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

Dorothy Machalek,1,2 Helen Rees,3 Admire Chikandiwa,3 Richard Munthali,3 Danielle Travill,2 Zizipho Mbulawa,4,5 Kathy Petoumenos,1 Sinead Delany-Moretliwe,3 John Kaldor,1 On behalf of the HOPE Study team

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 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.

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

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.
occur in low/middle-income countries (LMICs).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{7} High global uptake with effective HPV vaccines has been seen as the key to global control of cervical cancer.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10} The vaccines are highly effective in preventing infection and related cervical disease, including cancer.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16}

Despite substantial evidence for the benefits of HPV vaccines, uptake has been poor in many LMICs.\textsuperscript{17} The main barriers include vaccine cost, delivery cost and delivery complexity for the target age group.\textsuperscript{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.\textsuperscript{19} 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.\textsuperscript{20} Country programmes have adopted this recommendation, with 11–13 years being the most frequently targeted ages.\textsuperscript{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.\textsuperscript{11}

For many LMICs, even a two-dose schedule remains beyond reach, a problem compounded by a global shortage of HPV vaccine,\textsuperscript{20} and, more recently, the COVID-19 pandemic.\textsuperscript{21} There is growing evidence from retrospective analyses of incompletely dosed subgroups in randomised controlled trials\textsuperscript{22–24} and programmes,\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{30} An early evaluation of programme implementation suggested that first dose uptake in 2014 reached 87% of the target population.\textsuperscript{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%.\textsuperscript{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.\textsuperscript{34} Given the lead time of decades between the acquisition of HPV infection and the development of cancer,\textsuperscript{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. 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.

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), 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
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.

---

**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)
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. 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 flocked swab following guidance from the research staff. They then complete a validated self-administered questionnaire 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*

| Location                | 1st dose | 2nd dose |
|-------------------------|----------|----------|
| National                | 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.
including age, education level, area of residence, smoking status, age at first vaginal sex and hormonal contraception 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 (Seogene, Seoul, South Korea), a multiplexed quantitative PCR melting-curve assay for the detection of up to 28 HPV genotypes. Each test reaction includes a housekeeping 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 PRX100. 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 (≥50%), and 50% (RR=0.50; 95% CI: 0.34 to 0.74) if coverage is low (<50%).33 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. Most adverse events following immunisation (AEFIs) are minimal 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. In extremely rare cases, severe AEFI like anaphylaxis, which requires resuscitation and necessitates immediate hospitalisation, can occur. 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.

Author affiliations

1Kirby Institute, University of New South Wales-Kensington Campus, Sydney, New South Wales, Australia
2Centre for Women’s Infectious Diseases, The Royal Women’s Hospital, Parkville, Victoria, Australia
3Wits RHI, University of the Witwatersrand, Johannesburg, Gauteng, South Africa
4UCT-MRC Clinical Gynaecological Cancer Research Centre, University of Cape Town, Rondebosch, Western Cape, South Africa
5Department of Laboratory Medicine and Pathology, Walter Sisulu University, Mthatha, Eastern Cape, South Africa

Acknowledgements We would like to thank Admire Chikandiwa, Anna-Lise Williamson, Moira Beery and Yogan Pillay for their contributions to design and implementation during the early stages of the project.

Collaborators The HOPE study team includes Sinead Delany-Morettwe, Helen Rees, John Kaldor, Dorothy Machalek, Zizipho Mbulawa, Danielle Travill, Mojalefa Makae, Thandiswa Mzimela, Thembioble Mogodiri, Nontoko Zo Ntlou, Edwin Mkwansazi, Richard Munthali, Kathy Petoumenos, Andrew Valiley, Rebecca Guy, Suzanne Garland, Ian Frazer and Julia Brotherton.

Contributors The study was conceived by JK, DM, SD-M, HR and AC. All authors contributed to study design. SD-M led study implementation with support from HR and DT. ZM developed the initial HPV testing protocols. RM and KP led the statistics plan. DM, SD-M and JK drafted the initial manuscript which was critically revised by all the authors.

Funding This work was supported by the Bill and Melinda Gates Foundation (Opportunity ID: OPP11956557), and the National Health and Medical Research Council (Number: APP1164430).

Map disclaimer The inclusion of any map (including the depiction of any boundaries therein), or of any geographic or locational reference, does not imply the expression of any opinion whatsoever on the part of BMJ concerning the legal status of any country, territory, jurisdiction or area or of its authorities. Any such expression remains solely that of the relevant source and is not endorsed by BMJ. Maps are provided without any warranty of any kind, either express or implied.

Competing interests DM has received grants from Seqirus, non-financial support and honoraria donated to her institute from MSD, all more than 3 years ago. She has also received journal access sponsorship from Roche Diagnostics. All other authors report no conflicts of interest.

Machalek D, et al. BMJ Open 2022;12:e059968. doi:10.1136/bmjopen-2021-059968 7
REFERENCES

1. de Martel C, Plummer M, Vignat J, et al. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Cancer 2017;141:664–70.

2. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Health 2020;8:e191–203.

3. International Agency for Research on Cancer (IARC). GLOBOCAN, 2018. Available: https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf

4. Jansen EEL, Zielonke N, Gini A, et al. Effect of organised cervical screening on cervical cancer mortality in Europe: a systematic review. Eur J Cancer 2020;127:207–23.

5. Vacciarella S, Franceschi S, Zaridze D, et al. Preventable fractions of cervical cancer via effective screening in six Baltic, central, and eastern European countries 2017–40: a population-based study. Lancet Oncol 2016;17:1445–52.

6. Pimple SA, Mishra GA. Optimizing high risk HPV-based primary screening for cervical cancer in low- and middle-income countries: opportunities and challenges. Minerva Ginecol 2019;17:365–71.

7. Stelzle D, Tanaka LF, Lee KK, et al. Estimates of the global burden of cervical cancer associated with HIV. Lancet Glob Health 2021;9:e161–9.

8. World Health Organization. Global strategy to accelerate the elimination of cervical cancer as a public health problem, 2020. Available: https://www.who.int/publications/i/item/9789240014107

9. PATH. Global HPV vaccine introduction overview, 2021. Available: https://www.path.org/resources/global-hpv-vaccine-introduction-overview/

10. Bergman H, Buckley BS, Villanueva G, et al. Comparison of different human papillomavirus (HPV) vaccine types and dose schedules for prevention of HPV-related disease in females and males. Cochrane Database Syst Rev 2019;2019. doi:10.1002/14651858.CD013479. [Epub ahead of print: 22 11 2019]

11. Drotlet M, Bernard Eloitje, Perez N, et al. Population-Level impact and herd effects following the introduction of human papillomavirus vaccination programmes: updated systematic review and meta-analysis. Lancet 2019;394:497–509.

12. Lei J, Ploner A, Elfsrom KM, et al. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med 2020;383:1340–8.

13. Falcars M, Castaño A, Nidela B, et al. The effects of the National HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. Lancet 2021;398:2084–92.

14. Wellings K, Cobourn M, Slaysmayer E, et al. Sexual behaviour in context: a global perspective. Lancet 2006;368:1706–28.

15. Pinto LA, Diliner J, Beddows S, et al. Immunogenicity of HPV prophylactic vaccines: serology assays and their use in HPV vaccine evaluation and development. Vaccine 2018;36:4792–9.

16. Human papillomavirus vaccines: WHO position paper, May 2017. Wkly Epidemiol Rec 2017;92:241–68.

17. Bruni L, Saura-Lázaro A, Montoliu A, et al. HPV vaccination introduction worldwide and WHO and UNICEF estimates of national HPV immunization coverage 2010-2019. Prev Med 2021;144:106293.

18. Shin MB, Liu G, Mugo N, et al. A framework for cervical cancer elimination in Low-and-Middle-Income countries: a scoping review and roadmap for interventions and research priorities. Front Public Health 2021;9:670032.

19. Human papillomavirus vaccines: WHO position paper, October 2014. Wkly Epidemiol Rec 2014;89:465–91.

20. World Health Organisation. Global market study: HPV, 2020. Available: https://www.who.int/immunization/programmes_systems/procurement/mia4/platform/modules/HPV_Global_Market_Study_Public_Summary-Nov2020.pdf?ua=1

21. Toh ZQ, Russell FM, Garland SM, et al. Human papillomavirus vaccination after COVID-19. JNCI Cancer Spectr 2021;5:skab011.

22. Kreimer AR, Herrero R, Sampson JN, et al. Evidence for single-dose protection by the bivalent HPV vaccine-Review of the Costa Rica HPV vaccine trial and future research studies. Vaccine 2018;36:4774–82.

23. Basu P, Malvi SG, Joshi S, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. Lancet Oncol 2021;22:1519–29.

24. Kreimer AR, Struyf F, Del Rosario-Raymundo MR, et al. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica vaccine and PATRICIA trials. Lancet Oncol 2015;16:775–86.

25. Batmunkh T, Dalmaz MT, Mukhsaikhan M-E, et al. A single dose of quadrivalent human papillomavirus (HPV) vaccine is immunogenic and reduces HPV detection rates in young women in Mongolia, six years after vaccination. Vaccine 2020;38:4316–24.

26. Brotherton JM, Budd A, Rompolis C, et al. Is one dose of human papillomavirus vaccine as effective as three?: a national cohort analysis. Papillomavirus Res 2019;8:100177.

27. Burger EA, Campos NG, Sy S, et al. Health and economic benefits of single-dose HPV vaccination in a Gavi-eligible country. Vaccine 2018;36:4823–9.

28. World Health Organisation. Weekly epidemiological record. No 47 2019, 94, 541–560. Available: https://apps.who.int/iris/bitstream/handle/10665/329962/WER9447-eng-fre.pdf?ua=1

29. PATH. Technical synthesis of the current published evidence for single-dose HPV vaccination (December 2020). Available: https://www.path.org/resources/technical-synthesis-current-published-evidence-single-dose-hpv-vaccination/

30. Barnabas RV, Brown ER, Onono M, et al. Single-Dose HPV vaccination efficacy among adolescent girls and young women in Kenya (the KEN she study): study protocol for a randomised controlled trial. Trials 2021;22:661.

31. Baisley KJ, Whitworth HS, Changalucha J, et al. A dose-reduction HPV vaccine immunobridging trial of two HPV vaccines among adolescent girls in Tanzania (the DoRIS trial) - Study protocol for a randomised controlled trial. Contemp Clin Trials 2021;101:106266.

32. Delany-Moretffle S, Kelley KE, James S, et al. Human papillomavirus vaccine introduction in South Africa: implementation lessons from an evaluation of the National school-based vaccination campaign. Glob Health Sci Pract 2018;6:425–38.

33. World Health Organisation. WHO/UNICEF joint reporting form on immunization (JRF): human papillomavirus (HPV) vaccination coverage. Available: https://immunizationdata.who.int/pages/coverage/hpv.html?CODE=ZAFANTIGEN&YEAR= [Accessed 19 Nov 2021].

34. World Health Organisation. Weekly Epidemiological Record, 2010, vol. 85, 25 [full issue], Weekly Epidemiological Record = Revêlé épidémiologique hebdomadaire, 85 (25), 237-248, 2010. Available: https://apps.who.int/iris/handle/10665/241594

35. Schiffman M, Wentzensen N, Wacholder S, et al. Human papillomavirus testing as the prevention of cervical cancer. J Natl Cancer Inst 2011;103:368–85.

36. Brotherton JML, Wheeler C, Clifford GM, et al. Surveillance systems for monitoring cervical cancer elimination efforts: focus on HPV infection, cervical dysplasia, cervical screening and treatment. Prev Med 2021;144:106293.

37. LCZK S, Zungu N. HIV impact assessment summary, Cape town: HSRC press, 2017. Available: http://www.hsrc.ac.za/uploads/pageContent/9234/

38. Rehle TM, Hallett TB, Shisana O, et al. A decline in new HIV infections in South Africa: estimating HIV incidence from three national HIV surveys in 2002, 2005 and 2008. PLoS One 2010;5:11094.

39. Kelly HA, Sawadogo B, Chikandiwa A, et al. Epidemiology of high-risk human papillomavirus and cervical lesions in African women living with HIV/AIDS: effect of anti-retroviral therapy. AIDS 2017;31:273–85.

40. Tabrizi SN, Brotherton JML, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. Lancet Infect Dis 2014;14:86–96.

41. National Department of Health. National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and...
the management of HIV in children, adolescents and adults. South Africa: National Department of Health, 2014.

42. Mbulawa ZZA, van Schalkwyk C, Hu N-C, et al. High human papillomavirus (HPV) prevalence in South African adolescents and young women encourages expanded HPV vaccination campaigns. *PLoS One* 2018;13:e0190166.

43. Mbulawa ZZA, Coetzee D, Williamson A-L. Human papillomavirus prevalence in South African women and men according to age and human immunodeficiency virus status. *BMC Infect Dis* 2015;15:459.

44. Brisson M, Bénard Élodie, Drolet M, et al. Population-Level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. *Lancet Public Health* 2016;1:e8–17.

45. Meeting of the global Advisory Committee on vaccine safety, 7–8 June 2017. *Wkly Epidemiol Rec* 2017;92:393–402.