quality rating</b>	<b>Fair (8)</b>	<b>Fair (9)</b>	<b>Fair (9)</b>	<b>Good (11)</b>	<b>Fair (6)</b>	<b>Good (10)</b>	<b>Fair (6)</b>	<b>Fair (5)</b>	<b>Fair (8)</b>	<b>Fair (9)</b>

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

## Respiratory syncytial virus: enhanced understanding of the burden of disease and developments in active and passive immunisation

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### Abstract

*Respiratory syncytial virus (RSV) is a major cause of respiratory tract infection in infants and young children worldwide. Improvements in diagnostic testing have led to increased recognition of RSV infection in children in various settings as well as recognition of RSV as a significant cause of serious respiratory infections in older adults with underlying conditions. The burden of disease is significant with 33.0 million RSV-associated acute lower respiratory infection episodes globally in children younger than 5 years. Infants in the first 3 months of life bear the brunt of severe RSV disease. Recently a more effective and longer lasting monoclonal antibody targeting RSV F protein has been approved for use in infants, while maternal immunisation with a prefusion F protein-based (RSVpreF) vaccine provides effective protection against medically attended RSV-associated lower respiratory tract illness for infants during their first 3- 6 months of life. A number of other vaccines are in development that may offer protection for various age groups in the future.*

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## Introduction

Respiratory syncytial virus (RSV) has been well known to clinicians for many years, having first been described in 1956. It has long been recognised as a highly infectious virus and is a major cause of respiratory tract infections including bronchiolitis, pneumonia and apnoea in infants and young children worldwide.

RSV is ubiquitous and most children are exposed within the first few years of life. The initial primary infection is the most severe, with infants under 6 months of age, especially premature babies, at risk for life threatening disease. Re-infections are common throughout early childhood, but generally become less severe with increasing age and number of infections. In older children and adults RSV infections chiefly affect the upper respiratory tract, but can also cause bronchitis, pneumonia and exacerbations of chronic obstructive pulmonary disease (COPD) and asthma. Older adults > 65 years are at increased risk of lower respiratory tract involvement.

To date no effective directed therapy for RSV infection exists and treatment remains supportive, primarily consisting of humidified oxygen. (1) Similarly, no preventive measures are available for most children, especially those in lower middle-income countries (LMICs).

Although RSV can be detected by variety of older laboratory methods, including viral culture, immunofluorescence, antigen detection and serology, the development and increasing availability of polymerase chain reaction (PCR) testing has greatly facilitated the rapid diagnosis of RSV infection. This has led to the increased recognition of RSV infection in children in various settings as well as recognition of RSV as a significant cause of serious respiratory infections in older adults with underlying chronic conditions, on a level approaching that of influenza. (2)

The objectives of this review are to highlight progress in the understanding of the burden of RSV disease and to the development of preventative strategies that aim to potentially reduce its impact.

### **Enhanced understanding of the burden of disease**

Recent studies have provided more detailed updates on the burden of disease due to RSV. It is estimated that in 2019, there were 33.0 million RSV-associated acute lower respiratory infection episodes globally leading to 26 300 RSV-associated acute LRTI in-hospital deaths and 101 400 RSV-attributable overall deaths, in children younger than 5 years.(3) There were also an estimated 3.6 million -associated acute LRTI hospital admissions globally in the same year.

Infants aged 0-6 months account for 20% of acute episodes, 39% of hospital admissions and 51% of in-hospital deaths. (3) whilst infants in the first 3 months of life bear the brunt of severe RSV disease. (4) The disease burden is also markedly skewed towards low or middle-income countries where more than 95% of acute LRTI episodes and more than 97% of in-hospital deaths occur.(3)

Relying on traditional hospital-based surveillance significantly underestimates RSV associated mortality. A community- based post-mortem study in Lusaka, Zambia among children 0-6 months showed that about two thirds of all RSV-associated deaths occurred in the community, and that RSV caused at least 2.8% of all infant deaths in this age group. (5)

Infants at highest risk include those born very prematurely or with underlying chronic predisposing conditions such as congenital heart or lung or neurological conditions.(6) In contrast, in LMICs the majority of deaths occur in previously well infants.

RSV is also a common potentially under recognised cause of nosocomial LRTI infection. A recent global case series using an on-line RSV mortality registry (7) showed that 20% of all deaths where information on site of acquisition was available, were nosocomial in origin. This proportion was lower in LMICs compared to wealthier countries, which given that the burden of nosocomial infection is generally recognised as being significantly higher in LMICs (8), may suggest under reporting.

RSV is also associated with important long-term consequences, including recurrent LRTI, wheezing, asthma, and impaired lung function.(9, 10)

### **Prevention of RSV infection**

#### ***Passive immunisation for neonates***

The first monoclonal antibody, paluzimab, was licensed in 1998. (11) Given as a monthly intramuscular injection, it provides effective protection for high-risk neonates. More recently next generation monoclonal antibodies have been developed with more effective neutralising activity and a much longer half-life. Nirsevimab for example (12) which targets the prefusion conformation of RSV F protein can

be given as a single dose for the whole RSV season. It was approved in UK and EU at the end of 2022 and in the USA in July 2023 for use in infants and young children on the basis of trials showing significant protection against medically attended RSV infection in otherwise healthy infants. The improved protection and easier logistics mean that nirsevimab and similar future monoclonal antibodies might now be a viable option for prophylaxis for most infants in HICs in their first RSV season, rather than being applicable only to very high-risk infants. Unfortunately, the cost of monoclonal antibodies means that these are not feasible for LMICs with the highest burden of disease.

### ***Vaccination***

Development of RSV vaccines has been hampered by the negative experience of vaccine enhanced disease that was associated with the 1960s formalin- inactivated viral vaccine. (13). RSV naïve recipients of this vaccine experienced more severe disease on subsequent RSV infection through a process of antibody dependent enhancement, associated with the development of poorly neutralising antibodies and a T Helper Type 2 biased T cell response.(14)

A further complicating factor has been that immunity to RSV following natural infection is incomplete with re-infection occurring throughout life. To date neither the underlying immune response nor the correlates of protection to RSV infection are fully understood. However, cell mediated immunity, mucosal IgA and neutralising antibodies are all recognised to be associated with protection. (6)

Greater understanding of the epitopes targeted by highly neutralising antibodies in general and success in stabilising the prefusion conformation of F protein in particular has led to a recent explosion of focused vaccine development, with over 30 vaccine candidates in clinical development including a number in advanced or recently reported phase 3 clinical trials. A variety of vaccine types, including subunit, particle-based, live attenuated, recombinant vector, chimeric and nucleic acid vaccines are being tested, targeting mainly prefusion F antigen but also other antigens such as RSV G protein involved in initial viral attachment.(6)

To avoid vaccine enhanced disease RSV naïve infants will need a vaccine that generates potent neutralising antibodies, whereas older infants > 6 months and children can potentially receive a variety of vaccines that boost immunity after primary infection, including live attenuated vaccines. (6) Vaccines for pregnant women such as protein- based subunit vaccines generate protective antibodies that can be transferred to the fetus, a sort of natural delivery of passive immunisation. A recently reported Phase 3 trial in pregnant women using a single dose of a bivalent RSV prefusion F protein-based (RSVpreF) vaccine showed significant protection against medically attended RSV-associated lower respiratory tract illness for infants during their first 3- 6 months of life.(15). The only currently licensed RSV vaccines are in fact two preF subunit vaccines recently licensed for use in adults > 60 years of age based on high vaccine efficacy rates reported in recent trials in this population. (16, 17)

The rapid progress in RSV vaccine development is likely to continue in the next few years and there are hopes that effective RSV vaccines may be on the horizon. Nucleic acid or mRNA vaccines in particular have advanced quickly to late phase trials, buoyed by the success of COVID mRNA vaccines, which was in turn built on knowledge previously acquired in RSV vaccine development. (6)

Considerable work is going into preparatory studies at country or regional level that could assist in introducing and maximising benefit from future maternal vaccination and neonatal monoclonal antibody programs.(18) Access and affordability will be critical for LMICs or under resourced areas, and methods to reduce costs could be beneficial. For example, RSV causes seasonal outbreaks in the majority of countries away from the equator, including 75% of 52 LMIC countries studied. (19). Infants are at greatest risk of hospital admission for RSV if born 1-2 months before peak RSV activity. In countries with a seasonal disease pattern, seasonal use of maternal vaccines given only for the months shortly before and during the RSV season could prevent more cases of disease per dose administered, and therefore be more cost effective and feasible than year-round administration(19)

Following an adequate maternal immune response, efficient transfer of these antibodies across the placenta is required for successful maternal immunization. Since the most abundant immunoglobulin, IgG1, mainly crosses the placenta in the last 4 weeks of pregnancy, preterm infants may receive inadequate antibodies. In addition, a number of maternal factors, such as hypergammaglobulinaemia, HIV infection and placental malaria may impair transplacental transfer of antibodies. Unfortunately, all these conditions are more common in LMICs, and are not necessarily reversed by treatment of the underlying maternal condition and could impact on future maternal vaccination programs. (20)

Unexpected adverse events can derail vaccines even at late stages of development. A trial of a GlaxoSmithKline preF RSV vaccine in pregnant women was halted in 2022 because of higher rates of preterm delivery in the vaccine arm. (21) No safety concerns were identified in the Pfizer study of a similar target vaccine recently reported.(15) However, in that study the rate of preterm delivery before 37 weeks was higher in the vaccine group than in the placebo group (5.7% versus 4.9%) although this was not statistically significant given the relatively small numbers.

This all suggests that further studies will be needed to confirm effectiveness and safety of future potential vaccines, and also to determine how to implement them in different age groups and different epidemiological settings. Passive immunisation whether via monoclonal antibodies or maternal vaccination or a combination thereof will likely delay first episodes of RSV infection. How a potential delay will affect the severity of subsequent RSV infection is not entirely clear, while determining the optimal timing for active vaccination of infants following an initial period of protection via passive immunisation is also unclear.

## Conclusion

In summary whilst there are still many unknowns in the methods for the prevention of RSV disease, there is excitement that there is potential “light at the end of the tunnel” or that this is the “beginning of the end” for this pathogen that casts such a heavy burden on vulnerable children and older adults.(22) There is much work to be done to facilitate rapid uptake of new preventative methods in LMICs as soon as possible. (23)

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## CASE REPORT

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### A case of empyema necessitans in a paediatric patient with *Mycobacterium tuberculosis*

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Empyema necessitans,  
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#### Abstract

*Empyema necessitans* is a rare complication of pneumonia in which pus formed in the pleural cavity extends into the surrounding tissue. In children it is mostly caused by *Mycobacterium tuberculosis* but other bacterial organisms are implicated occasionally. Early diagnosis through appropriate imaging, cultures and molecular diagnostic tests of samples taken from the lesion is recommended. Outcome is good provided appropriate medical and surgical treatment are provided.

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#### Introduction

Empyema necessitans (EN) is a rare condition that results from infection of the soft tissues of the thoracic wall due to a sinus tract from empyema and is usually accompanied by pneumonia and osteomyelitis.

The term has its origin from the Greek word 'Em' meaning in or into and 'puon' which means pus and the Latin term necessitans meaning unavoidable or compulsion. (1)

EN is a complication of pneumonia with *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Actinomyces* and *Nocardia* being the most commonly described causes. (2- 4) Following the development of antibiotics and their use for pneumonia the incidence of EN has decreased significantly. It is rarely seen in the paediatric population (3). In 2018 there was one case reported from Cape Town, South Africa of a six month old girl with EN secondary to *Mycobacterium tuberculosis*. (4) A 3 year old male child was also reported to have EN due to *Aspergillus* in Kenya in 2019. (5)

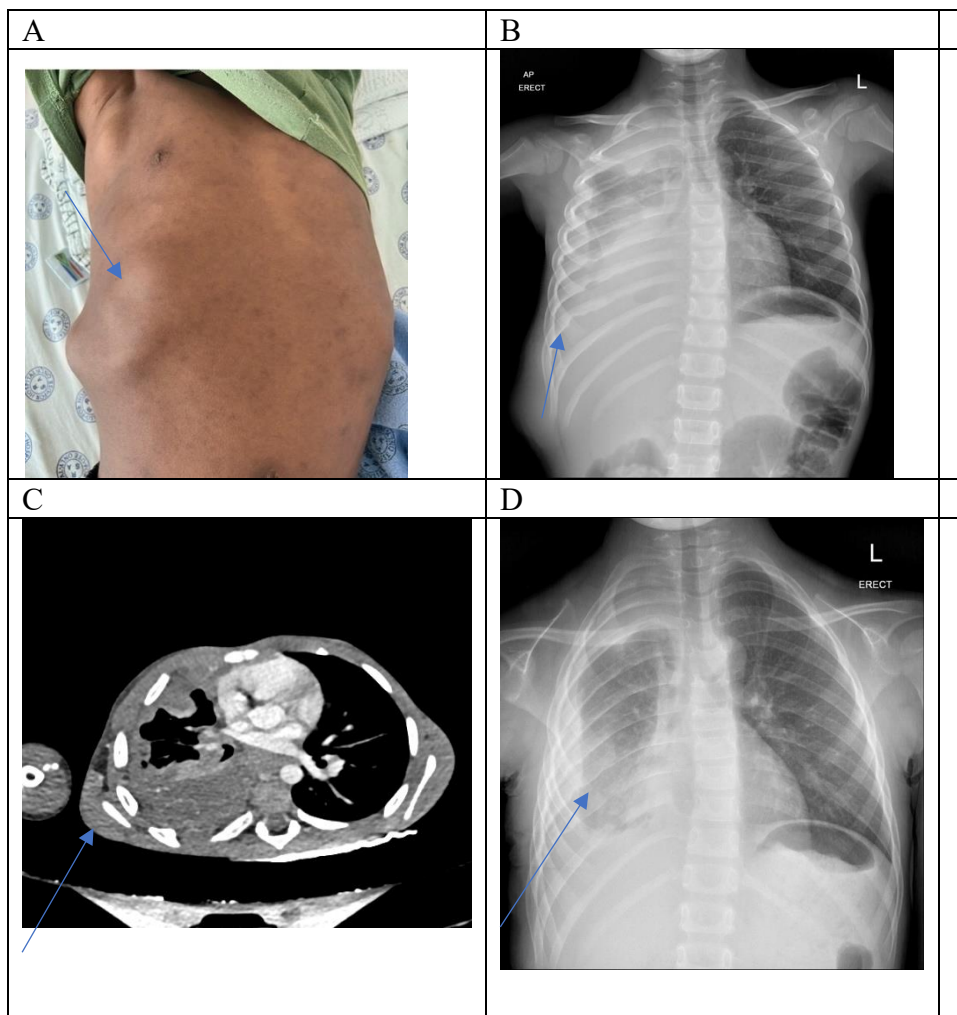
Due to its uncommon presentation, there is the need to create awareness in health care workers to help make early diagnosis, treat promptly, and prevent further complications. We present a case of EN due to *Mycobacterium tuberculosis*.



## Case report

A 6-year-old, previously well, HIV negative boy presented to our hospital with a 2-week history of anterior chest wall swelling that had progressively increased in size. There was no history of trauma to the chest wall or associated fever or pain, but he was coughing and was losing weight. In addition, a household contact diagnosed with pulmonary tuberculosis (TB) was identified.

**Figure 1,** A: Arrow indicates a 6cm x 4cm chest wall mass on the lower right chest wall extending posteriorly and inferiorly from the mid-axillary line of the 8<sup>th</sup> rib. B: Frontal chest radiograph demonstrating a complex right-sided pleural fluid collection extending to the apex of the lung with associated chest wall soft tissue mass and erosion of 5<sup>th</sup> - 10<sup>th</sup> ribs. C: Axial contrast-enhanced CT-scan of the chest in the mediastinal window confirms a complex rim-enhancing pleural fluid collection with extension through the chest wall into the soft tissue. The right lower lobe is collapsed secondary to the mass effect of the fluid collection and ipsilateral hilar lymphadenopathy with central necrosis is present. D: Post operative chest radiograph exhibits a residual right sided pleural fluid collection and rib erosions with expansion of the right lower lobe and diminished soft tissue swelling.



On examination the child did not appear acutely ill. There was no pallor or jaundice, and he did not have finger clubbing, but there were multiple enlarged lymph nodes in the right cervical, submandibular and axillary regions. These lymph nodes measured 1 to 2 cm, were mobile and non-tender. A BCG scar was present. The examination of the chest wall showed a 6cm x 4cm non-tender



fluctuant mass, located at the right costal margins in the midclavicular line, Figure 1A. On respiratory examination the oxygen saturation in air was 98% and the respiratory rate was normal with no chest indrawing. On auscultation air entry was reduced in right middle and lower zones anteriorly with stony dullness to percussion in the same zones. No added sounds were heard. The rest of the assessment was within normal limits.

Chest radiograph demonstrated a soft tissue mass on the right chest wall, collapse of the right lower zone and a complex pleural effusion with erosion of the costal margins of the fifth to tenth ribs, Figure 1B. Contrast enhanced computerized tomography of the chest (CT chest) confirmed a rim enhancing complex pleural fluid collection with punctate calcifications extending through the chest wall into the soft tissue of the chest wall. The mass effect of the fluid resulted in collapse of the right lower lobe. Additionally, there was central necrosis of the subcarinal, ipsilateral paratracheal, hilar and axillary nodes, Figure 1C.

Biopsy of the right lower lobe for cytology showed necrotizing granulomatous inflammation and there were no malignant cells on the pleural fluid. Xpert MTB/RIF Ultra on sputum was negative but positive on pleural aspirate and sensitive to rifampicin. Subsequent TB culture of the pleural fluid was also positive and a PCR/Line Probe assay for the cultured isolate confirmed rifampicin susceptible but isoniazid resistant tuberculosis.

The patient was treated with isoniazid, rifampicin, pyrazinamide, ethambutol and levofloxacin for 6 months with the possibility to extend therapy according to response. In addition, a right sided posterolateral thoracotomy was done to perform a decortication of the right lung. At surgery a thickened pleura with multiple areas of thick pleural granuloma and a granuloma that ruptured into the pleural space was observed. Post operative chest radiograph exhibited a residual right sided pleural fluid collection with expansion of the right lower lobe and diminished soft tissue swelling, Figure 1D.

## **Discussion**

EN is caused by long standing untreated pneumonia with extension of pus from the pleural space to the chest wall. It can occur in both immunocompetent and immunosuppressed children.

EN can present as a painful or non-painful chest wall swelling with other associated constitutional symptoms depending on the causative organism. It can go unnoticed with late presentation and diagnosis because the swelling can be painless, and it grows insidiously.

Diagnosis of EN includes chest X-ray, CT scan and magnetic resonance image (MRI) where available, with ultrasound guided aspiration of the pus for PCR and culture to identify the organisms involved.

Treatment is both medical and surgical. Medical treatment involves administration of appropriate antimicrobial therapy whilst surgical treatment involves drainage of the pus and decortication with closure of the fistula to restore pulmonary function.

Treatment for severe TB includes 4 drugs with isoniazid, rifampicin, pyrazinamide and ethambutol. Ethambutol is used as it has good bone penetration. This child had multiple lobes involved and so falls into the severe category of the new WHO classification and hence does not qualify for a short course of therapy. (6) The child in this case report had an additional drug levofloxacin added as isoniazid resistance due to an *inhA* mutation was detected. In the current era of drug resistant TB it is important that both genotypic and phenotypic testing is carried out as part of the TB investigations to ensure appropriate drugs are administered.

Clinicians should have a high index of suspicion for empyema necessitans in any child who presents with symptoms of pneumonia with chest wall swelling and ensure appropriate investigations are carried out including investigating for tuberculosis to ensure early and prompt treatment in order to avoid complications such as bone and soft tissue erosion.

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## CASE REPORT

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### Does a feeding nasogastric tube cause hypoxaemia?

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#### Abstract

*The use of feeding nasogastric tube has been very beneficial in management of sick infants to ensure optimal intake but is not without untoward effects. Persistent hypoxaemia is not well known to be associated with nasogastric tube feeding. We report two cases of persistent hypoxaemia in tube-fed patients with resolution on removal. Clinicians need to have a high index of suspicion for possible association between nasogastric tube feeding and persistent hypoxaemia after excluding common causes of hypoxaemia. Regular pulse oximetry and prompt removal of the tube is recommended once patient can take considerable quantity of feeds and fluid orally.*

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### Introduction

Poor feeding is a common manifestation of severe illness, and this includes infants and children with severe community-acquired pneumonia (CAP), who are vomiting everything or refusing feeds.<sup>1</sup> An age long alternative is the use of nasogastric tube (NGT) or orogastric feeding until they are able to take adequately, as also used in early phase of nutritional rehabilitation.<sup>2</sup> This method of feeding is associated with a few complications, which include vomiting, gagging, aspiration pneumonitis, and hypoxaemia, especially during insertion.<sup>1,3</sup> But it is not clear if it causes persistent hypoxaemia. There have been contradictory reports on the possible association between use of NGT and hypoxaemia among neonates, with scanty mention among infants and children.<sup>3-5</sup> We observed persistent hypoxaemia and oxygen dependence in two patients with successfully treated severe CAP while on NGT feeding, and resolution of the hypoxaemia on removal of the tube.

### Case presentation 1

OA, a 14-month-old male toddler presented to our facility on account of a fever of 4 days' duration, cough of 2 days and difficulty with breathing of one day. Fever was high grade, intermittent, associated with reduced appetite and refusal of feeds except breast milk. Cough was paroxysmal but non-barking. There was neither post-tussive vomiting, nor nasal discharge.

He subsequently developed difficulty with breathing. He had a positive history of cough in his older sibling which started earlier. No history suggestive of aspiration of a foreign body, choking on feeds or bluish discolouration of the lips or extremities.

At the onset of the illness, the mother gave paracetamol syrup; and oral dispersible artemether /lumefantrine. When the symptoms persisted, he was taken to a primary healthcare centre (PHC), where he was given oral cefuroxime 5 ml twice a day; and ibuprofen 5mls three times a day. However, on persistence of difficulty in breathing, he was taken to Adeoyo Maternity Teaching Hospital, Yemetu, Ibadan (AMTHYI) from where he was referred to the University College Hospital (UCH), Ibadan Nigeria due to a lack of bed space.

The pregnancy, labour, and delivery history was unremarkable. He was exclusively breastfed for 4 months. The mother commenced pap (porridge) and water at 4 months, other family diet at 6 months of age and he is currently on family diet and breastfeeding.

He was fully immunized according to the National Programme on Immunization schedule. The developmental history was appropriate for age.

On examination, he was febrile (axillary temperature, 38.1°C), anicteric, not pale, acyanosed, well hydrated and had no pedal oedema. The tonsils were slightly enlarged and hyperaemic. His weight was 9.7kg (0.1 z-score), length was 84cm (2.42 z-score.), mid-upper arm circumference was 14cm (-0.28 z-score.), and occipito-frontal circumference was 47cm (1 z-score).

There was no stridor, wheezing, or grunting. His chest was symmetrical. He was mildly dyspnoeic, tachypnoeic (respiratory rate, 54 breaths per minute), and has vesicular breath sounds both lung fields. The transcutaneous haemoglobin oxygen saturation (SpO<sub>2</sub>) was 89% on room air. His pulse was 140 beats per minute, regular and full volume. The first and second heart sounds were heard and there was no murmur.

The abdomen was full, moved with respiration, soft, and with no area of tenderness. The liver was palpable 4 cm below the right costal margin, firm, smooth and non-tender. No other abnormality was observed.

The diagnosis was acute severe CAP not in heart failure, and acute tonsillopharyngitis. He was placed on supplemental oxygen 1l/min, and intravenous antibiotics (cefuroxime 50mg/kg/dose 8 hourly and gentamycin 5mg/kg/day).

The chest radiograph showed situs solitus, levocardia, right perihilar adenopathy, patchy opacities on both lung fields, the cardiophrenic and costophrenic angles were clean and intact. The packed cell volume (PCV) was 31%; malaria rapid diagnostic test (RDT) was negative, and the full blood count (FBC) showed leucocytosis (16,000/μL) with neutrophil predominance (neutrophils, 66.1%; lymphocytes, 26.4%; monocytes, 6.3%); eosinophil, 1.2% and platelets, 280,000/ μL). The blood culture was sterile. The serum chemistry results showed metabolic acidosis of 10 mmol/L, Na-134mmol/L, K-3.7mmol/L, Cl-100mmol/L, Urea- 32mg/dl, and Cr-0.9mg/dl. The Gene X-pert test for *Mycobacterium tuberculosis* complex using gastric lavage was negative.

During the first 15 hours of admission, the patient's SpO<sub>2</sub> was between 95% and 99% on 1l/min of oxygen. An NGT was passed because he was not tolerating feeds orally. Correct placement of the NGT was confirmed by aspirating gastric content (checking that the pH was between 1-5) and hearing a whooshing sound when a stethoscope was placed over the patient's epigastrium while instilling a 30cc air bolus. He was subsequently weaned off oxygen. The SpO<sub>2</sub> on room air was between 95% and 98% for the subsequent 5 hours (26 hours into admission). However, 27 hours into admission, the patient desaturated (SpO<sub>2</sub> 88% on room air) shortly after being fed via NGT, and aspiration pneumonitis was suspected. He was recommenced on intranasal oxygen at 1L/min.

Between day 2 and 6 on admission, the patient remained mildly dyspnoeic (mild lower chest wall indrawing), and he was still on oxygen support. The breath sounds were vesicular with few coarse crackles on the right middle and lower lung zones. He was saturating between 95 and 100% on oxygen.

On day 7 of admission, the patient was afebrile, breath sounds were normal, respiratory rate ranged between 42 and 46 breaths/min, with no added sounds but still desaturating on room air while the NGT was *in situ*, and thus oxygen was continued at 1l/min. Possibility of impairment of oxygenation due to subtle obstruction from NGT was suspected during the consultant ward round. The NGT was removed, saturation improved significantly and remained normal (between 95 and 99% on room air) till discharge on the following day. The patient was discharged on day 8 with SpO<sub>2</sub> of 96% on room air.

## Case presentation 2

AA was a 15-week-old (real age, 5 weeks + 5 days) preterm female infant who presented with cough of two days' duration, fast breathing of 12 hours and 2 episodes of vomiting.

She developed cough 2 days prior to presentation. Cough was neither barking nor paroxysmal. Fast breathing started 12 hrs after onset of cough, no choking on feeds, no bluish discoloration of skin or extremities. She had associated vomiting (2 episodes), which contained recently ingested feeds and not bloody. No passage of loose stool, and no fever. She had had BCG and Hepatitis B vaccine at 8 weeks. Other aspects of history were not remarkable.

At presentation, examination revealed a small-for-age infant, axillary temperature was 36.7°C, mild pallor, anicteric, acyanosis, optimal hydration status and no peripheral oedema. The SpO<sub>2</sub> was 90% on room air.

The anthropometry was within normal limits: weight, 3.1 kg (-2.78 z-score); length, 50 cm (-2.49 z-score); and occipitofrontal circumference, 38 cm (0.66 z-score). There were abnormalities only in the respiratory system. There was neither stridor nor wheezes. She was not grunting, but dyspnoeic with subcostal recession; tachypnoeic with respiratory rate 72 breaths/min, breath sounds were normal, and there were bilateral coarse crackles. Other systems were essentially normal. The diagnosis was preterm female neonate, severe pneumonia not in heart failure. The differential diagnosis was aspiration pneumonitis.

On admission, the random blood glucose was normal (78mg/dl). FBC and differentials showed leucocytosis (14,200/ $\mu$ L) and normal differential counts (neutrophils, 17.1%; lymphocytes, 74.4%; monocytes, 7.3%, eosinophils, 1.2%), platelets were 430, 000 cells/ $\mu$ L. Pre-transfusion PCV was 23 %, and 32% after about 30mls of blood transfusion the next day. The malaria RDT was negative, and blood film showed no malaria parasites. The chest radiograph revealed areas of widespread patchy opacities and near homogenous opacity involving the right middle lung zone, Figure 1. The electrocardiogram showed left ventricular hypertrophy, but echocardiography was essentially normal. The serum electrolytes, urea and creatinine showed metabolic acidosis of 15mmol/L while other parameters were essentially normal (Na- 130mmol/L, Cl-104mmol/L, K-4.7mmol/L, Urea-5mg/dl, and Cr-0.3mg/dl).

She was treated thus: oxygen administered via nasal prong at 0.5l/min, which increased the SpO<sub>2</sub> from 90% to 98%; intravenous(iv) cefuroxime 150mg/kg/day 8hourly, iv gentamycin 5mg/kg daily, and iv metronidazole for 1 week.

She had persistent diarrhoea and was managed with tablets zinc sulphate 10 mg daily for 10 days, and oral rehydration solution. Throughout admission, she was euglycaemic. The antibiotics were changed to iv ceftriaxone because of poor clinical improvement, persistent fever, and worsening respiratory distress. The ceftriaxone was also changed after six days of use to iv meropenem and iv clindamycin for eight days; there was a sustained improvement but remained dependent on oxygen.

She was commenced on NGT feeding because of inadequate intake from direct breast-feeding with associated weight loss. She remained hypoxaemic for most of this time and was continued on intranasal oxygen at 1-2 l/min. On the 16<sup>th</sup> day on admission, temperature had remained normal, dyspnoea subsided, respiratory rate was 52 breaths/min, but she remained hypoxaemic and dependent on oxygen. Possibility of NGT contributing to the hypoxaemia was suspected. The NGT

was removed, and hypoxaemia resolved, and improvement maintained till patient was discharged home after spending 18 days on admission.

**Figure 1**, chest radiograph of case 2 at presentation



## Discussion

These two cases suggest the possibility of subtle and undetected episodes of hypoxaemia in infants on NGT feeding. Anatomically, the narrowest portion of the respiratory tract (the anterior nasal valve) is found just posterior to the nares, and since the tube is often passed through the upper respiratory passage, and then into the oesophagus, there is a possibility of it causing impairment of oxygenation and inadequate ventilation especially in such patient with severe pneumonia with significant lung consolidation; but this is expected to resolve following treatment with resolution of the infective process.<sup>3,6</sup>

Many decades ago, Bevan et al<sup>4</sup> demonstrated significant improvement of about 20% in the forced expiratory volume in one second (FEV<sub>1</sub>) following removal of nasogastric tube in eight adult patients after operation, which support the belief that an NGT unfavourably affects pulmonary ventilation in adult patients.<sup>4</sup> This belief has not been proven irrefutably to be so in infants or children. Some researchers<sup>2</sup> have also hypothesised that nasogastric route of placing a feeding tube is associated with higher incidence of hypoxaemia and bradycardia in preterm infants compared to orogastric route, but Bohnhorst et al<sup>5</sup> and Watson et al<sup>2</sup> found no difference in the effect of route of placement on development of hypoxaemia.<sup>2</sup>

However, Shiao et al<sup>3</sup> found some degree of breathing compromise in preterm infants with nasogastric tube feeding compared to those on continuous sucking, and recommended close monitoring of oxygen saturation, and heart rate during feeding via NGT.<sup>3</sup> These cases have been presented is to draw attention to the possibility of this interaction among infants especially those with other co-morbidities like pharyngitis as seen in the first case that can cause partial obstruction to the

upper airway.<sup>6</sup> The impact of prematurity on the development of hypoxaemia as seen in the second case reported is not so clear, but warrants further studies as available reports in the systematic review by Watson et al<sup>2</sup> are too few to influence practice. It is still not clear whether this association is by chance or if it only occurs in association with cases of pneumonia with significant lung consolidation, and thus requiring further studies. Nonetheless, clinicians need to have a high index of suspicion for the possibility of NGT feeding causing hypoxaemia, when hypoxaemia is persistent than expected, and also ensure more frequent pulse oximetry on patients with NGT feeding and prompt removal once adequate oral/direct intake is established.

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**Competing interests:** The author declares no competing interests.

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# Journal of the African Society for Paediatric Infectious Diseases (JAfSPID)

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*JAfSPID* is the official publication of the African Society for Paediatric Infectious Diseases. It was launched as an online newsletter called the *AfSPID Bulletin* in April 2013. In April 2022 it became a peer-review journal. In March 2023 the name was changed from The AfSPID Bulletin to *Journal of the African Society for Paediatric Infectious Diseases (JAfSPID)*. It publishes educational and research articles on all aspects of infectious diseases in neonates, children, and adolescents. The journal publishes a wide variety of manuscripts including commentaries, reviews, research manuscripts, case reports, medical images, conference reports and editorials. All articles are published under the Creative Commons CC-BY licence.

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