Alternative HPV vaccination schedules in Latin America

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Abstract

In 2008, the first HPV vaccination program in Latin America started in Panama, targeting girls aged 10-11 years with a 3-dose vaccine schedule, an initiative that was to be followed by other Latin American countries after local feasibility and population acceptability evaluations were completed. A 3-dose vaccine regimen over six months was originally chosen for HPV vaccines, copying the Hepatitis B vaccine schedule (0, 1-2, 6 months). Alternative vaccine schedules have been proposed afterwards based on: i) noninferior immunogenicity or immune response levels compared to those at which clinical efficacy has been proven (i.e., those observed in a 3-dose HPV vaccine schedule in women aged 15-26), and, ii) proven efficacy in clinical trials and/or effectiveness among women who were provided less than three doses due to a lack of adherence to a 3-dose vaccine schedule. In 2014, based on the available evidence and the potential increase in coverage by expansion of vaccination target groups, particularly in low and middle income countries (LMIC), the World Health Organization recommended a 2-dose schedule with at least a 6-month interval between doses for females up to 15 years of age and a 3-dose schedule for older women. More recently, it has been suggested that 1-dose HPV vaccination schemes may provide enough protection against HPV infection and may speed up the introduction of HPV vaccination in LMIC, where most needed.

Keywords: VPH vaccination; vaccination schedules; number of vaccine doses

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Resumen

En 2008, se inició en Panamá el primer programa de vacunación contra el virus del papiloma humano (VPH), dirigido a niñas de 10 a 11 años, utilizando un esquema de tres dosis en seis meses, iniciativa que fue adoptada por otros países de la región tras evaluar la aceptabilidad en la población y la viabilidad de llevar a cabo el programa. Inicialmente, el esquema de tres dosis para las vacunas contra el VPH se basó en el utilizado en la vacunación contra la hepatitis B (0, 1-2, 6 meses). Posteriormente, se han propuesto esquemas de vacunación alternativos, utilizando evidencia sobre: i) la inmunogenicidad o niveles de respuesta inmune no inferiores a aquéllos con los cuales la eficacia clínica de la vacuna fue probada (es decir, aquéllos observados con tres dosis en mujeres de 15 a 26 años); y ii) la eficacia demostrada en ensayos clínicos y efectividad demostrada en mujeres a quienes se vacunó con menos de tres dosis debido a falta de adherencia al esquema completo de tres dosis. En 2014, la Organización Mundial de la Salud recomendó un esquema de dos dosis con al menos seis meses de intervalo entre dosis para mujeres de hasta 15 años de edad y uno de tres dosis para mujeres mayores. La recomendación se basó en la evidencia disponible hasta entonces y a un posible aumento en cobertura mediante la ampliación de los grupos etarios a vacunarse, particularmente en países de ingresos bajos y medios (PIBMs). Más recientemente, se ha sugerido un esquema de vacunación contra el VPH de una sola dosis, el cual podría proporcionar suficiente protección contra la infección por VPH y así acelerar la introducción de la vacunación contra el VPH en PIBMs donde más se necesita.

Palabras clave: vacunación contra VPH; esquemas de vacunación; número de dosis de vacunas

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Cervical cancer is the second most common type of cancer in Latin America, with about 70 000 new cases occurring every year in the region.[1] The identification of certain oncogenic types of human papillomavirus (HPV) as a necessary cause of cervical cancer[2] has provided a great opportunity to prevent disease on two fronts: by immunization with HPV vaccines and by screening using HPV DNA assay, and it is clear that implementation of universal HPV vaccination of adolescent girls is the best prospect to control cervical cancer, although a reduction of cervical cancer burden is unlikely to be observed, even in young women, for at least several decades, given the latency between HPV infection and cervical cancer.[3]

In 2006, the first human papillomavirus vaccine (HPV vaccine) was marketed aiming to prevent cervical cancer. To date, two additional vaccines have been marketed (table I), which include additional HPV types, and there is now compelling evidence that HPV vaccination is efficacious and/or effective against: i) HPV-cervical, -vulvar, -vaginal, -anal and -oral infections; ii) precancerous cervical lesions; and, iii) genital warts.[4-8]

National immunization programs in Latin America have been very effective, contributing to the success of several accelerated disease control initiatives, such as the one for rubella.[9] In 2008, the first HPV vaccination program started in Panama targeting girls at age 10-11 with a 3-dose vaccine schedule, an initiative that was followed by other Latin American countries. In some countries, such as Peru and Argentina, local feasibility and population acceptability evaluations prior to establishing HPV vaccination programs were carried out. In Peru, ahead of establishing the program in 2011-13, the Ministry of Health, in collaboration with PATH, carried out operational research in 2007-8, that showed that large-scale school-based HPV vaccination was feasible to implement without major changes in the existing health system.[10] HPV vaccination was approved in Argentina in 2006, but only introduced in the national immunization program in 2011. This was supported by positive results from a population-based acceptability survey of women aged 18-49 years, of whom around 75% were willing to be vaccinated and 74% of those with at least one daughter would get their daughters vaccinated if they were offered the vaccine.[11]

A report on worldwide HPV vaccination coverage estimated that from 2006 to 2014, 118 million women had been targeted through these programs, with only 1% of them being from low-income or lower-middle-income countries.[12] Furthermore, an HPV vaccination program should have high coverage (at least 70%) for it to be cost-effective[13] and sustainability of the program should be guaranteed. Dose-reduction with inherent cost-reduction per vaccinated subject may drive increases in coverage worldwide, particularly in less-developed regions.

In fact, it has been shown that vaccine efficacy is not substantially affected by reducing the number of doses from three to two, and data suggest that efficacy will not be substantially affected even when reducing to one dose. This potential reduction to a single dose and the possibility of applying it at the most beneficial point in time, not only from a protective angle but also from practical delivery issues, may strongly incentivate HPV vaccination start in countries where the vaccine is most needed and where current competing health needs may be prioritized ahead of HPV vaccination.

In this manuscript, we summarize: the evidence for implementing different HPV vaccination schedules in Latin America over time, and the available evidence (efficacy, effectiveness and immunogenicity) for a reduced number of HPV vaccination doses.

Number of doses

Vaccine dosage schedules are initially established empirically based on the vaccine characteristics and composition. HPV vaccines contain proteins that assemble together resembling the virus without containing the viral DNA, which in theory elicit lower immune responses than live viral vaccines. Thus, a three-dose vaccine regimen over six months was originally chosen

Table I
FDA-approved HPV vaccines

	Quadrivalent (Gardasil)	*Nonavalent (Gardasil-9)*	*Bivalent (Cervarix)*
Manufacturer	Merck & Co., Inc		GlaxoSmithKline
HPV types	16, 18, 6, 11	16, 18, 6, 11, 31, 33, 45, 52, 58	16, 18
Adjuvant	Aluminiumhydroxy-diphosphosulfate		Aluminiumhydroxide with monophosphorylipid AS04
Schedule	3 doses (0, 2, 6 months)		3 doses (0, 1, 6 months)

for HPV vaccines copying the Hepatitis B vaccine schedule (0, 1-2, 6 months). Alternative vaccine schedules have been proposed afterwards based in: i) noninferior immunogenicity or immune response levels compared to those at which clinical efficacy has been proven (i.e., those observed in a 3-dose vaccine schedule in women aged 15-26); and, ii) proven efficacy in clinical trials and/or effectiveness among women who were provided less than three doses due to a lack of adherence to a 3-dose vaccine schedule.

In 2007, the *Comité sur l'Immunisation du Québec* published a report containing the initial arguments, both immunological and operational, for an extended HPV vaccination schedule at months 0, 6 and 60.[14,15] The immunological arguments were: i) high immunogenicity of vaccines with consequent higher production of antibody titers than those induced by natural infections; ii) higher immune responses after two vaccine doses in girls 9-11 years than after three doses in women 16-26 years in whom clinical efficacy of the vaccine had been proven; iii) lack or limited manufacturers' justification for the 3-doses standard schedule (over six months); and, iv) higher immune response yielded by a booster dose at five years compared to that of the initial immunization, a booster that could be provided when most needed, at sexual debut ages. The operational arguments included: i) potentially higher acceptance rates; and, ii) easier logistics when applying only two doses to girls during a school year.

Following this report, a randomized trial in three Canadian provinces confirmed that among girls who received two doses of the quadrivalent vaccine six months apart, immune responses to HPV 16 and HPV 18 one month after the last dose were noninferior to those among young women who received three doses of the vaccine within six months. Durability of the noninferiority up to 36 months was assessed and although antibody responses in girls were noninferior after two doses compared to three doses for all four vaccine genotypes at month seven, evidence for noninferiority was lost for HPV 18 by month 24 and for HPV 6 by month 36.[16] The immunogenicity and the safety of a booster of either vaccine (quadrivalent Gardasil or bivalent Cervarix) were also examined. Girls who were vaccinated at age 9-10 with two doses of the quadrivalent vaccine were randomized (1:1) to receive a booster of either vaccine at ages 12-13 (three years later); increased antibody titers were observed one month post-booster with either vaccine. The magnitude of the immune response was vaccine dependent and had the same pattern as reported after initial vaccination with the corresponding vaccine. Anti-HPV 16 and HPV 18 geometric means of antibody titers (GMT) were significantly higher after a booster with the bivalent vaccine than with the quadrivalent one. This difference is consistent with the higher immunogenicity of the bivalent compared to the quadrivalent vaccine after primary vaccination with a 3-dose at 0, 1-2 and 6 months HPV vaccine schedule, previously suggested to be due to different vaccine adjuvants. As the immune response was only assessed one month post-booster given at 18-36 months post-second dose when an antibody plateau is expected, long-term data are needed to further evaluate the effect and persistence of immunity after a booster dose.[17]

The information above was subsequently used in 2009 by an External Assessment Committee established for advising on the introduction of HPV immunization in Mexico. The Committee recommended vaccination with a 0-6-60 months schedule based on the facts above and the additional benefits of its application: simplified logistics and infrastructure, higher coverage using the same amount of resources and potential combined strategy of third dose administration at sexual debut ages within a sexual education intervention. Monitoring of immunogenicity was also recommended.[18]

The extended vaccine schedule was adopted by other countries, such as Colombia and Brazil, afterwards. While in 2013 the Colombian National Immunization Program changed from a 3-dose within six months scheme to the 0-6-60 HPV vaccine schedule allowing expansion of the target vaccination cohort of girls 9 years old into females aged 9-17,[19] Brazil's National HPV Vaccination Program started with the extended 0-6-60 vaccine schedule in 2014.[20]

In fact, by 2014, based on noninferior immunogenicity evidence, several countries had already approved the use of a 2-dose schedule in girls up to around 14 years of either vaccine. In view of its potential for cost-saving and programmatic advantages, the World Health Organization recommended a 2-dose schedule with at least a 6-month interval between doses for females up to 15 years old and a 3-dose schedule for older women.[21] Since then, countries initiating HPV vaccination programs have directly implemented a 2-dose schedule at months 0 and 6, such as Ecuador[22] and Dominican Republic[23] or Chile, with a 2-dose schedule at months 0 and 12.[24]

Among countries on a 3-dose HPV vaccination extended schedule, only Mexico should have provided the third dose from 2014 since the program started in 2009; however, a governmental regulation allowing the use of 2-dose HPV vaccination schemes was approved before the end of 2014, preventing the application of a third dose.[25]

Immunogenicity data

In this manuscript, we include immunogenicity data on 2- and 1-dose vaccination schedules. The detailed data by vaccine type is provided in table II.[16,26-32] Immunogenicity data on alternative 3-dose schedules and data on 2-dose schedules with alternative formulations can be found elsewhere.[33,34]

There are seven studies reporting data on immunogenicity of less than three doses; the bivalent vaccine was applied in five of them, while the quadrivalent vaccine was used in the other three. Among these studies, there are five clinical trials (three with the bivalent and two with the quadrivalent vaccine) originally designed to assess alternative vaccine schedules and three bivalent vaccine studies where immunogenicity in less than three doses was assessed ad-hoc given the incompleteness of vaccine doses (losses to follow-up or regulatory reasons).

The ratio of the GMT of an alternative vaccine schedule against the standard one is often used to compare them. In most HPV-immunogenicity studies, noninferiority of 2-dose and 1-dose against 3-dose schedule (denominator) is statistically accepted if the lower bound of the CI of the GMT ratio is more than 0.5, or, inversely, if the upper bound of the 95%CI when comparing the 3-dose standard (numerator) against the alternative schedule is lower than two.

Based on the above noninferiority criteria, clinical trials purposely designed to evaluate noninferiority of less than 3-dose schedules and the Indian study[16,26-29,32] have consistently demonstrated that the immunological responses to 2-dose HPV vaccination administered at months 0 and 6 to girls up to age 14 were noninferior to those elicited by 3-dose HPV vaccination at age 15 or older when measured at 21 months follow-up or onwards.[16,27-29]

Additional observed findings include: a) up to 60 months sustained noninferiority of 2-dose HPV 16 and HPV 18 antibody levels in 9-14 years old compared to women aged 15-25 receiving three doses in the Canadian/Germany trial;[27] b) noninferiority of a two-dose schedule when the second dose was given at 12 months[29] in addition to that shown with a 6-month second dose in the multicentric multinational trial in Germany, Taiwan and Thailand; c) noninferiority of 2-dose against 3-dose vaccination in women 18-25 years for HPV 16 and HPV 18 and GMT levels for 1-dose or 2-doses higher than those elicited by natural infection in the CVT (Costa Rican trial), and d) antibody measurements suggesting potential long-term protection (four years in the CVT[30] and 2-3 years in Uganda[31]), after one single dose of HPV vaccine, despite not achieving noninferiority of 1-dose to more doses schedules.[30,31] Moreover, CVT participants have been continuously followed-up, and results showing that protection against incident HPV 16/18 infection continues after seven years of-follow-up have been very recently published.[35]

Efficacy and effectiveness data

Published evidence on efficacy (under control conditions, such as a clinical trial) and effectiveness (real-life conditions) for less than 3-dose HPV vaccination is provided in table III.[36-42] Among all published studies, there is only one on vaccine efficacy, the pooled analysis of the CVT (Costa Rican RCT) and the PATRICIA trial. This CVT/PATRICIA study assessed the efficacy of the bivalent vaccine against incident HPV 16/18 infections (one-time detected, persistent over 6 or 12 months).[36] The remaining studies assessed vaccine effectiveness, two of the bivalent vaccine and four of the quadrivalent vaccine, against a variety of endpoints (genital warts, cytological abnormalities and histologically confirmed cervical lesions) using different study designs (cross-sectional, case-control, retrospective cohorts) and consequently reporting different measures of association.

In addition to the CVT/PATRICIA, two studies using routinely collected data in Scotland have evaluated vaccine efficacy against HPV 16/18 prevalent infections[37] and against precancerous cervical lesions (CIN1, CIN2 and CIN3).[38] Overall, the four studies on the bivalent vaccine have demonstrated that one, two and three doses of the bivalent vaccine reduce the incidence of persistent HPV 16 and HPV 18 infections[36] and prevalence of HPV 16 and HPV 18 infections.[37] However, reduced risk of cervical lesions (CIN1-3) at first cervical screen has only been observed in 3-dose vaccine schedules.[38]

As for the quadrivalent vaccine, one study in Sweden[39] reported significant reduced incidence rates of genital warts for one, two and three doses of the quadrivalent vaccine compared to no vaccination, and three studies using HPV immunization and cervical screening that routinely collected data in two Australian states, Queensland and Victoria, have reported effectiveness against cervical precancerous lesions.[40-42] A case-control study nested within the Queensland Health Pap smear registry[40] observed reduced odds of both low- and high-grade cervical lesions with one, two and three doses compared to no vaccination, although results for 1-dose were not statistically significant. A retrospective cohort of women screened between 2007 and 2011 was selected in Victoria, and their vaccination status (including number of administered doses) was gathered from: 1) those up to 17 years in 2007 and 2) those up to 26 years of age.[41,42] Results consistently showed decreased risk of

Table II

STUDIES ASSESSING IMMUNOGENIC NONINFERIORITY OF LESS THAN THREE DOSES COMPARED THREE DOSES VACCINE SCHEDULES AT DIFFERENT TIME POINTS

Study identification	*Vaccination age: number of participants (vaccine schedule)/time of reported endpoints*	*Main noninferiority findings*
Noninferiority purposely clinical trials		
Canada, Germany Bivalent HPV vaccine (NCT00541970) Romanowski *et al.*[26,27]	Age 9-14: 78 (2d), 82 (3d) Age 15-19: 82 (2d), 76 (3d) Age 20-25: 80 (2d), 81 (3d)	1. Noninferiority of 2d in 9-14 yo *vs* 3d in 15-25 yo for HPV 16 and HPV 18 GMTs at M7, M24, M36, M48 and M60 2. Noninferiority of 2d in 15-19 yo *vs* 3d in 15-25 yo for HPV 16 and HPV 18 GMTs at M7 and M60 3. Noninferiority of 2d in 20-25 yo *vs* 3d in 15-25 yo for HPV 18 GMTs but not for HPV 16 GMTs at M7
Mexico Bivalent HPV vaccine (NCT01717118) Lazcano-Ponce *et al.*[28]	Age 9-10: 1 026 (2d), 474 (3d) Age 18-24: 500 (3d)	1. Noninferiority of 2d in 9-10 yo *vs* 3d in 9-10 yo for HPV 16 and HPV 18 GMTs at M21 2. Noninferiority of 2d in 9-10 yo *vs* 3d in 18-24 yo for HPV 16 and HPV 18 GMTs at M21
Canada, Germany, Italy, Taiwan, Thailand Bivalent HPV vaccine (NCT01381575|HPV-070) Huang *et al.*[29]	Age 9-14: 524 (2d), 39 ($2d^{A}$; 0,12) Age 15-25: 443 (3d)	1. Noninferiority of 2d in 9-14 yo *vs* 3d in 15-25 yo for HPV 16 and HPV 18 GMTs at M36 2. Noninferiority of $2d^{A}$ in 9-14 yo *vs* 3d in 15-25 yo for HPV 16 and HPV 18 GMTs at M36
Canada Quadrivalent HPV vaccine (NCT00501137) Dobson *et al.*[16]	Age 9-13: 259 (2d), 261 (3d) Age 16-26: 310 (3d)	1. Noninferiority of 2d in 9-13 yo *vs* 3d in 16-26 yo for HPV 16, HPV 18, HPV 6 and HPV 11 GMTs at M7, M18, M24 and M36 2. Noninferiority of 2d in 9-13 yo *vs* 3d in 9-13 yo for HPV 16 and HPV 11 GMTs at M7, M18, M24 and M36 3. Noninferiority of 2d in 9-13 yo *vs* 3d in 9-13 yo for HPV 18 at M7 but not at M18, M24 and M36 4. Noninferiority of 2d in 9-13 yo *vs* 3d in 9-13 yo for HPV 6 GMTs at M7, M18 and M24
Ad -hoc studies		
Costa Rica Bivalent HPV vaccine (NCT00128661) Safaeian *et al.*[30]	Age 15-25 yo (original study) 78 (1d), 52 (2d), 140 ($2d^{B}$; 0,1), 120 (3d), 113 (natural infection)	1. Noninferiority of 2d *vs* 3d in 18-25 yo for HPV 16 and HPV 18 GMTs at M48 2. In addition: a. Compared to natural infection, $2d^{B}$ HPV 16 GMTs were 24 times higher and $2d^{B}$ HPV 18 GMTs were 14 times higher at M48 b. Compared to natural infection, 1d HPV 16 GMTs were 9 times higher and 1d HPV 18 GMTs were 5 times higher at M48
Uganda Bivalent HPV vaccine (NA, cross-sectional study) LaMontagne *et al.*[31]	Age 10-11 yo 36 (1d), 145 ($2d^{B}$; 0.1), 195 (3d)	1. Noninferiority was not shown for 1d and $2d^{B}$ vs 3d for HPV 16 and HPV 18 GMTs, however: a. Compared to minimum antibody levels in 3d, 86% of HPV 16 and 98% of HPV 18 $2d^{B}$ antibody levels were higher b. Compared to minimum antibody levels in 3d, 61% of HPV 16 and 86% of HPV 18 1d antibody levels were higher
India Quadrivalent HPV vaccine (NCT00923702) Sankaranarayanan *et al.*[32]	Age 10-18 yo 4 950 (1d), 4 979 (2d), 3 452 ($2d^{C}$; 0,2), 4 348 (3d) (Immunogenicity assessed in a representative convenient sample)	1. Noninferiority of 2d *vs* 3d in 10-18 yo for GMTs of four vaccine types at M7, M18, M36 and M48, except for HPV 18 GMTs at M48 2. In addition: a. Noninferiority of $2d^{C}$ *vs* 3d in 10-18 yo for HPV 16 GMTs at M36 but not at M18 and for no other vaccine types b. Noninferiority of 1d *vs* $2d^{C}$ in 10-18 yo for all vaccine types was not achieved

yo: years old; GMT: geometric mean titers; M: month. 1d: one-dose vaccination; 2d: vaccination at M0 and M6; $2d^{A}$: vaccination at M0 and M12; $2d^{B}$: vaccination at M0 and M1; $2d^{C}$: vaccination at M0 and M2; 3d: vaccination at M0, M1 and M6 for the bivalent vaccine and at M0, M2 and M6 for quadrivalent vaccine; NA: not applicable

Antibody detection was done with ELISA (Enzyme-linked immunosorbent assay) for all bivalent vaccine studies and by Luminex-based assays for quadrivalent vaccine ones

A less than three dose schedule was considered noninferior to a three dose schedule if the lower limit of the 95%CI of GMT ratio (<3d/3d) > 0.5 or the upper limit of the 95%CI of GMT ratio (3d/<3d) < 2.0; except in the Uganda study in which a 97.5% CI was used to account for type-specific adjustment

Table III

VACCINE EFFICACY AGAINST HPV INFECTION, GENITAL WARTS OR CERVICAL PRECANCEROUS LESIONS AFTER ADMINISTRATION OF 1, 2 OR 3 DOSES OF HPV VACCINE, BY VACCINE TYPE

Study identification	*Study design*	*Study population/ No. of participants per vaccine dose*	*Results*
CVT/PATRICIA Kreimer *et al.*[36]	Clinical trial (pooled data) 15 to 25yrs	Women aged 15-25 yo with 4fuy/ 3d: 13 296 TVC-naive (6 662 HepA, 6 634 HPV) 2d: 549 TVC-naive (276 HepA, 273 HPV) 1d: 238 TVC-naive (100 HepA, 138 HPV)	Vaccine efficacy against: 1. Incident one-time detection of HPV16/18 infection - 3d *vs* 3d HepA: 81.4% (95%CI 78.7-83.8) - 2d *vs* 2d HepA: 81.2% (95%CI 59.5-92.3) - 1d *vs* 1d HepA: 85.7% (95%CI 60.9-97.1) 2. Incident 6 months persistent HPV16/18 infection - 3d *vs* 3d HepA: 93.6% (95%CI 91.2-95.5) - 2d *vs* 2d HepA: 87.9% (95%CI 54.0-98.1) - 1d *vs* 1d HepA: 100% (67.4-100) 3. Incident 12 months persistent HPV16/18 infection - 3d *vs* 3d HepA: 92.6% (95%CI 89.2-95.1) - 2d *vs* 2d HepA: 83.7% (95%CI 35.7-97.5) - 1d *vs* 1d Hep A: 100% (95%CI 41.1-100)
Scotland Cuschieri *et al.* [37]	Cross-sectional; routine data linkage of the Scotland HPV Surveillance and Cervical Screening Programs	1988-93 birth cohorts attending for first cervical smear / 3d: 1 853; 2d : 300; 1d: 177; 0d: 3 619	Adjusted vaccine efficacy against prevalent HPV 16/18 infection* 3d *vs* 0d: 48.2% (95%CI 16.8-68.9) 2d *vs* 0d: 54.8% (95%CI 30.7-70.8) 1d *vs* 0d: 72.82% (95%CI 63.8-80.3)
Scotland Pollock *et al.*[38]	Cross-sectional; routine data linkage of the Scotland HPV Surveillance and Cervical Screening Programs and Colposcopy data	All women born in 1988-92 in the HPV Surveillance System with an abnormal cervical smear until May 2013 / 3d: 25 897; 2d: 2 725; 1d: 1 315; 0d: 76 113	Adjusted Relative Risk for screen-detected cervical lesions‡ 1) CIN1 - 3d *vs* 0d: 0.71 (95%CI 0.58-0.87) - 2d *vs* 0d: 0.65 (95%CI 0.42-1.01) - 1d *vs* 0d: 0.98 (95%CI 0.59-1.63) 2) CIN2 - 3d *vs* 0d: 0.50 (95%CI 0.40-0.63) - 2d *vs* 0d: 0.81 (95%CI 0.54-1.22) - 1d *vs* 0d: 1.03 (95%CI 0.62-1.71) 3) CIN3 - 3d *vs* 0d: 0.45 (95%CI 0.35-0.58) - 2d *vs* 0d: 0.77 (95%CI 0.49-1.21) - 1d *vs* 0d: 1.42 (95%CI 0.89-2.28)
Sweden Herweijer *et al.*[39]	Population-based cohort 10 to 24 yo; efficacy data for women 10-19 yo	Women 10-19 yo with average 3.8 fuy/ 3d: 89 836; 2d: 107 338; 1d: 115 197; 0d: 1 045 157 Average follow-up: 3.8 years	Incidence Rate Ratios of genital warts per 100 000 pyrs§ - 3d *vs* 0d: 0.20 (95%CI 0.17-0.23) - 2d *vs* 0d: 0.32 (95%CI 0.26-0.40) - 1d *vs* 0d: 0.54 (95%CI 0.43-0.68)
Australia (Queensland) Crowe *et al.*[40]	Case control nested within Queensland Health Pap smear registry; Routine data linkage with the Queensland Health Vaccination registry	Women 11 to 27 yo (vaccination target) in 2007 attending for first cervical smear in 2007-2011: 96 404 controls (only negative cytology over study period) with median 2.2 fuy/ 3d: 22 987; 2d: 10 850; 1d: 9 535; 0d: 53 032 10 887 CIN2+ on histology (including ungraded CIN) with median 1.8 fuy/ 3d: 2 013; 2d: 1 123; 1d: 1 230; 0d: 6 521 1 062 <CIN2 on histology/ASC-US+ cytology with median 2.1 fuy/ 3d: 119; 2d: 100; 1d: 114; 0d: 729	Adjusted odds ratios# of cervical lesions at first screening visit 1) CIN2+ - 3d *vs* 0d: 0.54 (95%CI 0.43-0.67) - 2d *vs* 0d: 0.79 (95%CI 0.64-0.98) - 1d *vs* 0d: 0.95 (95%CI 0.77-1.16) 2) <CIN2 or ASC-US+ cytology - 3d *vs* 0d: 0.66 (95%CI 0.62-0.70) - 2d *vs* 0d: 0.79 (95%CI 0.74-0.85) - 1d *vs* 0d: 0.95 (95%CI 0.89-1.02)

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Australia (Victoria) Gertig *et al.*[41]	Population-based retrospective cohort; routine data linkage of the Victorian Cervical Cytology and the National HPV Vaccination Program Registries	Women ≤17yo in 2007 with screening records in 2007-2011 with average 1.5 fuy / 3d: 21 199; 2d: 3 412; 1d: 2 568; 0d: 15 192	Hazard Ratios[&] of cervical lesions at first screening visit 1) CIN2+ - 3d *vs* 0d: 0.61 (95%CI: 0.48-0.78) - 2d *vs* 0d: 1.02 (95%CI: 0.68-1.53) - 1d *vs* 0d: 1.47 (95%CI 0.97-2.23) 2) High-grade cytology - 3d *vs* 0d: 0.71 (95%CI 0.61-0.83) - 2d *vs* 0d: 0.95 (95%CI 0.73-1.23) - 1d *vs* 0d: 0.85 (95%CI: 0.62-1.17) 3) Low-grade cytology - 3d *vs* 0d: 0.79 (95%CI 0.75-0.84) - 2d *vs* 0d: 0.64 (95%CI: 0.57-0.72) - 1d *vs* 0d: 0.67 (95%CI: 0.59-0.76)
Australia (Victoria) Brotherton *et al.*[42]	Population-based retrospective cohort; routine data linkage of the Victorian Cervical Cytology and the National HPV Vaccination Program Registries	Women ≤26yo in 2007 with screening records in 2007-2011 with average 2.9 fuy/ 3d: 45 358; 2d: 8 638; 1d: 6 938; 0d: 133 055 Average follow-up: 2.9 years	Hazard Ratios[∞] of cervical lesions after average follow-up of 2.9 years in women who received their final vaccination dose before first screen: 1) CIN2+ - 3d *vs* 0d: 0.71 (95%CI 0.64-0.80) - 2d *vs* 0d: 1.21 (95%CI 1.02-1.44) - 1d *vs* 0d: 1.19 (95%CI 0.99-1.43) 2) High-grade cytology - 3d *vs* 0d: 0.53 (95%CI 0.47-0.60) - 2d *vs* 0d: 0.63 (95%CI 0.50-0.80) - 1d *vs* 0d: 0.44 (95%CI 0.32-0.59) 3) Low-grade cytology - 3d *vs* 0d: 0.73 (95%CI 0.68-0.78) - 2d *vs* 0d: 0.52 (95%CI 0.44-0.61) - 1d *vs* 0d: 0.48 (95%CI 0.40-0.58)

yo: years old; pyrs: person-years old; 95%CI: 95%confidence interval; 1d: one-dose vaccination; 2d: vaccination at months 0 and 1 for the bivalent vaccine and at months 0 and 2 for quadrivalent vaccine; 3d: vaccination at months 0, 1 and 6 for the bivalent vaccine and at months 0, 2 and 6 for quadrivalent vaccine; fuy: follow-up years. CIN: cervical intraepithelial neoplasia; CIN2+: High grade histological abnormalities

* Vaccine efficacy estimated as: 1-the adjusted odds ratio of comparing prevalent infection of vaccinated women with 1, 2 or 3 doses versus unvaccinated women, adjusted for deprivation score and age at first dose
‡ Relative risk adjusted for cohort year, deprivation score and age
§ Incidence rate ratios adjusted for follow-up time, year of birth, and measures of socioeconomic status and remoteness
# Odds ratios adjusted for follow-up time, year of birth, and measures of socioeconomic status and remoteness
& Hazard ratios adjusted for age at first screening, socioeconomic status and remoteness
∞ Hazard ratios adjusted for age in 2007, socioeconomic status and remoteness

low- and high-grade cytological abnormalities, irrespective of age and number of doses, compared to unvaccinated women, though in the analysis performed in women up to age 17, only three doses showed significant risk reduction. For CIN2 or worse lesions (histological CIN2+), only 3-dose vaccination showed a protective effect, while two doses showed no effect and one dose even a non-significant increased risk irrespective of age. A similar result was observed in the Scottish analysis of cervical disease for risk of CIN3 after 1-dose of bivalent vaccine compared to no vaccination.[38] Thus, no vaccine efficacy by either vaccine have been shown for CIN2 or worse endpoints so far; indeed, in three studies, an apparent increased risk of CIN2+ in partially vaccinated subjects has been reported.[38,41,42] Nonetheless, caution should be taken when interpreting these results, as it is possible that partially vaccinated women who interrupted their 3-dose vaccine schedule, might have been at a higher underlying risk of HPV infection due to behavioral differences than those who completed their schedules.

Finally, the previously described immunogenicity study in India31 has recently reported, after seven years of follow-up, 1.6% (95%CI 6.2; 5.0-7.6) cumulative incidence of HPV infection in girls who received a single dose of the quadrivalent vaccine and 6.2% (95%CI 1.1-2.3) in those not vaccinated. No comparative measure was reported. However, the observed proportions suggest a 1-dose protective effect.[43]

Conclusions and further research needs

The FDA-approved HPV vaccines (bivalent, quadrivalent, nonavalent) have demonstrated to be highly

efficacious against infections with targeted HPV types and are in use in more than 70 countries around the world. However, there is a clear need to increase world HPV vaccination coverage, particularly in LMIC where unfortunately many lives are lost due to cervical cancer.

Many countries are nowadays using two-dose HPV vaccine schedules, based on strong supporting immunogenicity and efficacy evidence. Further reduction to a single dose HPV vaccination will represent a major impulse towards implementation of new HPV vaccination programs, to add birth cohorts to those already covered in countries and to contribute to the sustainability of existing HPV vaccination programs.

Current evidence on 1-dose HPV vaccination is inconclusive, both in immunological and efficacy studies. All three studies on immunogenicity data[30-32] reported inferior GMT levels of 1-dose HPV vaccination when compared to those elicited by either 2- or 3-dose vaccination; nonetheless 1-dose elicited higher antibody levels than those obtained by natural HPV infection.[30] To date, the minimum antibody levels required to provide protection against HPV-related infection is not established; however, it has been observed that among unvaccinated women, those with lower antibody levels are at a higher risk of HPV infection and cervical precancer lesions.[44] In terms of efficacy, while evidence suggests that 1-dose HPV vaccine may be sufficient to protect against HPV infection[36,37] and low-grade cytological abnormalities,[41,42] reduced, null or even increased risk of high-grade cytological and histological abnormalities after 1-dose vaccination has been reported.[40-42] It is however worth noting that only the CVT-PATRICIA pooled analysis assessed efficacy of 1-dose HPV vaccine against new HPV 16/18 one-time detected, six- and 12-month persistent infections. The results showed similar protection independently of the number of doses (compared to similar doses of Hepatitis A vaccine) but with less precision as the number of doses decreased.[36] In addition, the remaining studies assessing 1-dose schedule have been done using programmatic data in countries with vaccinated cohorts already attending screening; that is, with no random allocation of the number of doses, and hence, prone to bias.[37-42] Despite limitations, these initial results encouraged further evaluations to confirm the efficacy of one dose.

Thereupon, the ESCUDDO trial, evaluating noninferiority of 1-dose compared to 2-dose schedules in the prevention of new HPV 16/18 cervical HPV infections, has recently started in Costa Rica.[45,46] Twenty thousand girls 12 to 16 years old will be randomly allocated to one of four arms receiving one or two doses of the bivalent or nonavalent vaccine. The results from the ESCUDDO trial are very much awaited, if 1-dose of either HPV vaccine (bivalent or nonavalent) proved to be sufficiently efficacious, it could be recommended for prevention of HPV-related cancers, and even in the case that 1-dose is not fully efficacious, its impact in the reduction of disease and herd immunity may be significant, by allowing vaccination for many more people, rather than vaccinating fewer people with more doses.

Alternative vaccine schedules are also under evaluation for older women. The FASTER-Tlalpan study is currently assessing the efficacy of a combined strategy of HPV screening with one or two doses of the bivalent or quadrivalent vaccine in women aged 25-45.[47] Its results will provide valuable data for the HPV-FASTER strategy,[48] that aims to accelerate the reduction in cervical cancer burden, if demonstrated, in a single screen-and-vaccine visit.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer, 2013 [cited 2014, Jan 12]. Available from: http://globocan.iarc.fr

2. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, *et al.* Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12-9. https://doi.org/10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F

3. Almonte M, Sasieni P, Cuzick J. Incorporating human papillomavirus testing into cytological screening in the era of prophylactic vaccines. Best Pract Res Clin Obstet Gynaecol. 2011;25(5):617-29. https://doi.org/10.1016/j.bpobgyn.2011.05.003

4. Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, *et al.* Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PloS One. 2013;8(7):e68329. https://doi.org/10.1371/journal.pone.0068329

5. Lehtinen M, Dillner J. Clinical trials of human papillomavirus vaccines and beyond. Nat Rev Clin Oncol. 2013;10(7):400-10. https://doi.org/10.1038/nrclinonc.2013.84

6. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, *et al.* A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372(8):711-23. https://doi.org/10.1056/NEJMoa1405044

7. Drolet M, Bénard É, 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. https://doi.org/10.1016/S1473-3099(14)71073-4

8. 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. 2016;63(4):519-27. https://doi.org/10.1093/cid/ciw354

9. Tambini G, Andrus JK, Fitzsimmons JW, Roses-Periago M. Regional immunization programs as a model for strengthening cooperation among nations. Rev Panam Salud Publica. 2006;20(1):54-9. https://doi.org/10.1590/S1020-49892006000700012

10. Penny M, Bartolini R, Mosqueira NR, LaMontagne DS, Mendoza MA, Ramos I, *et al.* Strategies to vaccinate against cancer of the cervix: feasibility of a school-based HPV vaccination program in Peru. Vaccine. 2011;29(31):5022-30. https://doi.org/10.1016/j.vaccine.2011.04.078
11. Arrossi S, Maceira V, Paolino M, Sankaranarayanan R. Acceptability and uptake of HPV vaccine in Argentina before its inclusion in the immunization program: a population-based survey. Vaccine. 2012;30(14):2467-74. https://doi.org/10.1016/j.vaccine.2012.01.032
12. Bruni L, Diaz M, Barrionuevo-Rosas L, Herrero R, Bray F, Bosch FX, *et al.* Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. Lancet Glob Health. 2016;4(7):e453-63. https://doi.org/10.1016/S2214-109X(16)30099-7
13. Canfell K, Chesson H, Kulasingam SL, Berkhof J, Diaz M, Kim JJ. Modeling preventative strategies against human papillomavirus-related disease in developed countries. Vaccine. 2012;30(Suppl 5):F157-67. https://doi.org/10.1016/j.vaccine.2012.06.091
14. Duval B, Gilca V, Sauvageau C (eds.). Advice of the Institut National de Santé Publique Du Québec on Human Papillomavirus Vaccines. Montréal, Québec: Institut National de Santé Publique du Québec, 2008 [cited 2017 Feb, 9]. Available from: http://www.deslibris.ca/ID/213867
15. Dubé È, Institut National de Santé Publique du Québec, Direction des Risques Biologiques Environnementaux et Occupationnels, Comité sur l'immunisation du Québec. Prevention by vaccination of diseases attributable to the human papilloma virus in Quebec. Montréal, Québec: Institut National de Santé Publique du Québec, Direction des Risques Biologiques, Environnementaux et Occupationnels, 2008 [cited 2017, Feb 9]. Available from: http://www.deslibris.ca/ID/214673
16. Dobson SRM, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, *et al.* Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA. 2013;309(17):1793-802. https://doi.org/10.1001/jama.2013.1625
17. Gilca V, Sauvageau C, Boulianne N, De Serres G, Crajden M, Ouakki M, *et al.* The effect of a booster dose of quadrivalent or bivalent HPV vaccine when administered to girls previously vaccinated with two doses of quadrivalent HPV vaccine. Hum Vaccines Immunother. 2015;11(3):732-8. https://doi.org/10.1080/21645515.2015.1011570
18. Lazcano-Ponce E, Salmerón-Castro J, García-Carrancá A, Aranda-Flores C, Madrid-Marina V, Gómez-Altamirano CM, Martínez-Montañez OG. Recomendaciones para la definición de la política de vacunación contra el virus del papiloma en México. Salud Publica Mex. 2009;51(4):336-41.
19. Ministerio de Salud y Protección Social de Colombia. Vacunación contra el Virus Papiloma humano - VPH en Colombia, para la prevención del cáncer de cuello uterino y verrugas genitales. Bogotá: Munsalud, 2012 [cited 2017, Jan 30]. Available from: https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/IA/INCA/1-vacunacion-contra-virus-papiloma%20humano-verrugas-genitales.pdf
20. Ministério da Saúde. Presidente Dilma e ministro Chioro iniciam vacinação contra HPV. Ministério da Saúde: Portal da Saúde, 2014 [cited 2017 Feb, 9]. Available from: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/10035-postos-de-saude-e-escolas-iniciam-vacinacao-contra-hpv
21. World Health Organization. Human papillomavirus vaccines: WHO position paper. Wkly Epidemiol Rec. 2014;89(43):465-92.
22. Ministerio de Salud Pública de Ecuador. Vacuna contra el virus del papiloma humano previene cáncer uterino en el Ecuador. Quito: Ministerio de Salud Pública, 2014 [cited 2017, Oct 20]. Available from: http://www.salud.gob.ec/vacuna-contra-el-virus-del-papiloma-humano-previene-cancer-uterino-en-el-ecuador/
23. Ministerio de Salud Pública de República Dominicana. Resolución no. 000023 que incorpora la vacuna contra el virus del papiloma humano (HPV) al esquema basico de inmunización del programa ampliado de inmunización. Santo Domingo: Ministerio de Salud Pública, 2016 [cited 2017, Oct 10]. Available from: http://www.msp.gob.do/oai/documentos/Resoluciones/2016/RESOLUCION-000023-QUE%20INCORPORA%20LA%20VACUNA%20CONTRA%20EL%20VIRUS%20ZICA%20DEL%20PAPILOMA%20HUMANO%20HPV%20EL%20ESQUEMA%20BASICO%20DE%20INMUNIZACION%20DEL%20PROGRAMA%20AMPLIADO%20DE%20INMUNIZACION.pdf
24. Ministerio de Salud, Gobierno de Chile. Vacunación contra el Virus del Papiloma Humano. Santiago: Ministerio de Salud, 2017 [cited 2017, Oct 20]. Available from: http://web.minsal.cl/vacunacion-contra-el-virus-del-papiloma-humano/
25. Secretaría de Salud. Proyecto de Norma Oficial Mexicana PROY-NOM-036-SSA2-2014, Prevención y control de enfermedades. Aplicación de vacunas, toxoides, faboterápicos (sueros) e inmunoglobulinas en el humano. Gobierno de la República: DOF, 2014 [cited 2017, Feb 9]. Available from: http://www.dof.gob.mx/nota_detalle.php?codigo=5369071&fecha=21/11/2014
26. Romanowski B, Schwarz TF, Ferguson LM, Peters K, Dionne M, Schulze K. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. Hum Vaccin. 2011;7(12):1374-86. https://doi.org/10.4161/hv.7.12.18322
27. Romanowski B, Schwarz TF, Ferguson L, Peters K, Dionne M, Behre U. 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. 2016;12(1):20-9. https://doi.org/10.1080/21645515.2015.1065363
28. Lazcano-Ponce E, Stanley M, Muñoz N, Torres L, Cruz-Valdez A, Salmerón J . Overcoming 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. https://doi.org/10.1016/j.vaccine.2013.11.059
29. Huang LM, Puthanakit T, Cheng-Hsun C, Ren-Bin T, Schwarz T, Pellegrino A, *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. 2017;215(11):1711-9. https://doi.org/10.1093/infdis/jix154
30. Safaeian 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). 2013;6(11):1242-50. https://doi.org/10.1158/1940-6207.CAPR-13-0203
31. LaMontagne DS, Mugisha E, Pan Y, Kumakech E, Ssemaganda A, Kemp TJ, *et al.* Immunogenicity of bivalent HPV vaccine among partially vaccinated young adolescent girls in Uganda. Vaccine. 2014;32(47):6303-11. https://doi.org/10.1016/j.vaccine.2014.08.071
32. Sankaranarayanan R, Prabhu PR, Pawlita M, Gheit T, Bhatla N, Muwonge R. 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. 2016;17(1):67-77. https://doi.org/10.1016/S1470-2045(15)00414-3
33. Stanley MA, Sudenga SL, Giuliano AR. Alternative dosage schedules with HPV virus-like particle vaccines. Expert Rev Vaccines. 2014;13(8):1027-38. https://doi.org/10.1586/14760584.2014.935767
34. Romanowski B, Schwarz TF, Ferguson LM, Ferguson M, Peters K, Dionne M. Immune response to the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 4 years after vaccination: results from a randomized study. Hum Vaccines Immunother. 2014;10(5):1155-65. https://doi.org/10.4161/hv.28022
35. Safaeian M, Sampson JN, Pan Y, Porras C, Kemp TJ, Herrero R, *et al.* Durability of protection afforded by fewer doses of the HPV16/18 vaccine: the CVT trial. J Natl Cancer Inst. 2018;110(2). https://doi.org/10.1093/jnci/djx158
36. Kreimer AR, Struyf F, Del Rosario-Raymundo MR, Hildesheim A, Skinner SR, Wacholder S, *et al.* Efficacy of fewer than three doses of an

HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA trials. Lancet Oncol. 2015;16(7):775-86. https://doi.org/10.1016/S1470-2045(15)00047-9

37. Cuschieri K, Kavanagh K, Moore C, Bhatia R, Love J, Pollock KG. Impact of partial bivalent HPV vaccination on vaccine-type infection: a population-based analysis. Br J Cancer. 2016;114(11):1261-4. https://doi.org/10.1038/bjc.2016.97

38. Pollock KG, Kavanagh K, Potts A, Love J, Cuschieri K, Cubie H, *et al.* Reduction of low- and high-grade cervical abnormalities associated with high uptake of the HPV bivalent vaccine in Scotland. Br J Cancer. 2014;111(9):1824-30. https://doi.org/10.1038/bjc.2014.479

39. Herweijer E, Leval A, Ploner A, Eloranta S, Simard JF, Dillner J. Association of varying number of doses of quadrivalent human papillomavirus vaccine with incidence of condyloma. JAMA. 2014;311(6):597-603. https://doi.org/10.1001/jama.2014.95

40. Crowe E, Pandeya N, Brotherton JML, Dobson AJ, Kisely S, Lambert SB, Whiteman DC. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. BMJ. 2014;348:g1458. https://doi.org/10.1136/bmj.g1458

41. Gertig DM, Brotherton JML, Budd AC, Drennan K, Chappell G, Saville AM. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. BMC Med. 2013;11(1):227. https://doi.org/10.1186/1741-7015-11-227

42. Brotherton JML, Malloy M, Budd AC, Saville M, Drennan KT, Gertig DM. 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. 2015;(1):59-73. https://doi.org/10.1016/j.pvr.2015.05.005

43. Sankaranarayanan R, Joshi S, Muwonge R, Esmy PO, Basu P, Prabhu P, *et al.* Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. Vaccine. 2018;36(32 Pt A):4783-91. https://doi.org/10.1016/j.vaccine.2018.02.087

44. Castellsagué X, Naud P, Chow SN, Wheeler CM, Germar MJ, Lehtinen M, *et al.* Risk of newly detected infections and cervical abnormalities in women seropositive for naturally acquired human papillomavirus type 16/18 antibodies: analysis of the control arm of PATRICIA. J Infect Dis. 2014;210(4):517-34. https://doi.org/10.1093/infdis/jiu139

45. Kreimer AR, Sherman ME, Sahasrabuddhe VV, Safaeian M. The case for conducting a randomized clinical trial to assess the efficacy of a single dose of prophylactic HPV vaccines among adolescents. J Natl Cancer Inst. 2015;107(3):pii:dju436. https://doi.org/10.1093/jnci/dju436

46. National Cancer Institute (NCI). Scientific evaluation of one or two doses of the bivalent or nonavalent prophylactic HPV vaccines. ClinicalTrials.gov, 2017 [internet] [cited 2017, Aug 18]. Available from: https://clinicaltrials.gov/ct2/show/NCT03180034

47. Salmerón J, Torres-Ibarra L, Bosch FX, Cuzick J, Lörincz A, Wheeler CM. HPV vaccination impact on a cervical cancer screening program: methods of the FASTER-Tlalpan Study in Mexico. Salud Publica Mex. 2016;58(2):211-9. https://doi.org/10.21149/spm.v58i2.7790

48. Bosch FX, Robles C, Díaz M, Arbyn M, Baussano I, Clavel C, *et al.* HPV-FASTER: broadening the scope for prevention of HPV-related cancer. Nat Rev Clin Oncol. 2016;13(2):119-32. https://doi.org/10.1038/nrclinonc.2015.146