Early use of the HPV 2-dose vaccination schedule: Leveraging evidence to support policy for accelerated impact

Vladimir Gilca a,b,⇑, Jorge Salmerón-Castro c,h, Chantal Sauvageau a,b, Gina Ogilvie d,e, Monique Landry f, Monica Naus d,g, Eduardo Lazcano-Ponce c

a Quebec Public Health Institute, Quebec, Canada
b Laval University Research Hospital Center, Quebec, Canada
c Centro de Investigación en Salud Poblacional, Instituto Nacional de Salud Pública, Cuernavaca, Morelos, Mexico
d University of British Columbia, Vancouver, Canada
e BC Women’s Hospital and Health Centre, Vancouver, Canada
f Quebec Ministry of Health and Social Services, Montreal, Canada
g British Columbia Centre for Disease Control, Vancouver, Canada
h Unidad Académica en Investigación Epidemiológica, Centro de Investigación en Políticas, Población y Salud, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico

A R T I C L E   I N F O

Article history:
Available online 7 June 2018

Keywords:
Human papillomavirus (HPV)
HPV vaccine
Alternative vaccination schedule
Single dose
Cervical cancer

A B S T R A C T

Although human papillomavirus (HPV) vaccines were initially licensed based on efficacy after three-dose regimens in women aged 15–26 years, it was recognized early in clinical development that comparable immunogenicity could be obtained after just two doses when administered to younger girls. In both Canada and Mexico, public health authorities made the decision to administer two doses 6 months apart with a planned additional dose at 60 months, while simultaneously doing further study to determine if the third dose would confer meaningful additional benefit. This delayed third dose approach permitted a more cost-effective program with opportunities for improved compliance while minimizing injections and leaving open the opportunity to provide a full three-dose vaccination series. It required close cooperation among many governmental and civil society leadership bodies and real-time access to emerging data on HPV vaccine effectiveness.

Although still limited, there is increasing evidence that even one-dose vaccination is sufficient to provide prolonged protection against HPV infection and associated diseases. Ongoing clinical trials and ecological studies are expected to consolidate existing data regarding one dose schedule use. However, to accelerate the preventive effect of HPV vaccination some jurisdictions, in particular those with limited resources may already consider the initiation of a one dose vaccination with the possibility of giving the second dose later in life if judged necessary. Such an approach would facilitate vaccination implementation and might permit larger catch-up vaccination programs in older girls (or as appropriate, girls and boys), thereby accelerating the impact on cervical cancer and other HPV-associated diseases.

© 2018 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Two main factors dictate the success of a vaccination program: vaccine effectiveness and vaccine uptake. A decade of experience with HPV vaccines has shown they are safe and effective, with the potential to prevent the majority of HPV-related diseases [1–5]. Despite these important characteristics, vaccine uptake remains suboptimal with less than half of countries (82 of 195) implementing HPV vaccination programs [6,7]. This situation is due to several factors including high vaccine prices, operational difficulties of multi-dose vaccination schedules, targeted age groups outside of infant and early childhood routine schedules, anti-vaccination concerns specific to HPV vaccines including its association to sexual activity, and ignorance about the relevance of precancerous clinical endpoints assessed in clinical trials. In many countries the main barriers are related to operational and financial difficulties, including the multi-dose vaccination schedule [8,9].

2. Vaccination schedules

Pre-licensure clinical trials of HPV vaccines assessed their immunogenicity and efficacy in three-dose vaccination schedules...
In Canada, healthcare is a provincial/territorial jurisdiction and each province and territory can make healthcare decisions including vaccination programs [20,21]. This results in variation of schedules for public immunization programs across Canada where implementation of HPV vaccination programs for school-aged girls varied from 2007 to 2010 [22], using quadrivalent vaccine in main vaccination programs and quadrivalent or bivalent vaccine in catch-up campaigns. At the time of writing nine of ten Canadian provinces use a two-dose schedule and one province continues with three doses [22]. Age cohorts eligible for HPV vaccination also vary across provinces from 9 to 14 years, some provinces/territories vaccinating only girls, and some both girls and boys.

3.1. The Quebec approach

Since 1990 the province of Quebec (population 8 M) has had a provincial immunization committee (QIC – Comité sur l’immunisation du Québec) whose active members with voting rights are public health experts, pediatricians and infectious disease specialists. This advisory committee makes recommendations to the Ministry of Health regarding the use of new vaccines and the optimization of existing programs. As prevention of HPV-related diseases exceeds the field of traditional infectious diseases the usual 16 QIC membership was extended to 36 with experts in gynecology, sexual transmitted diseases, cancer prevention, virology, anthropology and psychology. In 2005, with the imminent approval of HPV vaccines by Health Canada, an HPV working group created at the initiative of the Quebec Public Health Institute prepared an advisory report for future recommendations.

Quebec developed a vaccine decision-making framework including disease burden, vaccines characteristics, potential strategies for vaccination programs, program cost-effectiveness, acceptability, feasibility, capacity to evaluate, equity, ethics, and conformity [23]. By 2007 the quadrivalent HPV vaccine was available in Canada and the bivalent HPV vaccine was with the Health Canada regulatory board for approval so the use of one or both vaccines was not ruled out before the final decision. Thus, the characteristics of both vaccines were reviewed and compared [24].

At that time no efficacy data after one or two vaccine doses was available, so special attention was paid to immunogenicity data. As immunogenicity in adolescents and preadolescents was used by vaccine manufacturers as “bridging criteria” from efficacy data in women for HPV vaccines licensing for preadolescents and adolescents, it was thought that it could also serve for two- versus three-dose comparisons. Existing data indicated that one month post-second dose of quadrivalent vaccine (given 2 months post first dose) in 10–15 year-old girls the seroconversion rates (>97.5%) were similar to those reported one month post-third dose administered to 16–23 year-old women [25]. In the same study antibody titers as measured by GMTs post-second dose in 10–15 year-olds were higher than post-third dose in 16–23 year-olds in which high efficacy against the infections, pre-cancerous lesions (CIN2/3) and anogenital warts was reported. Presented in scientific conferences but not published at that time, data from clinical trials with two doses of the bivalent HPV vaccine in 10–14 year-old girls were also promising. Fivefold higher antibody titers were reported 18 months post-vaccination of 10–14 years-old girls when compared with those observed in 15–25 year-old women [26]. These data were discussed by experts from across Canada at the Canadian Human Papillomavirus Vaccine Research Priorities Workshop and different HPV research questions were ranked by importance. The immunogenicity and efficacy/effectiveness of two-dose schedules was voted as the most important question in the category “Intervention Research” [27], and participants questioned the need of the second dose in the 0, 2, 6 months schedule when vaccinating preadolescents and adolescents. Generally, with recombinant vaccines, an excellent priming is obtained after a single dose. The second dose induces higher antibody titers when administered 6–12 months after first dose when compared to 1–2 months interval.

While all other Canadian provinces/territories adopted the schedule recommended by the vaccine manufacturer (0, 2 and 6 months), in its 2007 report on HPV vaccination the QIC recommended an extended three-dose schedule (0, 6 and 60 months) noting that “the third dose will be given if judged necessary” [24,28]. The six months interval between the first two doses was based both on immunological expectations which were later confirmed and on operational reason (allowed co-administration with the combined hepatitis A and B vaccine). After approval by the extended QIC the report was sent for consultation to associations of provincial pediatricians, gynecologists, infectious disease and sexual transmitted disease specialists, and nurses to obtain their support for program implementation. This approach also familiarized these health professionals with immunological and operational reasons which justify the use of an extended schedule.

Consequently, in 2008 Quebec implemented a school-based HPV immunization program (0, 6 and 60 months) targeting Grade 4 girls (9–10 years-old) in the routine immunization program. This specific age group was chosen because preadolescents generally respond better to vaccination than older age groups, are more compliant with vaccination schedules, are not yet sexually active, and because a successful school-based hepatitis B immunization program in this age group had been in place since 1996 [29].

4. The global transition to two-doses HPV schedules in girls

At a WHO meeting in 2013 interim immunogenicity data from ongoing 2-dose schedule clinical trials in Canada, India, and Mexico, as well as first data on effectiveness of fewer than three-doses were presented [30]. The interim data from clinical trials with two doses given 6-month apart to 9–10 year-old girls showed non-inferior GMTs when compared to those observed in young
women after three doses of vaccine. Most effectiveness studies used population registries of immunization and cervical cancer screening programs. Due to the limits related to such real-world data analyses from available vaccine registries (i.e., the two doses were given at a short interval, many girls were already sexually active and potentially infected at the time of vaccination), the results were relatively ambiguous. However, when analyses were limited to more circumscribed data, including a “buffer period” with exclusion of cases of anogenital warts and/or precancerous lesions which were diagnosed during the first 6–12 months post-vaccination, the results observed after the two-dose vaccination series were encouraging [31–33]. Thus, the data accumulated during the first 4–5 years post-program implementation supported the initial hypotheses regarding the adequacy of two doses of HPV vaccine in preadolescents and adolescents and significantly diminished initial uncertainties. In July 2013, the Pan American Health Organization was the first to recommend the use of a 2- or 3-dose extended HPV immunization schedules for girls aged 9–13 years [34].

Consequently, in 2013 the QIC decided that the third dose of vaccine initially planned in the extended schedule (0, 6 and 60 months) was not relevant when vaccinating preadolescents and adolescents and recommended a two-dose schedule (0 and 6 months). It was judged that the two-dose schedule would improve the vaccine uptake and compliance with the vaccination schedule, reduce the number of injections related to immunization and correspondingly the probability of adverse events, while significantly improve the program’s cost-effectiveness, facilitating some catch-up campaigns and eventually uptake of the vaccine in an HPV program for boys [35]. Thus, the province of Quebec was the first jurisdiction in the Americas and the second in the world (after Switzerland) to recommend a two-dose HPV vaccination program. This preceded the first updated licensure for 2 dose HPV vaccination schedule for girls which was December 2013 in Europe and July 2014 in Canada. By 2017, 23 low- and middle-income countries and 25 high-income countries had adopted a two-dose vaccination schedule [36].

5. Importance of evaluation and monitoring

In 2008, monitoring of new scientific data and a comprehensive program evaluation plan were initiated to inform the decision of the need for the third dose of vaccine in Grade 9 (5 years after vaccination with two doses). Funding for this was foreseen in the budget prepared by the Quebec Ministry of Health for the implementation of a new program [35]. A randomized immunogenicity clinical trial with two doses of HPV vaccine and concomitant or separately administered combined hepatitis A and B vaccine was started at the time of HPV vaccination program implementation [29], as was a multi-provincial non-inferiority immunogenicity clinical trial on two versus three doses of HPV vaccine [37]. Rapid real-time sharing of ongoing evaluation studies data at large national and international conferences was established and the results of these studies along with newly available Canadian and international data were used by the QIC when deciding about the pertinence of the third dose of vaccine in 2012–2013. Finally, a long-term randomized clinical trial to assess the efficacy of two- versus three-dose schedules (ICI-VPH) against persistent infections in Quebec was initiated in 2013 [38], together with a multi-provincial larger non-randomized trial (QUEST) on the same issue under the leadership of a British Columbia team [39]. In these two studies a total of 5823 girls were vaccinated at the age of 9–12 years and will be followed for 10 years. More recently important efforts have been made at international level to assess the efficacy and effectiveness of less than three-dose schedules [40–43].

6. The Mexican context

Mexico has a tradition of innovative evidence-based public health policies. The first School of Public Health in Latin America was created 95 years ago, and was incorporated into the National Institute of Public Health of Mexico (INSP in Spanish) 30 years ago. Since its inception, the INSP has influenced health policies in Mexico such as the implementation of smoke-free closed spaces via the application of local laws based on scientific evidence provided by INSP research groups [44]. Since 2006, Mexico has pioneered the introduction of human papillomavirus (HPV) DNA testing using data obtained from population based studies. Alternative schedules of HPV vaccine (i.e., the 0-6-60 month strategy) were implemented in Mexico as a vaccination policy to increase coverage anticipating that scientific evidence would soon be available to give guidance for the use of the third dose.

6.1. The Mexican experience

Mexico adopted an evidence-based public health practice for cervical cancer prevention and control, including HPV screening and vaccination, for all regions and socioeconomic groups. After introduction of the 0-6-60-month extended schedule among girls under 14 years of age in Quebec a similar vaccination program was initiated in Mexico, following recommendations by a group of experts coordinated by the INSP [45,46]. Universal HPV vaccination for girls between 10 and 11 years of age was introduced in Mexico in 2012 using an extended alternative vaccine schedule (0-6-60 months) that was recommended by the INSP as the immune response to HPV vaccines is especially strong among 9–11 year-old girls [47]. An INSP-implemented clinical trial in Mexico to evaluate the immunogenicity and non-inferiority of alternative HPV vaccination schedules found antibody titers against both available at that time vaccines were significantly higher after administration of two doses in 9–10-year-old girls than after three doses in 18–24-year-old women [45]. Based on the available evidence, Mexico adopted an alternative two-dose vaccination schedule in April 2014 without intention for a third dose, which has been proven to be not inferior to the traditional schedule in terms of immunogenicity [48]. Meanwhile, a follow-up long term immunogenicity study is ongoing in Mexico. In this study 1447 girls vaccinated with two doses of bivalent vaccine (0, 6 months) at the age of 9–10 years, and 428 women vaccinated with three doses of the same vaccine (0, 1, 6 months) at the age of 18–24 years are followed up. Preliminary, unpublished yet results suggest that a non-inferiority in antibody titers between two study groups persists for at least 5 years.

7. Can a similar step-wise policy approach be used to leverage encouraging single-dose HPV data?

Over a decade of experience with HPV vaccines with data on post-implementation surveillance results in non-compliant individuals who received a single dose of vaccine, as well as on immunogenicity and efficacy data reported in some clinical trials [33,40,43,49–52] suggests that even one dose might be sufficient for protection against related diseases. However, the question is how much data is needed to decide whether to switch to one-dose vaccination, with or without the option of giving an additional dose later in life. Existing data after one dose of HPV vaccine shows seropositivity rates close to 100% but with antibody titers which are inferior to those observed after 2 or 3 doses, therefore immunogenicity bridging is not possible [49,52]. However, without consensus on the seroprotective threshold it is difficult to interpret observed differences in antibody titers.
after one or more doses of vaccine. Recent data suggest that naturally acquired HPV-16 antibodies are associated with up to 90% reduction in incident infection, 6-month persistent infection, and atypical squamous cells of undetermined significance or greater (ASCUS+) [53]. In this context, the ~9-fold higher antibody titers reported 7 years after vaccination with a single dose of bivalent vaccine when compared to antibodies acquired after a natural infection are reassuring [54]. Previously reported data indicate that even vaccinees who did not seroconvert or became seronegative as antibodies waned are still protected against the disease [55,56]. This suggests that the lower limit of quantitation of current serological tests might be above the seroprotective threshold or that post-vaccination cellular immunity plays a crucial role in protection [57]. However, the opposite cannot be completely excluded and some decrement in efficacy may happen when using a one-dose schedule. Countries which for different reasons have no HPV vaccination programs and have a high burden of HPV-related diseases may be more favorably inclined to implement one-dose vaccination to prevent most but not all of the burden related to HPV genotypes included in the vaccines. Alternatively, countries which have two- or three-dose programs in place might be willing to use a one-dose schedule if such an approach increases vaccine uptake and creates the budgetary possibility to add additional age or gender groups to the existing program. Many countries which implemented HPV vaccination programs also have cervical cancer screening programs, and in the future a single screening test may be all that is necessary in the life-time of HPV-vaccinated cohorts, so a theoretical for the time being slight decrement in vaccine efficacy should have minimal impact on the burden of disease. Furthermore, lower vaccine efficacy does not necessarily mean lower vaccination program effectiveness; increasing vaccine uptake by moving to a one-dose schedule might increase the program effectiveness.

8. Further questions over one-dose HPV vaccination

Other important questions about a similar approach for reduced dose schedules is what decrement in vaccine efficacy would trigger the administration of an additional dose in an extended 1 + 1 schedule, and in which age group is it reasonable to use such an extended schedule? Similar questions were raised when deciding about the use of two-dose or extended 2 + 1 schedules. Approaches used then can be re-applied for eventual one-dose or 1 + 1 extended schedules. The interval between doses should allow for the accumulation of evidence regarding the efficacy/effectiveness of a one-dose schedule (not necessarily in the same age group), and the risk of infection and of the disease should be minimal during the interval between first and second doses. This implies that the first dose should be given as early as possible (e.g. to 9–10 or even 7–8 year-olds); an age when vaccinees have not yet been exposed to HPV, and where the probability of exposure during the 4–5 years post-first dose remains low. Alternatively, because data from Costa Rica [54] and India [52] support single-dose efficacy for at least 7 years in older girls and women, it could be argued that such an extended interval dosing could be appropriate now for a similar population with this “umbrella” of protected time. These ongoing follow-up studies and recently initiated studies are expected to consolidate and extend existing knowledge about the duration of the protection ensured by one dose of vaccine. Additionally, the results from ecological studies conducted ten and more years after vaccination with less than three doses are expected to be available in the near future.

The decrement level which triggers administration of a second dose may vary substantially. In countries with an important HPV-related disease burden and no vaccination or screening programs in place, a reduction of 60–70% of the burden after one-dose vaccination might be an excellent choice when compared with the current situation. But in countries with two- to three-dose programs in place it might be difficult to accept even a 10% reduction in vaccine efficacy with a change to a one-dose schedule. Although HPV vaccination is expected to substantially reduce the burden of the disease, it cannot eradicate the disease as not all HPV genotypes are covered by the existing vaccines (70–90% of HPV-related cancers are covered), implying that a certain risk will persist regardless of the vaccination schedule.

Each jurisdiction will decide how existing resources should be better spent, including one-dose vaccination versus no vaccination or one-dose vaccination of more age cohorts and/or both genders versus more limited two- or three-dose programs. The mathematical models used when looking at different potential scenarios of two- versus three-dose schedules can be relatively easily applied to a one-dose schedule. Such data will help when making recommendations.

9. Summary

While there are strong operational justifications and immunologic expectations for harmonized vaccine schedules for adolescents and infants, experience over the last two decades shows initially approved multi-dose schedules may be optimized to better suit the local epidemiology and health service constraints. Public health authorities have a moral responsibility and in many countries a legal mandate to evaluate existing and new potential immunization programs. HPV vaccines are among the most thoroughly investigated vaccines with 10 years of field experience and more than 15 years of experience in large clinical trials indicating they are safe, highly immunogenic and protect against the related diseases. The ambitious, but carefully planned and evaluated two-dose HPV vaccination schedule became a standard used in many countries, and further data, although limited, now suggest that one-dose schedules might be sufficient. The ongoing and planned studies are expected to consolidate existing evidence-based data and to help the decision-making process regarding the use of a single-dose vaccination schedule. The use of extended 1 + 1 schedules may bridge the time period up until when more conclusive data is available in a policy approach similar to what was applied in Canada and Mexico for the transition to a 2-dose HPV vaccine schedule. To accelerate the preventive effect of HPV vaccination, some jurisdictions, in particular those with limited resources may already consider the initiation of a one dose vaccination with the possibility of giving the second dose later in life if judged necessary.

References

[1] Drolet M, Renard E, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2015;15(5):565–80.
[2] Jach R, Basta A, Kotarski J, Markowska J, Paszkowski T, Debinski R, et al. Ten years of anti-HPV vaccinations: what do we know? Przegląd Menopauzalny Menopauze Rev 2016;15(3):170–5.
[3] Markowitz LE, Liu G, Hariri S, Steinau M, Dunne EF, Unger ER. Prevalence of HPV after introduction of the vaccination program in the United States. Pediatrics 2016;137(3):1–9.
[4] Markowitz LE, Hariri S, Lin C, Dunne EF, Steinau M, McQuillan G, et al. Reduction in Human Papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States. National Health and Nutrition Examination Surveys, 2003–2010. J Infect Dis 2013;208(3):385–93.
[5] Garland SM, Kjaer SK, Muñoz N, Block SL, Brown DR, DiNubile MJ, et al. Impact and effectiveness of the quadrivalent human papillomavirus vaccine: a systematic review of 10 years of real-world experience. Clin Infect Dis Off Publ Infect Dis Soc Am 2016;63(4):519–27.
[6] Ginsburg O. Global disparities in HPV vaccination. Lancet Glob Health 2016;4(7):e428–9.
Gertig DM, Brotherton JM, Budd AC, Drennan K, Chappell G, Saville AM. Impact of HPV vaccination programs: a systematic review and meta-analysis. *Vaccine* 2016;34(10):1188–202.

Kreimer AR, Struyf F, Del Rosario-Raymundo MR, Hildesheim A, Skinner SR, Block SL, Nolan T, Sattler C, Barr E, Giacoletti KE, Marchant CD, et al. HPV vaccine effectiveness against incident cervical intraepithelial neoplasia grade 2 and grade 3: a systematic review and meta-analysis. *Vaccine* 2016;34(17):1956–67.

Msyamboza KP, Mwagomba BM, Vallee M, Chiumia H, Phiri T. Implementation of a population-based HPV vaccination program on cervical abnormalities: a population-based HPV vaccination program on cervical abnormalities: a cross-sectional study. *Ann Hum Biol* 2017;44(2):191–9.

Sauvageau C. Vaccination to prevent HPV infections: from promise to practice. *Plos Med* 2017 Jun 14;14(6):e1002325.

Moyanoa KP, Mwagomba BM, Vallee M, Chiumia H, Phiri T. Implementation of a human papillomavirus vaccination program project in Malawi: experiences and challenges. *BMJ Public Health* 2017;17(1):386–9.

Centers for Diseases Control and Prevention. Recommended immunization schedule for children and adolescents aged 18 years or younger, United States, 2017. Available from: http://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html [accessed Aug 18, 2017].

World Health Organisation. Table 2: Summary of WHO position papers - 2017 [Internet]. 2017 [cited 2017 Aug 7]. Available from: http://www.who.int/immunization/policy/Immunization_routine_table2.pdf [accessed Aug 18, 2017].

Plotkin SA, Orenstein WA, Offit PA. Vaccines. 6th ed. Philadelphia: Saunders Elsevier; 2012. p. 1550.

Pichichero ME. Challenges in vaccination of neonates, infants and young children. *Vaccine* 2014;32(31):3886–94.

McCollors JA, Dunn JD. Advances in vaccine technology and their impact on managed care. *PT Peer Rev* Formula Manage 2008;33(1):35–41.

Junewicz A, Brateanu A, Nielsen C. Do patients who received only two doses of hepatitis B vaccine need a booster? *Clev Clin J Med* 2014;81(6):346–8.

Merck Canada Inc. Highlights of prescribing information [Internet]; 2017 [cited 2017 Aug 7]. Available from: http://www.merck.com/product/us/a/685266/labeling.html [accessed Aug 18, 2017].

Stuuran AM, Marano C, Burns EG, De Moerloose L, Shoulav D. Impact of universal mass vaccination with monovalent inactivated hepatitis A vaccines - a systematic review. *Hum Vaccines Immunother* 2017;13(1):13–26.

Centers for Disease Control and Prevention. Hepatitis A Questions and Answers for Health Professionals | Division of Viral Hepatitis | CDC [Internet]; 2017 [cited 2017 Aug 7]. Available from: http://www.cdc.gov/hepatitis/hav/answers.htm [accessed Aug 18, 2017].

Urueña A, González JE, Rearte A, Pérez Carrega ME, Calli R, Pagani MF, et al. Effectiveness of less than three doses of quadrivalent human papillomavirus vaccine against cervical intraepithelial neoplasia when administered using a standard doses pacing schedule: Observational cohort of young women in Australia. *Papillomavirus Res* 2015;1:59–73.

Msyamboza G, Pimple SA, Hepatitis A HPV vaccine: One, two, or three doses for cervical cancer prevention? *Indian J Med Paediatr Oncol* Off J Indian Soc Med Paediatr 2015;36(4):201–6.

Basu P, Bhattacharya N, Gomu T, Sankaranarayanan R. Less than three doses of the HPV vaccine - review of efficacy against cervical and disease end points. *Hum Vaccines Immunother* 2016;12(6):1394–402.

Reynales-Shigematsu LM. Tobacco and cancer: epidemiology and new perspectives of prevention and monitoring in Mexico. *S Caldwell Publica Mex* 2016;58(2):251–60.

Hernández-Avila M, Torres-Ibarra L, Stanley M, Salmerón J, Cruz-Valdés A, Muñoz N, et al. Evaluation of the immunogenicity of the quadrivalent HPV vaccine using 2 versus 3 doses at month 21: an epidemiological surveillance mechanism for alternate vaccination schemes. *Hum Vaccines Immunother* 2016;12(1):30–8.

Lazcano-Ponce E, Stanley M, Muñoz N, Torres L, Cruz-Valdés A, Salmerón J, et al. Re-assessing barriers to HPV vaccination: non-inferiority of antibody response to human papillomavirus 16/18 vaccine in adolescents vaccinated with a two-dose vs. a three-dose schedule at 21 months. *Vaccine* 2014;32(6):725–32.

Lazcano-Ponce E, Salmerón-Castro J, García-Carrancá A, Aranda-Flores C, Madrid-Molina V, Gómez-Añorbeiro CM, et al. Recommendations for the definition of a policy on vaccination against papillomavirus in Mexico. *Strategic Advisory Group of Experts of the World Health Organization. Salud Publica Mex* 2017;60(1):88–101.

Neuzil KM, Cano do G, Thiem VD, Jam Johannes A, Huang VM, Tang T, et al. Immunogenicity and reactogenicity of alternative schedules of HPV vaccine in Vietnam: a cluster randomized noninferiority trial. *JAMA* 2011;305(14):1424–31.

Saafaeian M, Porras C, Pan Y, Kreimer A, Schiller JT, Gonzalez P, et al. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. *Cancer Prev Res (Phila Pa)* 2013 Nov;6(11):1242–50.

Stanley M. Preventing cervical cancer and genital warts - how much protection is enough for HPV vaccines? *J Infect* 2016;5:72 Suppl:S32–8.

Navarro-Illana E, López-Lacort M, Navarro-Illana P, Vilata J, Diez-Domingo J. Immunogenicity and HPV infection after one, two, and three doses of HPV Vaccine in Catalonia: a multicentre prospective cohort study. *Lancet Oncol* 2016;17(1):67–77.

Sankaranarayanan R, Prabhuj PR, Paulwita M, Gheit T, Bhathal N, Mwewoge R, et al. Immunogenicity and HPV infection after one, two, and three doses of HPV vaccine in Tanzania: a cross-sectional study. *Lancet Oncol* 2017;18(1):117–25.

FUTURE I/II Study Group, Dilnjer J, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen O-E, et al. Four year efficacy of prophylactic human papillomavirus type 2 vaccine against low grade cervical, vulvar, and vaginal...
intraepithelial neoplasia and anogenital warts: randomised controlled trial. BMJ 2010;341:c3493.

Haghshenas MR, Mousavi T, Kheradmand M, Afshari M, Moosazadeh M. Efficacy of human papillomavirus L1 protein vaccines (Cervarix and Gardasil) in reducing the risk of cervical intraepithelial neoplasia: a meta-analysis. Int J Prev Med 2017;8:44.

Stanley M, Pinto LA, Trimble C. Human papillomavirus vaccines–immune responses. Vaccine 2012;30(30 Suppl 5):F83–7.