


BMJ Open Impact of one and two human papillomavirus (HPV) vaccine doses on community-level HPV prevalence in South African adolescent girls: study protocol and rationale for a pragmatic before–after design

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ABSTRACT

Introduction Vaccines against human papillomavirus (HPV) are the key to controlling cervical cancer in low/middle-income countries (LMICs) where incidence is highest, but there have been limited data from these settings on programme impact on HPV prevalence, and none in a population with endemic HIV infection. Furthermore, for many LMICs, the currently recommended two-dose schedule is difficult to deliver at scale, so there is mounting interest in a single-dose schedule.

Methods and analysis The Human Papillomavirus One and Two-Dose Population Effectiveness Study is a hybrid impact evaluation of the national South African HPV vaccination programme, which has targeted grade 4 girls aged at least 9 years in public schools with two doses of vaccine since 2014, and a single-dose vaccine ‘catch-up’ programme delivered in one district in 2019. Impacts of both schedules on the prevalence of type-specific HPV infection will be measured using repeat cross-sectional surveys in adolescent girls and young women aged 17–18 years recruited at primary healthcare clinics in the four provinces. A baseline survey in 2019 measured HPV prevalence in the cohort who were ineligible for vaccination because they were already above the target age or grade under either the national programme or the single-dose programme in the selected district. HPV prevalence surveys are repeated in 2021 in the selected district, and in 2023 in all four provinces. We will calculate prevalence ratios to compare the prevalence of HPV types 16 and 18 in the single-dose (2021) and two-dose (2023) cohorts, with the vaccine-ineligible (2019) cohort.

Ethics and dissemination The project was approved by the University of the Witwatersrand Human Research Ethics Committee (HREC #181005), and the University of New South Wales HREC (#181-005). Findings will be disseminated through peer-reviewed journals, scientific meetings, reports and community forums.

Strengths and limitations of this study

- The before–after design aims for reproducible cross-sectional samples to allow for the detection of changes over time in human papillomavirus (HPV) prevalence in populations that are comparable apart from vaccine schedule.
- The sampling frames, recruitment procedures, and HPV detection and genotyping methodologies have been validated and successfully implemented by members of the research team in different settings.
- The evaluation design is pragmatic and real world, so has the potential to provide information within the next 3 years on community-level impacts of both the one-dose and two-dose schedules compared with no vaccination.
- A limitation of the design is that sentinel clinics may reach a subgroup of adolescent girls who are more sexually active than the general population, so absolute HPV prevalence estimates may not be readily generalisable to other adolescent populations, but the estimates of relative reduction will be.
- A further limitation is that a proportion of adolescent girls vaccinated in the one-dose programme may have been sexually active and have acquired prevalent infection at the time of vaccination, which could bias vaccine impact estimates towards the null.

INTRODUCTION

Persistent infection with human papillomavirus (HPV) is a necessary cause of nearly all cervical cancer cases, as well as a fraction of cancers of the vulva, vagina, penis, anus, and head and neck.¹ There are an estimated 630 000 HPV-related cancers each year globally, of which 84% are cancers of the cervix, the fourth most common malignancy in women.^{1 2} Nearly all (84%) of these cancers



occur in low/middle-income countries (LMICs).² The impact of HPV is particularly striking for Southern and Eastern Africa, where age-standardised incidence rates for cervical cancer are 36 and 40 per 100 000 women, respectively, three to four times higher than the global average.³ This global inequality in cervical disease burden has been primarily due to disparities in access to screening and effective treatment. Delivered through well-organised programmes, screening based on cytological Pap testing has been highly successful in reducing cervical cancer incidence and mortality in high-income countries.^{4,5} However, LMICs have generally been unable to implement the clinical and laboratory infrastructure, quality assurance protocols, follow-up and linkage to treatment needed for an effective screening programme.⁶ In African countries, an additional factor driving HPV-related malignancies is the high rate of HIV infection, which can prevent effective immune control of HPV infection.⁷ High global uptake with effective HPV vaccines has been seen as the key to global control of cervical cancer.⁸

Since licensure in 2006, highly efficacious prophylactic HPV vaccines have been introduced into national immunisation programmes in over 110 countries, with the primary goal of preventing cervical cancer.⁹ There are three commercially available HPV vaccines in widespread use globally. The bivalent and quadrivalent vaccines protect against oncogenic HPV types 16 and 18, which cause 70% of cervical cancers. The nonavalent vaccine targets five additional oncogenic types, which account for a further 20% of cases. The quadrivalent and nonavalent vaccines also protect against HPV types 6 and 11, which cause most genital warts.¹⁰ The vaccines are highly effective in preventing infection and related cervical disease including cancer.^{11–13} However, they are not effective against pre-existing disease, so should be administered before exposure to HPV, ideally before sexual debut, which occurs at a median age of 17–20 years in most countries.^{10 11 14} Immunological bridging studies have demonstrated that antibody responses were non-inferior in those aged 9–15 years old compared with 16–26 years old, in whom protective efficacy against cervical disease has been established.¹⁵ Accordingly, the WHO recommended that vaccination be delivered at age 9–14 years to ensure that recipients are unlikely to be sexually active at the time of vaccination.¹⁶

Despite substantial evidence for the benefits of HPV vaccines, uptake has been poor in many LMICs.¹⁷ The main barriers include vaccine cost, delivery cost and delivery complexity for the target age group.¹⁸ Consequently, reducing the number of doses in the HPV schedule has become a key strategy to improve global vaccine coverage. Studies have shown that two doses administered to pre-adolescents with wider spacing between doses is serologically equivalent to three doses in adult women.¹⁵ Based on these data, the WHO recommended a two-dose schedule for girls under 15 years, with an interval of at least 6 months between doses in 2014.¹⁹ Country programmes have adopted this recommendation, with 11–13 years

being the most frequently targeted ages.¹⁷ However, there is limited research on the population impact of the reduced schedule, its potential to generate herd protection or cross-protection against non-vaccine types, as has been demonstrated for the three-dose schedule.¹¹

For many LMICs, even a two-dose schedule remains beyond reach, a problem compounded by a global shortage of HPV vaccine²⁰ and, more recently, the COVID-19 pandemic.²¹ There is growing evidence from retrospective analyses of incompletely dosed subgroups in randomised controlled trials^{22–24} and programmes,^{25 26} suggesting that a single dose is likely to generate satisfactory immune responses and, hence, protection against new HPV infections, and ultimately cervical cancer. These observations foreshadow potentially huge implementation advantages for cost-savings and coverage, particularly for LMIC settings,²⁷ and have informed recent suggestions by WHO for countries (in the context of supply and implementation constraints) to consider flexibility in the timing of the second dose for up to 3–5 years after the first dose.²⁸ However, this strategy constitutes off-label use of the vaccine, and evidence is not yet sufficient to support a formal recommendation to switch to a single dose.²⁹ Several individually randomised trials currently in progress will provide head-to-head evidence on immunogenicity and protection against infection of various combinations of dose numbers and valency.^{29–31}

South Africa introduced HPV vaccination with two doses of the bivalent vaccine in 2014 for grade 4 girls aged at least 9 years, becoming one of the first large African countries to introduce a national school-based programme.⁹ An early evaluation of programme implementation suggested that first dose uptake in 2014 reached 87% of the target population.³² Since 2014, available data indicate that while the programme has achieved first-dose coverage of at least 70% each year, course completion rates have lagged by 15%–20%.³³ The programme presents a unique opportunity to assess key issues related to population-level impact. First is the effectiveness of a schedule that differs from that investigated in randomised efficacy trials and high-income country programmes in regard to both the number of doses (2 vs 3) and the target age group (9 years vs 11–13 years). Second is the context in which the programme is being implemented, with extreme socioeconomic diversity, variable healthcare access and high HIV prevalence, all of which may influence programme impact. Finally, there is an opportunity to evaluate a one-dose schedule in a population of girls who were just older than the first vaccine-eligible age cohort but who are still in early adolescence and may benefit from vaccination.

Anticipated outcomes of HPV vaccination include reductions in circulating HPV infections, precursor cervical lesions and, in the long term, cervical cancer.³⁴ Given the lead time of decades between the acquisition of HPV infection and the development of cancer,^{34 35} earlier endpoints are needed to ensure that programmes are likely to have the intended impact. Tracking cervical

pre-cancer, which occurs earlier, has been used in high-income settings, but many countries do not have centralised population screening programmes, let alone large-scale registries. Furthermore, the population at risk may not have yet attained the age at which they would be also targeted for screening. Given these difficulties, a feasible means of early monitoring of vaccine programme impact has been the use of repeat cross-sectional surveys of type-specific HPV prevalence in selected populations.³⁶ Such surveys have been used to measure declines in HPV prevalence in vaccine-eligible cohorts following programme introduction and the levels of herd and cross-protection.¹¹

Using this approach, the Human Papillomavirus One and Two Dose Population Effectiveness (HOPE) Study aims to evaluate the impact of the two-dose schedule delivered through the national programme, as well as single-dose schedule delivered as a ‘catch-up’ in one district of the country, on community-level HPV prevalence in South African adolescent girls and young women (AGYW), both HIV negative and HIV positive. This paper describes the design and methodology of the study.

Primary objectives

Among South African AGYW aged 17–18 years:

- ▶ Measure the population impact of the national two-dose vaccine programme, delivered in grade 4 girls aged at least 9 years old, in protecting against infection with HPV 16 and 18.
- ▶ Measure the population impact of a single-dose vaccine schedule, delivered as a catch-up, to AGYW in grade 10 in one district, in protecting against infection with HPV 16 and 18.

Secondary objectives

- ▶ Determine whether HIV infection status affects the impact of the single-dose and two-dose HPV vaccine schedules.
- ▶ Measure the extent of vaccine cross-protection and herd protection of the national two-dose school programme.
- ▶ Identify sociodemographic and behavioural correlates of HPV vaccine uptake and impact of both vaccine schedules.

METHODS AND ANALYSIS

Study design and overview

The HOPE Study design is a hybrid impact evaluation of the South African national HPV vaccination programme and a ‘catch-up’ single-dose programme delivered to girls in grade 10 in a selected district. A surveillance network has been established at existing healthcare clinics in four provinces, including in the Lejweleputswa district of the Free State province where the catch-up programme took place. At each surveillance round, AGYW aged 17–18 years attending participating clinics are invited to self-collect a specimen for HPV testing and to complete a short questionnaire. Impacts of both schedules on protection against

infection will be measured by comparing HPV prevalence between birth cohorts of AGYW who were vaccine eligible with prevalence in a preceding cohort who were not. An overview of the study design is presented in [figure 1](#).

Objective 1 will be achieved by comparing HPV prevalence between AGYW aged 17–18 years recruited in 2019 and 2023 at participating study clinics in all four provinces. The survey conducted in 2019 provided an estimate of HPV prevalence in the cohort that was at least 3 years too old to have been eligible for vaccination in the national programme and at least 2 years too old to have been eligible for the single-dose catch-up programme in Lejweleputswa (see next paragraph). The survey in 2023 will obtain an estimate of HPV prevalence among AGYW in the first cohort to have been eligible for the national two-dose programme at age 9 years through their schools, in 2014 (see [figure 1](#)).

Objective 2 will be achieved by comparing HPV prevalence between AGYW aged 17–18 years recruited in 2019 and 2021 through participating clinics located in the Lejweleputswa district of the Free State province, where a single dose of the bivalent vaccine was offered to girls in grade 10 attending public schools in the first half of 2019, as described in more detail below. The 2019 baseline study population will be the subset of AGYW recruited from clinics in the Lejweleputswa district in that year, as described in the preceding paragraph. The survey in 2021 will measure HPV prevalence in AGYW aged 17–18 years who would have been eligible for the single-dose catch-up in Lejweleputswa (see [figure 1](#)).

Implementation of the single-dose catch-up in Lejweleputswa district, Free State

Setting

The single-dose catch-up was a one-off campaign conducted between February and May 2019. It was designed and overseen by the research team with research ethics approval. One dose of the bivalent HPV vaccine was offered to adolescent girls in year 10 at all public schools in the Lejweleputswa district of the Free State province (see [figure 2](#)). This setting was chosen for several reasons:

- ▶ The province has among the highest vaccine coverage rates in the national school-based programme (83% and 74% for one and two doses in 2017, respectively) (internal communication with South African National Department of Health). High coverage ensures that any difference in relative HPV prevalence between the dosing schedules will be predominant due to differences in protection.
- ▶ The district is located in a province with high HIV prevalence (25.2% overall),³⁷ increasing the likelihood of reaching target numbers of HIV-positive AGYW in the surveys.
- ▶ The study team had previously established an excellent working relationship with district authorities, health services and education authorities in this province, including a large-scale multiyear health

Objective 1: Compare HPV prevalence to measure impact of school programme (Four provinces)

Objective 2: Compare HPV prevalence to measure impact of single dose catch-up programme (Free State province only)

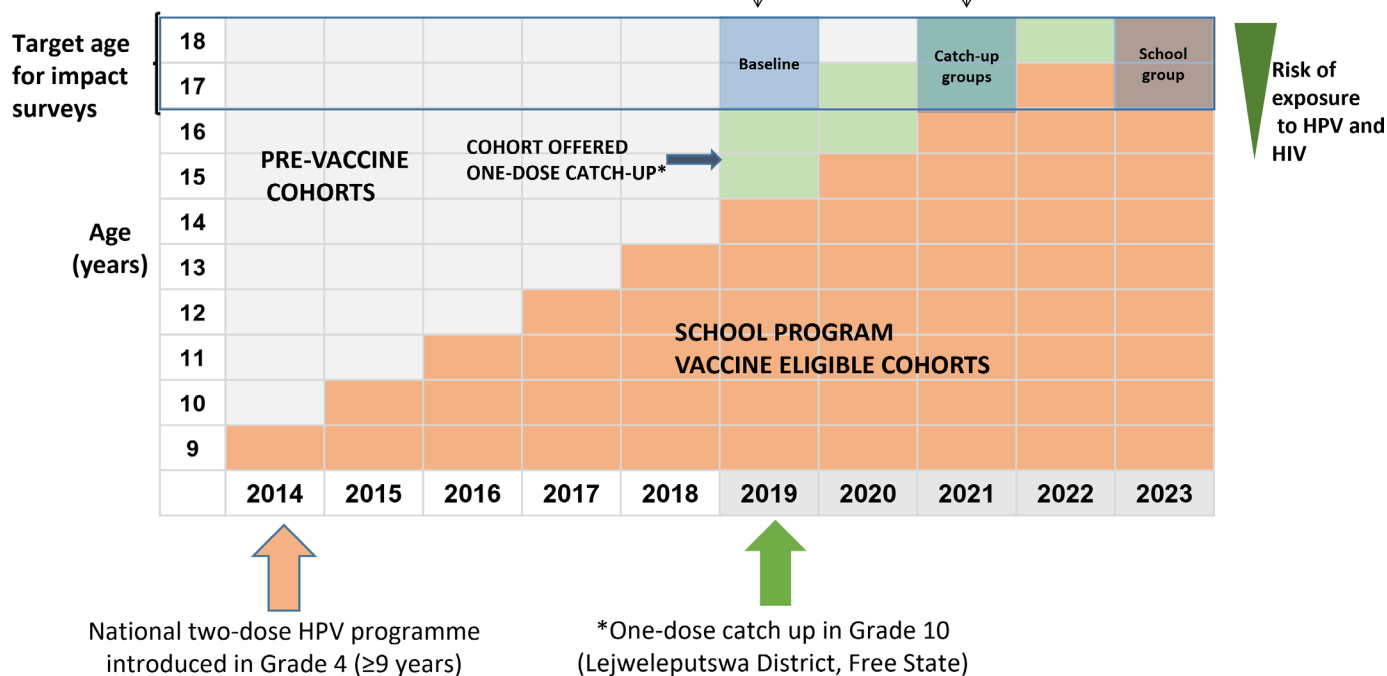


Figure 1 Timing of one-dose catch-up programme, the timing of cohorts offered two doses of HPV vaccine in schools and timing of impact surveys. HPV, human papillomavirus.

system-strengthening initiative, increasing the likelihood of successful implementation.

Target population

An estimated 6700 adolescent girls attending 66 public high schools in the district were offered a single dose of the bivalent HPV vaccine (Cervarix). Girls attending these schools were eligible if they were in year 10, had never received any HPV vaccine doses and provided written consent. Girls were excluded if they reported a history of severe illness or were ill on the day of vaccination, or disclosed that they were pregnant or breast feeding.

Vaccination campaign

The study team worked with both the national and provincial Departments of Health and Departments of Basic Education, to align the campaign as much as possible with principles and procedures used in the national two-dose programme. The research team provided all resources required for the catch-up campaign, including vaccine doses, staff support, fridges, cooler boxes, transport and other logistical support. At each school, study vaccination teams worked with educators to implement the campaign. Study-specific information and consent forms were distributed at schools a few weeks before the scheduled vaccination dates. Written informed parent or guardian consent, and learner assent were both required by the Departments of Health to participate.

Individual doses administered at each school were recorded on electronic registers held by the research team. Information collected included full name, date of birth, date of vaccination and vaccine batch number. To track progress, summary sheets were generated weekly containing, for each school, enrolment numbers for girls in grade 10 and the total number of girls vaccinated as recorded in the study register. The target coverage for each school was 80%, in line with one-dose coverage in the national programme.

Implementation of HPV prevalence surveys

Setting

The provinces of Gauteng, North West, Mpumalanga and Free State (see figure 2) were selected to reflect geographical and sociodemographic diversity and variation in coverage achieved through the national HPV vaccination programme (see table 1). Within each province, publicly funded clinical sites were selected based on the following considerations:

- ▶ *High numbers of target population:* clinics that target young women, particularly adolescents.
- ▶ *High HIV caseload in the target population, including adolescents:* clinics are located within 27 districts prioritised for sexual health services due to higher HIV prevalence in AGYW.

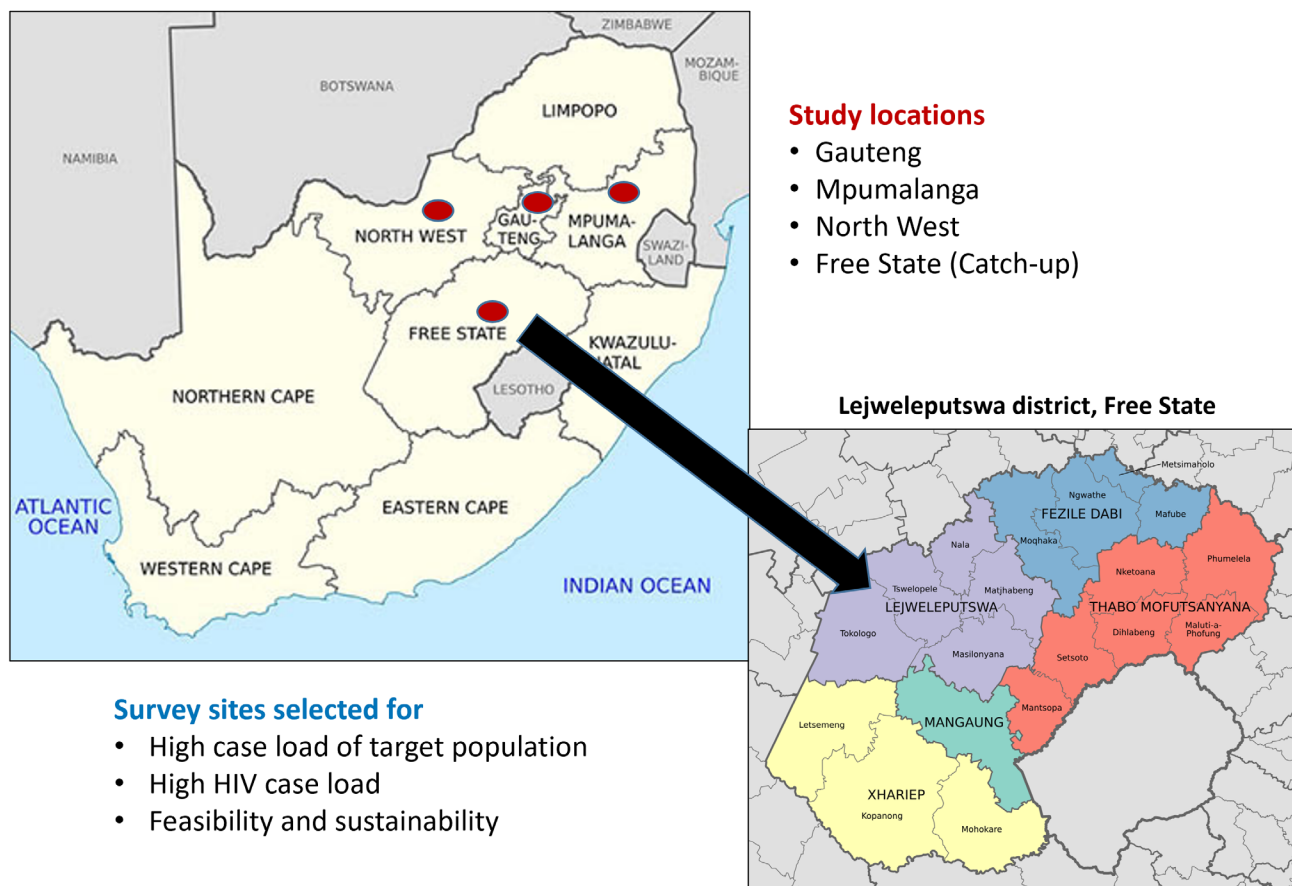


Figure 2 Location of study clinics.

- ▶ *Capacity to act as study sites throughout the project and beyond:* clinics have experience with conducting surveillance activities and a strong history of research collaboration activities with the study team, including organisation of self-collection of vaginal swabs by young women.

Target population

Available population-based data suggest that between 30% and 50% of South African adolescent girls report having had sexual intercourse, with the average age at first sex ranging from 16 to 18 years.³⁸ Accordingly, targeting the surveys to AGYW aged 17–18 years will ensure they are likely to have become sexually active and at risk of HPV

infection at the time of recruitment and therefore, in the vaccine-eligible cohorts, potentially able to benefit from the vaccination.

Recruitment

The procedures to recruit survey participants are identical at all clinics across the three survey periods. Research staff identify consecutive age-eligible AGYW attending health services for routine care. Invitation to participate depends on the research staff's judgement that there is sufficient time to discuss the study without disrupting the clinical care of the patient. Written informed consent is obtained from all participants. For those aged 17 years, South African law generally requires consent for research participation from a parent. However, a waiver of parental consent was granted by the Witwatersrand Human Research Ethics Committee for the study. The project aims to recruit a total of 3950 AGYW. Each survey is conducted over a period 9–10 months to ensure sufficient numbers of AGYW with HIV are recruited (see table 2).

Study procedures

Consenting participants self-collect a vaginal sample for HPV testing using a dry flocced swab following guidance from the research staff. They then complete a validated self-administered questionnaire³⁹ covering questions on HPV vaccination history and correlates of HPV prevalence

Table 1 Location of study clinics and coverage estimates through the school-based programme, 2017*

	1st dose	2nd dose
<i>National</i>	81%	64%
Gauteng province	82%	67%
North West province	85%	74%
Mpumalanga province	75%	43%
Free State province	84%	70%

*Internal communication with South African National Department of Health.

Table 2 Maximum target enrolment numbers per survey, stratified by HIV status

	2019		2021		2023	
	All provinces	Free State only	All provinces	Free State only	All provinces	Free State only
HIV negative	550	400	–	1000	1300	1000
HIV positive	300	210	–	350	450	360

including age, education level, area of residence, smoking status, age at first vaginal sex and hormonal contraceptive use.⁴⁰

Participants are asked to provide their HIV status based on recent test results. AGYW who have not had an HIV test in the past 3 months are offered HIV counselling and testing.⁴¹ AGYW who test positive receive post-test counselling and are linked to care as per national guidelines.⁴¹ For participants known to have HIV, data on HIV diagnosis date, treatment regimen, viral load and CD4 count (where available) are abstracted from clinical records, with participant consent.

Participants are reimbursed with an R100.00 voucher for the time contributing to the survey.

HPV detection and genotyping

All samples are stored at 4°C or lower (depending on availability) before being transported to the central laboratory for processing and long-term storage at –20°C. Swabs are swirled in 1000 µL of phosphate-buffered saline or transport medium to suspend cellular material. After nucleic acid extraction, all specimens are tested for HPV DNA and genotyped using Seegene Anyplex II HPV28 (Seegene, Seoul, South Korea), a multiplexed quantitative PCR melting-curve assay for the detection of up to 28 HPV genotypes. Each test reaction includes a house-keeping beta-globin gene detected as an internal control to monitor extraction efficiency, cell adequacy and PCR inhibition.

Validation of individual HPV vaccine doses

Doses administered in the catch-up will be validated against records in the study register. For doses administered in the national programme, data on HPV vaccination history, including the date of each dose, will be extracted from provincial Departments of Health vaccination registers.

Statistical considerations

Primary outcomes and broad statistical plan

The primary outcome measure is the prevalence of vaccine-targeted HPV types 16 and 18 and will be calculated along with 95% CIs at each survey round. Binomial log-linear regression or generalised linear models will be used to estimate prevalence ratios with 95% CIs to compare outcomes between survey periods (see figure 1), adjusted for any characteristics that are found to vary between the surveys ($p < 0.1$). All tests will be two sided ($\alpha = 0.05$). Overall vaccine impact for each dosing schedule will be estimated using the formula 1-adjusted

PR \times 100. Differences in the prevalence of HPV types other than 16 and 18 will be used as a marker of between-cohort differences in sexual behaviour. Differences in impact between HIV-positive and HIV-negative participants will be assessed by stratification and testing for interactions, to account for the possibility that HPV prevalence may differ by HIV status.

As this is a real-world programmatic evaluation of vaccine impacts using a before–after methodology, the study was designed to compare cohorts who received the vaccine (either in the catch-up or the school campaigns) with those who did not. The main comparisons will be limited to these two groups. Any differences in relative HPV prevalence between one-dose and two-dose schedules will only compare the two resulting impact estimates as described above, without formal statistical testing.

Sample size

The prevalence of HPV types 16 and 18 among HIV-negative and HIV-positive South African AGYW aged 17–18 years has been estimated to be approximately 19%⁴² and 30%,⁴³ respectively. With these baseline estimates, the study has 80% or more power to detect post-vaccine prevalence estimates of 11.4% among HIV-negative and 18.0% among HIV-positive females, a relative reduction of 0.6 (40%), as significantly different at the 0.05 level. Meta-analyses of vaccine impact data from countries that have implemented three-dose schedules suggest relative reductions in HPV 16/18 prevalence among vaccine-eligible female adolescents aged 15–19 years within 1–4 years following programme implementation are 72% (Relative Risk [RR]=0.28; 95% CI: 0.19 to 0.41) if coverage is high ($\geq 50\%$), and 50% (RR=0.50; 95% CI: 0.34 to 0.74) if coverage is low ($< 50\%$).¹¹ Strong population-level impacts can be expected with coverage as low as 20%.⁴⁴

Patient and public involvement

The National Department of Health was involved in project development from inception in 2018 and is a named collaborator on the funding applications. Once funding was secured, an inception meeting was held that involved stakeholders from the national, provincial and district Departments of Health and Basic Education. The team also conducted stakeholder consultations with community members in all four provinces. All stakeholders were consulted about the study design and implementation, and their feedback was incorporated throughout the study design process.

In the Free State, the study team conducted outreach to 961 parents and 4790 AGYW across 66 schools before implementing the catch-up. A community advisory board was also established. An information dissemination plan was developed in consultation with the key stakeholders, including provincial Departments of Health, Department of Basic Education, parent associations, school governing bodies, teachers and principals. Information on the campaign was disseminated prior to commencement of vaccination through multiple mechanisms (ie, posters, fact sheets, education sessions and meetings, and email lists).

During the design of the HPV prevalence surveys, efforts were made to minimise the burden on existing health staff in clinics and to ensure that clinic visits for AGYW are efficient and comprehensive, responding to all their health needs in a single visit.

ETHICS AND DISSEMINATION

Ethical and safety considerations

The bivalent vaccine is approved for use in females aged 9 through 45 years and has an excellent safety profile.⁴⁵ Most adverse events following immunisation (AEFIs) are minor and include headaches, muscle aches, nausea or local reactions (redness, swelling, pain at the injection site). In rare instances, fainting or syncope may occur. There is no evidence that the HPV vaccine increases the risk of syncope, but post-vaccination syncope in adolescents receiving the HPV vaccine has been reported.⁴⁵ In extremely rare cases, severe AEFI like anaphylaxis, which requires resuscitation and necessitates immediate hospitalisation, can occur.⁴⁵ All reported adverse events following administration of the catch-up HPV vaccine dose were recorded, per national guidelines. These were all minor. There were no serious AEFIs that resulted in hospitalisation.

The single-dose HPV vaccine schedule is currently outside the standard recommendation, and can only be given in a research context. Its use in this project is supported by the growing evidence of the protective benefits of a single dose, the highly favourable side effect profile and the consideration that those in the catch-up would have otherwise received no vaccine doses at all. If study results and other evidence suggest that a single dose does not provide adequate protection, a delayed second HPV vaccine dose will be offered to participants. This was clearly stipulated in the consent forms.

The HPV survey procedures are considered to be extremely low risk. Responses to sensitive questions are collected using a computer-assisted self-interview to minimise any social discomfort. Visual aids are used to demonstrate how participants can self-collect a swab with minimal discomfort. Being tested for HIV may subject participants to stigma and discrimination if inadvertently revealed to persons outside the study. Patient confidentiality and anonymity is maintained at all times to minimise the risk of possible disclosures.

Survey participants may become distressed if they learn they have a positive HPV test. They are counselled before sample collection about the meaning of a positive test and any requirements for longer-term screening and follow-up access. They are asked whether they would like to receive their HPV results and, if so, how. Those who wish to receive their results are contacted by study staff with the option of receiving results and counselling over the phone or in person. Participants with positive results for oncogenic HPV types are advised that their HPV infection may be self-limiting and resolve without immediate treatment. However, as an additional safety measure, they are offered a referral for a further screening test to be performed after 12 months.

Dissemination plan

A communication plan was developed to map ongoing communication to stakeholder groups across the study life cycle. The dissemination process will consider scientific, policymakers and general population audiences. Interim and final results will be presented to the scientific community through conference presentations and publications in scientific journals. Efforts will be made to ensure that results are available in open-access journals wherever possible.

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