Factors Affecting Compliance with Clinical Practice Guidelir Screening among Healthcare Providers in Africa: Systemati Meta-Summary of 2045 Individuals

Etienne Asonganyi, Meenakshi Vaghasia, Clarissa Rodrigues, Amruta Phadtare, Anne Ford, Ricardo Pietrobor

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Abstract

Background

Although the importance of the Pap smear in reducing cancer incidence and mortality is known, many countries in A cancer screening programs. The World Health Organization (WHO) has published Clinical Practice Guidelines (CP however, there is a gap between expectations and clinical performance. Thus, the aim of this study was to conduc factors affecting compliance with CPGs for Pap screening among healthcare providers in Africa.

Methods

And Findings: MEDLINE, Scirus, Opengate and EMBASE databases were searched in January 2012. Studies in outcome measured any factors that affect medical personnel from using a Pap smear to screen for cervical cance titles and abstracts, then full-texts, extracted data and assessed quality of the included studies. A descriptive anal Frequency effect sizes (FES) for each finding and Intensity effect sizes (IES) for each article to represent their ma studies were included (2045 individuals). Six different themes related to the factors affecting compliance with CPG awareness (FES = 82%), Negligence/Misbeliefs (FES = 82%), Psychological Reasons (FES = 73%), Time/Cost C (FES = 45%) and also no reason given (FES = 36%). IES for articles ranged between 33 and 83%.

Conclusions

These results suggest that prevention initiatives should be comprehensive to include education and resources neec strategies on costing, and practitioner time studies.

Figures

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Introduction

Cervical cancer is the second most common cancer among women worldwide, and the leading cause of cancer-re 2008, 453,000 new cases and 242,000 deaths occurred from cervical cancer, with 83% of the cases of cervical c effectiveness of the Pap smear in reducing cervical cancer incidence and mortality has already been demonstrated disparity in rates of screening for cervical cancer in developing countries with the average screening coverage rate developing countries [5]. In the developing world, women at highest risk for developing cervical cancer are among Health Organization (WHO) published clinical practice guidelines (CPGs) on cervical cancer screening in developin initiated widespread national cervical cancer screening programs. A WHO report on cervical cancer screening in S most affected by cervical cancer, it has access to less than 5% of the global resources for cervical cancer prevent to promote, restore, or maintain health, requires the translation of WHO guidelines into national guidelines and the

In African countries, not only is the incidence of cervical cancer high but a large proportion of patients present with that in African countries there is a lack of a successful large scale screening programs. Despite the significant lack been no previous systematic reviews to identify the factors leading to compliance or non-compliance with CPGs o

Physician behavior, specialty and gender have all shown to play an important role in patient compliance [10,11]. In clinical practice guidelines, the authors noted many factors could limit adherence like lack of awareness, familiarity well as inertia of previous practice. However, the authors emphasize that, since barriers may differ from setting to

In Africa, factors that have been shown to affect physicians' compliance include but are not limited to: busy clinics transport to care and opposition to care by men [13]. Another review investigating guideline compliance concluded clinical performance but did not investigate the reasons for this disparity [14]. These studies did not address the c objective of this systematic review is to identify factors affecting compliance with Clinical Practice Guidelines for P

Reference	Country	Study Design	No of Individuals	Occupation
Mutyaba T. , et al (2006) [20]	Uganda	Descriptive Cross-Sectional Survey	288	Medical Officers = 39 (13.5%), Nurses = 1((58.0%), Specialists = 19 (6.6%), Students (21.9%)
Dim CC. , et al (2009) [21]	Nigeria	Survey Questionnaires	79	Fellows = 17 (22%), Senior Residents = 16 Junior Residents = 17 (22%), Medical Offic (18%), Interns = 15 (19%)
Udigwe GO. , et al (2006) [22]	Nigeria	Self-administrated Questionnaire Survey	140	Nurses
Gharoro EP. , et al (2006) [23]	Nigeria	Survey	184	Doctors = 16 (8.7%), Nurses = 109 (59.2% Pharmacists = 4 (2.2%), Lab. Technicians = (2.2%), Hospital Maids = 41 (22.3%), Radi = 3 (1.6%), Others = 7 (3.8%)
Nwobodo EI. , et al (2005) [24]	Nigeria	Cross-Sectional Survey	159	Doctors = 18 (11.3%), Nurses = 127 (79.9% Pharmacists = 4 (2.5%), Lab. Scientists = 7 Social Workers = 3 (1.9%)
Anya SE. , et al (2005) [25]	Nigeria	Questionnaire Survey	144	Doctors = 21 (14.6%), Nurses = 76 (52.8% Pharmacists = 20 (13.9%), Lab. Scientists (18.8%)

Reference	Country	Study Design	No of Individuals	Occupation
Tarwireyi F. , et al (2003) [26]	Zimbabwe	Cross-Sectional Survey	60	Doctors = 1 (1.7%), Nurses = 34 (56.7%), Aide = 22 (36.6%), Allied = 3 (5.0%)
Aboyeji PA. , et al (2004) [27]	Nigeria	Cross-Sectional Survey	483	Nurses = 405 (83.9%), Doctors = 31 (6.4% Pharmacists = 12 (2.5%), Lab. Scientists =
Olaniyan OB. , et al (2000) [28]	Nigeria	Cross-Sectional Survey	166	Doctors = 15 (9.0%), Nurses = 118 (71.1% Pharmacists = 10 (6.0%), Lab. Scientists = (10.2%), Social Workers = 6 (3.6%)
Urasa M. , et al (2011) [29]	Tanzania	Descriptive Cross-Sectional Study	137	Enrolled Nurses = 70 (51.0%), Registered 67 (49.0%)
Ayinde OA. , et al (2003) [30]	Nigeria	Survey	205	Doctors = 45 (22.0%), Nurses = 90 (43.9% Maids = 70 (34.1%)

Table 1. Characteristics of the included studies.

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Methods

Protocol and Registration

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Review and M the study can be found in File S1, and the PRISMA check list in Table S1.

Eligibility Criteria

The following inclusion criteria were considered: 1) Studies involving medical personnel; 2) Studies whose outcome personnel from using a Pap smear to screen for cervical cancer, 3) Studies conducted in Africa, and 4) Observatio retrospectively analyzed clinical trial data, unpublished articles, dissertations, and abstracts without full text. In add or Portuguese were not included in the review.

Information Sources

We searched the following electronic databases for published literature up until January 2012: PubMed, Scirus, O EMBASE. We did not use limits for language when searching the databases. The references of the included article analysis of the included studies using Google Scholar, and also sought experts' suggestions through email commu

Articles and Assessment Criteria	Mutyaba T. , et al (2006) [20]	Dim CC. , et al (2009) [21]	Udigwe GO. , et al (2006) [22]	Gharoro EP. , et al (2006) [23]	Nwobodo EI. , et al (2005) [24]	Anya SE. , et al (2005) [25]	Tarwirey F. , et al (2003) [26]
Are the criteria for inclusion of subjects described?	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Has the study sample been clearly described in	No	Yes	Yes	Yes	No	Yes	Yes

Articles and Assessment Criteria	Mutyaba T. , et al (2006) [20]	Dim CC. , et al (2009) [21]	Udigwe GO. , et al (2006) [22]	Gharoro EP. , et al (2006) [23]	Nwobodo EI. , et al (2005) [24]	Anya SE. , et al (2005) [25]	Tarwirey F. , et al (2003) [26]
terms of sample size and demographic characteristics such as age, race, gender, location, socioeconomic status, etc?							
Is the study sample appropriate to the problem being studies or the hypotheses being tested?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the study sample large enough to test the hypotheses?	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear
How was the study sample selected (random, haphazard, consecutive patients presenting with a particular disease, all subjects in a particular group, etc)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Is the design of the study clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Does the design of the study adequately test the hypotheses?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
How was random selection of subjects achieved? Was any other method besides the use of random numbers table used?	No	Yes	No	No	No	No	No
Have the measurement of the outcome, independent, and control variables been clearly described?	Yes	Yes	No	Yes	No	Yes	No
Are the variables measured with appropriate and accurate methods?	Yes	Unclear	Unclear	Yes	Unclear	Yes	Unclear

Articles and Assessment Criteria	Mutyaba T. , et al (2006) [20]	Dim CC. , et al (2009) [21]	Udigwe GO. , et al (2006) [22]	Gharoro EP. , et al (2006) [23]	Nwobodo EI. , et al (2005) [24]	Anya SE. , et al (2005) [25]	Tarwirey F. , et al (2003) [26]
Do the operational definitions match the theoretical variables?							
Have the laboratory tests, instruments and/or questionnaires used to measure the variables undergone validity and reliability testing?	No	No	No	No	No	No	No
Have the procedures or methods undergone standardization for a particular population that is being studied?	No	No	No	No	No	No	No
Were the outcomes variables measured using appropriate blinded methods?	No	No	No	No	No	No	No
Have the number of non-respondents,	Yes	Yes	No	Yes	Unclear	Yes	Yes

Table 2. Risk of bias assessment.

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Search

The initial search comprised the following Mesh terms "*Vaginal Smears*", *and* "*Africa*" and the related entry terms. database is shown in Table S2.

Study Selection

Titles and abstracts of the retrieved articles were independently evaluated by two reviewers (E.A. and M.V.). Abst eligibility criteria were kept for full-text evaluation. Reviewers independently evaluated full-text articles and determi consensus and if disagreement persisted, we sought a third reviewer's opinion (A.J.).

Quality of Studies

Several tools have been proposed for evaluation of methodological quality of observational epidemiological studies checklist specific for evaluating cross-sectional studies [17], which is based on 15 items. We chose this checklist b which recommends to use checklists rather than scales, as well as to use a tool as specific as possible, consideri

Data Extraction

Two reviewers (E.A. and M.V.) independently conducted data extraction and disagreements were also solved by t was pre-tested by the two reviewers and alterations were made as necessary. General characteristics of the stuc

and setting where the study took place, number of health care providers, health providers characteristics. In additi affecting compliance with CPGs for Pap smear screening among healthcare providers in Africa.

Data Analysis

We performed a descriptive analysis of factors affecting healthcare provider compliance with CPGs for Pap smea affecting compliance were grouped by similarity, and within each group, brief descriptions of the findings were gen adapted the methodology proposed by Sandelowski M, et al (2007) [19]. Frequency effect sizes (FES) were gene theme by the total number of studies in our final list and multiplied by 100. The themes with higher FES are the one the magnitude of each report, intensity effect sizes (IES) were calculated. Specifically, for each study, the number number of findings with frequency effect size >25%. Additionally, for each study, the number of themes it cited was studies with higher IES are the ones presenting more themes. As the lowest FES identified was 36%, and both IE each study.

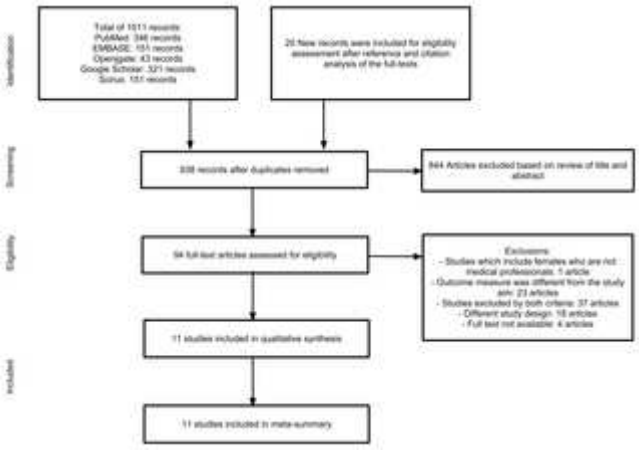

Figure 1. PRISMA flowchart.
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Results

Characteristics of included studies

A total of 1011 records were identified and screened with 94 full-text articles assessed for eligibility based on the included in the qualitative synthesis and meta-summary. Figure 1 illustrates the search and article selection proces during the article selection phases of this project.

Reference	Studies Findings
Mutyaba T. , et al (2006) [20]	Knowledge: 81% had knowledge about whether cervical cancer is curable, 29% had knowledge about risk had knowledge about Pap smear screening, 26% had knowledge about eligibility for screening, and 39% screening interval. Attitudes: 93% thought cancer of the cervix was a public health concern, 68% thought of the participant females did not think they were susceptible to cervical cancer themselves, 60% of males susceptible. Most nurses and midwives thought that speculum examination and Pap smear were doctors' students thought they were for senior doctors only, doctors in disciplines other than gynecology thought th activity for gynecologists only, lack of vaginal specula and absence of indication for speculum examinatior screening patients, among the females respondents, reasons for not having been screened included: not carelessness, fear of vaginal examination, lack of interest, test being unpleasant and not yet being of risky female respondents said that they would only accept a vaginal examination by a female health worker. Me strongest reason for not performing Pap smears. Responses were: 35% thought they were not allowed, 1 thought it was for senior doctors and 26% did not know how to do one. Practices: routine management of

Reference	Studies Findings
	performing vaginal examinations -62%, speculum use during vaginal examinations -12%, females respond screened themselves -19%, male respondents whose partners have ever been screened -26%, don't ask and don't refer patients for screening -78%.
Dim CC. , et al (2009) [21]	Reasons for non-use of Pap smear by female medical practitioners: poor health consciousness -2 (3%), d cancer -6 (9%), scared of the outcome -4 (6%), too busy to screen -15 (23%), just lazy about screening -1 -1 (2%), awaiting menopause -1 (2%), no reason -21 (23%), and non-accessibility of Pap smear – zero.
Udigwe GO. , et al (2006) [22]	Reasons for not undergoing Pap smear: ignorance of availability -26 (18.6%), fear of outcome -21 (15.0% (25.0%), financial implication -1 (0.7%), no reason -52 (37.1%), and not applicable -8 (5.7%).
Gharoro EP. , et al (2006) [23]	More than 65% of the respondents were aware of the disease, cervical cancer, and approximately 64% w Pap smear awareness level significantly varied among the categories of the female health workers. A min smear test. There was a significant variation in utilization of Pap smear test across the various categories significant correlation between Pap smear awareness and utilization. The majority, 89%, believed that the cervical cancer. The self-reported utilization of Pap smear test among health workers was low. While there between Pap smear test awareness and utilization, screening uptake was very poor due to a combination misapprehension, and deficient knowledge.
Nwobodo EI. , et al (2005) [24]	Reasons for not having Pap smear: no physician referral -98 (64.5%), did not feel susceptible to cancer o believe in the test -7 (4.6%), have no knowledge of Pap smear -5 (3.3%), did not know where to have the (2.0%), and no reason given -9 (5.9%).
Anya SE. , et al (2005) [25]	Knowledge of cervical cancer and Pap smear: 91.7% had heard of cervical cancer while 80.6% knew it wa vaginal bleeding, 22.2% could not list any risk factor for cervical cancer, 32.6% believed it was potentially be prevented, and 77.8% reported they had heard of Pap smear.
	Attitudes: 88.6% who had heard of cervical cancer considered it a serious problem, 89 respondents who k 92.1% would recommend regular Pap smear if these were affordable, only 9% had ever had a Pap smear were the two determinants of likelihood to have had a Pap smear. Doctors and divorced/separated women smears. Reasons for non-uptake of Pap smears among those knew its purpose: not available -39 (51.3%) (22.4%), cannot afford it -14 (18.4%), and no personal risk of cervical cancer -6 (7.0%).
Tarwireyi F. , et al (2003) [26]	Knowledge of risk factors: early sexual intercourse -21 (35%), using vaginal herbs and chemicals -51 (85% papilloma virus -17 (28.3%), HIV infection -6 (10%), multiple sexual partners -26 (43.3%), and multiple pre of pre-cervical cancer treatments options: cryotherapy -17 (28.3%), knife cane biopsy -9 (15.0%), electro- zero, and laser – zero.
Aboyeji PA. , et al (2004) [27]	Reasons for not wanting to be screened: cannot have cervical cancer -137 (52.5%), fear of detecting of c screening against religious belief -38 (14.6%), screening expense -35 (13.4%), my husband is against it -2 reason -34 (13.0%).
Olaniyan OB. , et al (2000) [28]	Reasons for not having Pap Smear: no physician referral -57 (54.3%), did not feel susceptible to cancer -2 have the test -6 (5.7%), would require husband's permission -2 (1.9%), did not believe in test -2 (1.9%), a
Urasa M. , et al (2011) [29]	Knowledge of causes of HPV: HPV infection -53 (38.7%), genetic predisposition -32 (23.4%), certain food infectious -103 (75.2%). Knowledge of Transmission of HPV: sexual intercourse -83 (60.6%), direct genita -137 (100%), body fluids -112 (81.8%), drinking unsafe water -135 (98.5%), mother to child transmission - (99.3%). Knowledge of risks of cervical cancer: smoking -28 (20.4%), alcohol -123 (89.8%), multiple sexua HPV infection -60 (43.8%), early sexual debut -51 (37.2%), impaired immunity -11 (8.0%), use of Intrauteri hygiene -136 (99.3%). Knowledge of symptoms of cervical cancer: post-coital bleeding -63 (46%), inter-m blood stained vaginal discharge -73 (53.3%), fever -134 (97.8%), headache -136 (99.3%), pelvic pain -26 -52 (38%), and painful coitus -59 (43.1%).

Reference	Studies Findings
Ayinde OA. , et al (2003) [30]	Knowledge about cancer of the cervix was highest among doctors, followed by nurses and hospital maids previous Pap smear. Reasons for not having Pap smear in those who have never had it: cost considerati about test -83 (43.5%), lack of awareness about locations where the test is performed -17 (8.9%), reluctar exposed -6 (3.1%), belief in not being prone to cervical cancer -5 (2.6%).

Table 3. Factors affecting compliance with CPGs for Pap smear screening identified in each study.

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Themes	No of Studies - FÈS (%)*	Reference
Insufficient Knowledge/ Lack of awareness	9 (82)	Mutyaba, et al. (2006) [20], Dim CC, et al (2009) [21], Udigwe GO, et a [24], Tarwireyi F, et al (2003) [26], Olaniyan OB, et al. (2000) [28], Uras
Negligence/ Misbeliefs	9 (82)	Mutyaba, et al. (2006) [20], Dim CC, et al (2009) [21], Udigwe GO, et a [24], Anya SE. , et al (2005) [25], Aboyeji PA. , et al (2004) [27], Olaniy
Psychosocial Reasons	8 (73)	Mutyaba, et al. (2006) [20], Dim CC, et al (2009) [21], Udigwe GO, et a [24], Aboyeji PA. , et al (2004) [27], Olaniyan, et al. (2000) [28], Ayinde,
Time/Cost Constraint	4 (36)	Dim, et al. (2009) [21], Udigwe, et al. (2006) [22], Anya, et al. (2005) [2
Insufficient infrastructure/ training	5 (45)	Mutyaba T. , et al (2006) [20], Gharoro, et al. (2006) [23], Anya, et al. ([29]
No reason given	4 (36)	Dim, et al. (2009) [21], Udigwe, et al. (2006) [22], Aboyeji PA. , et al (20

Table 4. Themes identified in the included studies and the respective Frequency effect sizes (FES).

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Studies Characteristics

Included studies had a total of 2045 individuals. Sample sizes varied from 60 to 483 with a mean of 185.9 of which The characteristics for the studies included in this analysis are shown in Table 1.

Quality of Studies

Table 2 demonstrates the risk of bias assessment of the included studies. There was prevalence of “Yes“, which n were ‘Unclear’ in their presentation of some items, representing moderate risk of bias (33/165). Also, some studie as high risk of bias (39/165).

Reference
Mutyaba T. , et al (2006) [20]
Dim CC. , et al (2009) [21]
Udigwe GO. , et al (2006) [22]
Gharoro EP. , et al (2006) [23]
Nwobodo EI. , et al (2005) [24]
Anya SE. , et al (2005) [25]
Tarwireyi F. , et al (2003) [26]
Aboyeji PA. , et al (2004) [27]
Olaniyan OB. , et al (2000) [28]
Urasa M. , et al (2011) [29]
Ayinde OA. , et al (2003) [30]

Table 5. Intensity effect sizes (IES) for each report.

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Synthesis of Results

Factors affecting compliance with CPGs for Pap smear screening identified in the articles are presented in Table 3 for factors affecting non-compliance with CPGs for Pap screen including: insufficient knowledge/awareness, negli constraints and insufficient infrastructure.

The results of the meta-summary demonstrated all findings reported a FES > 25, ranging range from 82% to a lov more relevant. Non-compliance factors had the highest FES, meaning the most common findings amongst studies Negligence/Misbeliefs. Each of these themes and their corresponding FES are displayed in Table 4.

The IES for each of the included articles is displayed in Table 5. The results demonstrate IES ranging from 50 to 8 largest number of findings, in contrast to the study of Tarwireyi F, et al (2003), which had the lowest number of fin

Discussion

To our knowledge, this is the first systematic review describing the factors that affect compliance with CPGs for P Our review identified 11 studies that cited factors for noncompliance with Pap smear protocols including Insufficier Psychological Reasons, Time/Cost Constraints and Insufficient Infrastructure/Training.

The factors found in our study to be most cited and therefore that had the highest FES were Insufficient Knowledg complying with Pap smear guidelines. Surprisingly, even among professionals with knowledge on Pap smear and c This result is in agreement with another study that found that improved awareness of Pap smear may not affect its Pap smear but only 18% had used it before [31]. In South Africa, a national study evaluating 20,603 women in pub never had a Pap smear [32]. In this South African context, barriers to effective screening programs are further cor education and literacy levels, health infrastructure and access to health services, thus representing a considerable

Previous studies have evaluated cervical cancer and Pap smear awareness in different populations [34-42]. A rece of awareness of cervical cancer and Pap smear test, and factors associated with the utilization of Pap test among participants had cervical cancer awareness while 39% were aware of Pap smear testing. In addition, the study de and hospitals as their source of information about cervical cancer and Pap smear, thus showing their important rol highlight that a health education program about cervical cancer that incorporates media might be very impactful in and Pap smear awareness among undergraduate students showed that 71% of the students were aware of cervi [36].

In this context, previous study carried out in Nigeria among sexually active woman demonstrated that only 26% of and in addition, only 47% of the aware group knew that the test was to screen cervical cancer. The authors report knowledge of Pap test, but not in relation to the test utilization [39].

Another study determining the level of awareness and uptake of cervical screening in Owerri, Nigeria has demonst aware of cervical screening and that 7.1% had ever done the test. The main reasons for not doing it were “no nee and fear and anxiety over a positive result [35].

Although our results demonstrate high IES throughout the studies (greater than 25%), meaning that the themes ide quality assessments demonstrated that not all studies presented some of the assessed items or it was unclear, re Specifically, most studies did not have a representative sample and blinding of the outcome assessment. These lin extracted from these studies, the size of the effect.

Findings from our study suggest though that while Insufficient Knowledge/ Lack of Awareness is a large limitation, must be more comprehensive to further address Negligence/Misbeliefs and Psychological Reasons and well as the Infrastructure/Training. Given the high incidence of advanced stage cervical cancer in Africa, there is an urgent nee guideline compliance. These findings support adopting a multifaceted approach, not only addressing provider educ and psychosocial concerns. In addition, future work in this area should be performed to further understand the ext and the validity of these reasons from the perspective of the patient. Secondly, further understanding of cost, time should be undertaken.

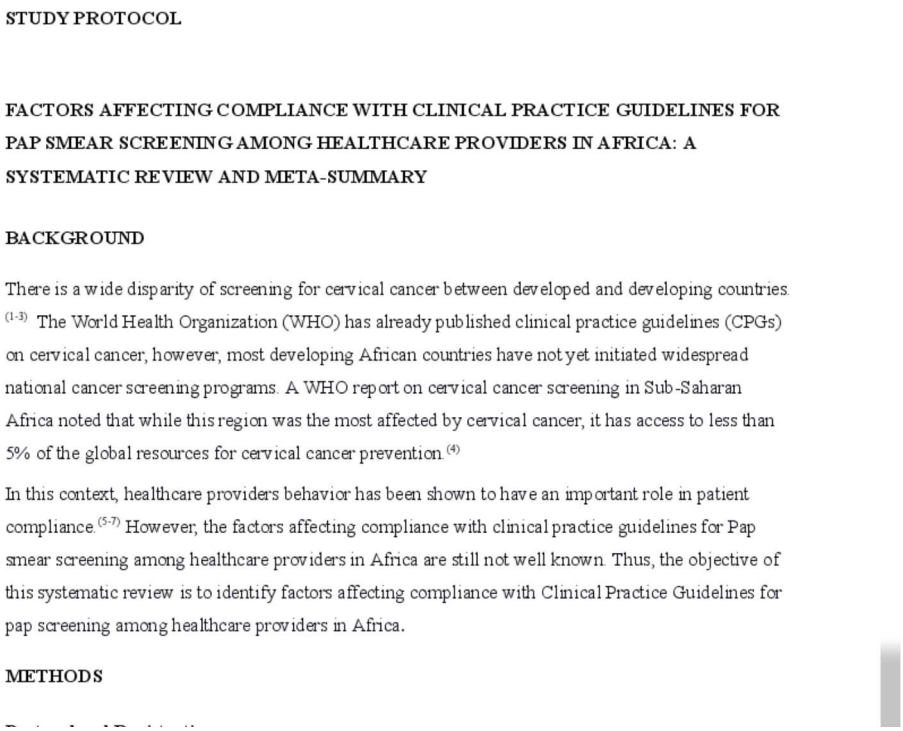
Our data coincide with a previous study that reported implementing multifaceted approaches are needed to achiev Such approaches should involve improvement of health workers and community knowledge by implementing then e

as establishing appropriate structure and guidelines, and developing new technologies [33]. Research has been co technologies in low-resource setting, which would require fewer resources and infrastructure, thus having the pote implementation [43]. However, it has been demonstrated that technological interventions and innovations alone are Other concerns intrinsic to health systems in Africa include human resources concerns such as training, increasing should be addressed concurrently within a comprehensive workforce development strategy, alongside work to mal task shifting would be limited [44].

In conclusion, studies that have evaluated factors affecting healthcare provider clinical practice guideline adherenc demonstrating that the themes identified were consistent across the studies. The studies suggest provider non-co about protocols, time and cost constraints, and lack of infrastructure or training on performing Pap smears. These multifaceted including education, resource needs assessments and improvement, Pap smear testing training as we

Supporting Information

File_S1.docx



STUDY PROTOCOL

FACTORS AFFECTING COMPLIANCE WITH CLINICAL PRACTICE GUIDELINES FOR PAP SMEAR SCREENING AMONG HEALTHCARE PROVIDERS IN AFRICA: A SYSTEMATIC REVIEW AND META-SUMMARY

BACKGROUND

There is a wide disparity of screening for cervical cancer between developed and developing countries.[1-3] The World Health Organization (WHO) has already published clinical practice guidelines (CPGs) on cervical cancer, however, most developing African countries have not yet initiated widespread national cancer screening programs. A WHO report on cervical cancer screening in Sub-Saharan Africa noted that while this region was the most affected by cervical cancer, it has access to less than 5% of the global resources for cervical cancer prevention.[4]

In this context, healthcare providers behavior has been shown to have an important role in patient compliance.[5-7] However, the factors affecting compliance with clinical practice guidelines for Pap smear screening among healthcare providers in Africa are still not well known. Thus, the objective of this systematic review is to identify factors affecting compliance with Clinical Practice Guidelines for pap screening among healthcare providers in Africa.

METHODS

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File S1. Study Protocol.
doi:10.1371/journal.pone.0072712.s001
(DOCX)

Table S1. PRISMA checklist.
doi:10.1371/journal.pone.0072712.s002
(DOC)

Table S2. PubMed Search Strategy.

doi:10.1371/journal.pone.0072712.s003
(DOCX)

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Author Contributions

Conceived and designed the experiments: EA CGR AP RP JA CL. Performed the experiments: EA MV CGR AP. A reagents/materials/analysis tools: AF RP JA CL. Wrote the manuscript: EA CGR AF CL.

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