Papillomavirus Research 8 (2019) 100190

Contents lists available at ScienceDirect

Papillomavirus Research

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

Rationalizing the HPV vaccination schedule: A long road to a worthwhile destination

Traditional sub-unit protein based vaccines require an adjuvant and multiple doses in a primary series, followed by booster doses as required, to stimulate the immune response adequately to provide sustained disease protection – for example diphtheria-tetanus-pertussis vaccines. These principles guided the initial trialing of human papillomavirus (HPV) vaccines using a three dose schedule of 0,1–2,6 months in order to provide sufficient time from the initial priming dose for stimulation and maturation of B cells prior to the final boosting dose to maximise the potential for the vaccines to induce a sustained effective immune response [1]. As with all vaccines at the point of implementation, duration of protection was unknown – an important issue given that the peak HPV infection rates occur in young women and the prophylactic vaccine was targeted to early adolescent girls, prior to exposure.

It is now apparent that vaccine induced protection occurs even with very low levels of detectable antibody, with protection sustained for over a decade in vaccinated cohorts even in individuals in whom the nominal 'seroconversion' threshold is no longer met (there is still no known immune correlate of protection.) [2,3] Sustained protection in the long term is likely [4]. The three HPV vaccines (bivalent, quadrivalent and nonavalent) are all clearly highly immunogenic, possibly due to the repetitively spaced presentation of the L1 protein antigen on the virus like particle, which mimics the conformation of the actual virus [5].

In a parallel with the use of hepatitis B vaccines, two dose schedules, using a wider spacing between the doses, in younger adolescents were developed based on the observation of higher titres generated with younger age. Trials supported the immunogenicity of such an approach with comparable titres, kinetics and avidity of antibodies with those of older women who had received three doses and in whom efficacy had been demonstrated [2,6–9]. In 2014, WHO recommended the use of two dose schedules in younger adolescents < 15 years on the basis of immunobridging [10]. At the same time, evidence had accumulated that the benefits of HPV vaccination on herd protection and speed of impact could be accelerated through the use of multi-cohort vaccination strategies across a wider initial age range, such as successfully demonstrated in the Australian mass catch up program [11]. However currently three doses remains the standard recommendation for those aged 15 and older at first vaccine dose and for all those with immunosuppression. Whilst the question of whether in fact just one dose of HPV vaccine could be adequate to provide protection is being actively pursued globally through RCTs and with slowly accumulating observational data [12], what evidence do we need to determine whether we could move to similarly spaced two dose schedules for a wider age range now? This is an important question as we face a global HPV vaccine supply crisis, currently limiting our ability to scale up HPV vaccination in countries who need it most, and because delivering three doses of vaccine is both expensive and logistically challenging, the latter probably all the more so in middle and late adolescence than in children.

The paper by Basu et al. in *Papillomavirus Research* provides further evidence in the form of infection outcomes to support the use of two dose schedules for 15–18 year olds, building on an earlier publication of trial data published in *Papillomavirus Research* in 2018 [13,14]. This paper is the most recent analysis of data from an Indian study that was established originally as a cluster randomized controlled trial to explicitly compare the immunogenicity and efficacy of two doses of quadrivalent HPV vaccine, spaced at 6 month apart, with three doses spaced at 0,2,6 months across the age range of 10–18 years. Unfortunately the study was suspended, for reasons unrelated to the study, when 17,729 of 21,258 (83.4%) eligible girls in 178 of 188 clusters had been recruited, creating an observational cohort. At suspension of vaccination, there were four default vaccine groups: three dose schedule completed (25%), two dose schedule complete (28%), two dose default (first two of three dose schedule planned complete) (19%) and one dose (28%). This unplanned event has had some surprising benefits for knowledge, creating an opportunity to observe the impact of one dose of vaccination and the study authors are to be commended for strategic use of the data and the subsequent recruitment of a control group to provide a reference point for effectiveness against HPV infection amongst similar women. Data supporting efficacy of one dose of HPV vaccine against infection from the cohort have been published elsewhere [15,16].

The present paper builds on the earlier publication by Bhatla et al. [14] which demonstrated similar antibody kinetics post vaccination and equivalent L1 16/18/6/11 antibody titres amongst 15–18 year olds one month after the last dose whether they had received two doses spaced at 180 days or three doses. Avidity indices were non-inferior to three dose recipients at age 10–14 years for both two and three dose groups [14]. The two dose group had non-inferior neutralizing antibody titres at month 18 against HPV16 and 6, but type 18 titres were inferior in the two dose recipient group (type 11 not assessed). In Basu et al., at a median follow up of 7 years, the rates of incident vaccine targeted HPV infection were not significantly different between married two dose schedule (180 days +) and three dose recipients and were lower than in the control group [13]. Persistent infections were rare in both groups and more common in the control group. Types against which there may be cross protection (31/33/45) were less common in the two and three dose recipients than control women whereas other sexually transmitted HPV types occurred with similar frequency [13]. In order to interpret these data, an assessment needs to be made as to whether these data can sufficiently address, without unintended bias, the original study hypothesis of equivalence of two and three dose schedules in adolescent girls up to age 18, given that the randomization was

https://doi.org/10.1016/j.pvr.2019.100190
Received 14 October 2019; Received in revised form 20 November 2019; Accepted 20 November 2019
Available online 21 November 2019

interrupted.

Randomization is intended to randomly distribute both known characteristics of participants that may potentially be associated with the outcome as well as unknown characteristics. In doing so, it provides maximal reassurance and power to identify and quantify a true effect of the study intervention. In this case, the intervention is the receipt of two as opposed to three doses of quadrivalent HPV vaccine and the outcomes of interest are measures of the immune response to vaccination and HPV infection rates. Arguably the most important known determinants of the immune response to HPV vaccines and the likelihood of HPV infection are age, sexual exposure and immunosuppression, so it is important that we seek whatever data are available to reassure us that these characteristics are likely to be evenly distributed between the two and three dose groups. All girls needed to be ambulant and in good health at recruitment, with exclusion of those 'in poor health and with severe or debilitating illness' [15]. This criteria may provide some reassurance in relation to a low likelihood of immunosuppressed girls being recruited to either arm. Notably however the control group was never part of the original randomization and added post-hoc, meaning that an assessment of how similar or different the control group are to both vaccinated groups is important in order to assess the effectiveness findings.

Demographic characteristics of the two and three dose groups are provided by the authors in the 2018 paper (Table 1) [14]. These are summarised as 'Age and dose groups are comparable for all these variables.' However no statistical tests are provided. Recruitment by cluster complicates simple comparisons and should the randomization and recruitment have been completed, all analyses would have needed to account for the cluster design. A statistical summary of baseline characteristics was provided in a previous paper reporting across all dose groups and unvaccinated controls as showing 'all characteristics had non-significant Pearson chi-square p value from hierarchical log-linear modelling using iterative proportional fitting, with conditional dependency of characteristics on randomization cluster' (footnote Table 1 [16]). It is unclear if this statistical analysis included the unvaccinated group who were not randomized and who had some apparent differences in summary characteristics reported compared to all vaccinated women (obviously older at recruitment due to design, but also more likely to be middle income, less likely to be low income, more likely to live in a thatched roof home and more likely to have had no education) [16].

In regard to the two dose vs three dose 15–18 year old groups, no information is given regarding whether the distribution by single year of age 15–18 is comparable. At one site (Mumbai), girls were only recruited into the two dose group (n = 157/1795, 8.7% of two dose 15–18 year old recipients) and not the three dose group, meaning that any underlying systematic difference in HPV risk related to socio-demographic characteristics of girls resident in Mumbai may not be balanced between the two arms [14]. Minor differences are apparent in distribution of religion between the groups, which could be important if there are major differences in risk by religion. There are also minor differences in the distribution of indictors of socioeconomic status, with slightly more girls living in thatched roof houses in the three dose group and slightly more girls in the three dose group were in the lowest household income group and slightly fewer in the wealthiest [14]. It is difficult to assess the importance or otherwise of the minor differences in the distribution of these variables and a univariate analysis of associations between HPV positivity and these characteristics would be helpful to understand whether they are likely to confound the association between dose groups and outcome. No baseline HPV infection status was collected from participants, complicating interpretation of vaccine effectiveness compared to other trials with infection as an outcome. However baseline HPV serostatus was collected in a subgroup of participants for HPV6/11/16/18 and found not to differ between the two and three dose groups at baseline, providing some reassurance of the comparability of baseline risk between groups [14].

At the date of analysis, median duration of follow up was the same between dose groups and a similar number of girls in each 15–18 year old group (860/1515 56.8% three dose, 901/1795 50.2% two dose) and 10–14 year old group (617/2833 21.8% three dose, 611/3184 19.2% two dose) had married, and then been included in the HPV infection analysis (first specimen collected at 18 months post marriage or 6 months post birth of first child, whichever was earlier.) [13].

So how should policy makers weight the findings? Are these data robust enough to reassure policy makers that, although the gold standard of randomized data are not available, that the data are sufficient to move to a two dose recommendation for 15–18 year olds? In favour of acceptance of the findings is the overall similarity in demographic characteristics between two and three dose groups, similar baseline seropositivity suggesting similar baseline risk, and the fact that, unlike in population based studies of two vs three dose impact, there was no decision making on the part of the woman or clinician as to whether she received two and three doses. This selection bias is marked in observational real world studies where women who only received one or two of three doses have characteristics associated with higher HPV risk [17,18]. Counterbalancing those data are the lack of baseline HPV infection data, detailed sexual history information and other risk factor data (eg smoking, contraceptive use) and a lack of specific reassurance regarding whether the minor apparent differences in some baseline characteristics could result in confounding. It is unclear to what extent the control group are truly comparable to the vaccinated women (their demographic characteristics suggest they could be at higher risk) so their baseline risk of HPV infection may be somewhat different. Countering this concern is the reassurance provided by the fact that the observed differences in HPV infection are relatively vaccine type specific, with incident 6/11/16/18 infection rates in the two and three dose groups 6–7x lower than in the control group, with a smaller difference in rates of other types (approx 1.4 times higher in control than 15–18 year old vaccine groups). Within the power of the study, there is no significant difference in rates of vaccine preventable infection between the two and three dose groups, although there is still some uncertainty given that the point estimate for 16/18 infection is 0.8% (95% CI 0.3–1.7) for three doses vs 1.6% (0.9–2.6) for the two dose group [13]. Notably both of these rates are very low for young sexually active women.

Are these data congruent with what is known elsewhere about HPV vaccination dose spacing? They are consistent with the immunogenicity findings from a randomized bivalent HPV vaccine study comparing two and three dose schedules, which found non-inferior antibody titres at month 7 using a standard three dose schedule (0,1,6 months) vs a two dose schedule (0,6 months) in 15–19 year females [19] They are also supported in principle by immunological evidence from Scherer et al., [20] which suggested that dose spacing with the licensed three dose quadrivalent HPV vaccine schedule is suboptimal in adult women. Those data found that the high vaccine induced antibodies from dose 1 and 2 may be interfering with stimulation, expansion and maturation of B memory cells after the third dose. This suggests that a more rationally designed immunisation schedule would provide wider spacing between doses for all recipients regardless of age.

Given the WHO recommendation for use of the two dose schedule in those aged 14 and under was based on bridging immunogenicity data alone, which may be subject to less biases in measurement and confounding compared to effectiveness data, the immunogenicity findings of non-inferiority (albeit from a single study) may be sufficient for policy makers and advisory bodies to support a move to a two dose schedule in 15–18 year olds. Indeed as yet there are still no effectiveness data available following implementation of two dose pre-adolescent schedules. Ultimately decision makers deal with imperfect data on many occasions and the question is what is the clinical risk vs benefit in expanding the two dose schedule to the older age group. The major uncertainty remains lack of information about long term durability of such a schedule. All available evidence suggests that HPV vaccination is

optimally delivered at a younger age, when comparative immune responses are greater and most likely to stimulate long term durable responses, potentially even after one dose [21,22]. It is likely that if indeed more than one dose of vaccine is necessary, that two doses spaced further apart could be more effective at generating a sustained immune response in 15–18 year olds than receiving only two of three intended doses spaced closer together will be. Many countries have failed to effectively deliver three doses in this age group. In Australia at present, although catch up vaccination is available to the age of 19 years, because the national policy is to provide two doses before age 15, those who require a third dose are required to pay for it themselves. Should clinicians advise women being vaccinated aged between 15 and 18 in Australia to space their second dose out further knowing that many young women will never return and pay for the third dose? Probably.

In the face of HPV vaccine supply constraints, high vaccine cost, and the difficulties of delivering three doses in catch up programs for women 15–18, I would argue that policy makers would be justified in recommending a more rational and achievable two dose schedule for all adolescents to the age of 18 at this time. The issue of longevity of protection is not new and, until an immune correlate of protection is established or time passes, is not easily addressed. The similarity in antibody avidity and kinetics post two doses compared to three provides reassurance that the likelihood of long term protection is not being significantly compromised. Further results with longer follow up and disease endpoints will also be valuable. Whatever schedule a country uses, all countries should have, as recommended by WHO, long-term records of HPV vaccine doses given and the possibility of recalling women for booster doses in the future should they ever be required.

Declaration of competing interest

Julia Brotherton was an investigator on investigator-initiated research grants that provided funding for laboratory testing for a study of cervical cancers (Seqirus) and recurrent respiratory papillomatosis (Merck) more than three years ago, but has never received personal financial benefits.

References

[1] M.A. Stanley, S.L. Sudenga, A.R. Giuliano, Alternative dosage schedules with HPV virus-like particle vaccines, Expert Rev. Vaccines 13 (8) (2014) 1027–1038, https://doi.org/10.1586/14760584.2014.935767.

[2] E. Meites, A. Kempe, L.E. Markowitz, Use of a 2-dose schedule for human papillomavirus vaccination — updated recommendations of the advisory committee on immunization practices, MMWR Morb. Mortal. Wkly. Rep. 65 (2016) 1405–1408, https://doi.org/10.15585/mmwr.mm6549a5external icon.

[3] M. Lehtinen, C. Lagheden, T. Luostarinen, et al., Ten-year follow-up of human papillomavirus vaccine efficacy against the most stringent cervical neoplasia endpoint-registry-based follow-up of three cohorts from randomized trials, BMJ Open 7 (8) (2017), https://doi.org/10.1136/bmjopen-2017-015867 e015867. Published 2017 Aug 18.

[4] M. Stanley, Tumour virus vaccines: hepatitis B virus and human papillomavirus, Philos. Trans. R. Soc. Lond. B Biol. Sci. 372 (1732) (2017) 20160268, https://doi.org/10.1098/rstb.2016.0268.

[5] J. Schiller, D. Lowy, Explanations for the high potency of HPV prophylactic vaccines, Vaccine 36 (32 Pt A) (2018) 4768–4773, https://doi.org/10.1016/j.vaccine.2017.12.079.

[6] B. Romanowski, T.F. Schwarz, L. Ferguson, et al., Sustained immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine administered as a two-dose schedule in adolescent girls: five-year clinical data and modeling predictions from a randomized study, Hum. Vaccines Immunother. 12 (1) (2016) 20–29, https://doi.org/10.1080/21645515.2015.1065363.

[7] L.M. Huang, T. Puthanakit, C. Cheng-Hsun, et al., Sustained immunogenicity of 2-dose human papillomavirus 16/18 AS04-adjuvanted vaccine schedules in girls aged 9-14 Years: a randomized trial, J. Infect. Dis. 215 (11) (2017) 1711–1719, https://doi.org/10.1093/infdis/jix154.

[8] O.E. Iversen, M.J. Miranda, A. Ulied, T. Soerdal, E. Lazarus, et al., Immunogenicity of the 9-valent HPV vaccine using 2-dose regimens in girls and boys vs a 3-dose regimen in women, J. Am. Med. Assoc. 316 (22) (2016 Dec 13) 2411–2421, https://doi.org/10.1001/jama.2016.17615.

[9] S.R.1 Dobson, S. McNeil, M. Dionne, M. Dawar, G. Ogilvie, et al., Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial, J. Am. Med. Assoc. 309 (17) (2013 May 1) 1793–1802, https://doi.org/10.1001/jama.2013.1625.

[10] World Health Organization, Human papillomavirus vaccines: WHO position paper, October 2014, Weekly Epidemiol. Record WER 43 (89) (2014) 465–492 http://www.who.int/wer/2014/wer8943.pdf?ua=1 , Accessed date: 29 May 2019.

[11] M. Drolet, J.-F. Laprise, J.M.L. Brotherton, B. Donovan, C.K. Fairley, H. Ali, E. Bénard, D. Martin, M. Brisson, The impact of human papillomavirus catch-up vaccination in Australia: implications for introduction of multiple age cohort vaccination and post-vaccination data interpretation, JID (J. Infect. Dis.) 216 (10) (2017 Dec 5) 1205–1209, https://doi.org/10.1093/infdis/jix476.

[12] M. Stanley, P. Dull, HPV single-dose vaccination: impact potential, evidence base and further evaluation, Vaccine 36 (32 Pt A) (2018 Aug 6) 4759–4760, https://doi.org/10.1016/j.vaccine.2018.02.076 Epub 2018 May 10.

[13] P. Basu, R. Muwonge, N. Bhatla, B.M. Nene, S. Joshi, et al., Two-dose recommendation for Human Papillomavirus vaccine can be extended up to 18 years - updated evidence from Indian follow-up cohort study, Papillomavirus Res. 7 (2019 Jan 31) 75–81, https://doi.org/10.1016/j.pvr.2019.01.004.

[14] N. Bhatla, B.M. Nene, S. Joshi, P.O. Esmy, U.R.R. Poli, et al., Are two doses of human papillomavirus vaccine sufficient for girls aged 15-18 years? Results from a cohort study in India, Papillomavirus Res. 5 (2018 Jun) 163–171, https://doi.org/10.1016/j.pvr.2018.03.008 Epub 2018 Mar 22.

[15] R. Sankaranarayanan, P.R. Prabhu, M. Pawlita, T. Gheit, N. Bhatla, et al., Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study, Lancet Oncol. 17 (1) (2016 Jan) 67–77, https://doi.org/10.1016/S1470-2045(15)00414-3 Epub 2015 Dec 2.

[16] R. Sankaranarayanan, S. Joshi, R. Muwonge, P.O. Esmy, P. Basu, et al., Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study, Vaccine 36 (32 Pt A) (2018 Aug 6) 4783–4791, https://doi.org/10.1016/j.vaccine.2018.02.087 Epub 2018 Mar 15.

[17] L.E. Markowitz, M. Drolet, N. Perez, M. Jit, M. Brisson, Human papillomavirus vaccine effectiveness by number of doses: systematic review of data from national immunization programs, Vaccine 36 (32 Pt A) (2018 Aug 6) 4806–4815, https://doi.org/10.1016/j.vaccine.2018.01.057 Epub 2018 May 22.

[18] J.M.L. Brotherton, M. Malloy, A. Budd, M. Saville, K. Drennan, D.M. Gertig, Effectiveness of less than three doses of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia when administered using a standard dose spacing schedule: observational cohort of young women in Australia, Papillomavirus Res. 1 (2015) 59–73.

[19] B. Romanowski, T.F. Schwarz, L.M. Ferguson, K. Peters, et al., Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared to the licensed 3-dose schedule, Hum. Vaccine 7 (12) (2011) 1374–1386, https://doi.org/10.4161/hv.7.12.18322.

[20] E.M. Scherer, R.A. Smith, J.J. Carter, G.C. Wipf, D.F. Gallego, M. Stern, A. Wald, D.A. Galloway, Analysis of memory B-cell responses reveals suboptimal dosing schedule of a licensed vaccine, J. Infect. Dis. 217 (4) (2018 Jan 30) 572–580, https://doi.org/10.1093/infdis/jix566.

[21] K.K. Smolena, L. Gelinasa, L. Franzenb, S. Dobson, M. Dawar, et al., Age of recipient and number of doses differentially impact human B and T cell immune memory responses to HPV vaccination, Vaccine 30 (2012) 3572–3579.

[22] V. Gilca, C. Sauvageau, G. Panicker, G. De Serres, J. Schiller, et al., Long intervals between two doses of HPV vaccines and magnitude of the immune response: a post-hoc analysis of two clinical trials, Hum. Vaccines Immunother. (2019), https://doi.org/10.1080/21645515.2019.1605278.

Julia ML. Brotherton*

VCS Population Health, VCS Foundation, East Melbourne, Victoria, Australia

Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia

E-mail address: jbrother@vcs.org.au.

* VCS Population Health, VCS Foundation, East Melbourne, Victoria, Australia.