Combining cervical cancer screening for mothers with schoolgirl vaccination during HPV-vaccine implementation in South Africa: Results from the VACCS1&2 trials

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PRECIS:

This study demonstrates successful linking of school-based HPV-vaccination, knowledge transfer and maternal cervical screening within a developing nation setting, using a transferable model.

HIGHLIGHTS:

Key findings and impact

- A vaccine acceptance rate of ~60% was reached in an opt-in programme requiring parental signed informed consent
- Use of oral presentations almost doubled the number of mothers with knowledge about cervical cancer
- Cervical self-screening was accepted by 47% of previously unscreened mothers of vaccine recipients

KEY WORDS: vaccine implementation; linkage of health interventions; screening uptake; HPV vaccination; HPV screening

ABSTRACT

Objective

The platform provided by HPV vaccination for linked public health interventions to improve cervical cancer prevention remains incompletely explored. The Vaccine And Cervical Cancer Screen (VACCS) cross sectional observation trials aimed to evaluate the efficacy of HPV school-based vaccination linked with maternal cervical cancer screening.

Methods

Girls from 29 schools in two provinces in South Africa were invited in writing to receive HPV vaccination. Two approaches to informed consent were compared, namely an audio-visual presentation (VACCS1) and in written format (VACCS2). Markers of vaccine uptake and coverage were calculated, namely uptake among the invited and consented cohorts, and rates of completion and sufficient vaccination. Mothers and female guardians received educational material about cervical cancer, and either a self-sampling device or an invitation to attend existing screening facilities. Knowledge was assessed in structured questionnaires (before and after), screening uptake was self-reported and directly assessed and compared between these approaches.

Results

Vaccine acceptance among 5137 invited girls was similar for the two methods of consent; 99.3% of consented girls received first dose; overall completion rate was 90.5% More girls were vaccinated using two-dose [974/1016 (95.9%)] than three-dose regimen [1859/2030 (91.6%)]. The questionnaire (n=906) showed poor maternal knowledge which improved significantly ($p<0.05$) after health education; only 54% of mothers reported any previous screening. The offer of a self-sampling device (n=2247) was accepted by 43.9% of mothers,

but only 26% of those invited to screen at existing facilities (n=396) reported subsequent screening.

Conclusion

Successful linking of primary health interventions to control cervical cancer was demonstrated. School-based HPV-vaccination, linked to health education, self-sampling and molecular screening resulted in significant improvements in knowledge and screening.

INTRODUCTION

Among women aged 15 to 44 years in South Africa, cervical cancer is the most common cancer, estimated to annually affect more than 10 000 women.[1,2] The high prevalence, as well as late presentation and poor survival of cervical cancer in South Africa have been attributed to the HIV epidemic, deficits in health infrastructure and the screening programme, poverty and lifestyle factors which all contribute to high rates of HPV infection and persistence, pre-cancerous lesions and cancer.[1-6] South Africa urgently needs a functional, integrated and effective cervical cancer prevention programme to revert this epidemic. Both primary and secondary prevention strategies are essential to address the cancer risk of current and future generations.[7]

In view of its efficacy and cost-effectiveness, school-based HPV vaccination is a major health priority for South Africa. Examples of successful cytology-based screening programmes in the developing world are rare or absent. In South Africa, coverage of the screening programme is low and has limited success to reach groups at highest risk. Several studies have demonstrated a lack of knowledge and awareness of the disease, which may contribute to poor health seeking behaviour.[8-10] In addition, failure to communicate and treat after positive screening is common. Finding alternative methods to reach the screening target population, improve their knowledge and communicate results must be a priority and will require innovative approaches.

School-based HPV vaccination programmes may serve as a novel platform to offer education and screening to adult female relatives, but the optimal way to link these preventive methods has not been determined.[11-13] We therefore conducted two cross sectional observation trials as part of the VACCS-initiative (Vaccine And Cervical Cancer Screen trials) to study different approaches to the potential linkage between HPV vaccination, education, and screening.

The primary objective of this study was to evaluate whether HPV vaccine implementation can be linked successfully with other health interventions to improve maternal cervical cancer knowledge and screening. The secondary objective was to describe determinants of adolescent HPV vaccine uptake and completion. This is a combined report of the VACCS1 and VACCS2 trials which were both conducted in the Gauteng and Western Cape provinces of South Africa.[14-16] Following the initial reports of these studies, HPV vaccine roll-out to primary school girls was initiated by the National Department of Health.

METHODS

Study protocols and procedures were approved by the institutional human research ethics review committees of the Universities of Pretoria (VACCS1: 219/2009; VACCS2: 90/2013) and Stellenbosch (N11/01/008). Approval to conduct the trials at primary public schools was obtained from national and provincial Departments of Health and Basic Education and local school governing bodies. Written informed consent was obtained from all subjects, the parents or legal guardians for minor subjects. The selection and recruitment of schools and the vaccination procedures for the first two studies were similar and previously reported.[14,15] Study size was based on the availability of donated vaccine dosages. The intention during VACCS1 was vaccination with the standard registered three doses of either quadrivalent or bivalent vaccine.

During VACCS2 only the bivalent vaccine was used and intended as two doses with a six-month interval. At the time, data convincingly demonstrated that two doses were sufficient for young girls.[17]

Vaccination

Parents could provide consent for vaccination of their daughters during the education events or without attending (first study) or were asked to complete and sign consent documents which were sent home (remote consent, second study). No girl was vaccinated without her own written and implied assent. Girls younger than 12 years needed parental consent by law. The vaccination process has been described earlier.[14,15]

Health Education

In VACCS1, parents received a printed invitation to an after-hours health education event at the school. During these events, information about the disease, its development, clinical presentation and prevention by vaccination and screening was shared using an audio-visual presentation. During VACCS2, extensive information about cervical cancer prevention options and about the study was offered to parents in a printed format, delivered home by the girl herself.

A questionnaire was developed, tested and validated in a small pilot study for use in VACCS1. Using this administered questionnaire, information from parent participants was acquired on demographics, knowledge of cervical cancer symptoms and prevention, as well as health care behaviour. The same questions were repeated after 3 months to determine changes in knowledge and participant-reported screening behaviour to evaluate efficacy of the educational intervention.

Screening

Mothers were invited to screen using three approaches: invitations to attend existing facilities (VACCS1); tampons and transport medium (with information to use) handed out directly for self-collected screening (VACCS1); and Evalyn® self-samplers sent home in a sealed package (VACCS2, both provinces). Screening was indicated for any woman with a uterus without recollection of previous screening in the last five years.

Information from the questionnaires were used to describe the demographics of the screening cohort and to calculate the size of the unscreened cohorts. All self-collected samples were tested with HPV DNA tests, while samples collected at existing facilities were tested in the standard way using cytology. We determined changes in screen behaviour using self-reporting and by calculating participation in HPV and cytological screening options.

Data Management

For analysis and comparison of the vaccination data of VACCS1 and VACCS2, girls enrolled in the targeted grades made up the invited cohort, and those with written parental and child consent made up the consented cohort. We defined the consented cohort for these studies as all those who consented to receive the vaccine. The vaccinated cohort were all girls who received at least one dosage, while all who received at least two doses, six months or more apart, were considered sufficiently vaccinated.[14] Uptake, completion and sufficiently vaccinated rates were calculated for the different cohorts and compared between the studies, using the relevant cohort denominator.

The two questionnaires were compared per participant to determine the impact of the project on knowledge and behaviour as previously described.[18] The number of women who attended existing screening facilities (VACCS1) after the health education event was determined by accessing data from the local screening registry.

The total target group for screening were all adult women available to participate; the unscreened target group was calculated from the percentage of participants indicating no screening in the last five years. The screened cohort included everyone who reported an improvement in screening to the previous 12 months (VACCS1) and women who handed in self-collected samples (VACCS1 and VACCS2). The invited cohort were all women verified

to have received an invitation to participate in screening. Uptake rates and positive screening rates were calculated using these different cohorts, as well as the test results.

Statistical analysis was performed using Statistica statistical software. A p-value <0.05 was considered statistically significant. In accordance with the journal's guidelines, all data required for the reproducibility of this study in other centres, will be provided if requested.

RESULTS

We invited 3465 primary school girls attending 19 schools during VACCS1 (2011-2013) and 1672 girls in ten schools in the same districts during VACCS2 (2013-2014). From these, 2619 mother-daughter pairs were invited from Gauteng Province and 2518 pairs from the Western Cape. Vaccination data are shown in Table 1.

Vaccination

Written parental consent and child assent for vaccination were obtained from 3068 of 5137 (59.7%) girls. Invited uptake rates were 59.0% for VACCS1 versus 61.1% for VACCS2, with no difference between the two strategies to inform and invite girls to this opt-in programme. Almost 90% of parents who attended a health education event, consented, but this was offset by relatively low attendance rates (Table 1).

Only 22 (0.7%) children with parental consent never received the first vaccine dosage, resulting in an overall uptake rate for consented children of about 99.3%. The completion rate of the two-dose regimen was significantly higher than the three-dose regimen (95.9% vs. 87.8%; p<0.0001). A larger percentage of girls were sufficiently vaccinated in the second project where two doses were intended (95.9% vs. 91.6%; p<0.0001) (Table 1).

Health Education

The questionnaires demonstrated a lack of knowledge about cervical cancer symptoms and prevention among mothers that improved significantly after attending health education events about the disease. (Table 2: knowledge). Data about knowledge improvement after receiving written information was not available, but information were distributed to more households when provided in printed format (100% vs. 28.6%) (Table 2).

The median age of mothers/female guardians of girls in grade four to seven was 38 years and of participants that accessed screening was 38.7 years (SD 7.7). Levels of education varied widely (primary school: 10%; tertiary education: 21 %) as did employment data (salaried: 50%; self-employed: 6.8%). Parents with children attending Gauteng schools were significantly younger and better educated[16] (data not shown).

Screening

Self-reported screening behaviour scores were similar for the different sites and improved in the total study after the invitation to participate. This data; however, did not correlate well with confirmed participation in screening (Table 3).[18] We could confirm the screening uptake and participation of those who accepted the invitation to self-sample and deliver the specimen at the school (Table 4).

The best estimate of screening uptake when participants were simply reminded to use existing facilities was the self-reported improvement of 24.5% in the second questionnaire translating into 10.7% of unscreened women. Screening uptake reached 43.9% of the study participants (28.6% of the total unscreened target group) when self-screening was offered either at a health education event (64.5%) or was sent home (32.8%) ($p<0.0001$) (Table 4).

Women who received self-screening kits at a health education event, were much more likely to use it than when it was sent home (31.8% vs. 16.4%; $p<0.0001$). Self-sampling kits were equally unused in large numbers during both studies, by women who elected to take it home

(VACCS1) and by those who received it at home in an envelope (VACCS2). Both methods resulted in 14.8% of the total target group being screened, translating to about 29.0% of the unscreened women (Table 4).

Throughout the project, about 19.1% of screening tests were positive for high-risk HPV (hrHPV) and 8.6% positive for HPV 16 and/or 18. As expected, tampon collected samples tested with Roche Linear Array was slightly more sensitive than brush collected samples tested with Roche Cobas. Although numbers were small, Western Cape samples appeared to have a lower prevalence of abnormalities compared to Gauteng (Table 5).

DISCUSSION

Summary of Main Results

During this HPV vaccine implementation study at primary schools, the overall vaccine uptake was 59.7%, and the need for parental informed consent (the opt-in model) was a significant barrier to vaccination. The consented uptake rate was near 100%; vaccine completion rates and the rate of sufficiently vaccinated participants were best with the two-dose regimen.

Vaccination was successfully linked with knowledge transfer and screening of mothers using self-sampling and molecular tests, which were abnormal in 27.7% of women. Self-screening was superior to using the existing health facilities, which may still have been over-reporting as not all tests could be confirmed via electronic access to the national screening database.[19] Women may not recall the time since their last screening test accurately and the results of these questions may also be influenced by social desirability bias. The age distribution of screened women mirrored the ideal screening target group, with most women between 30 and 49 years of age.

Results in the Context of Published Literature

Reported vaccine acceptance for the target group varies from 10% to >90%.[20] In a review of low- and middle income countries, half of all opt-in studies reported uptakes above 90%; 33% reported uptakes of 70-90%, while opt-out or implied consent was more successful.[21] In the current study, using an opt-in consent approach, requiring both written informed parental consent and child assent, vaccine uptake was lower than most other reports, but probably is realistic and reflects a true-life situation without campaigns to motivate. While multiple factors are reported to influence uptake (type of vaccination programme, coercion, time period of the study, income level of the participants, social media campaigns, or method to obtain consent), the true reasons for poor uptake are largely speculative.[22]

When vaccination rates are calculated per consented cohort, the vaccination rates of more than 99% compares with that reported in another early South African implementation study.[23] Heterogeneity regarding reported completion rates, or "follow-through rates," challenge comparison with the completion and sufficiently vaccinated rates calculated in the current study, which report on both two-dose and three-dose implementation.[22] The rates of sufficiently or completely vaccinated girls in the two-dose leg of the study, compares favourably with published data.[24]

Our demographic data confirm that mothers of vaccine recipients are an ideal target group for cervical cancer education and screening. Poor knowledge of disease detection and prevention has often been linked to high prevalence and late diagnosis of cervical cancer, but evidence about interventions that effectively addresses this problem is limited.[25] Consistent with previous reports, the present study confirmed that South African women lack this basic knowledge.[26,27] Importantly, in this report simple health education during a vaccine

implementation project had a measurable and significant positive effect on the knowledge of mothers of primary school children. Furthermore, it was demonstrated that increased knowledge scores can be linked to improved screening behaviour when screening was easy to access.[16]

Many methods have been tested to reach the unscreened population via self-sampling. In a meta-analysis which was performed according to the type of invitation used, participation rates varied widely. Door-to-door invitations in developing settings reached most women (92.4%), mailed self-sampling kits reached 20.7% and mailed opt-in invitations had participation rates of only 9.7%.[28] The overall screening participation rate among unscreened women in this study (29.5%) was similar for both methods to deliver sampling kits, and compares favourably to previously reported rates using mailed kits. Poor attendance was obtained using reminder invitation to existing screening facilities; this is in accordance with other reports.[29]

Strengths and Weaknesses

This school vaccine implementation project was performed in a real-life setting and linked to maternal education and screening. The study was performed in two provinces with very different demographics and in 29 schools to allow for the heterogeneity of the South African population. Other strengths include that different methods of inviting participation, and different dosing regimens were used and compared.

Limitations include the shortcomings of administered questionnaires, difficulties to accurately assess knowledge and attitudes and the potential inaccuracy of self-reported data. Determinants of parental consent could not be studied because questionnaire results were unavailable for non-consenting parents. The self-reported response of participants invited to screen at existing clinics was probably an overestimate and was not supported by other data sources.

Implications for Practice and Further Research

HPV vaccination campaigns can be used to offer health education and screening. Written and audio-visual material can effectively address the education gap; self-sampling kits can reach unscreened mothers via this platform. The positive attitude among parents toward vaccination, and health-seeking-behaviour for their children will hopefully contribute to wide-spread acceptance of HPV vaccine programmes in South Africa and similar developing countries. Further research should explore reasons for relatively poor vaccine uptake in opt-in programmes and methods to improve this uptake.

CONCLUSIONS

HPV vaccine programmes can enable linked primary and secondary prevention of cervical cancer, targeting schoolgirls and mothers. Education, vaccination and screening for cervical cancer control were all successfully combined in a single programme. Mothers of primary school children are socially and economically critically important and at the ideal age for cervical screening. HPV vaccine programmes can reach unscreened mothers via self-collected molecular tests and school-based logistics.

In this study, parental informed consent was the major determinant of vaccine uptake, while the number of required doses was the major determinant of vaccine completion. The distribution of information was most successful when sent home in a written format, but there was a poor response to the request for remote consent. During educational events, we obtained excellent parental consent rates and showed an improvement in knowledge, but attendance was relatively poor. The final consent rate was therefore similar between the two approaches. The two-dose regimen reached the best vaccine completion and sufficiently vaccinated rates.

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- Nurse research assistants and medical students: questionnaires and vaccination
- All participating schools, management teams, girls, parents and guardians.

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Table 1. Vaccine coverage

		Invited cohort	Consented cohort	Invited uptake rate (%)	Vaccinated cohort	Consented uptake rate (%)	Single dose	First two of intended three doses	Vaccine completion rate	Sufficiently vaccinated rate
Study	**Provincial sites**	**Target group = enrolled girls (n)**	**Girls with consent and assent (n)**		**Received at least one dose (n)**		**Received only one vaccine dosage (n)**	**Received two dosages, less than 6 months apart (n)**	**Received intended number of doses (n (%))**	**Received minimum 2 doses, 6 months apart (n (%))**
VACCS1	GP	1654	1059	64.0	1053	99.4	9	103	870 (82.6)	941 (89.4)
	WC	1811	987	54.5	977	99.0	10	49	912 (93.3)	918 (94.0)
	Total	**3465**	**2046**	**59.0**	**2030**	**99.2**	**19**	**152**	**1782 (87.8)**	**1859 (91.6)**
VACCS2	GP	965	519	53.7	518	99.8	23	n/a	495 (95.6)	495 (95.6)
	WC	707	503	71.1	498	99.0	19	n/a	479 (96.2)	479 (96.2)
	Total	**1672**	**1022**	**61.1**	**1016**	**99.4**	**42**	**n/a**	**974 (95.9)**	**974 (95.9)**
Project total		**5137**	**3068**	**59.7**	**3046**	**99.3**	**213**		**2756 (90.5)**	**2833 (93.0)**

GP = Gauteng Province; n/a = not applicable; VACCS = Vaccine And Cervical Cancer Screen; WC = Western Cape

Table 2. Questionnaire results

Vaccine acceptance			
Parental consent method	**Invitation to health education event (n (%))**	**Information letter sent home (n (%)) (n = 1 672)**	**p-value**
Households reached with information	906 / 3171 (28.6)	1672 (100)*	**<0.0001**
Acceptance per informed households	498 / 568 (87.7)#	1022 (61.1)	**<0.0001**
Acceptance per total target group	2046 / 3465 (59.0)	1022 (61.1)	0.2295

Knowledge about cervical cancer before and after intervention					
	Knowledge before health education event (n)		**Knowledge after health education event (n)**		**Significance of change**
	Inadequate	Adequate	Inadequate	Adequate	(p-value)
Symptoms	239	538	115	662	**<0.005**
Screening	539	238	288	489	**<0.005**
Vaccination	640	137	149	628	**<0.05**
Total	1418	913	552	1779	

*Assuming that all households received the letter; # data incomplete.

Bolded values indicate statistically significant findings

Table 3. Self-reported screening before and after the intervention (VACCS1)

	Screening experience before invitation (n)		**Screening experience after invitation (n)**		**Significance of change**
	Never	Ever	Never	Ever	(p-value)
Lifetime	338	391	227	502	<0.005
Past year	555	174	465	264	<0.005
Total	893	565	692	766	

Bolded values indicate statistically significant findings

VACCS, Vaccine And Cervical Cancer Screen

Table 4. Screening coverage.

Screening method			**Total target group**	**Unscreened target group**	**Invited cohort**	**Screened cohort**	**Invited uptake rate**	**Unscreened uptake rate**	**Newly screened#**	**Positive screen**	**Screening uptake rate**
Method of sampling	Method of screening	Method of invitation	Women targeted * (n)	Unscreened cohort (n (%)) $	Women receiving invitation (n)	Women screened during study (n)	Acceptance among invitees (n (%))	Acceptance among unscreened invitees (n (%))	Acceptance per unscreened study participants * (%)	Positive tests (n (%))	Previously plus newly screened (%)
HCW sampling	**Conventional cytology**	**Letter**	1811	909	396	97 *	97* / 396 (24.5)	97 / 909 (10.7)	19.6 *	17 * (17.5)	55.2 *
Self-sampling	**HPV genotyping on tampon sample**	**Personal**	1654	827	795	253	253 / 795 (31.8)	253 / 392 (64.5)	47.9	75 (29.6)	65.3
	HPV partial genotyping on brush sample	**Letter**	1672	836	1452	238	238 / 1452 (16.4)	238 / 726 (32.8)	46.6	61 (25.6)	64.2
Project total			**5137**	**2572 / 5137 (50.1)**	**2643**	**588**	**588 / 2643 (22.2)**	**588 / 2027 (29.0)**	**N/A**	**153 (26.0)**	**N/A**

$ calculated as 50.1% of all mothers as reported in questionnaire

*unverified; self-reported

#per unscreened study participants

HCW = healthcare worker; HPV = human papillomavirus; NA = not available

Table 5. Screening results

		Total number screened (n)	**Only other hrHPV (n (%))**	**HPV 16 and/or 18 (n (%))**
Region:	Gauteng Province	413	79 (19.1)	38 (9.2)
	Western Cape	78	15 (19.2)	4 (5.1)
Collection:	Tampon	253	52 (20.6)	23 (9.1)
	Brush	238	42 (17.6)	19 (8.0)
Test:	Genotyping	253	52 (20.6)	23 (9.1)
	Partial genotyping	238	42 (17.6)	19 (8.0)

HPV = human papillomavirus; hrHPV = high-risk HPV.