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Strong reduction in prevalence of HPV16/18 and closely related HPV types in sexually active adolescent women following the introduction of HPV vaccination in Argentina

Joaquín Víctor González [a], Gerardo Daniel Deluca [b], Rita Mariel Correa [a], Domingo Javier Liotta [c,d], Jorge Alejandro Basiletti [a], María Dolores Fellner [a], María Celeste Colucci [a], Olga Gabriela Alzogaray [e], Nathalia Katz [f], Juan José Carmona [g], Néstor Fabián Tappari [g], Enrique Berner [h], Viviana Cramer [h], Paula Real [h], Carlota Viviana López Kaufman [i], Gabriela Judit Kosoy [i], Lucía Katabian [i], María Silvia Severino [j], Ricardo Enrique Aboslaiman [e], Cecilia Chami [k], María Elina Totaro [c], Carolina Rogoski [g], Alejandra Julia Giurgiovich [l], Gloria Lilian Martínez [l], Liliana Marisol Plana [l], Carla Vizzotti [m], María Alejandra Picconi [a,*]

[a] *Servicio Virus Oncogénicos, Laboratorio Nacional y Regional de Referencia para HPV, Instituto Nacional de Enfermedades Infecciosas -ANLIS "Dr. Malbrán", Av. Velez Sársfield 563, C1282AFF, Buenos Aires, Argentina*

[b] *Facultad de Medicina, Universidad Nacional Del Nordeste, Mariano Moreno 1240, W3400ACX, Corrientes, Argentina*

[c] *Laboratorio de Biología Molecular Aplicada, Facultad de Ciencias Exactas, Quimicas y Naturales, Universidad Nacional de Misiones, Av. Mariano Moreno 1375, N3300, Posadas, Misiones, Argentina*

[d] *Instituto Nacional de Medicina Tropical- ANLIS "Dr. Malbrán", Neuquén y Jujuy S/n, N3370, Puerto Iguazú, Misiones, Argentina*

[e] *Centro Integral de Salud La Banda, Av. San Martín 449, G4300, La Banda, Santiago Del Estero, Argentina*

[f] *Dirección de Control de Enfermedades Inmunoprevenibles, Ministerio de Salud de La Nación, Rivadavia 875, C1002AAG, Buenos Aires, Argentina*

[g] *Servicio Ginecología, Hospital Escuela de Agudos "Ramón Madariaga", Av. Marconi 3736, N3300, Posadas, Misiones, Argentina*

[h] *Servicio de Adolescencia, Hospital General de Agudos "Dr. Cosme Argerich", Gral. Urquiza 609, C1221 ADC, Buenos Aires, Argentina*

[i] *Sección Adolescencia, Hospital General de Agudos "Bernardino Rivadavia", Av. Gral. Las Heras 2670, C1425ASQ, Buenos Aires, Argentina*

[j] *Servicio Adolescencia, Hospital General de Agudos "Carlos Durand", Av. Díaz Vélez 5044, C1405DCS, Buenos Aires, Argentina*

[k] *Sub Programa Salud Integral Del Adolescente, Ministerio de Salud de Santiago Del Estero, Av. Belgrano Sur 2050, Santiago Del Estero, G4200, Argentina*

[l] *Consultorio de Adolescencia, Hospital Zonal General de Agudos "Evita Pueblo", Calle 136 3008, B1884, Berazategui, Provincia de Buenos Aires, Argentina*

[m] *Secretaría de Acceso a La Salud, Ministerio de Salud de La Nación, Av. 9 de Julio 1925, C1073ABA, Buenos Aires, Argentina*

1. Introduction

Persistent infection with a high-risk (HR) human papillomavirus (HPV) type is a necessary cause of cervical cancer (CC) and has been shown to be associated with other cancers in women and men. Two of these HR-HPV types, HPV16 and HPV18, are present in around 71% of CC worldwide. Infection with low-risk (LR) HPV6 or HPV11 has been shown to be associated with the vast majority of genital warts [1,2].

Three prophylactic HPV vaccines are globally available: a quadrivalent vaccine first licensed in 2006, a bivalent vaccine in 2007 and a nonavalent vaccine in 2014. All of them protect against infection with HPV16 and 18, while the most recent one also protects against five

* Corresponding author. Servicio Virus Oncogénicos, Laboratorio Nacional y Regional de Referencia de HPV, Instituto Nacional de Enfermedades Infecciosas -ANLIS "Dr. Malbrán". Av. Velez Sársfield 563, C1282AFF, Buenos Aires, Argentina.

E-mail addresses: joavicgon1969@gmail.com (J.V. González), delucagd@gmail.com (G.D. Deluca), mcorrea@anlis.gob.ar (R.M. Correa), javierliotta@gmail.com (D.J. Liotta), jbasiletti@gmail.com (J.A. Basiletti), mdfellner@anlis.gob.ar (M.D. Fellner), celecolucci@gmail.com (M.C. Colucci), ogalzogaray12@hotmail.com (O.G. Alzogaray), nkatz@dicei.msal.gob.ar (N. Katz), juanchocarmona@hotmail.com (J.J. Carmona), fabiantappari@hotmail.com (N.F. Tappari), enriqueberner@gmail.com (E. Berner), draviviana@gmail.com (V. Cramer), palireal@gmail.com (P. Real), lkaufman@fibertel.com.ar (C.V. López Kaufman), gabriela.kosoy@hotmail.com (G.J. Kosoy), lkatabian@gmail.com (L. Katabian), docseverino@hotmail.com (M.S. Severino), rikiaboslaiman@hotmail.com (R.E. Aboslaiman), ceciliachami@hotmail.com (C. Chami), mtotaro@hotmail.com (M.E. Totaro), carorogoski@hotmail.com (C. Rogoski), alejandragiurgiovich@yahoo.com.ar (A.J. Giurgiovich), martinez-lulu@hotmail.com (G.L. Martínez), solplana@yahoo.com.ar (L.M. Plana), cvizzotti@gmail.com (C. Vizzotti), mapicconi@gmail.com, mapiccconi@anlis.gob.ar (M.A. Picconi).

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additional HR-HPV types (HPV31, 33, 45, 52, and 58). Current evidence suggests the three vaccines offer comparable efficacy in CC prevention from the public health perspective [3].

HPV vaccination of young females was introduced in 2007 under the national immunization programs, using the first two licensed vaccines. More recently, some countries have added routine adolescent male vaccination with the quadrivalent vaccine. Although vaccines were highly effective in clinical trials, monitoring real-world effectiveness is important for programme and policy strategies. Because of the long interval between infection and cancer development, efforts are under way to evaluate impact on more immediate outcomes.

Aiming at CC prevention, in October 2011 Argentina launched the most comprehensive government-funded national HPV prevention program in Latin America, incorporating the bivalent HPV vaccine, with a 0-1-6-month schedule, for girls 11 years of age, born after January 2000 [4]. This intervention also involved reinforcing CC screening in women aged 30–64 as a secondary prevention strategy, with the gradual introduction of HPV testing as primary screening [5]. In 2014, the programme switched to the quadrivalent vaccine, and was extended to males and females aged 11 to 26 living with HIV and transplanted individuals with a 3-dose schedule (0, 2 and 6 months) kept up to the present time [6]. In 2015 the number of doses was reduced to two for girls aged 11, and two years later, vaccination was extended to boys aged 11 (born after 2006) also with a 2-dose scheme [7].

In Argentina, the three-dose coverage has been moderate, the average coverage being 85.2%, 69.9% and 55.8% for first, second and third doses, respectively, for the girls vaccinated from 2011 to 2014; while for those immunized between 2015 and 2018, the averages for the first and second doses were 83.3% and 51.1% respectively. Argentina is a federal country with twenty-four autonomous jurisdictions, which define the most convenient vaccination strategy. In general, a mixed strategy is applied (school and on-demand in vaccination centers). Since its incorporation into the national calendar in 2011, the access rate for the HPV vaccine has been satisfactory but the dropout rate is high (around 30%). Multiple factors were identified; in the jurisdictions whose strategy is based at the school level, the main ones are the shortage of human resources to meet the vaccination schedule before school year end.

Data on the impact of HPV vaccine through national vaccination programmes are largely described for immunized females, including catch-up cohorts from Australia, Europe and North America [8]; however, there are still no publications reporting vaccine surveillance data from Latin America.

In Argentina, women are convened for governmental cervical screening from age 30; hence the earliest effect of vaccination on the incidence of cervical abnormalities is expected to be seen by 2030 when the first cohort of vaccinated women have access to cervical screening.

The present study was conducted to compare HPV DNA type-specific distribution in sexually active unvaccinated and vaccinated adolescent girls, recruited in six public hospitals from Argentina, to provide information on the early impact of HPV vaccination. Vaccine effectiveness is also explored by analysing HPV prevalence according to reports of vaccination and potential cross-protection against related but non-vaccine HPV types.

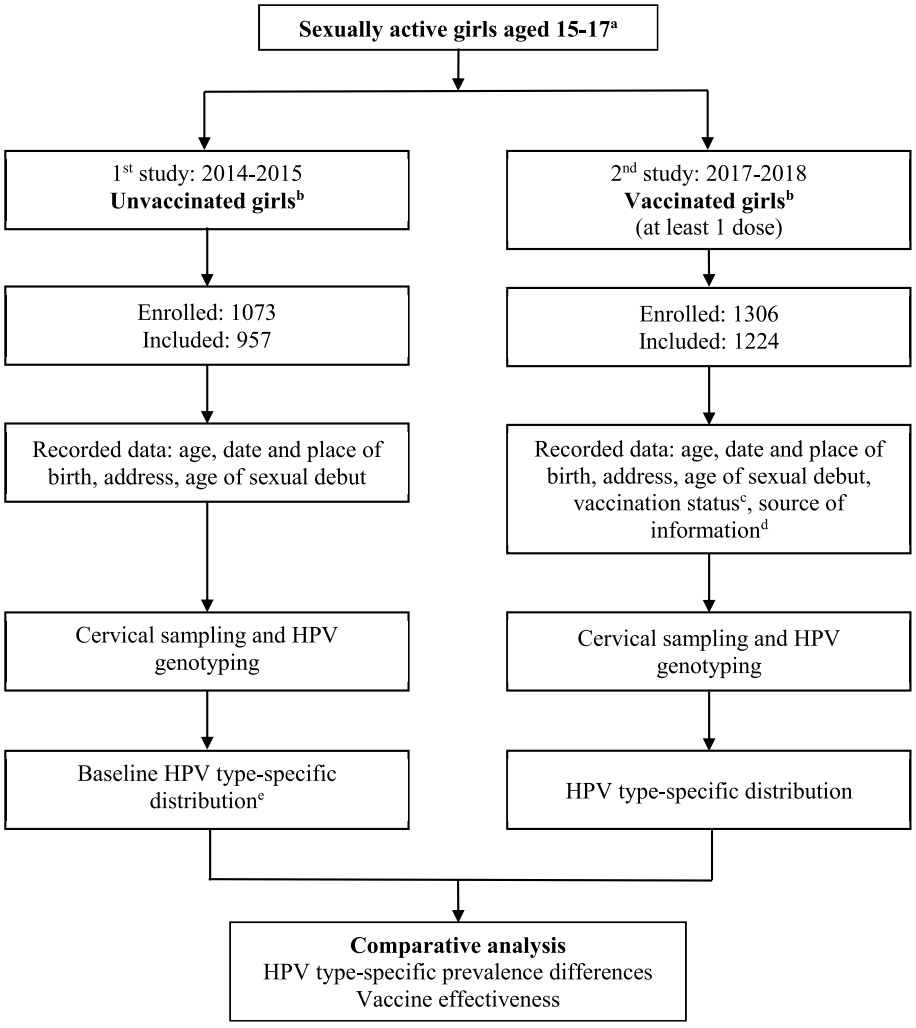

Fig. 1. Flow diagram summarizing the steps of both studies and the final comparison for the vaccine efficacy analysis. [a] Samples for both studies were collected from girls recruited in the same six public hospitals from Argentina.[b] Identical procedures for recruitment, specimen and data collection, and HPV genotyping were used for both groups. [C] Vaccination status: type of vaccine and number of received doses.[d] Source of information: card, clinical history or self-report.[e] González JV, et al. (Ref. 9).

2. Materials and methods

2.1. Study design, enrolment and samples

Two cross sectional studies were conducted by the National and Regional Reference HPV Laboratory (N&R–HPV Lab) (Oncogenic Viruses Service, National Institute of Infectious Diseases, ANLIS Malbrán, Buenos Aires); both of them enrolled sexually active girls (sexual activity starting at least 6 months before the recruitment), aged 15–17 (Fig. 1). The first one included unvaccinated girls (UV) (who did not receive any dose of HPV vaccine) (April 2014 and October 2015) [9], while the second one enrolled vaccinated girls (VA) (who received at least one HPV vaccine dose) (February 2017–November 2018).

The lower age range limit to be studied was established in 15 years, considering it the average age at which adolescents start sexual activity in Argentina [10].

Samples for both studies were collected from girls recruited in the same six public hospitals, located in three regions of Argentina:

- Area Metropolitana de Buenos Aires (AMBA; which includes Buenos Aires, the capital city of Argentina, and the surrounding area in the Province of Buenos Aires): *Hospital Evita Pueblo* (Berazategui, Province of Buenos Aires); *Hospital Argerich, Hospital Rivadavia* and *Hospital Durand* (Buenos Aires city) (East-central region of the country)
- Posadas, Province of Misiones: *Hospital Madariaga* (Northeastern region of the country)
- La Banda, Province of Santiago del Estero: *Centro Integral de Salud La Banda* (north-central region of the country)

The girls who met the inclusion criteria (Fig. 1), were invited to join the study by the Adolescent Service gynaecologists when they sought medical counselling, particularly about contraception. The participants signed an informed consent and answered a short questionnaire including basic information on age, date and place of birth, current address, and age of sexual debut; in the case of VA, data on the vaccination status (type of vaccine and number of doses received) and the source of information (vaccination card, electronic clinical history or self-report) were also recorded.

Identical procedures for recruitment, specimen and data collection, and HPV genotyping were used for the UV and VA groups.

In order to standardize the collection, storage and transfer of the samples obtained in the different centers, a Standard Operating Procedure was developed and distributed in each centre during the training workshops carried out before starting the project. Audit visits were also made to evaluate the progress of these processes.

Cervical samples were obtained from both the endocervix and the exocervix, using a Cytobrush (hc2 DNA Collection Device, Qiagen) that was introduced in the cervical canal and rotated 360°, 5 times. The cellular material was placed in a vial containing STM medium (Qiagen) and stored at +4 °C until its shipment (within fifteen days) to the N&E-HPV Lab for processing.

Prior to shipment, specimens were unlinked from any patient-identifiable data and anonymised.

2.2. Laboratory methods

Procedures for DNA extraction and HPV genotyping strategy have been previously described for the UV survey conducted in 2014–2015 [9]. Briefly, DNA was extracted from 200 µl of *STM* sample using commercial columns (Qiagen) on a robotic system (QIAcube system, Qiagen), following manufacturer's instructions.

HPV detection and genotyping was performed using a polymerase chain reaction (PCR) with Broad-Spectrum General Primers (BSGP) 5+/6+ biotin-labelled designed to amplify a highly conserved 140 bp fragment of the HPV-L1 gene. The DNA amplification is combined with a reverse line hybridization which identifies 36 HPV genotypes (6, 11, 16, 18, 26, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 66, 68, 70, 71, 72, 73, 81, 82, 83, 84 and 89) [11].

2.3. Statistical analysis

All data were entered and analysed in a specially designed database and subsequently processed using IBM® SPSS® Statistics 23.0.0.3 statistical software.

We compared the prevalence of HPV genotypes in UV and VA to estimate the size of any reduction in prevalence after HPV vaccination. For this purpose, we used a logistic regression analysis (binomial log lineal regression), and the confidence interval (CI) was established with an $\propto = 0.05$ in all cases. We tested statistical significance at the 0.05 level and throughout the analyses. Vaccine effectiveness was calculated as (1 – Odds Ratio) x100.

2.4. Ethical and legal considerations

Both UV and VA studies were approved by the Research Ethical Board of the ANLIS Malbrán and the Ethics Committee of each participating hospital, ensuring confidentiality and anonymity. Written informed consent was obtained prior to enrolment of study participants.

Under the Argentine legal system, adolescents over 14 years of age have the right to be assisted and receive health-related care without being accompanied by an adult or guardian, as well as to decide to participate in research projects and sign their consent.

Because the teenage girls invited to participate in the study were not within the age range for CC screening, special care was taken to warn them that it was a research study. The opportunity was taken to teach basic concepts about HPV infection and health care, which included the age at which screening should begin, to avoid generating alarm and/or an inappropriately early CC screening initiation.

3. 3. Results

3.1. Study population

A total of 1306 cervical cell samples from VA were collected, 82 were excluded because some of the established criteria were not met. The HPV results obtained from the remaining 1224 VA samples were compared with those previously analysed from 957 UV [9].

Table 1 describes the number of included samples by age and place of recruitment, from UV and VA girls. The average ages were 15.6 (SD 0.64 years) and 16.8 (SD 0.87 years) for UV and VA, respectively. In VA, adolescents born in 2000 (33.4%), 2001 (37.0%), 2002 (22.2%), and 2003 (6.3%) were included, i.e. they were immunized between 2011 and 2014, although in most cases the exact vaccination date is not available. Therefore, the vast majority of target cohorts received the bivalent vaccine, available until 2014 in the National Vaccination Programme.

The mean ages of sexual debut were: 13.8 years (95%CI 13.7–13.8) for UV and 14.9 years (95%CI 14.7–14.9) for VA ($p < 0.001$).

Information about the type of vaccine and number of doses received is detailed in Table 2. Most of the girls said they had received the bivalent vaccine (almost 80%) and claimed having received all 3 doses almost 60%.

The source of information in relation to the vaccine status was 70.8% self-reported, 27.7% obtained from Immunization Cards and 1.7% from medical history records.

Through address georeferencing of the recruited girls, it was established that the vast majority of both groups corresponded to the same neighbourhoods, close to the hospitals that assist them.

3.2. HPV type-specific distribution

Data about HPV prevalence broken down by sample collection site

Table 1
Collected samples by age and recruitment site, among unvaccinated and vaccinated sexually active girls from Argentina.

Sample collection site	Unvaccinated girls				Vaccinated girls			
	Age				Age			
	15y	16y	17y	Total	15y	16y	17y	Total
	N (%)				N (%)			
Area Metropolitana de Buenos Aires (AMBA[a])	259 (27.1)	300 (31.3)	11 (1.1)	570 (59.6)	74 (6.0)	124 (10.1)	174 (14.2)	372 (30.4)
Posadas, Misiones	78 (8.1)	84 (8.8)	10 (1.0)	172 (17.9)	82 (6.7)	132 (10.8)	203 (16.6)	417 (34.1)
La Banda, Santiago del Estero	65 (6.8)	133 (13.9)	17 (1.8)	215 (22.5)	102 (8.3)	133 (10.9)	200 (16.3)	435 (35.5)
Total	402 (42.0)	517 (54.0)	38 (4.0)	957 (100)	258 (21.1)	389 (31.8)	577 (47.1)	1224 (100)

[a] AMBA: Area Metropolitana de Buenos Aires, which includes Buenos Aires city and the adjacent area in the Province of Buenos Aires.

Table 2
Type of vaccine and number of doses received among vaccinated adolescent girls from Argentina.

Vaccine	1 Dose (%)	2 Doses (%)	3 Doses (%)	Unknown[b] (%)	Total (%)
Bivalent	75 (6.1)	235 (19.2)	622 (50.8)	38 (3.1)	970 (79.2)
Quadrivalent	3 (0.2)	43 (3.5)	46 (3.7)	6 (0.5)	98 (8.0)
Unknown[a]	22 (1.8)	19 (1.5)	77 (6.3)	38 (3.1)	156 (12.7)
Total	100 (8.2)	297 (24.3)	745 (60.9)	82 (6.6)	1224 (100)

[a] Girls who stated having been vaccinated but did not remember which vaccine they had received.
[b] Girls who stated having been vaccinated but did not remember the number of doses received.

are shown in Table 3. When comparing the total rates obtained for UV vs. VA, significant reductions were noted in the prevalence of HPV infection of any type (from 56.3% to 49.8%; $p = 0.002$); HPV16/18 (from 15.2% to 1.2%; $p < 0.001$); and HPV 6/11/16/18 (from 22.5% to 6.4%; $p < 0.001$).

The frequencies of the different genotypes estimated for UV and VA are presented in Fig. 2a. In the case of multiple infections, each type was counted independently. The differences in type-specific HPV prevalence between VA and UV are shown in Fig. 2b.

The prevalence of vaccine and selected non-vaccine HR- HPV types for UV and VA are presented in Table 4. Although the drops observed in VA were much stronger for HPV16 (from 11.1% to 0.8%; $p < 0.001$) and HPV18 (from 6.0% to 0.4%; $p < 0.001$), the prevalence of some HR- HPV types related to HPV16 and 18, as HPV31 (from 7.1% to 1.6%; $p < 0.001$) and 45 (from 4.6% to 0.5%; $p < 0.001$) were also significantly reduced. In the case of HPV33, although not significantly, a downward trend was also seen (from 3.1% to 1.7%; $p < 0.032$).

Regarding multiple infections, a significant decline was found from 36.3% (95% CI 33.3–39.4] for UV to 25.4% (95% CI [22.9–27.8]) for VA ($p < 0.001$); [OR = 0.604, (95%CI, 0.503–0.727) ($p < 0.001$)]. This trend is particularly clear in infections by 4 or more different HPV types (data not shown).

According to the HPV prevalence data obtained in the UV vs VA groups, vaccine effectiveness was estimated for protection against vaccine and some specific non-vaccine HR-types (Table 5), this being above 93% for HPV 16 and HPV18.

4. Discussion

This comparative study between unvaccinated and vaccinated sexually active adolescent girls, aged 15–17, recruited in consecutive periods (2014–2015 and 2017–2018, respectively) was the first evidence of a strong reduction in HPV16 and 18 prevalence after implementation of the National HPV Vaccination Programme in Argentina; also, a cross-protective effect for HPV31 and 45 was shown.

Though the recruited adolescents were between 15 and 17 years old, the age distribution was not homogeneous in both groups, since in the vaccinated group there was a higher proportion of girls aged 17 than in the unvaccinated group (age average 15.6 for UV vs. 16.8 for VA); but there was also a 1-year shift in the average age of sexual debut (13.8 for UV vs. 14.9 years for VA). In other words, in the VA group there would be older girls but who began sexually a little later, which could indicate that in both groups the time of potential exposure to the infection from their sexual beginning would be similar, favoring their comparability.

Although we cannot assure that both groups had identical epidemiological characteristics since this information was lacking, efforts were made for them to be as similar as possible. Because the samples were collected in the same hospitals in both periods, the participants came from the neighbourhoods closest to the hospital, leading to the assumption that all of them belong to a similar socioeconomic level.

Moreover, as reported by the National Survey on Sexual Health and Reproduction conducted in Argentina in 2015, the number of women's lifetime sex partners, a known risk factor for HPV infection, has grown since 2000 [12]; although cohort differences in addition to vaccination cannot be excluded with absolute certainty, it would seem more likely that the effect of the vaccine has been underestimated in our study, reducing the bias associated to changes in HPV-risk-related characteristics between both periods. Likewise, the fact that there was definitely circulation of HPV in vaccinated girls as demonstrated by the considerable prevalence of all types except vaccine types (Fig. 2) using identical sample collection and genotyping methods across both studies, supports the results. Therefore, the comparison between both groups would lead to consider the reduction observed in HPV prevalence as a true biological effect related to vaccination and not due to changes in sexual behaviour or other demographic factors.

Since Argentina still lacks a fully Nominal Vaccine Registry, in this study self-reporting was the prevalent source of information. Most of the vaccinated teenagers reported they had received the bivalent vaccine (almost 80%) in 3 doses (60%). These data are reasonable and consistent with the real setting, considering that: 1) Most of the girls were vaccinated when the National Vaccination Programme provided the bivalent vaccine, which was mandatory and free (2011–2014), although in 2014, in the transition period, there was an overlap with the quadrivalent, and 2) the national average for the 3-dose coverage was 70.4% for girls vaccinated in 2011–2014. Although the lack of an official vaccination registry would evidence a study weakness, the startling reduction in HPV16/18 reflects the veracity of participants' reports, based on the trust patients felt for the Adolescent Services' medical doctors.

In this study, the overall HPV prevalence in adolescent girls declined slightly but significantly between UV and VA (56.3% and 49.8%, respectively), which is comparable to what was noted in Australia (60% vs. 49% in the pre and post-vaccine implementation groups, respectively, for women aged 18–24) [13]. Similarly, in 18–26 year-old

Table 3
Prevalence of HPV infection of any type, HPV 16/18, and HPV 6/11/16/18 by site of recruitment, among sexually active 15–17 year old girls from Argentina.

HPV Status	Total					Metropolitan Area of Buenos Aires (AMBA)[a]					Posadas, Misiones					La Banda, Santiago del Estero				
	UV (N = 957; 100%)		VA (N = 1224; 100%)		p value	UV (N = 570; 59.6%)		VA (N = 372; 30.4%)		p value	UV (N = 172; 18.0%)		VA (N = 417; 34.1%)		p value	UV (N = 215; 22.5%)		VA (N = 435; 35.5%)		p value
	N (%)	95%CI	N (%)	95%CI		N (%)	95%CI	N (%)	95%CI		N (%)	95%CI	N (%)	95%CI		N (%)	95%CI	N (%)	95%CI	
HPV Positive	539 (56.3)	53.1–59.5	609 (49.8)	47.0–52.6	0.002	297 (52.1)	48.0–56.2	183 (49.2)	44.1–54.3	0.38	106 (61.6)	54.3–68.9	196 (47.0)	42.2–51.8	0.001	136 (63.3)	56.8–69.7	230 (52.9)	48.2–57.6	0.012
HPV 16/18 Positive	145 (15.2)	12.9–17.4	15 (1.2)	0.61–1.84	<0.001	72 (12.6)	9.9–15.4	3 (0.8)	−0.1–1.7	<0.001	36 (20.9)	14.8–27.0	5 (1.2)	0.2–2.25	<0.001	37 (17.2)	12.2–22.3	7 (1.6)	0.4–2.8	<0.001
HPV 6/11/16/18 Positive	215 (22.5)	19.8–25.1	78 (6.4)	5.0–7.7	<0.001	113 (19.8)	16.6–23.1	28 (7.5)	4.8–10.1	<0.001	47 (27.3)	20.7–34.0	24 (5.7)	3.5–8.0	<0.001	55 (25.6)	19.7–31.4	26 (6.0)	3.8–8.2	<0.001

UV: Unvaccinated girls; VA: Vaccinated girls; CI: Confidence interval.
[a] AMBA: Metropolitan Area of Buenos Aires, which includes Buenos Aires city and the adjacent area in the Province of Buenos Aires.

women from Scandinavia, the HPV prevalence dropped slightly from 36.5% (pre-vaccine baseline) to 34.5% (post-vaccination period) [14]; while in a school-based HPV vaccination study from Norway, the decrease was less pronounced among unvaccinated and vaccinated girls 18–20 years of age (41.1% vs 38.5%) [15], as well as in females aged 14 to 19 of the NHANES survey (USA) (32.9% vs 29.0%) [16]. Given the relative low contribution of vaccine types to the overall HPV prevalence in the population and because co-infections occur, a decrease in the prevalence of any HPV due to the declines in vaccine types may go unseen or discretely observed, particularly if there is an increase in the population's sexual risk behaviour [16].

The present work reports an impressive fall of HPV16 and 18 prevalence in vaccinated 15–17 year old girls, which is consistent with previous studies conducted over different time frames and in different populations and settings, which support the real-world effectiveness of the bivalent and quadrivalent HPV vaccines, especially in younger age groups and countries with high vaccination coverage [16–21]. In England, eight years after the introduction of the national HPV vaccination programme, a large surveillance which included HPV results from over 15,000 samples, evidenced a substantial fall in HPV16/18, from 8.2% to 1.6% in 16–18-year olds [22]. A series of over 12,000 samples from 13 to 22-year-old women from Sweden showed a reduction in HPV16 (from 14.9% pre-vaccination to 8.7% post-vaccination) and HPV18 (7.9%–4.3%) [23]. In Norway, a single-cohort delivery of HPV vaccine to 12 to 13-year-old girls was associated with a decrease in vaccine types of 90% (95% CI, 86%–92%) in vaccinated girls 5 years after vaccination [24]. Scotland reported similar results to those attending cervical screening at age 20–21, with a reduction of HPV types 16 and 18 rates from 30.0% (95% CI 26.9–33.1) in unvaccinated to 4.5% (3.5–5.7) among those vaccinated at age 12–13 [25]. A systematic review and meta-analysis which includes 65 articles from 14 high-income countries demonstrated, in the first 9 years after the start of HPV vaccination, that the prevalence of HPV16 and 18 decreased significantly by 83% (RR 0.17, 95% CI 0.11–0.25) among girls aged 13–19 [26]. This reduced prevalence of HPV16 and HPV18 is likely to translate into a significant decline of cervical cancer in the future (and probably other HPV-associated cancers from different anatomic locations other than the cervix), considering that both HPV genotypes are known to have lower clearance rates and higher malignant progression probability [27].

In our study, the HPV prevalence decline clearly extends to non-vaccine-carcinogenic types HPV31 (alpha 7 genus) and 45 (alpha 9 genus), with close phylogenetic relationships to HPV16 or 18, respectively, suggesting cross-protection. Evidence of changes in the non-vaccine types is less consistent across different studies depending on the vaccine type, age group and study population. A meta-analysis conducted by Malagon et al. found that the quadrivalent vaccine was efficacious against outcomes associated with HPV31, and the bivalent vaccine against those associated with HPV31, 33, and 45; the efficacy against persistent infections with HPV31 and 45 decreased over time, suggesting waning cross-protection [28]. A systematic review and meta-analysis which considered changes in individual non-vaccine types only, demonstrated reductions in HPV31 in women aged ≤19, but not HPV33 or HPV45 [29]. A more recent related meta-analysis conducted by Drolet et al. showed for HPV31, 33, and 45 non significant decreases in prevalence in the first 4 years of vaccination, among girls aged 13–19; however, after 5–8 years of vaccination, the prevalence of HPV31, 33, and 45 declined significantly by 54% (RR 0.46, 95% CI 0.3–0.66) in this group [26]. Interestingly, Bogaards et al. have reported for the bivalent vaccine, sustained cross-protection up to 8 years post-vaccination in the Netherlands, suggesting that cross-protection is better explained by genomic distance than by distance measures based on capsid antigens only; taken together, the bivalent vaccine is predicted to provide partial cross-protection against HPV31, 33, 35, 45, 52, and possibly 58, all phylogenetically related to HPV16 or 18 [30]. Although the cross-protection data described in the present study are encouraging, assessing the absolute prevalence of precancerous cervical lesions

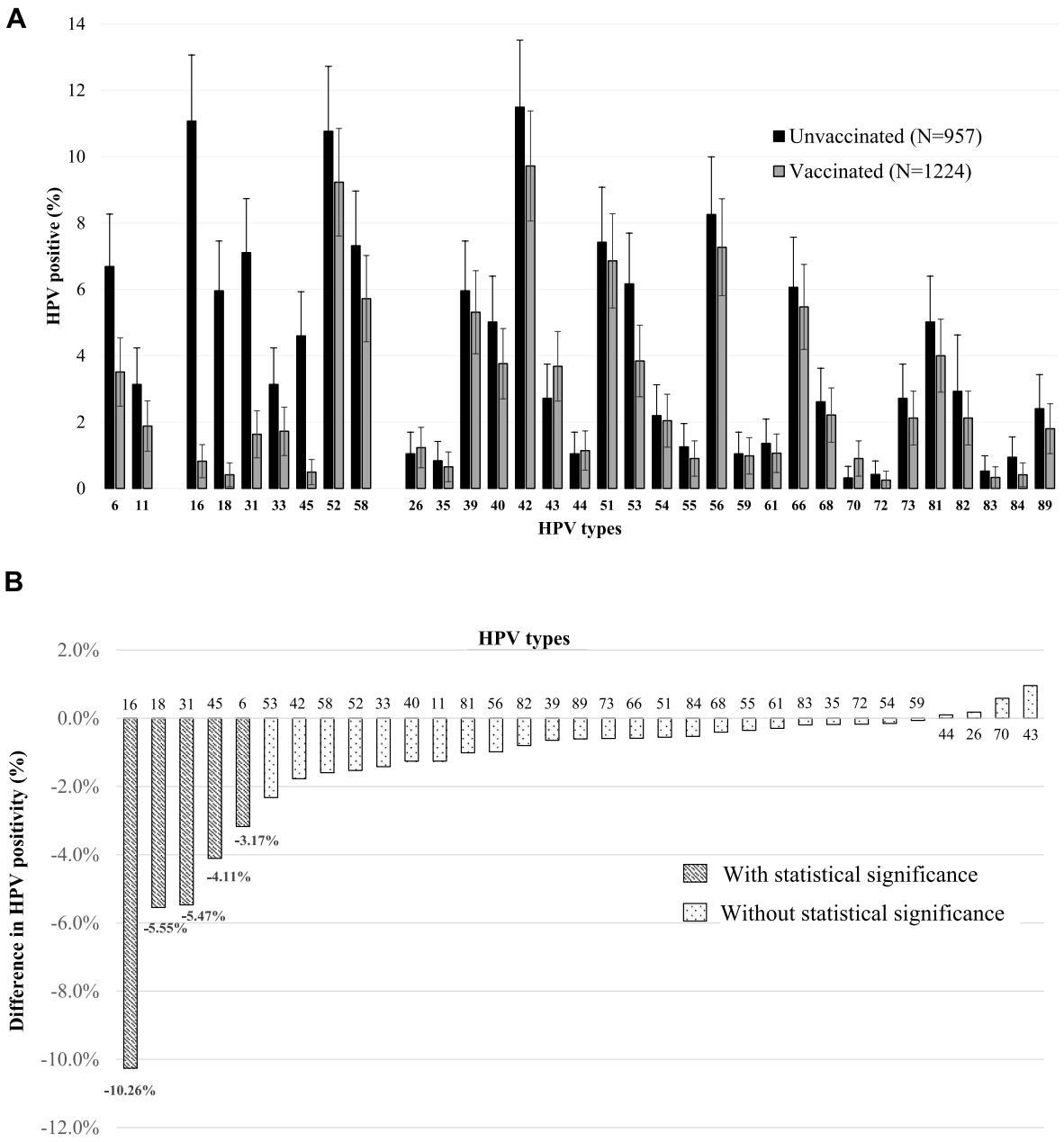

Fig. 2. a. Distribution of HPV genotypes in unvaccinated and vaccinated adolescent girls from Argentina. b. Type-specific HPV prevalence differences between vaccinated and unvaccinated adolescent girls from Argentina.

attributed to each potential cross-protective HR-HPV type will allow expanding the knowledge about vaccination's true additional benefits in our population.

In this work, the prevalence of the other three HR-HPV components of the nonavalent vaccine, HPV33, 52 and 58 dropped in vaccinated girls, although not statistically significant, as in reports from other studies [21,29,31]. This observation should be interpreted with caution because of the limited size of our series. Furthermore, a decrease in the prevalence of non-vaccine HPV types may take several years to be noted, as reported by Drolet et al. [26]. Of note, the additional five HR-types included in the nonavalent vaccine cause substantially less HPV-associated cancer than HPV16/18 because they are less likely to progress to cancer [32]. In Argentina, it was estimated that 77.1% of cervical cancers are attributable to HPV16 and 18 which enhances the role of these high-risk genotypes in the disease burden [33]; although, the nonavalent vaccine might probably help prevent the development of CC and other HPV-related cancers in a larger number of people.

It is important to state that the reduced but yet considerable level of HPV positivity (predominantly HR types) seen in this study in vaccinated girls reinforces the continuing need for cervical screening.

In relation to low risk HPV types, in this work a significant drop in HPV6 prevalence was detected in vaccinated girls. Previous surveillance data from England showed an unexpected reduction in genital warts' diagnoses [34]. This observation, together with findings of moderate efficacy against some low-risk HPV types in data from bivalent vaccine clinical trials had led to hypothesise that this vaccine may induce a modest cross-protective effect against HPV 6/11 and genital warts [35]. However, Sonnenberg et al. have more recently reported that there was no evidence of population protection against genital warts conferred by the bivalent vaccine [36]. Although in our study the decrease of HPV6 could relate to the 8% of girls who reported having received the quadrivalent vaccine, the results do not create sufficient statistical power to consider this argument; moreover, the reduction was found only in HPV6 and not in HPV11. Furthermore, no information is available on

Table 4
Prevalence of selected vaccine and non-vaccine HPV types and groups of types among unvaccinated and vaccinated adolescent girls from Argentina.

HPV types	Unvaccinated girls (N = 957)		Vaccinated girls (N = 1224)		OR (95% CI)	P value
	N (%)	(95%CI)	N (%)	(95%CI)		
Bivalent/Quadrivalent vaccine						
HPV 16	106 (11.1)	(9.1–13.1)	10 (0.8)	(0.3–1.3)	0.066 (0.034–0.127)	<0.001
HPV 18	57 (6.0)	(4.5–7.5)	5 (0.4)	(0.1–0.8)	0.065 (0.026–0.162)	<0.001
HPV 16,18	145 (15.2)	(12.9–17.4)	15 (1.2)	(0.6–1.8)	0.069 (0.041–0.119)	<0.001
HPV 6	64 (6.7)	(5.1–8.3)	43 (3.5)	(2.5–4.5)	0.508 (0.343–0.755)	0.001
HPV 11	30 (3.1)	(2.0–4.2)	23 (1.9)	(1.1–2.6)	0.592 (0.341–1.026)	0.061
HPV 6,11	91 (9.5)	(7.7–11.4)	63 (5.2)	(3.9–6.4)	0.516 (0.370–0.721)	<0.001
HPV 6,11,16,18	215 (22.5)	(19.8–25.1)	78 (6.4)	(5.0–7.7)	0.235 (0.178–0.309)	<0.001
HR-HPV 16/18 related types[a]						
HPV31	68 (7.1)	(5.5–8.7)	20 (1.6)	(0.9–2.4)	0.217 (0.131–0.260)	<0.001
HPV33	30 (3.1)	(2.0–4.2)	21 (1.7)	(1.0–2.4)	0.539 (0.307–0.948)	0.032
HPV45	44 (4.6)	(3.3–5.9)	6 (0.5)	(0.1–0.9)	0.102 (0.043–0.241)	<0.001
HPV52	103 (10.8)	(8.8–12.7)	113 (9.3)	(7.6–10.9)	0.843 (0.636–1.117)	0.235
HPV58	70 (7.3)	(5.7–9.0)	70 (5.7)	(4.4–7.0)	0.769 (0.546–1.083)	0.132

Abbreviations: HR: High risk; LR: Low risk; OR: Odds ratio; CI: Confidence interval.
[a] Additional HR HPV types of nonavalent vaccine.

Table 5
Estimated vaccine effectiveness in vaccinated adolescent girls from Argentina.

HPV type	Vaccine effectiveness (95% CI)
HPV16	93.4 (87.3–96.6)
HPV18	93.5 (83.8–97.4)
HPV16/18	93.1 (88.1–96.0)
HPV16/18/31/45	89.3 (84.7–92.5)

Abbreviation: CI Confidence interval.

the surveillance of genital warts in our country, which also limits our analysis.

In Argentina, three-dose coverage has been moderate, with 70% average for the girls vaccinated from 2011 to 2014, which would enable a herd protection analysis [26]. In this study, samples from the baseline cohort (UV) were collected between 2014 and 2015, 3–4 years into the HPV immunization program; while samples from adolescents belonging to the first vaccinated cohorts (VA) were collected 6–7 years from the implementation of immunization (period 2017–2018). Although no proof is available on herd protection, perhaps both analyses may have been somewhat influenced by this effect. Although it is difficult to speculate in this regard, the sharp drop in HPV16/18 frequencies in vaccinated cohorts confirms the success of immunization on the vaccine viruses' circulation in the evaluated population.

Our data showed an overwhelming decrease in HPV16/18 leading to high levels of vaccine effectiveness, which was also reported by many authors and well summarised in the meta-analysis published by Garcia Perdomo et al. [37]. The outstanding surveillance carried out in Scotland and England, where immunization started with the bivalent vaccine as in Argentina, reported vaccine effectiveness values were 82.0% and 89.1% for HPV16/18, respectively [22,23,25]. In this study, the estimated vaccine effectiveness was slightly higher (93% for HPV16/18), which is remarkable given the fact that vaccination was established as having received ≥1 dose (i.e., not necessarily the complete vaccination series) and, since it was mostly self-reported, there could have been an underestimation of incomplete scheme cases. Although we were not able of presenting data on effectiveness by number of dose, our report would somehow agree with a recent review suggesting that one HPV vaccine dose may be as effective in preventing HPV infection as multi-dose schemes in healthy young women [38]; however, results are expected from ongoing clinical trials assessing the efficacy and immunogenicity of single-dose HPV vaccination compared to currently-recommended schemes.

While type replacement seems to be unlikely with HPV vaccination, studies in several countries have been monitoring type-specific HPV prevalence since the vaccine introduction for increases in any non-vaccine HR types. Some reports suggest type-replacement may be occurring [29,39,40], while others demonstrate the opposite [18, 41–44]. In our analysis, there were no significant increases in any non-vaccine HPV types among vaccinated girls despite which continued monitoring of non-vaccine HPV genotypes is advisable.

Besides the above-mentioned epidemiological insights, our study has important additional strengths. To our knowledge, this is the first study of HPV vaccine monitoring in Latin America. The huge heterogeneity of the populations and resources available at global level prioritises the importance of local/regional studies as a way to evaluate specific determining factors and make the best public policy decisions. All HPV surveillance and vaccine monitoring studies reported so far come from high-income countries, so that information cannot be directly and accurately extrapolated to low- and middle-income countries where there may be substantially different HPV epidemiology, sexual behaviour and disease cofactors.

However, the study also has limitations. First, a sampling frame based on hospital attenders at selected locations, which was chosen for practical reasons, and cannot be claimed to represent the wider female population. Second, running the study in sexually active adolescent girls to obtain earlier data on the impact of HPV vaccination limited the number of samples collected, since this age group is difficult to approach, and obtaining data on sexual behaviour is not easy (unadjusted comparisons should be interpreted with caution). And third, the vaccination history was mostly self-reported and over or under-reporting could have occurred.

In conclusion, during the first 7 years post HPV vaccine introduction in Argentina, the prevalence of vaccine-type HPV16/18 decreased by >93% in vaccinated sexually active girls, demonstrating high effectiveness; we have also noted cross-protective effects for HPV31 and HPV45, which could add to the success of the Argentine national HPV vaccination programme.

With the highly vaccinated cohorts moving into adulthood, reductions in cervical abnormalities, with subsequent drops in treatments, and ultimately a decrease in the burden of disease and death from cervical and other HPV-related cancers, should grow further. Continued HPV infection surveillance among the new cohorts of girls and boys receiving the quadrivalent vaccine will be critical to fully assess its impact as vaccination efforts continue.

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CRediT authorship contribution statement

Joaquín Víctor González: Conceptualization, Validation, Investigation, Data curation, Writing - review & editing. **Gerardo Daniel Deluca:** Data curation, Formal analysis, Writing - review & editing. **Rita Mariel Correa:** Investigation, Visualization, Writing - review & editing. **Domingo Javier Liotta:** Resources, Writing - review & editing. **Jorge Alejandro Basiletti:** Writing - review & editing. **María Dolores Fellner:** Writing - review & editing. **María Celeste Colucci:** Investigation. **Olga Gabriela Alzogaray:** Resources. **Nathalia Katz:** Resources, Writing - review & editing. **Juan José Carmona:** Supervision. **Néstor Fabián Tappari:** Resources. **Enrique Berner:** Supervision. **Viviana Cramer:** Resources. **Paula Real:** Resources. **Carlota Viviana López Kaufman:** Supervison. **Gabriela Judit Kosoy:** Resources. **Lucía Katabian:** Resources. **María Silvia Severino:** Resources. **Ricardo Enrique Aboslaiman:** Resources. **Cecilia Chami:** Resources. **María Elina Totaro:** Resources. **Carolina Rogoski:** Resources. **Alejandra Julia Giurgiovich:** Resources. **Gloria Lilian Martínez:** Resources. **Liliana Marisol Plana:** Resources. **Carla Vizzotti:** Conceptualization, Funding acquisition, Writing - review & editing. **María Alejandra Picconi:** Conceptualization, Investigation, Project administration, Funding acquisition, Supervision, Writing - original draft, Writing - review & editing, All authors have approved the final article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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