A single dose of quadrivalent HPV vaccine is highly effective against HPV genotypes 16 and 18 detection in young pregnant women eight years following vaccination: an retrospective cohort study in Fiji

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Summary

Background In 2008/9, Fiji vaccinated >30,000 girls aged 9–12 years with the quadrivalent human papillomavirus (4vHPV) vaccine coverage for at least one dose was >60% (one dose only was 14%, two dose only was 13%, three doses was 35%). We calculated vaccine effectiveness (VE) of one, two and three doses of 4vHPV against oncogenic HPV genotypes 16/18, eight years following vaccination.

Methods A retrospective cohort study was undertaken (2015–2019) in pregnant women ≤23 years old, eligible to receive 4vHPV in 2008/9, with confirmed vaccination status. The study was restricted to pregnant women due to the cultural sensitivity of asking about sexual behavior in Fiji. For each participant a clinician collected a questionnaire, vaginal swab and genital warts examination, a median eight (range 6–11) years post vaccination. HPV DNA was detected by molecular methods. Adjusted VE (aVE) against the detection of vaccine HPV genotypes (16/18), the comparison group of non-vaccine genotypes (31/33/35/39/45/51/52/56/58/59/66/68), and genital warts were calculated. Covariates included in the adjusted model were: age, ethnicity and smoking, according to univariate association with any HPV detection.

Findings Among 822 participants the prevalence of HPV 16/18 in the unvaccinated, one, two and three-dose groups were 13.3% (50/376), 2.5% (4/158), 0% (0/99) and 1.6% (3/189), respectively; and for the non-vaccine high-risk genotypes, the detection rate was similar across dosage groups (33.2%–40.4%, p = 0.321). The aVE against HPV 16/18 for one, two and three doses were 81% (95% CI; 48–93%), 100% (95% CI; 100–100%), and 89% (95% CI; 64–96%), respectively. Prevalence of HPV 16/18 was lower among women with longer time since vaccination.

Interpretations A single dose 4vHPV vaccine is highly effective against HPV genotypes 16 and 18 eight years following vaccination. Our results provide the longest duration of protection for reduced dose 4vHPV schedule in a low- or middle-income country in the Western Pacific region.

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Research in context

Evidence before this study

Post-hoc analysis from clinical trials showed that a single dose of HPV vaccine to be as effective as two or three doses. However, the data from observation studies is limited. We searched PubMed for evidence of HPV vaccine effectiveness following a single dose on HPV detection or cervical changes using the following terms in combination "HPV" "vaccine" "detection" "genotype" "cervical neoplasia" "effectiveness" "dose*" "efficiency". A total of 297 titles were screened. We identified 15 observational studies which have assessed the effectiveness of one dose of HPV vaccine and no clinical trials. Six of these assessed the outcome of HPV detection. Two were from a LMIC. The Mongolian study had a six year follow up time post 4vHPV introduction and the Indian study had a nine year follow up time. Four were from two high-income countries (HIC), USA using 4vHPV and Scotland using 2vHPV, the longest follow up time was 12 years post vaccination in USA. There were 11 studies in six HIC, USA, Australia, Canada, Scotland Denmark and Sweden which assessed the effectiveness of a single dose against cervical dysplasia, the longest follow up time was 14 years post HPV vaccination in Denmark and Sweden.

Of the studies assessing the effectiveness of a single dose on HPV 16/18 detection, five of the six showed that a single dose had similar protection to two or three doses, including the LMIC settings. There were two studies in Scotland, one demonstrated that a single dose was not as effective as two or three doses, while the other found it to be as effective. The VE for protection against HPV 16/18 of a single dose ranged from 5% to 95%.

Of the studies assessing the effectiveness of a single dose on cervical changes, four of the 11 studies demonstrated effectiveness from a single dose. Generally VE against cervical changes is lower than against HPV detection, and the VE of a single dose ranged from 35% to 62% across these studies.

Added value of this study

Our study complements the results from the previous studies which demonstrated a high level of protection following a single dose of HPV vaccine against HPV detection. As there is heterogeneity in results therefore adding to this body of evidence is important, partially for LMIC where there is a paucity of data and the burden is high. Our data has the longest follow up time from a LMIC country in the Western Pacific region. The Pacific region has a high burden of cervical cancer.

Implications of all the available evidence

A single dose schedule has important implications for policy makers in LMIC considering introducing HPV vaccine, as well as those which have already introduced the HPV vaccine. Simplification of the schedule will have a significant impact on cost and logistics. Our findings support the current WHO Position Statement of the use of a single dose of HPV vaccine and is of particular importance following the WHO Director-General call for action to eliminate cervical cancer as a public health matter and when there is a limited global vaccine supply.

Introduction

Currently, there are three WHO licensed HPV vaccines (bivalent [2vHPV; Cervarix®, GlaxoSmithKline; HPV16/18] quadrivalent [4vHPV; Gardasil®, Merck; HPV6/11/16/18] and nonavalent [9vHPV; Gardasil 9®, Merck; 6/11/16/18/31/33/45/52/58]) and one WHO prequalified vaccine [2vHPV; Cecolin®, Innovax; HPV16/18]. All licensed vaccines are highly immunogenic and protective against vaccine-related HPV type detection and associated cervical neoplasia in clinical trials[1–4] and post-licensure vaccine effectiveness studies.[5,6] Initially recommended as a three-dose schedule, the WHO then in 2014, updated HPV vaccination schedule recommendations to a two-dose schedule as studies showed that reduced doses were noninferior serologically compared to three.[7] Thus far, national immunisation programs have adopted a two-dose schedule at least six months apart reducing the cost and simplifying the logistics of vaccine delivery. The longest follow-up of observational studies assessing long term protection from a two-dose schedule against HPV infection is 12 years following 4vHPV in the USA[8] and against cervical dysplasia is 14 years post 4vHPV vaccination in Denmark and Sweden.[9]

For cost and logistic reasons a single-dose schedule is now being explored, particularly in low- and middle-income countries (LMIC).[10] Simplification of the regimen for HPV vaccine could bring significant advantages to LMIC where an estimated 85% of cervical cancer deaths occur.[11] Early evidence is supportive; observational studies and randomised control trials (RCT) have shown that a single dose may be effective[12–14]; and clinical trial follow up data from RCTs in India (using 4vHPV) and Kenya (using 9vHPV) demonstrated >90% effectiveness against high-risk HPV 16/18 detection nine years and 18 months post-vaccination, retrospectively.[14,15] In recent SAGE WHO recommendations in June 2022, a permissive recommendation for one or

two doses given for girls <15 years old was made.[16] Recently, Australia and Ireland have made announcements to change to a single dose schedule.[17]

Fiji is a small country in the South Pacific Ocean and has a high burden of cervical cancer. The incidence rate of cervical cancer (2003–2009) was 28 per 100,000 women.[18] In 2008–2009, Fiji received a donation of the 4vHPV vaccine (Merck, Gardasil®) which was sufficient to vaccinate four birth cohorts (30,338 girls aged 9–12 years) with a three-dose schedule. Vaccines were delivered in a school-based program, but not all girls received the full course due to absenteeism from school and other reasons.[19] National vaccine coverage estimates for 4vHPV was >60% for at least one dose (14%, 13% and 35% for one, two and three doses, respectively).[20] It was estimated that <1% received the vaccine privately.

Previously, we reported on the immunogenicity levels of one to three doses of 4vHPV six to eight years post vaccination in Fiji and found that two doses were comparable to three doses. In addition, providing a subsequent single dose booster with 2vHPV (Cervarix®) at eight years post 4vHPV vaccination, resulted in similar increased immunogenicity levels as two or three doses for HPV genotypes 16/18.[21]

The aim of this study is to determine the effectiveness of one, two and three doses of 4vHPV against high-risk (HR) vaccine genotypes 16/18 and genital warts, eight years following vaccination in young, pregnant women in Fiji.

Methods

Study site

Fiji is an upper middle-income country in the South Pacific with an estimated population of 884,887 in 2017, with 62% indigenous (iTaukei) and 32% Fijians of Indian descent, and 66% of the population living in urban areas.[22] We undertook a retrospective cohort study in young pregnant women attending routine antenatal care clinics in Fiji from October 2015 to March 2019, 6–11 years following vaccination. Pregnant women were chosen to ensure a sexually active cohort, while avoiding culturally inappropriate questions on sexual activity. In 2017, 90% of women received antenatal care in government-funded hospitals. We recruited from the major public antenatal clinics: the Colonial War Memorial Hospital (CWMH), the main tertiary hospital in Suva, where approximately 9000 (45%) of the 20,000 total births in Fiji occur each year; the nearby Nausori Maternity Hospital which has about 2000 births (10% of all births) per year; Lautoka hospital which has about 4500 births per year; Sigatoka and Ba hospitals which both have about 550 births per year.

All available HPV immunisation registers from the 2008/2009 4vHPV vaccination campaign were retrieved. Registers were available from three of the four Divisions (the largest administrative unit in Fiji) and urban populations accounted for 71%. Individual level data included in the registers were; name, date of birth, the number of doses and the date received or reason for non-receipt.

Study procedures

Pregnant women who were age-eligible to receive 4vHPV during the 2008/2009 campaign and attended antenatal clinics were screened for eligibility by study staff. Inclusion criteria were: aged 15–23 years of age, 4vHPV vaccination status was verifiable in the HPV immunisation register. Exclusion criteria were: inability to consent due to mental illness or other reason, contraindication for collection of a vaginal swab and lack of vaccination data in a school register. Following written informed consent by participants and/or guardians, women were screened for eligibility based on the availability of verified 4vHPV vaccination status. Women who had not received 4vHPV, but met the eligibility criteria were included as the unvaccinated comparator group. Demographic factors (age, number of years since last 4vHPV dose, ethnicity (self-reported as iTaukei or Fijians or Indian descent), number of previous lifetime boyfriends (a proxy for the number of sexual partners), participant's mothers' education, smoking and type of house, cooking fuel and household items which were used to derive socioeconomic status) and 4vHPV vaccination status were recorded by the study staff.

To determine socioeconomic status, a short list was made of household assets (i.e. vehicle, refrigerator, computer, electricity, washing machine, and television) that were considered to be present in more affluent and less affluent households by local Fijian staff. Data on these assets were collected and possession of each asset was scored (one or zero). This score was weighted for consistency with other assets using principal components analysis as described by Filmer et al.,[23] and the quintiles were reported.

As part of routine antenatal care, a physical examination, including a vaginal examination is performed at the first antenatal visit. At this visit, the study midwife, blinded to the HPV vaccination status, examined the participant for genital warts and took a low vaginal swab (Regular nylon flocked specimen collection dry swab, 80 mm, cat. #552C; Copan Flock Technologies Srl, Brescia, Italy) by inserting the swab 2 cm into the vagina and rotating 10 times. Genital examination findings were recorded on a separate data collection form, to ensure the study midwife remained blinded to vaccination status. Agreement between whether genital warts were present or not was compared between the midwife and antenatal clinic obstetric doctor for the first 50 cases. There was 100% agreement between the midwife and antenatal clinic obstetric doctor genital wart examination for the first 50 participants. Thereafter, positive

genital warts examinations were confirmed by the obstetric doctor at the clinic.

Laboratory methods

Vaginal swabs were returned into their casing without medium, and immediately placed in a cool box. Samples were transported to the Public Health Laboratory, Centre of Communicable Diseases Laboratory, Suva, Fiji within 5–6 h, where swabs were swirled into 2000 μL of phosphate buffered saline and stored at minus 20 °C. Each week the stored samples were transferred to storage at minus 80 °C freezer. Samples were shipped on dry ice to the Western Pacific HPV reference laboratory as set up by WHO, at the Royal Women's Hospital molecular laboratory, Melbourne, for HPV detection and genotyping. The laboratory staff were blinded to participant vaccination status.

A 100 μL aliquot of the swab suspension was added to 1 mL of PreservCyt solution (Hologic) and tested for 14 oncogenic HPV genotypes using the Cobas 4800 HPV test (Roche Diagnostics; assay reports individual genotyping for 16 and 18 and a pooled high risk HPV result for 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68).[24] A 200 μL aliquot of the original swab suspension was extracted (MagNA Pure 96 DNA and Viral Nucleic Acid Small Volume kit, Pathogen Universal 200 protocol; Roche Diagnostics) and assessed for adequacy by qPCR detection of human β-globin gene.[24] Samples testing negative on the Cobas assay were screened for low risk HPV types by PCR using L1 consensus primer set PGMY-09-PGMY11, followed by ELISA detection.[24] Samples positive for either test were genotyped using the Linear Array HPV assay (detects 37 genotypes including LR genotypes 6/11; Roche Diagnostics), as previously reported.[25,26] Due to possible cross-reactivity of the HPV52 probe with genotypes 33, 35, and 58 amplicons, samples positive for ≥1 of these three probes were further tested for HPV52 using a genotype-specific PCR assay.[27] However, the Linear Array HPV assay was only available for the first 707 participants as kit production was discontinued from 2019.

Outcome definitions

There were three outcomes: detection of HPV 16/18 vaccine genotypes; detection of non-vaccine genotypes high-risk (31/33/35/39/45/51/52/56/58/59/66/68) as a control genotype group; and the presence of genital warts as detected clinically by the study midwife. For the 707 samples tested on Linear Array there were three additional outcomes; low-risk (LR) genotypes 6/11 which are contained in the 4vHPV vaccine; 9vHPV vaccine genotypes (6/11/16/18/31/33/45/52/58); and seven additional genotypes which are not contained in the 2vHPV vaccine (currently part of the routine schedule in Fiji), but in the 9vHPV vaccine (6/11/31/33/45/52/58).

Sample size

The sample size for each dosage group was selected to enable estimation of vaccine effectiveness (VE) (unvaccinated vs one-, two- and three-dose groups), and to estimate prevalence of genital warts. The study was designed with the primary comparison of interest as the two-dose vs unvaccinated group. Full details of sample size calculations and assumptions are included in the Supplementary material. A total sample size of 820 women was selected with the following dose groups: 370 unvaccinated participants, 160 one-dose participants, 100 two-dose participants and 190 three-dose participants.

Statistical analysis

All data collection forms were monitored by the study coordinator and double entered into Epidata, version 3.1 (The EpiData Association, JM Lauritsen). Data were analysed using STATA, version 14 (Stata Corporation, College Station, TX). The demographic characteristics and prevalence rates of HPV genotypes of the different dosage groups were described.

Outcome comparison groups were participants with and without high-risk and non-vaccine high risk HPV detection, respectively. Crude and adjusted prevalence rate ratios (aPRR) and 95% confidence intervals (CI) were calculated for HPV 16/18, the control non-vaccine high-risk genotypes (31/33/35/39/45/51/52/56/58/59/66/68) and genital warts by each dosage group and follow-up period using log-binomial regression. Covariates included in the adjusted model were selected according to univariate association with any HPV detection, covariates were: age, ethnicity and smoking. VE and 95% CI were calculated using (1– aPRR) × 100, adjusted for age, ethnicity and smoking. The 95% CI were estimated using generalised linear regression with a Gaussian distribution, log link and robust variance estimator, because of zero cells.

Ethics approval and role of the funding source

This study was conducted according to the protocol approved by The Fiji National Health Review Ethics Committee (2015.2 CEN) and The University of Melbourne Human Ethics Research Committee (1545198.1). Details of funding sources are included in the Supplementary material. The funders did not play any role in the study design, data collection, data analysis, interpretation, writing of the report.

Results

Participant recruitment and characteristics

From 5674 pregnant women screened for eligibility, 835 women were eligible. Of 822 participants enrolled in the study (Fig. 1) only one (0.1%) had an invalid laboratory result for all three assays, and therefore excluded from the analysis.

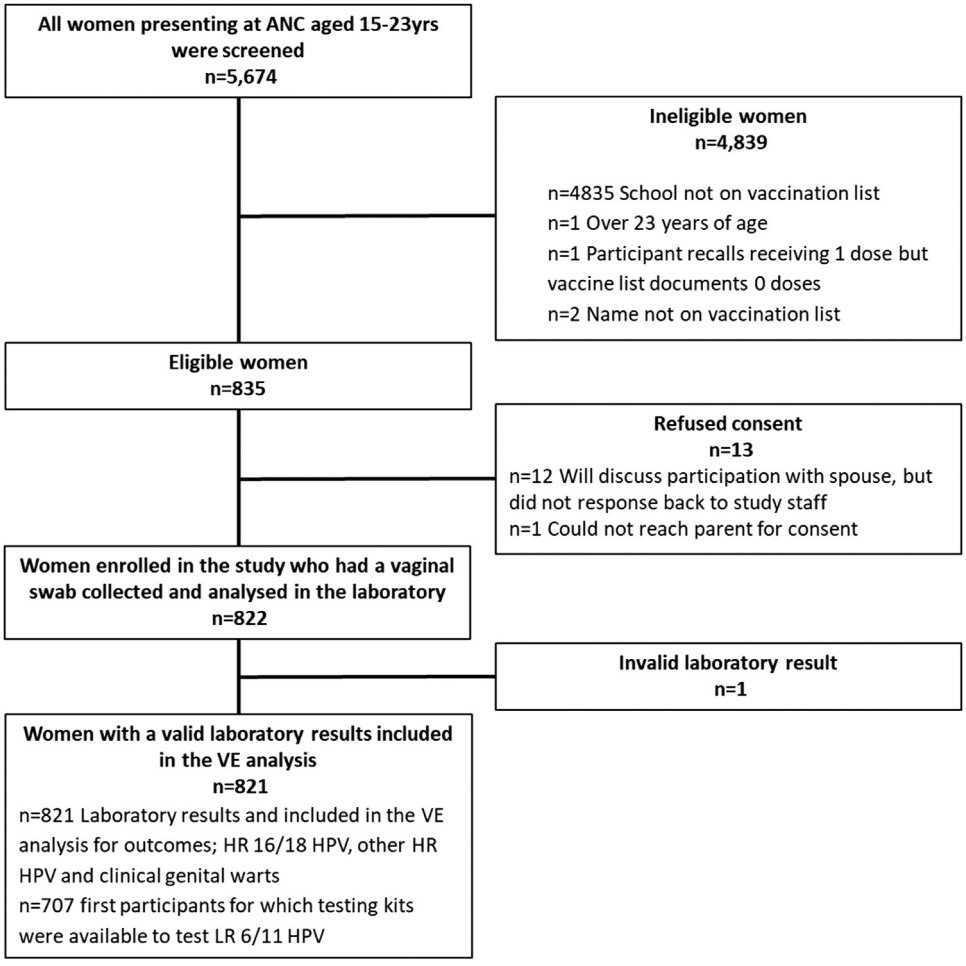

Fig. 1: Note, n = 1 for all laboratory assays. ANC = antenatal clinic; VE = vaccine effectiveness; HPV = human papillomavirus; HR = high-risk; LR = low-risk.

Demographic characteristics; age in years, years since last dose, ethnicity, number of lifetime boyfriends, participant's mothers' education, ever smoked cigarettes, socioeconomic status, were similar across dosage groups (Table 1).

Prevalence of HPV 16/18 and vaccine effectiveness dose

The crude prevalence of HPV 16/18 detection was higher in the unvaccinated group (13.3% (50/376)), compared to the one (2.6% (4/158)), two (0% (0/99)), and three (1.6% (3/189)) dose groups (Table 1). HPV 16/18 detection was lower in both the one-dose group vs the unvaccinated group (aPRR = 0.19%, 95% CI; 0.07–0.52%) and the three-dosage vs the unvaccinated group (aPRR = 0.11%, 95% CI; 0.04–0.36%) (Table 2). Among the two-dose group, HPV16/18 were not detected among any of the participants. The adjusted VE against HPV 16/18 for one-, two- and three-doses were 81% (95% CI; 48–93%), 100% (95% CI; 100–100%), and 89% (95% CI; 64–96%), respectively (Table 2).

Prevalence of 6/11 HPV and vaccine effectiveness by dose

Demographics for the group with full genotyping results (n = 707) were similar to those receiving partial genotyping (n = 115), with some difference in time since vaccination and dose number received (see Supplementary Table S2).

For the 707 participants with full genotyping results; LR 6/11 HPV prevalence was low in all groups: 2.4% (9/376), 0% (0/66), 1.3% (1/77) and 0.53% (1/188) for the unvaccinated, one-dose, two-dose and three-dose groups, respectively (Supplementary Table S2). The prevalence of high-risk 9vHPV vaccine genotype was 22.6% (85/376), 25.8% (17/66), 9.1% (7/77) and 12.2% (23/188) for the unvaccinated, one-dose, two-dose and three-dose groups,

Characteristics or outcome	4vHPV dosage group			
	Unvaccinated (n = 376)	1 dose (n = 158)	2 doses (n = 99)	3 doses (n = 189)
Age in years, median (IQR)	19.6 (20.4, 21.3)	20.5 (19.5, 21.2)	19.9 (19.0, 20.6)	19.0 (19.7, 20.3)
Years since last 4vHPV dose, median (IQR)	NA	8.8 (8.0, 9.8)	8.3 (7.6, 8.7)	7.9 (7.4, 8.4)
Ethnicity, n (%)				
iTaukei	293 (78)	117 (74)	76 (77)	152 (80)
Fijian of Indian descent or others	80 (22)	41 (26)	23 (23)	37 (20)
Number of boyfriends, n (%)				
1	262 (70)	128 (81)	79 (80)	143 (76)
2	64 (17)	19 (12)	10 (10)	24 (13)
3	28 (7)	5 (3)	6 (6)	15 (8)
>3	21 (6)	5 (3)	3 (3)	7 (4)
Participant's mothers' education, n (%)				
Secondary school or higher	336 (91)	146 (92)	93 (94)	178 (95)
Primary school	26 (7)	8 (5)	4 (4)	10 (5)
None	9 (2)	4 (3)	2 (2)	0 (0)
Ever smoked cigarettes, n (%)	116 (31)	39 (25)	20 (20)	56 (30)
Socioeconomic status,[a] n (%)				
1st quintile (less affluent)	71 (19)	31 (20)	24 (24)	39 (21)
2nd quintile	83 (22)	31 (20)	16 (16)	39 (21)
3rd quintile	74 (20)	31 (20)	16 (16)	44 (23)
4th quintile	106 (28)	42 (27)	29 (29)	45 (24)
5th quintile (more affluent)	42 (11)	23 (15)	14 (14)	22 (22)
HPV prevalence, n (%)				
All high-risk genotypes[b]	148 (39.4)	59 (37.8)	40 (40.4)	78 (41.3)
High-risk 2vHPV vaccine genotypes[c]	50 (13.3)	4 (2.6)	0 (0.0)	3 (1.6)
High-risk non-vaccine genotypes[d]	125 (33.2)	56 (35.9)	40 (40.4)	76 (40.2)
Genital warts	7 (1.9)	1 (0.63)	1 (1.0)	4 (2.1)
	n = 376	n = 66	n = 77	n = 188
High-risk 9vHPV vaccine genotypes[ef]	85 (22.6)	17 (25.8)	7 (9.1)	23 (12.2)
Low-risk genotypes[fg]	9 (2.4)	0 (0.0)	1 (1.3)	1 (0.5)
Seven additional genotypes[fh]	48 (12.8)	13 (19.7)	7 (9.1)	20 (10.6)

NA = not available. Number of years unavailable to be calculated as participants did not receive any 4vHPV doses. [a]Calculated using Principal Components Analysis. [b]All high-risk genotypes = 16/18/31/33/35/39/45/51/52/56/58/59/66/68. [c]High-risk 2vHPV vaccine genotypes = 16/18. [d]High-risk non-vaccine genotypes = 31/33/35/39/45/51/52/56/58/59/66/68 (genotype 66 is no longer classified as high-risk, however is still included in laboratory assays). [e]High-risk 9vHPV vaccine genotypes = 6/11/16/18/31/33/45/52/58. [f]Data is shown for the first 707 participants with results for low-risk genotypes 6/11 due to limitations on test availability. [g]Low-risk genotypes = 6/11. [h]Seven additional genotypes which are not contained in the 2vHPV vaccine (currently part of the routine schedule in Fiji) and are contained in the 9vHPV vaccine = 6/11/31/33/45/52/58.

Table 1: **Characteristics of study participants according to their respective dose (unvaccinated, one, two or three) of quadrivalent human papillomavirus (4vHPV) vaccine received (n = 822).**

respectively (Table 1). The prevalence of the seven additional genotypes which are contained in the 9vHPV vaccine and not contained in the 2vHPV vaccine which is currently the routine schedule in Fiji (6/11/31/33/45/52/58) was 12.8% (48/376), 19.7% (13/66), 9.1% (7/77) and 10.6% (20/188) for the unvaccinated, one-dose, two-dose and three-dose groups, respectively (Table 1). Due to the small number of LR 6/11 HPV cases there were too few cases to calculate an aPRR or VE.

Prevalence of non-vaccine high risk genotypes

Detection levels of non-vaccine high-risk genotypes (control genotypes) for all dosage groups were similar at 33–40%: the aPRR for the one-, two- and three-dose groups were 1.09% (95% CI; 0.85–1.40%), 1.16% (95% CI; 0.88–1.52%) and 1.10% (95% CI; 0.88–1.38%), respectively (Table 2).

Prevalence of genital warts

The prevalence of genital warts is shown in the Supplementary material.

Discussion

We found a single dose of pre-teen 4vHPV vaccine to be highly effective against detection of HPV16/18 genotypes among young Fijian women through to eight years following vaccination (VE of 81% single dose vs 100% two

	Crude prevalence ratio (95% CI)	Adjusted prevalence ratio (95% CI)	Adjusted vaccine effectiveness (95% CI[b])
High-risk 16/18 HPV genotypes			
1 vs unvaccinated	0.19 (0.07, 0.52)	0.19 (0.07, 0.52)	81% (48%, 93%)
2 vs unvaccinated[c]	0.00018 (0.00013, 0.00023)	0.000062 (0.000046, 0.000083)	100% (100%, 100%)
3 vs unvaccinated	0.12 (0.04, 0.38)	0.11 (0.04, 0.36)	89% (64%, 96%)
2 vs 1 doses[c]	0.00090 (0.00034, 0.0024)	0.00040 (0.00012, 0.0013)	100% (100%, 100%)
High-risk non-vaccine genotypes[d]			
1 vs unvaccinated	1.08 (0.84, 1.39)	1.09 (0.85, 1.40)	−9% (−40%, 15%)
2 vs unvaccinated	1.22 (0.92, 1.61)	1.16 (0.88, 1.52)	−16% (−52%, 12%)
3 vs unvaccinated	1.21 (0.97, 1.52)	1.10 (0.88, 1.38)	−10% (−38%, 12%)
1 vs 2 doses	1.12 (0.85, 1.47)	1.06 (0.77, 1.33)	−6% (−33%, 23%)

[a]Adjusted for age, ethnicity and smoking. [b]Calculated using (1 − aPR) × 100. [c]Estimated using generalised linear regression with a Gaussian distribution, log link and robust variance estimator. [d]High-risk non-vaccine genotypes = 31/33/35/39/45/51/52/56/58/59/66/68.

Table 2: **Unadjusted and adjusted[a] prevalence ratios of HPV detection and 4vHPV vaccine effectiveness[b] in young pregnant Fijian women.**

doses vs 89% three doses). While confidence intervals were wide (48–93% effective), this is consistent with similar observational vaccine effectiveness studies.[8,28] This study is the longest duration of follow up from a single 4vHPV dose in a LMIC. In the Western Pacific region prevalence of HPV16/18 genotypes in the unvaccinated, one-dose, two-dose and three dose groups was 13.3% (50/376), 2.6% (4/158), 0% (0/99) and 1.6% (3/189), respectively.

We are aware of six other observational studies assessing effectiveness of a single dose against HPV detection, two of which showed similar VE against HPV 16/18 detection to ours. Four studies assessed 4vHPV given to teenage girls; one was in India, and demonstrated a 95% (95% CI; 85–99.9%) VE against HPV 16/18 detection 10 years after receiving a single dose,[14] another in Mongolia demonstrated a 92% (95% CI; 44–99%) VE against HPV 16/18 detection six years after receiving a single dose.[28] Among women in USA, 4vHPV VE against HPV 16/18 detection was 94% (95% CI; 58–99%) for a single dose up to 12 years post vaccination.[29] Another USA study demonstrated the prevalence of HPV 16/18 was low and similar in the 1, 2, and three dose groups, but did not report VE.[30] For 2vHPV, there were two Scottish studies, which found that a single dose administered to teenage girls had a 48% and 5% (not significant) VE up to five years post vaccination.[31,32] These observational studies complement findings among women who did not receive the full vaccine series in the Costa Rica HPV Vaccine Trial, and the multi-centre PATRICIA study, which found a single dose had similar effectiveness (82% (95% CI; 40.2–97.0%) VE) as two or three doses of 2vHPV against HPV 16/18 detection 11 years following vaccination.[13] In addition, two observational studies in Fiji and Uganda have shown long-term immunogenicity from a single booster dose of 4vHPV vaccine six and two years following vaccination, respectively.[21,33] A recent RCT demonstrated 97% efficacy of a single dose of 2vHPV or 9vHPV against HPV 16/18 detection among young sexually active Kenyan women aged 15–20 years, 18 months post vaccination.[15]

Importantly, single dose HPV schedules have also been shown to reduce cervical dysplasia. There are 11 observational studies in six high income countries; USA, Australia, Canada, Scotland, Denmark and Sweden, which assessed the effectiveness of a single dose administered to adolescents against cervical dysplasia.[8,9,12,34–41] The longest follow up time was 14 years post HPV vaccination in Denmark and Sweden. All studies assessed 4vHPV apart from the Scottish study, which assessed 2vHPV. Four of the 11 studies demonstrated effectiveness from a single dose with VE results ranging from 35% to 62%.[8,34,36,38]

We found 100% aVE against HPV 16/18 detection following two doses of 4vHPV. The two doses were generally given one month apart, rather than the recommended 6-month interval for a two-dose schedule. There were two participants in the 3-dose group who had HPV 16/18 detected. It is unclear whether this demonstrates vaccine failure or whether this is due to deposition from a partner if sexual intercourse occurred within 72 h of swab collection. It is unlikely that it is due to persistent infection prior to vaccination as the girls were only 9–12 years of age at the time of vaccination, although this cannot be entirely ruled out. A similar study in the USA found 95% (95% CI; 61–99%) VE 12 years following vaccination with two doses of 4vHPV.[29] The two Scottish studies assessed HPV 16/18 genotypes eight years following 2vHPV vaccination: VE for two doses was 55% (95% CI; 31–71%)[32] and no effect.[31] Our estimate is higher than other studies, due to no events in the two-dose group, which may be a chance finding as the number of participants was small, although the pre-defined sample size was reached. This is supported by the VE of 81%, 100%, and 89% for 1, 2 and 3 dose-groups, respectively, while we would expect a monotonic dose-response relationship rather than a U shaped relationship. Other reasons for our high VE

results compared to other studies may be due to the use of a higher valency vaccine although the 2vHPV also provides some cross-protection to other high-risk HPV types (31, 33, 45), differences in vaccination coverage or confounders for HPV infection as the authors noted differences in risk factors, such as age or time from vaccination, between women across dosage groups and prior exposure to HPV infection.[31,32]

There were few cases of genital warts in our study, with very low prevalence in all dosage groups. The prevalence in Fiji is within the lower range of that documented in a systematic review of global data, which estimated the prevalence of genital warts to be 0.2%–5.1% among women aged 20–40 years based on genital examinations.[42] The prevalence of LR 6/11 HPV detection was is also low in our study at 2.4%, 0.0%, 1.3% and 0.5% in the unvaccinated, one-, two- and three-dose groups, respectively, which is similar to other settings.[43] The difference in prevalence rates across groups suggests a trend to vaccine effect, but due to the small numbers a VE could not be calculated. The low prevalence of genital warts and LR 6/11 HPV suggests no strong justification to switch from the 2vHPV to 4vHPV vaccine in Fiji. Among participants with clinical genital warts 23% (3/13) had LR HPV 6/11, and 54% (7/13) had multiple genotypes detected. This probably reflects high-risk behaviour rather than a causal association for which HPV detection results from a genital wart biopsy would be required.

Our study had limitations, the most important being that dose groups were not randomly assigned and therefore there is a risk of unmeasured confounding, a limitation common to all observational studies. However, our key bias indicator, the prevalence of non-vaccine high-risk HPV genotypes, was similar between dosage group. This suggests that HPV exposure was similar between the dosage groups. Although we were unable to ask the number of sexual partners due to cultural sensitivity, the number of lifetime boyfriends did not differ between dosage groups. There was little difference in the unadjusted and adjusted regression suggesting little confounding from the exposures included in the model, however there may have been unmeasured confounders. The availability of vaccination registers which may have affected the generalisability of the results. However, the registers were found from three of the four divisions (the largest administrative unit in Fiji) and the proportion of the population in urban areas (71%) similar although slightly higher than the general population (66%) therefore this impact is assessed to be minimal. A major strength of our study was that HPV vaccination was given at a young age and therefore most likely before sexual debut. Our study was conducted among pregnant women to overcome the cultural taboo of asking sexual activity in young women, which could affect the generalisability of our results. However, our recruitment sites were likely to be representative of pregnant young women in Fiji generally. Additional strength of our study is the length of the follow up time, eight years following immunisation, confirmation of vaccination status by written record and predefined outcomes.

In summary, we have demonstrated that a single dose of pre-teen 4vHPV vaccine administration offers high VE against HPV 16/18. We found no evidence of waning of VE over time, in fact prevalence of HPV 16/18 declined over time. There are substantial public health implications for a single dose schedule particularly at this time when there is limited global vaccine supply and a number of high-burden LMICs are currently considering introducing HPV vaccine. In May 2018 the WHO called for elimination of cervical cancer as a public health priority. Our study provides additional data to support the current WHO Position Statement regarding the use of a single dose schedule.

Contributors

FMR conceived, designed and initiated study and was the key manuscript reviewer; ET collected data and drafted the manuscript; RR contributed to the design of the study, analysed data, and drafted the manuscript; ST provided key study design inputs for sample collection and processing; JF and RD coordinated Ministry facilities. JF was CWMH leads in accessing data; ET, TR, and RR coordinated study staff especially data collection; SY collected the data; RR and CN led the statistical methods and performed statistical analysis; KJ provided logistical advice, intellectual, and physical support; SG, GM, and AC were responsible for laboratory analysis of samples and contributed to the manuscript; EKM and SG performed methodology and manuscript review; All authors approved the manuscript for submission.

Data sharing statement

RR and ET had full access to study data and FMR had final responsibility for the decision to submit for publication. The data that support the findings of this study are available on request from the corresponding author [FMR]. The data are not publicly available due to restrictions [e.g. their containing information that could compromise the privacy of research participants].

Declaration of interests

RR has nothing to declare.

ET has nothing to declare.

FTR has nothing to declare.

SY has nothing to declare.

SMG is a member of the MSD Global HPV Advisory Board, through her institution received an MSD grant for an Investigator Initiated grant and lecture fees for work performed in personal time. She is currently a recipient of an Australian National Health and Medical Research Council Leadership 3 Investigator grant APP1197951.

GM has nothing to declare.

AC has nothing to declare.

ST has nothing to declare.

CN is co-investigator on a Merck Investigator Studies Program grant on pneumococcal serotype epidemiology in children with empyema as well as being an investigator on a Pfizer Inc. funded clinical research collaboration of pneumococcal vaccination in Mongolia, both unrelated to this manuscript.

KJ has nothing to declare.

RD has nothing to declare.

KM is a member of the WHO SAGE committee and a co-investigator on the Pfizer-funded study of adult pneumococcal disease burden in Mongolia.

JF has nothing to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100798.

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