Vaccine 37 (2019) 412–416

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

Age-specific HPV prevalence among 116,052 women in Australia's renewed cervical screening program: A new tool for monitoring vaccine impact

Julia ML. Brotherton [a,b,*], David Hawkes [c,d], Farhana Sultana [a,b], Michael J. Malloy [a,b], Dorothy A. Machalek [b,e,f], Megan A. Smith [g], Suzanne M. Garland [e,f,h], Marion Saville [c,h]

[a] VCS Population Health, VCS Foundation, Level 6, 176 Wellington Parade, East Melbourne, VIC, 3002, Australia
[b] Melbourne School of Population and Global Health, University of Melbourne, Level 3, 207 Bouverie Street, Carlton, Victoria 3053, Australia
[c] VCS Pathology, VCS Foundation, 265 Faraday Street, Carlton South, Victoria 3053, Australia
[d] Department of Pharmacology and Therapeutics, The University of Melbourne, Victoria 3010, Australia
[e] Centre for Women's Infectious Diseases, The Royal Women's Hospital, Cnr Grattan St & Flemington Rd, Parkville, Victoria 3052, Australia
[f] Infection and Immunity, Murdoch Children's Research Institute, Parkville, Victoria, Australia
[g] Cancer Research Division, Cancer Council NSW, 153 Dowling St, Woolloomooloo, NSW 2011, Australia
[h] Department of Obstetrics and Gynaecology, The University of Melbourne, Parkville, Victoria 3010, Australia

ARTICLE INFO

Article history:
Received 20 September 2018
Received in revised form 23 November 2018
Accepted 26 November 2018
Available online 11 December 2018

Keywords:
Human papillomavirus
Prevalence
Cervical screening
Australia

ABSTRACT

Australia's transition to primary human papillomavirus (HPV) based cervical screening, has for the first time, provided a passive mechanism for monitoring the impact of vaccination on infection prevalence among women attending screening. We assessed oncogenic HPV prevalence by single year of age in the first 7 months of the program, using data collected from a large screening laboratory in Victoria, Australia, which is routinely screening using cobas 4800, cobas 6800 and Seegene assays. Among 116,052 primary screening samples from women aged 25–74, 9.25% (95%CI: 9.09–9.42%) had oncogenic HPV detected: 2.14% (95%CI: 2.05–2.22%) were 16/18 positive and 7.12% (95%CI: 6.97–7.27%) were positive for only non-16/18 HPV. Prevalence peaked at age 25–29 then decreased with age, but this was driven by non-16/18 types. HPV16/18 prevalence remained low and flat across ages, contrasting with pre-vaccination epidemiology when HPV16/18 peaked in young women. HPV-based screening can precisely monitor HPV prevalence.

1. Introduction

Understanding the epidemiology of human papillomavirus (HPV), in particular the age(s) when infection is acquired, cumulative probability of infection over time, persistence of infection in different populations, and how these correlate with cancer risk, has been key to determining how best to implement cervical cancer prevention strategies through vaccination and screening programs for maximum population impact [1]. The prevalence of HPV in a population provides a snapshot of past and present sexual behaviour across birth cohorts and provides information about the level of cervical cancer risk in that population [2]. A global meta-analysis of over 1 million women and 194 studies, found an overall HPV prevalence (including both oncogenic and low risk types) of 11.7% in women with normal cytology (5.0% prevalence for oncogenic types only) [3]. However, prevalence estimates have utilised varying sampling frames, assays and sample sizes. Obtaining representative samples has been challenging because HPV testing has not been routine and therefore consent based models, which are subject to selection bias, have frequently been required. Global HPV prevalence estimates are known to vary by region, study design, target population and calendar time. A likely source of variation lies in the different laboratory detection methodologies used (i.e. sensitivity, specificity and type-specific spectrum of assays), as well as true differences in the underlying risk of HPV exposure in the population studied [3,4]. Variation in prevalence by age reflects differences in sexual behaviour and mixing patterns within the population, in underlying risk factors for viral persistence, and

* Corresponding author at: VCS Population Health, VCS Foundation, Level 6, 176 Wellington Parade, East Melbourne, Victoria 3002, Australia.
E-mail addresses: jbrother@vcs.org.au (J.ML. Brotherton), dhawkes@vcs.org.au (D. Hawkes), fsultana@vcs.org.au (F. Sultana), mmalloy@vcs.org.au (M.J. Malloy), dorothy.machalek@mcri.edu.au (D.A. Machalek), Megan.Smith@nswcc.org.au (M.A. Smith), Suzanne.Garland@thewomens.org.au (S.M. Garland), msaville@vcs.org.au (M. Saville).

https://doi.org/10.1016/j.vaccine.2018.11.075
0264-410X/

change in these over time. In all populations, HPV prevalence in women rises rapidly in the years following sexual debut [3]. In many populations, it peaks in this period and falls to a lower stable level thereafter, presumably reflecting reduced risk of exposure as women typically enter more stable long-term relationships, in addition to the development of some natural immunity and the impact of screening and treatment of lesions. In some populations, there is a bimodal distribution with a second peak in later life, which may be due to changes in sexual behaviour (i.e. re-partnering) [5], reactivation of latent HPV with age or around menopause, or a cohort effect [3,6].

The move to HPV-based cervical screening programs, which utilise HPV nucleic acid testing (NAT) calibrated to detect HPV at a clinical threshold associated with the presence of underlying high grade cervical lesions, offers a means to precisely discern and monitor the prevalence of oncogenic HPV among females. Australia has recently transitioned to a primary HPV-based cervical screening program, which offers women 25 to 74 years of age 5 yearly HPV NAT with partial genotyping (separate identification of the most oncogenic types HPV16 and 18) and reflex cytology as triage for women who are positive for non-16/18 HPV types, whilst those 16/18 positive are referred directly for colposcopy [7]. This occurred upon a background of a 2nd yearly cytology-based screening program for women aged 20–69 years since 1991, and an ongoing school-based quadrivalent HPV vaccination program for 12–13 year old girls since 2007, including catch-up vaccination for women aged up to 26 years in the initial three years of the vaccination program. Here we present, for the first time, precise estimates of oncogenic HPV prevalence amongst females in a population by single year of age derived from routine screening data.

2. Methods

We utilised primary cervical screening samples collected in the renewed Australian National Cervical Screening Program (NCSP) between December 1st, 2017 and June 30th, 2018. Samples were processed in a single laboratory (VCS Pathology; Victoria, Australia), a specialist cervical screening laboratory performing approximately half of the cervical screening tests for Victorian women, at no cost to them. All samples were health care practitioner collected cervical samples from women aged 25 to 74 referred as 'Primary screening HPV test'. This category of specimen excludes tests from women who were symptomatic; undergoing a co-test for diagnostic purposes; in surveillance following an earlier cytological abnormality; or undergoing test-of-cure after treatment of a previous lesion. HPV results were obtained from the three different HPV assays in routine clinical use, specimens being randomly tested with one assay, in the laboratory: Roche Cobas 6800 HPV (60%), Roche Cobas 4800 HPV (39%) (Roche Diagnostics, Indianapolis, USA) and Seegene Anyplex II HR HPV (Seegene, Seoul, Korea) (1%). All three assays are calibrated for the detection of oncogenic HPV at clinically relevant levels (14 types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68; hereafter any oncogenic HPV) and meet the requirements for HPV assays to be used as part of the NCSP [8].

We estimated the prevalence and 95% confidence interval for: (1) any oncogenic HPV; (2) HPV 16 and/or 18 separately and together (with hierarchical reporting for separate types, where more than one type was detected i.e. HPV16, else HPV18, else other oncogenic HPV); and (3) oncogenic HPV types other than HPV 16/18 (without concurrent detection of HPV16/18), by single year of age and by age grouped into 5-year categories. We also reported the proportion of samples that were unsatisfactory (either due to insufficient cellularity or inhibition by substances such as lubricant or blood. Australian standards mandate that cervical screening tests must contain controls to detect these) [8]. All 95% confidence intervals were computed using the binomial exact method. All statistical analyses and graphs were derived using STATA version 12.1 (Stata Corp, College Station, Tx, USA).

Ethics approval for the use of de-identified laboratory results was given by Bellberry Human Research Ethics Committee.

3. Results

In the first seven months of the program, 116,169 eligible samples were tested. Of these, 117 (0.10%; 95%CI 0.08–0.12%) gave an unsatisfactory result, with no significant difference by age ($p = 0.36$) (Supplementary Table). Results by HPV group and single year of age for valid samples are presented in Fig. 1. As shown in Table 1, oncogenic HPV was detected in 9.25% (95%CI 9.09–9.42%) of satisfactory tests, with 16/18 detected in 2.14% (95%CI 2.05–2.22) and other oncogenic HPV (not 16/18) in 7.12% (95%CI 6.97–7.27%). HPV16 was more prevalent than HPV18 (HPV16 1.57% (95%CI 1.50–1.64%), HPV18 0.57% (95%CI 0.52–0.61%)). Prevalence of non-16/18 HPV peaked at 18.46% (95%CI 17.76–19.16%) amongst the youngest women (aged 25–29), before steadily declining with increasing age, whereas HPV 16/18 prevalence was highest amongst women aged 35–44, but was relatively flat across all ages (Table 1).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.11.075.

4. Discussion

We have utilised routine cervical screening samples to discern the prevalence of oncogenic HPV in women attending screening in Victoria, Australia. There were 2000–3000 specimens in each single-year age group from 26 to 63 years (with numbers just under 2000 in 25 year old women and those over 63). We found that any oncogenic HPV prevalence was highest among women aged 25–29 years and decreased with age, but this was driven by the infection patterns for non-16/18 HPV. In contrast, HPV16/18 prevalence was low, and stable across age groups. This pattern most certainly reflects the population-level impact of Australia's quadrivalent HPV vaccination program with high, multi-cohort uptake, which offered catch up vaccination to all women up to age 26 in the period 2007–2009 (now aged up to 37 years) [9]. Prior to the vaccination program, HPV16/18 prevalence (HPV 16 in particular) followed a similar age-specific pattern to that for non-16/18 types [10,11]. This dampening of the previously observed high peak of HPV16/18 infections in young women is consistent with other data on vaccine impact in Australia. Sentinel surveillance studies of screening women have noted a 92% decline in HPV16/18 prevalence in women aged 18–24 years and 90% in women aged 25–34 years by 2015, in comparison to baseline pre-vaccination data [12].

We also ascertained that unsatisfactory rates for HPV testing are very low (0.10%) across age groups, and notably much lower than for conventional cytology samples (between 2.2 and 2.6% in national data for the previous cytology-based program [13]). Samples for HPV testing can be unsatisfactory when there is insufficient cellular material present or inhibition of the amplification step of the assay, but these are clearly an uncommon problem with provider-collected cervical samples.

Prior to this analysis, Australia had a pre-vaccination baseline estimate of HPV prevalence across age groups, from a large national clinic-based study of screening women [11]. That study, including cervical samples from 1929 women aged 15 to 60 years,

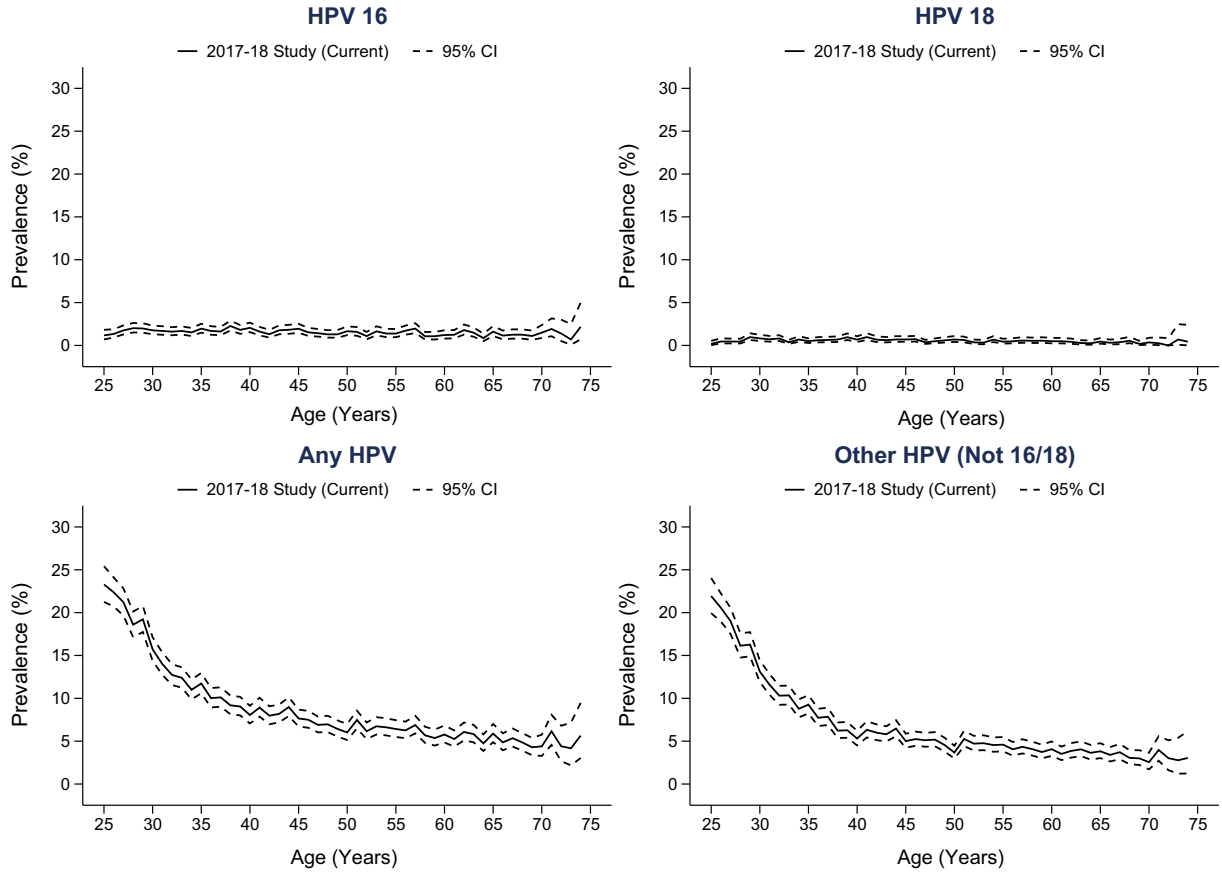

Fig. 1. Oncogenic HPV prevalence in 116,052 primary cervical screening samples from Victoria, Australia by single year of age (a) HPV 16 (b) HPV 18 (c) Any oncogenic HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) (d) Other oncogenic HPV (non 16/18).

Table 1
HPV prevalence (95% confidence interval) in the cervical screening population in Victoria, Australia, by 5 year age groups, 1 Dec 2017–30 June 2018.

Age groups (years)	Total screened	Any oncogenic HPV[€]		HPV 16		HPV 18		HPV 16/18		Non 16/18 oncogenic types	
		n	%, 95% CI	n	%, 95% CI	n	%, 95% CI	n	%, 95% CI	n	%, 95% CI
25–29	11,975	2478	20.69 (19.97–21.43)	204	1.70 (1.48–1.95)	64	0.53 (0.41–0.68)	268	2.24 (1.98–2.52)	2,210	18.46 (17.76–19.16)
30–34	14,444	1897	13.13 (12.59–13.70)	239	1.65 (1.45–1.88)	98	0.68 (0.55–0.83)	337	2.33 (2.09–2.59)	1,560	10.80 (10.30–11.32)
35–39	14,151	1421	10.04 (9.55–10.55)	265	1.87 (1.66–2.11)	96	0.68 (0.55–0.83)	361	2.55 (2.30–2.82)	1,060	7.49 (7.06–7.94)
40–44	13,618	1,147	8.42 (7.96–8.90)	234	1.72 (1.51–1.95)	99	0.73 (0.59–0.88)	333	2.45 (2.19–2.72)	814	5.98 (5.58–6.39)
45–49	14,328	1017	7.10 (6.68–7.53)	215	1.50 (1.31–1.71)	82	0.57 (0.46–0.71)	297	2.07 (1.85–2.32)	720	5.03 (4.67–5.40)
50–54	12,543	828	6.60 (6.17–7.05)	185	1.47 (1.27–1.70)	68	0.54 (0.42–0.69)	253	2.02 (1.78–2.28)	575	4.58 (4.22–4.96)
55–59	12,214	749	6.13 (5.71–6.57)	177	1.45 (1.24–1.68)	63	0.52 (0.40–0.66)	240	1.96 (1.73–2.23)	509	4.17 (3.82–4.54)
60–64	10,710	594	5.55 (5.12–6.00)	142	1.33 (1.12–1.56)	42	0.39 (0.28–0.53)	184	1.72 (1.48–1.98)	410	3.83 (3.47–4.21)
65–69	9,203	467	5.07 (4.63–5.54)	118	1.28 (1.06–1.53)	35	0.38 (0.27–0.53)	153	1.66 (1.41–1.95)	314	3.41 (3.05–3.80)
70+	2,866	142	4.95 (4.19–5.81)	45	1.57 (1.15–2.10)	9	0.31 (0.14–0.60)	54	1.88 (1.42–2.45)	88	3.07 (2.47–3.77)
Overall	116,052	10,740	9.25 (9.09–9.42)	1,824	1.57 (1.50–1.64)	656	0.57 (0.52–0.61)	2,480	2.14 (2.05–2.22)	8,260	7.12 (6.97–7.27)

[€] Any oncogenic HPV refers to detection of one or more of 14 types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Non 16/18 oncogenic type detection refers to specimens in which only these types, and not 16/18, were detected. For 16 and 18 detection, where a test was positive for more than one type, they are reported hierarchically as HPV16, else HPV18, else non 16/18.

used an HPV assay (Linear Array) that detects 37 HPV types (including non-oncogenic types) and that was epidemiologically calibrated to detect HPV more sensitively (i.e. below a clinical risk threshold) rather than clinically validated for primary HPV screening. It found high rates of HPV in young women, including HPV16 and 18; declining prevalence with increasing age; and a suggestion of a second smaller peak in prevalence around menopause [11]. We were unable to confirm this second peak in the current study, though note a suggestion of a minor non-statistically significant upwards fluctuation in prevalence around age 51 (Fig. 1), consistent with the average age of menopause in Australia [14]. This may be because of underlying differences in the characteristics and risk factor profiles of the two populations (one clinic-based, one population-based), but may also suggest that if latent HPV can reactivate around menopause [6], it is unlikely to produce infections associated with significant lesions detectable by HPV assays at the clinical threshold. Further analysis of screening results from women in this age group, to assess whether HPV

detected around menopause is any more or less likely to be associated with cytological abnormalities, may be useful. A direct comparison of findings from our study with the baseline study is given in Fig. 2.

Strengths of our study include use of a large population-based sample covering the full screening age range. Although samples were from one laboratory, this laboratory serves half of screening women in Victoria, including women from lower socioeconomic groups and rural areas, and utilises a range of HPV platforms. Inclusion of results from the Seegene system, just established in the laboratory, is promising for future analyses, given its ability to provide individual genotyping for 14 HPV types. This could facilitate detailed epidemiological surveillance by individual genotype using large volume routine screening results. This could be of enormous value in the ongoing monitoring of both the impact of the vaccination and screening programs. This will become increasingly important in monitoring the impact of the nonavalent HPV vaccine, which provides protection against the seven most common oncogenic HPV types (16,18,31,33,45,52,58) found in cervical cancers worldwide. The nonavalent vaccine was introduced in Australia in 2018, so nonavalent-vaccinated cohorts have not yet entered screening, but routine screening data could provide an important baseline measure and ongoing monitoring (ideally supplemented with sentinel surveillance using other samples in women under the age of 25, such as chlamydia screening samples, as an earlier measure of vaccine impact).

The screening program uses clinically validated tests, rather than highly sensitive assays, limiting our ability to directly compare results with prior epidemiological studies. However, some evidence suggests that clinical and epidemiological assays provide equivalent ability to detect the prevalence of different HPV types relative to each other in a population and trends over time in type-specific HPV prevalence [15]. Additionally, advantages of screening tests include their widespread routine use, facilitating greater efficiency and larger sample sizes than otherwise feasible, a reduced risk of selection bias if the requirement for consent based studies is removed, and with less expense and time required. Furthermore, as screening tests are calibrated to detect clinically-relevant infections and lesions, arguably they provide a more relevant measure of disease risk [16].

We also restricted our sample to routine screening tests only, in order to assess HPV prevalence amongst asymptomatic women attending for routine screening. The higher risk groups will be the subject of future dedicated analyses, as will analyses of HPV prevalence and screening results amongst women utilising the self-collection pathway for under and never screened women. Monitoring of HPV prevalence over time as vaccinated cohorts age will also inform how well HPV-based screening using partial genotyping, and differential management for HPV16/18 and non-16/18 infections, performs and adapts as vaccine-targeted HPV types become increasingly uncommon in the population.

In summary, routinely-collected de-identified data from HPV-based screening programs can provide unique, comprehensive information about population-level HPV prevalence with a precision that was previously beyond the reach and budget of research studies. This initial analysis of data from the first seven months of Australia's new program from one large laboratory confirms previous data indicating a high peak in HPV in young women in

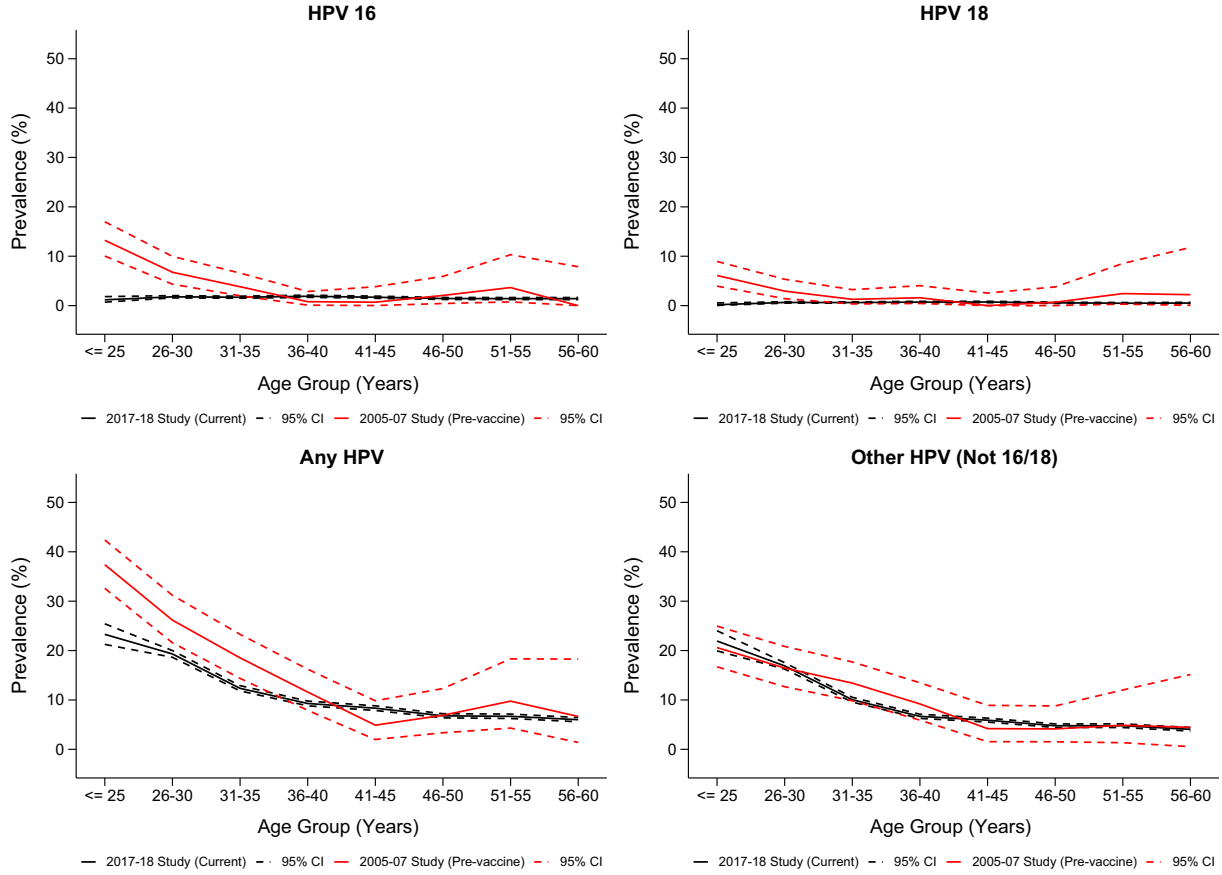

Fig. 2. Oncogenic HPV prevalence in two studies (A) 2017–2018 screening samples of 116,052 Victorian women and (B) 2005–2007 clinic recruited screening samples analysed using Linear Array of 1929 women by 5 year age groups [11] for (a) HPV 16 (b) HPV 18 (c) Any oncogenic HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) (d) Other oncogenic HPV (non 16/18).

Australia followed by a decline with age, with the notable exception of the most oncogenic types HPV16 and HPV18, indicating a quite remarkable impact of HPV vaccination on population-level epidemiology of HPV infection.

Funding

This work was supported by the National Health and Medical Research Council funded Centre for Research Excellence in Cervical Cancer Control (APP1135172), which provides partial salary support to David Hawkes, Farhana Sultana, Dorothy Machalek and Megan Smith. The funder had no role in study design, in the collection, analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

Acknowledgements

We thank laboratory staff at VCS Pathology.

Author contributions

The study was conceived by DH, JMLB and MS. DH extracted laboratory data which was analyzed by FS and MM. JMLB led the data interpretation and drafted the initial manuscript which was critically revised by all authors. All authors have approved the final article.

Declaration of interests

JMLB, MS and DH are investigators on the Compass trial for which VCS Foundation has received kits and partial funding from Roche. VCS Pathology has also received free test kits for unrelated projects from Roche, Seegene, Cepheid, and Becton Dickinson. JMLB, MS and SMG were investigators on a cervical cancer typing study with laboratory testing funded by Seqirus. JMLB and SMG were investigators on a recurrent respiratory papillomatosis surveillance study partially funded by an investigator initiated grant from MSD. DAM reports travel grants from Seqirus, travel funding and honoraria to her institute from Merck Sharp & Dohme (MSD), outside the submitted work. SMG has received grants to her institution from Merck and GSK (GlaxoSmithKline) to perform phase 3 clinical vaccine trials. She has received speaking fees from MSD for work performed in her personal time and Merck paid for travel and accommodation to present at Global HPV Advisory board meetings. FS, MJM and MAS declare no conflicts of interest.

References

[1] Moscicki AB, Schiffman M, Burchell A, Albero G, Giuliano AR, Goodman MT, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine 2012;30(Suppl 5):F24–33.
[2] Sharma M, Bruni L, Diaz M, Castellsagué X, de Sanjosé S, Bosch FX, et al. Using HPV prevalence to predict cervical cancer incidence. Int J Cancer 2013;132:1895–900.
[3] Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis 2010;202:1789–99.
[4] Li N, Franceschi S, Howell-Jones R, Snijders PJ, Clifford G. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. Int J Cancer 2011;128:927–35.
[5] Mercer CH, Tanton C, Prah P, Erens B, Sonnenberg P, Clifton S, et al. Changes in sexual attitudes and lifestyles in Britain through the life course and over time: findings from the national surveys of sexual attitudes and lifestyles (Natsal). The Lancet 2013;382(9907):1781–94.
[6] Gravitt P, Winer R. Natural history of HPV infection across the lifespan: role of viral latency. Viruses 2017;9:267.
[7] Cancer Council Australia Cervical Cancer Screening Guidelines Working Party. National Cervical Screening Program: Guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding, 2017.
[8] National Pathology Accreditation Advisory Council. Requirements for Laboratories Reporting Tests for the National Cervical Screening Program Canberra: Australian Government Department of Health, 2017.
[9] Drolet M, Laprise JF, Brotherton JML, Donovan B, Fairley CK, Ali H, et al. The impact of human papillomavirus catch-up vaccination in Australia: implications for introduction of multiple age cohort vaccination and postvaccination data interpretation. J Infect Dis 2017;216:1205–9.
[10] Garland SM, Brotherton JM, Condon JR, McIntyre PB, Stevens MP, Smith DW, et al. Human papillomavirus prevalence among indigenous and non-indigenous Australian women prior to a national HPV vaccination program. BMC Med 2011;9:104.
[11] Brotherton JM, Condon JR, McIntyre PB, Tabrizi SN, Malloy M, Garland SM. Human papillomavirus prevalence to age 60 years among Australian women prevaccination. Sex Health 2015 Aug;12(4):353–9. https://doi.org/10.1071/SH15035.
[12] Machalek DA, Garland SM, Brotherton JML, Bateson D, McNamee K, Stewart M, et al. Very low prevalence of vaccine human papillomavirus types among 18- to 35-year old Australian women 9 years following implementation of vaccination. J Infect Dis 2018;217:1590–600.
[13] Australian Institute of Health and Welfare. Cervical screening in Australia 2018, ed. Cat.no. CAN 111 Canberra: AIHW, 2018.
[14] Berecki-Gisolf J, Begum N, Dobson AJ. Symptoms reported by women in midlife: menopausal transition or aging? Menopause 2009;16:1021–9.
[15] Meites E, Lin C, Unger ER, Steinau M, Patel S, Markowitz LE, et al. Can clinical tests help monitor human papillomavirus vaccine impact? Int J Cancer 2013;133:1101–6.
[16] Arbyn M, Depuydt C, Benoy I, Bogers J, Cuschieri K, Schmitt M, et al. VALGENT: A protocol for clinical validation of human papillomavirus assays. J Clin Virol 2016;76(Suppl 1):S14–21.