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Original Article

Intention and Concerns about HPV Vaccination among In-School Adolescents in Ibadan, Oyo State, Nigeria.

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Abstract

Background: Human papillomavirus (HPV) is a very common sexually transmitted infection responsible for some cancers including cervical cancer. Despite nearly half of the Nigerian population being at risk (women <25), vaccination uptake against the infection is still less than 5%.

Methodology: This cross-sectional descriptive survey was conducted using a multi-stage sampling technique. A semi-structured questionnaire was administered to 300 in-school adolescents aged 15-19 years, across 15 private and public secondary schools in Ibadan-North and Ibadan North-West of Oyo State, whose parents gave consent. The data was analysed using descriptive and inferential statistics in SPSS v21. Cronbach's alpha coefficient was used to measure internal consistency reliability while categorical tables were compared using chi-square and regression analysis with a p-value <0.05.

Results: The mean age of respondents was 15.8 ± 0.84 years. Half of them were females (52.3%) and also attended private schools (56.3%). Very few of the respondents had heard about HPV (21.0%) and HPV vaccine (12.7%), however, more than half had heard about cervical cancer (55.3%). Few respondents had good knowledge (11.0%) and positive perception (27.0%) of HPV, cervical cancer and HPV vaccine. The major source of information was social media (46.2%). Half of the respondents reported intention to take the vaccine if recommended by their family doctor (56.3%) and if given parental approval (52.0%), however, many (60.7%) were concerned about the vaccine's side effects.

Conclusion: Findings show that parents and health workers influence adolescents' HPV vaccination uptake. The study thus recommends the prioritization of parental involvement in HPV vaccination. Parents and health workers should therefore be targeted as key stakeholders in driving the awareness of HPV and uptake of HPV vaccine among adolescents.

Keywords: HPV vaccine; Knowledge; Perception; Intention; Concerns; Uptake.

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Introduction

Human Papillomavirus (HPV) is the most common sexually transmitted infection (STI) that can be contracted by both genders. It can be contracted by having vaginal, anal or oral sex with an infected person or by having contact with an infected skin or mucosal surfaces [1]. HPV. There are over 100 types of Human papillomavirus that have been reported with 14 types capable of causing cancers of the cervix, anus, vulva, vagina, penis and oropharynx [2].

HPV prevalence occurs at its peak during adolescence and in young adulthood shortly after sexual debut [3] due to risky sexual behaviours such as early debut in sexual activities, sex with many partners, low and inconsistent use of condoms, anal sex and mouth to genital contact [4]. This places nearly half of the Nigerian population at possible risk of HPV infection [5]. Globally, eighty-five per cent of the burden of HPV infection which is the highest risk factor for cervical cancer has been reported in developing countries [6] with Africa having the second highest prevalence of 16.1% [7] and Nigeria reporting a prevalence of 18.6%[8].

The prophylactic human papillomavirus (HPV) vaccines have been discovered to prevent oncogenic types which are responsible for 70% of cervical cancer cases. Despite this finding and the vaccines' availability, there is still low vaccination uptake in Nigeria. This low uptake is suspected to be responsible for the high incidence of cervical cancer which is the second leading cancer among women in the country. Approximately 15,000 cases of cervical cancer with nearly 11,000 deaths were reported alone in 2019[9].

The World Health Organization (WHO) recommends that boys and girls be vaccinated at ages 9-14 with two doses of HPV vaccine before becoming sexually active while adolescents above 15 years including special populations such as those with Human Immunodeficiency Virus (HIV) be given three doses of the vaccine. WHO also recommends the inclusion of the HPV vaccination into the National Immunization Programmes (NIPs) by countries as part of an integrated and holistic strategy to mitigating HPV and cervical cancer [5].

Despite this commendable approach by the WHO, findings by Ndikom and Oboh (2017) revealed a low uptake of HPV vaccine among adolescents at 4.1%[10] while another study revealed an uptake rate of 1.4% among adolescent girls in Nigeria[11]. Another study also reported that only 2.6% have been vaccinated with the HPV vaccine [12]. The low uptake rate may be attributable to low intention and willingness [12-13]. However, in some countries, high intention has been reported; Malaysia (88.6%) and Rwanda (69.3%) [14-15]. Understanding the intention and concerns of HPV vaccination among in-school adolescents helps in identifying key factors limiting the vaccination uptake. Therefore, this study assessed the knowledge, perception, intention, and concerns about HPV vaccination among in-school adolescents.

Methodology

This study was a cross-sectional study among in-school adolescents from ages 15-19 years. The survey was administered by using a semi-structured questionnaire to collect data among in-school adolescents in two local government areas (Ibadan North and Ibadan North-West Local Government Areas) in Ibadan metropolis, Oyo State, Nigeria.

There are about 42 government schools and 57 private-owned schools: 13 government schools and 32 private-owned schools in IBNLGA and IBNWLGA respectively. A multistage sampling technique was used to arrive at the sample size. Ten (10) schools from Ibadan North and five (5) from Ibadan Northwest LGAs were selected using a 10% purposive selection of the total number of schools in each LGA. The schools were further stratified into private and public schools, using a proportionate ratio (4 government schools: 6 private-owned schools; 2 government schools: 3 private-owned schools for IBNLGA and IBNWLGA respectively). A simple random technique was then used to select the schools using balloting. Finally, 20 consenting students from each class were randomly selected among those who fit the criteria for this study.

The inclusion criterion included in-school adolescents between ages 15-19 that gave assent and whose parents have consented to participate in the study. In-school adolescents who were ill or did not give assent were excluded from the study. The sample size was calculated using the formula provided by Fisher *et al.,* (1998).

$$n = z^2 pq / d^2$$

Where:
n = the required sample size; z= 1.96 (95%) standard normal deviation at the required confidence interval; p=prevalence of HPV in targeted population; q= 1-p; $d^{2=}$ margin of error set at 0.05 (precision set at 5%); p= 18.6%[8]. n= 257, however, the sample size was increased to 300 to have a more representative sample size.

The data was collected using a 64-item semi-structured questionnaire. The questionnaire contained six sections. The first section contained information on the socio-demographic characteristics of the study respondents (9 questions). The second question collected data on the awareness and knowledge of HPV vaccination among study respondents (22 questions). The third question gathered information on the perception of HPV vaccination among study respondents (9 questions). The fourth question gathered information on the uptake of HPV vaccination among study respondents (6 questions). The fifth question collected information on the intention of HPV vaccination among study respondents (9 questions). The sixth question gathered data on the concerns of HPV vaccination among study respondents (9 questions). The internal consistency reliability of the scale used in this study measured by Cronbach's alpha coefficient was 0.74.

The data was entered directly into Statistical Package for Social Science (SPSS) version 21 software. The entries were cleaned and sorted. Independent variables such as socio-demographic variables were analysed using descriptive analysis (percentage, standard deviation, mean, frequency distribution) while dependent variables such as awareness, knowledge and perception were analysed using inferential statistics (chi-square and regression analysis) to show significant variables that predict or determine intentions and concerns on the uptake of the vaccine. Data was properly stored and passworded RWQin a computer which was only accessible to the authors.

Measures

To measure knowledge and perception, a 30-point scale was used with scores 0-8 categorized as poor knowledge, 10-19 categorized as fair knowledge and 20-30 categorized as good knowledge. An 18-point scale was used with scores <6 categorized as negative perception, 6-11 categorized as fair perception and 10-19 categorized as positive perception.

Ethics

Ethical approval was obtained and participation in the study was voluntary. Informed consent forms were earlier given to students to take home to their parents to indicate approval of their adolescents to take part in the study. Assents forms were then read and given to students whose parents had signed the consent forms to also get their approval. Confidentiality was ensured during the data collection and all identifiers were removed. Serial numbers were written on the copies of the questionnaire for easy identification, entry and recall. (OY/AD13/479/4063).

Result

A total of three hundred (300) in-school adolescents participated and completed the survey. The mean age of the respondents was 15.8 ± 0.84 years. There were more females (52.3%), private school attendees (56.3%), Christians (73.7%) and Yorubas (80.0%) among the respondents. More than half (52.0%) of the

respondents' mothers had tertiary education. The predominant occupation was trading for mothers and similarly for fathers; 50.3% and 54.0% respectively (Table 1).

Table 1: Socio-demographic characteristics of respondents

Characteristics	**Percentage (%)**	**Characteristics**	**Percentage (%)**
Age		Secondary	121(40.3)
15	126(42.0)	Tertiary	156(52.0)
16	118(39.3)	No formal education	14(4.7)
17	43(14.3)	Not sure	2(0.7)
18	13(4.3)	**Mothers/Guardians' occupation**	
Sex		Trading	151(50.3)
Male	143(47.7)	Artisan	51(17.0)
Female	157(52.3)	Civil service	46(15.3)
Type of School Attending		Health professional	10(3.3)
Private	169(56.3)	Teaching	30(10.0)
Public	131(43.7)	Banking	12(4.3)
Religion		**Fathers/Guardians' occupation**	
Christianity	221(73.7)	Trading	162(54.0)
Islam	79(26.3)	Civil service	70(23.3)
Ethnicity		Clergy	4(1.3)
Yoruba	240(80.0)	Teaching	14(4.7)
Igbo	42(14.0)	Artisan	18(6.0)
Hausa	8(2.7)	Health professional	6(2.0)
Others	10(3.3)	Retired	8(2.7)
Mother's Highest Level of Education		Engineering	5(2.6)
Primary	7(2.3)	Accounting and banking	11(4.6)

Awareness of HPV, Cervical Cancer and HPV Vaccine

Less than a third of the respondents had heard about HPV (21.0%) and they claimed to have heard about HPV from social media (39.7%), radio or TV (19.2%), health practitioners (16.7%), school/teachers (5.1%)

and other sources such as family and friends. Majority of the respondents (76.3%) have not heard of HPV vaccination, however, more than half of the respondents (55.3%) had heard of cervical cancer (Table 2).

Table 2: Awareness of HPV, Cervical Cancer and HPV Vaccine

Characteristics	Yes	No	Not Sure
Ever heard HPV	63(21.0)	203(67.7)	34(11.3)
Ever heard HPV vaccination	38(12.7)	229(76.3)	33(11.0)
Ever heard Cervical cancer	166(55.3)	111(37.0)	23(7.7)
Ever heard HPV vaccine to protect against cervical cancer	35(11.7)	234(78.0)	31(10.3)

Knowledge of HPV and HPV vaccine

Majority (82.0%) of the respondents did not know how HPV is transmitted as only 15.0% reported that HPV is transmitted through sexual intercourse. Regarding who HPV can affect, only 32.7% of the respondents reported that both boys and girls can be infected and very few (13.7%) of the respondents claimed to know HPV-infected individuals can be asymptomatic. Only 31.0% of the respondents reported that HPV vaccine can prevent HPV infection while 16.3% reported that HPV vaccine can prevent cervical cancer. Majority of the respondents (64.7%) reported that they were not sure if the HPV vaccine guarantees protection from cervical cancer. Only 24.3% of the respondents reported that the vaccine shots should be given before the first exposure to sexual activity while majority (67.7%) were not sure. Very few of the respondents (3.3%) knew that 9 years and above is the age range of the target population for HPV vaccine. More than half of the respondents (57.0%) knew that the vaccine can be obtained in health facilities. Majority (88.0%) of the respondents reported that they do not know the required number of shots for the HPV vaccine and if cervical cancer can be terminal (64.7%). Overall, the majority (80.0%) had fair knowledge of HPV infection, 9% had poor knowledge while only 11% had good knowledge (Table 3).

Table 3: Knowledge of HPV and HPV vaccine

Characteristics	Percentage (%)	Characteristics	Percentage (%)
HPV is transmitted through		**HPV vaccine can guarantee over 90% protection from cervical cancer**	
Sexual intercourse	45(15.0)	Yes	50(16.7)
Airborne transmission	5(1.7)	No	56(18.7)
Vector vehicle	4(1.3)	Not Sure	194(64.7)
Don’t know	246(82.0)	**HPV vaccine shot(s) should be given before the first exposure to sexual activity**	

HPV can affect		Yes	73(24.3)
Boys	0(0.0)	No	23(7.7)
Girls	10(3.3)	Not Sure	203(67.7)
Boys and girls	98(32.7)	Nonresponse	1(0.3)
Don't know	192(64.0)	**Required number of shots of the HPV vaccine**	
HPV infected individuals can be asymptomatic		1-2 shots	19(6.3)
Yes	41(13.7)	2-3 shots	13(4.3)
No	13(4.3)	3-4 shots	4(1.3)
Not Sure	246(82.0)	Don't Know	264(88.0)
Age range of the 9 years and above target population for HPV vaccine		**Cervical cancer can be associated with HPV infection**	
9 years and above	10(3.3)	Yes	103(34.3)
12 years and above	12(4.0)	No	37(12.3)
14 years and above	55(18.3)	Not Sure	160(53.3)
Don't know	223(74.3)	**Cervical cancer is a genetic disease**	
HPV vaccine can prevent cervical cancer		Yes	68(22.7)
Yes	49(16.3)	No	49(16.3)
No	18(6.0)	Not Sure	183(61.0)
Not Sure	233(77.7)		

The majority of the respondents (63.7%) were unsure if HPV infection can cause cervical cancer. Only 14.0% of the respondents agreed to be at risk of HPV once they have had sex. Less than half (41.3%) of the respondents agreed that HPV vaccine can protect them from HPV infection and a little over half (51.3%) agreed that both boys and girls should take the HPV vaccine. Majority were undecided (69.7%) whether cervical cancer can be prevented by the HPV vaccine while 27.0% agreed that early initiation of sex can expose them to HPV infection. Majority (61.0%) of the respondents were unsure if their parents would allow them to take the HPV vaccine. In addition, majority (63.3%) reported undecided to sexually active persons do not need to take the HPV vaccine. However, 33.7% agreed that protected sex can prevent HPV infection. Overall, the majority (73.0%) of respondents had fair perception while 27.0% had good perception (Table 4).

Table 4: Perception of HPV and HPV vaccine

Characteristics	Agree	Undecided	Disagree	Non-response
HPV infection can cause cervical cancer	82(27.3)	191(63.7)	27(9.0)	0(0.0)
I am at risk of HPV once I have sex	42(14.0)	184(61.3)	73(24.3)	1(0.3)
HPV vaccine can protect me from HPV	124(41.3)	160(53.3)	15(5.0)	1(0.3)
Both boys and girls should take the HPV vaccine	154(51.3)	127(42.3)	18(6.0)	1(0.3)
Cervical cancer cannot be prevented by the HPV vaccine	31(10.3)	209(69.7)	60(20.0)	0(0.0)
I think early initiation of sex cannot expose me to HPV	39(13.0)	180(60.0)	81(27.0)	0(0.0)
My parents would allow me to take the HPV vaccine	82(27.3)	183(61.0)	35(11.7)	0(0.0)
Sexually active persons do not need the HPV vaccine	14(4.7)	190(63.3)	95(31.7)	1(0.3)
Protected sex can prevent HPV infection	101(33.7)	165(55.0)	34(11.3)	0(0.0)

Uptake of HPV vaccination

Very few of the respondents (1.3%) reported having taken the HPV vaccine and all had taken 2 shots over a year ago. Only 3.3% of the respondents reported knowing someone who had taken the vaccine.

Intention of respondents on uptake of HPV vaccination

Only 26.3% of the respondents reported personal intention to take the HPV vaccine and 29.0% reported that their parents will allow them to take the HPV vaccine if the cost is subsidized. More than half of the respondents (52.0%) reported their intention to take the HPV vaccine if given approval by their parents. Very few (26.2%) of the respondents reported their intention to take the HPV vaccine if their friends also take it. Few of the respondents (37.3%) were unsure of their intention to take the vaccine even if their teachers advised them to and 57.3% reported that their parents will allow them to take the vaccine if they know its benefits. About half (49.3%) reported their intention to take the vaccine if it is available in health facilities around their homes. More than half of the respondents (56.3%) reported their intention to take the vaccine if recommended/prescribed by their family doctor while only 26.3% of the respondents reported intention to take the vaccine if peers in their religious organizations also get vaccinated (Table 5).

Table 5: Intention of respondents on uptake of HPV vaccination

Characteristics	Yes	No	Not Sure
Intend to take the HPV vaccine	79(26.3)	82(27.3)	139(46.3)
Parents will allow to take the HPV vaccine if the cost is subsidized	87(29.0)	63(21.0)	150(50.0)
Intend to take the HPV vaccine if parents give approval	156(52.0)	51(17.0)	93(31.0)
Intend to take the HPV vaccine if friends also take it	80(26.7)	127(42.3)	93(31.0)
Intend to take the HPV vaccine if teachers advise to	97(32.3)	91(30.3)	112(37.3)
Parents will allow to take the HPV vaccine if they know its benefits	172(57.3)	39(13.0)	89(29.7)
Will take the HPV vaccine if it is available in health facilities around you	148(49.3)	51(17.0)	101(33.7)
Will take the HPV vaccine if family doctor recommends it	169(56.3)	44(14.7)	87(29.0)
Will take the vaccine if peers in your religious organizations take it	79(26.3)	97(32.3)	124(41.3)

Concerns about HPV vaccination

Majority of the respondents (60.7%) were concerned about the side effects of the vaccine. Very few (16.3%) reported that their parents might be concerned about the effectiveness of the vaccine and the cost (14.0%) while 35.7% reported their parents might be concerned about the safety of the HPV vaccine. Only 32.0% reported being scared of vaccination pain while 14.3% reported being concerned that their peers will think they were sexually active if they take the vaccine. Very few (6.0%) reported that their religious organization is against obtaining vaccination (Table 6).

Table 6: Concerns on HPV vaccination

Characteristics	Yes	No	Not Sure
Concerned about the side effects of the HPV vaccine	182(60.7)	42(14.0)	76(25.3)
Parents might be concerned that the HPV vaccine is not very effective	49(16.3)	65(21.7)	186(62.0)
Parents might be concerned about the cost of the HPV vaccine	42(14.0)	88(29.3)	170(56.7)
Scared about the pain of the vaccination shot	96(32.0)	105(35.0)	99(33.0)
Concerned that peers will think you are sexually active if you take the vaccine	43(14.3)	147(49.0)	110(36.7)
Religious organization is against the uptake of the HPV vaccine.	18(6.0)	158(52.7)	124(41.3)
Parents might be concerned about the safety of the HPV vaccine	107(35.7)	52(17.3)	141(47.0)

Association between Variables

Chi-square test was used to show the relationship between the socio-demographic characteristics and the knowledge of the respondents. There was a statistically significant relationship between knowledge and sex ($X^{2:}$ 6.908; p-value: 0.03) and type of school attended ($X^{2:}$ 8.840; p-value: 0.01) (Table 7).

Table 7: Association between socio-demographic characteristics and knowledge of respondents

Characteristics	Poor knowledge	Fair knowledge	Good knowledge	X^2	P-value
Sex					
Male	13(4.3)	121(40.3)	9(3.0)		
Female	13(4.3)	119(39.7)	25(8.3)	6.908	0.032*
Type of School Attending					
Private	1(4.0)	145(48.3)	12(4.0)		
Public	14(4.7)	95(31.7)	22(7.3)	8.840	0.012*

Study findings showed a statistically significant relationship between knowledge and adolescents' intention to take the HPV vaccine (p-value: 0.034); if available in health facilities around their homes (p-value: 0.034); if advised by their family doctor (p-value: 0.000) and if their parents are aware of its benefits (p-value: 0.015) (Table 8).

Table 8: Relationship between knowledge and intentions of in-school adolescents on the uptake of HPV vaccine

Characteristics	Poor knowledge	Fair knowledge	Good knowledge	P-value
Intend to take HPV vaccine				
Yes	4(1.3)	59(19.7)	16(5.3)	
No	9(3.0)	68(22.7)	5(1.7)	
Not sure	13(4.3)	113(37.7)	13(4.3)	0.034*
Parents will allow you take the HPV vaccine if they know its benefits				
Yes	8(2.7)	10(3.3)	8(2.7)	
No	139(46.3)	26(.7)	75(25.0)	
Not sure	25(8.3)	3(1.0)	12(4.0)	0.015*
Will take the HPV vaccine if available in health facilities around you				
Yes	6(2.0)	112(40.7)	20(6.7)	
No	6(2.0)	43(14.3)	2(0.7)	
Not sure	14(4.7)	75(25.0)	12(4.0)	0.034*
Will take the HPV vaccine if your family doctor recommends				
Yes	5(1.7)	138(46.0)	26(8.7)	
No	7(2.3)	35(11.7)	2(0.7)	
Not sure	14(4.7)	67(22.3)	6(2.0)	0.000*

Discussion

This survey revealed that sex and type of school attended by adolescents was highly related to their knowledge of HPV and HPV vaccination. This was supported by a similar study where better knowledge was also found among females and students who attended private-owned schools [17]. There was a higher knowledge of HPV among females due to common and incomplete knowledge that HPV is only contracted by females. This was also highlighted in their response as the majority of the respondents did not know that HPV could affect both boys and girls. The result from this study also asserted that awareness of HPV and HPV vaccine was low among the respondents, and many were unaware that HPV vaccination could protect against cervical cancer [14,18]. Very few of the respondents reported that the vaccine shots should be given before the onset of sexual activity, the age range of the target population to be vaccinated and the required number of shots. These results were like previous and recent studies with reported low levels of awareness of HPV and HPV vaccine in Nigeria [10,18]. Although there was low awareness of HPV, there was an appreciable awareness of cervical cancer, although this did not translate into an increase in knowledge, given there was still an inadequate knowledge of its causation. Consequently, the poor level of awareness

and knowledge found in this study may be attributed to the little coverage given to the relationship between HPV and sexuality education in schools.

Furthermore, very few of the respondents reported having taken the HPV vaccine or having known someone who took the vaccine. This highlights gaps in the uptake of HPV vaccination in Nigeria [10], and also asserts low vaccination uptake among adolescents as only 4 of the 300 respondents were reported to have taken the HPV vaccine[12,22]. Uptake of HPV vaccination is linked to the awareness and knowledge of the human papillomavirus and sexually transmitted infections generally as well as the perception of the vaccine itself, coupled with its effectiveness.

Generally, the findings also showed that majority of the respondents were unsure of their intention to take the vaccine. This corroborates a study among females that reported low intention [12]. A low reportage on intention may be attributed to the low awareness and knowledge of HPV and HPV vaccine. Respondents also reported taking the vaccine if their parents gave them approval and if their parents also knew the benefits of taking the vaccine. This factor is important as mothers' knowledge of HPV vaccine is still low[20,21]. Low knowledge of HPV vaccine among mothers can be a limiting factor to the uptake of HPV vaccine among their adolescents. Hence, health education strategies should be targeted at mothers and parents to improve awareness and knowledge of the vaccination as uptake by their adolescents is largely dependent on their consent and approval. A higher proportion also reported intention to take the vaccine if available in health facilities around them and if recommended by their family doctor. This shows the importance of these stakeholders in increased uptake of HPV vaccine.

Study findings showed a significant relationship between knowledge and respondents' intention to take the vaccine; their parents allowing them to take the vaccine if the cost is subsidized, their parents allowing them to take the vaccine if they know its benefits, if vaccine is available in health facilities around their homes and if the vaccine is recommended by their family doctors. Although this study revealed that parents, teachers and health workers are key stakeholders in driving the awareness and uptake of HPV and HPV vaccine among adolescents, they have been reported to be the least sources of information in this study and in previous ones as well [10,17]. It is therefore crucial to target and develop health education strategies for these groups.

Regarding concerns of adolescents on HPV vaccine, majority of the respondents were concerned about the side effects of the HPV vaccine, and whether their parents were concerned about the vaccine's effectiveness, safety and cost. There is a poor knowledge of the actual cost of the vaccine and fear of affordability of general healthcare services due to the income level of families. Previous studies have also identified similar concerns about the HPV vaccine which could also serve as barriers to its uptake; this includes concerns about its side effects in relation to infertility, the safety of the HPV vaccine, and the availability of HPV vaccine in health facilities, among others [16,20]. From the study findings, it could be assumed that the level of knowledge and perception of in-school adolescents on HPV and HPV vaccine could influence their intention and concerns on uptake of HPV vaccine.

From the study findings, it is therefore recommended that school health education intervention should engage learning activities that could increase awareness and knowledge of HPV and HPV vaccine among students. These measures could include showing movies that pass messages on HPV and HPV vaccine, music composition, discussions, posters, and group presentations on common STIs. In addition, awareness creation among parents considering that they play a major role in making health decisions for their children. Hence, schools should also include parents in awareness education on HPV, and the need for cervical cancer screening while also passing across health information on HPV vaccine to their children. This could be done through Parent Teachers' Association, newsletters, parents' WhatsApp group chats and other modes of communication used to access parents/guardians. Lastly, health facilities and health professionals should ensure to recommend the HPV vaccine to parents during consultations and visits as this study highlighted intention for uptake if recommended by family doctors.

Conflicting Interests

The authors declare that they have no competing interests.

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