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EPIDEMIOLOGICAL DYNAMIC MODELING OF HUMAN PAPILLOMAVIRUS-RELATED DISEASES TO ASSESS VACCINATION STRATEGIES IN ARGENTINA

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Abstract Our objective was to develop and test a dynamic simulation model of human papillomavirus (HPV)-related diseases to assess rational vaccination strategies in Argentina. A dynamic stochastic transmission model for hetero- and homosexual transmission of HPV oncogenic and low-risk oncogenic types among females and males was developed. The model included HPV transmission and vaccination, the natural history of HPV-related diseases, disease outcomes, and cervical cancer screening. Considering all cervical cancers, covered or not by the current quadrivalent vaccine, the existing coverage rate would lead to 60% reduction in the global incidence of cervical cancer at 25 years, and to 79% at 50 years. Isolated current female vaccination without a screening program would need around 100 years to eliminate cervical cancer from the local population. Current coverage rate would lead to 59% reduction of vulvar cancer, 76% of vaginal cancer, 85% of anal cancer, and 87% of oropharyngeal cancer, estimated over a 25-year time prospect. Female HPV vaccination within the context of current cervical cancer screening should reach a minimum long-term mean coverage of 60% of girls, receiving at least a two-dose vaccine schedule, to significantly reduce or virtually eliminate cervical cancer at 50 years. Including vaccination to boys to improve herd immunity did not influence the incidence of cervical cancer over time, as long as female coverage did not fall below 50%. Regarding vulvar, vaginal, anal, penile, and some oropharyngeal cancers, current girls-only based vaccination could virtually eliminate these cancer types after 35-40 years, both in women and men.

Key words: human papillomavirus, vaccines, cancer, epidemiology, mathematical model

Resumen ***Modelo epidemiológico dinámico de enfermedades relacionadas al papilomavirus humano para evaluar estrategias de vacunación en la Argentina.*** Se desarrolló un modelo de simulación dinámica de enfermedades relacionadas con papilomavirus humano (VPH) para evaluar estrategias de vacunación. Se desarrolló un modelo dinámico estocástico para transmisión hetero/homosexual de VPH oncogénicos y de bajo riesgo oncogénico, entre mujeres y hombres. El modelo incluyó transmisión y vacunación contra VPH, historia natural de enfermedades relacionadas con VPH, mortalidad y programas de detección de cualquier cáncer de cuello uterino (CCU); teniendo en cuenta todos estos, con o sin vacunación cuadrivalente con la cobertura actual, la reducción sería 60% en la incidencia global de CCU en 25 años, y de 79% en 50 años. Vacunando solo mujeres, sin programa de detección precoz, necesitaría unos 100 años para eliminar el CCU localmente. La tasa de vacunación actual determinaría 59% de reducción del cáncer de vulva, 76% del cáncer vaginal, 85% del cáncer anal y 87% del cáncer orofaríngeo, a 25 años. La vacunación de mujeres, con el cribado actual del CCU, deberá alcanzar una cobertura media mínima a largo plazo del 60% de las niñas, con al menos dos dosis de vacunas, para reducir significativamente o eliminar el CCU en 50 años. La vacunación en niños para mejorar la inmunidad de grupo no influiría en la incidencia del CCU de no caer la cobertura femenina por debajo de 50%. Con respecto a cánceres de vulva, vagina, ano, pene y algunos orofaríngeos, la vacunación actual solo en niñas podría eliminar virtualmente estos tipos de cáncer después de 35-40 años, tanto en mujeres como en hombres.

Palabras clave: papilomavirus humano, vacunas, cáncer, epidemiología, modelo matemático

A comprehensive approach to the evaluation of preventive strategies for human papillomavirus (HPV)-related diseases in developing countries raises a number of technical challenges. These include accurate modeling of HPV transmission within the local population, the natural history of HPV-associated cancers, screening test performance and coverage, population access to treatment, and vaccination uptake[1]. Since an age-specific population-based vaccination strategy –such as the school mandate for HPV vaccination in Argentina– is expected to reduce HPV-associated cancers only within two or three decades, accurate local projections are needed to support current and future financial investments. From the point of view

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of both public health and ethics, identification of the most effective strategies is essential when access to health services is limited[2].

Although there are some general simulation models developed in high-income countries or supported by the pharmaceutical industry, country-specific data can affect the results of direct parametrization or calibration of progression and regression rates in local models. Nation-wide representative data, burden of HPV infection, screening coverage, urban/rural ratio population, and economic parameters could be the most changing factors between developed and developing countries. The first report from Argentina on a cost-effectiveness Markov model for HPV vaccination appeared in 2009 and it was rather linked to the industry that developed the HPV vaccine[3]. Other general cohort models involving Argentina[4] estimated the perspective of vaccination in Latin American countries exclusively from an economical point of view[5, 6]. For modeling, a Markov cohort process of HPV-related diseases usually simulates a simple birth cohort study tracing people through their lives. Therefore, it can only estimate the direct effect on vaccinated groups, and not the changing effect of vaccination over time on unvaccinated persons. This indirect benefit of vaccination is referred to as "herd immunity". That is why cohort models tend to underestimate the overall effectiveness of vaccination and herd immunity can be only captured with dynamic models in which HPV transmission is directly simulated in the whole population[7, 8]. Mathematically, dynamic modeling uses a set of differential equations to capture nonlinear interactions of disease transmission[9]. Basically, a dynamic simulation model assumes that the force of infection at time *t* is a function of the number of infectious individuals in the population at that time, and not a constant rate. Hence, mass immunization can reduce infectious individuals in the community and act on those who are not immunized[10, 11]. Conversely, because of their complexity, a weakness of the dynamic models is that they may appear as "black boxes" for decision makers.

HPV infection is also linked to other anogenital cancers (anus, vulva, vagina, and penis) and oropharyngeal cancers (tongue, tonsils, and oropharynx), whose incidence has increased in recent years in developed countries[12, 13]. Thus, it can be assumed that prophylactic vaccination would play a significant role in preventing these HPV-associated cancers, too. Until now, no general model evaluated vaccination strategies for these HPV-related diseases in Argentina, particularly using dynamic models to assess herd immunity impact.

The objective of this study was to develop and test a dynamic simulation model of HPV-related diseases to assess rational vaccination strategies in the Argentine population.

Materials and methods

The structure of a dynamic model is typically nonlinear, and differs from cohort models in that it does not track just a single cohort but rather the changing population over time. Hence, individuals constantly enter the model as they are born and exit as they die. In the model, vaccination reducing the prevalence of HPV infection over time means that susceptible individuals are less likely to become infected because there are fewer persons in the population to infect them with HPV. This indirect benefit is referred to as the herd immunity benefits of vaccination, and can be quantitatively evaluated only with dynamic models. In this study, we used the Stella software (v9.0.2, High Performance Systems, Hanover, NH) to develop dynamic stochastic transmission models for heterosexual and homosexual transmission of HPV oncogenic and low-risk oncogenic types 6/11/16/18/31/33/45/52 among females and males. The complete model included HPV transmission and vaccination, the natural history of HPV-related diseases, disease outcomes, and cervical cancer screening. Implementation was based on the schematic diagram of Figure 1. This model estimated the annual incidence of HPV-related precancerous lesions and invasive cervical cancer, as well as resulting cervical cancer deaths. In addition, other types of HPV-related male and female cancers were included in the model, such as vaginal, vulvar, anal, penile and oropharyngeal, as well as anogenital warts and recurrent respiratory papillomatosis (RRP). A steady-state solution was approached in the long run, until HPV-related cancers were virtually eliminated from the population. Model input data and assumptions, and Tables S1 to S3 are presented in the Appendix.

Because of the large number of equations and inputs, a sensitivity analysis was performed only on vaccination coverage since it was considered the most influential variable. The series of values obtained from sequential simulations were expressed as mean and standard deviation (SD), and comparisons were done with Student-*t* test assuming normal distribution. When a range of values was present, parameters were included in the model as random uniform probabilities between the minimum and maximum extremes of each parameter. Consequently, these stochastic simulations generated plots with visually saw wave time courses. For numerical analysis purposes, the Runge-Kutta 4th order method was used to solve the differential equations generated in the model. Although the equations' solution may differ with the method used, no significant differences were found when using either Euler or 2nd and 4th order Runge-Kutta approaches.

Results

An example of long-term stochastic dynamic simulation of the annual number of new cases of cervical cancer according to different scenarios is shown in Figure 2. The results suggest that in Argentina, maintaining the current mean vaccination coverage rate of 70% for a two-dose application, 24% for one-dose application, and 5% of catch-up coverage, the vaccination strategy including only girls aged 11 years would be enough to virtually eliminate cervical cancer within 50 years, as long as the current cervical screening program persisted. Considering all cervical cancers, covered or not by the current quadrivalent vaccine, the existing coverage rate would lead to 60% (SD: 12.8%) reduction in the global incidence of cervical

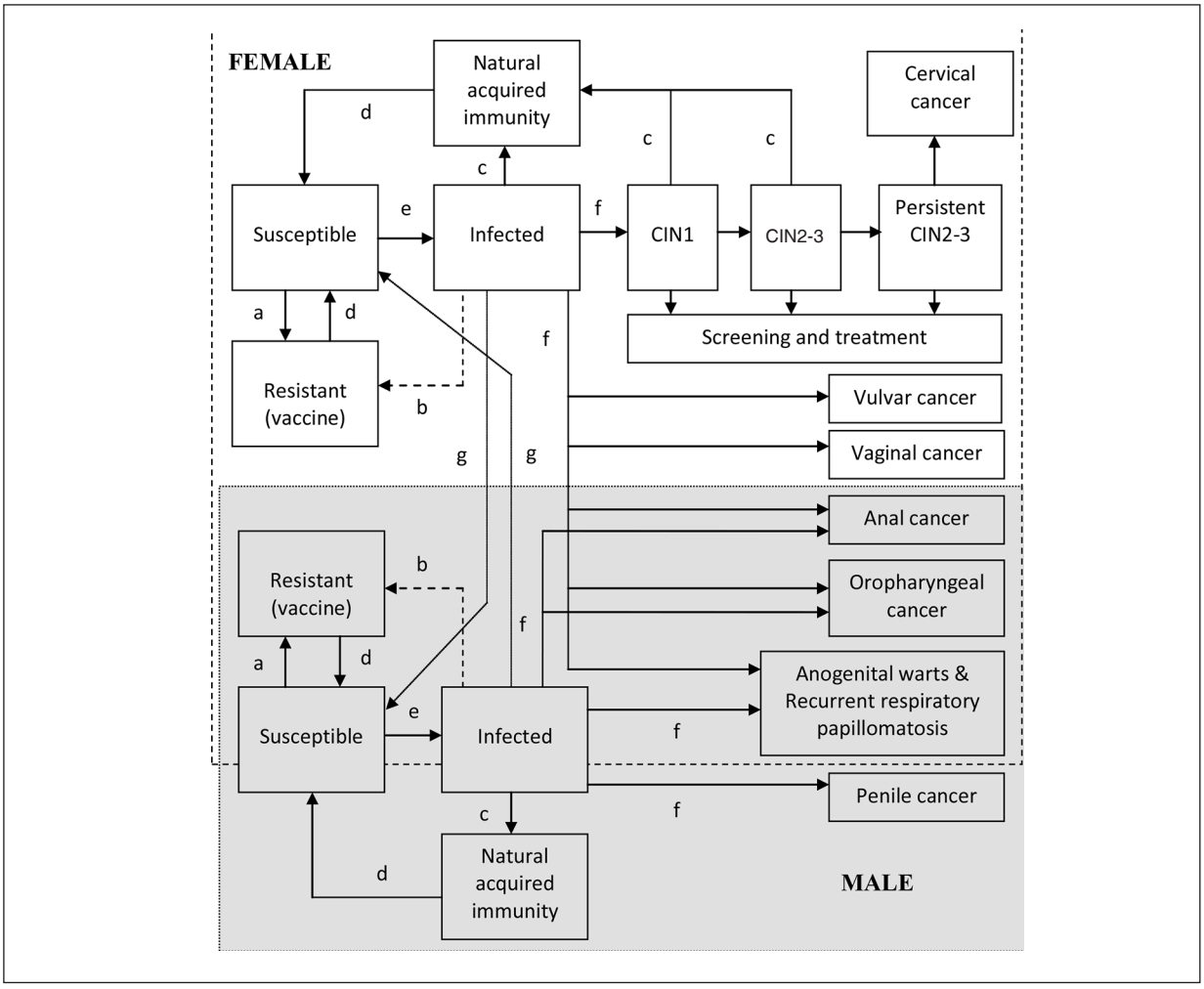

Fig. 1.– A simplified schematic diagram of HPV transmission and vaccination model for females and males, including the natural history of HPV infection, HPV-related disease outcomes, and cervical cancer screening. (a) Vaccination, (b) catch-up vaccination, (c) clearance, (d) immunity loss, (e) infectivity, (f) disease progression, (g) male/female cross-contagion. Individuals enter into the susceptible compartment according to birth and immigration rates. Through hetero- or homosexual contact, a susceptible host may be infected with HPV. An infected person can clear infection and become immune. Susceptible girls and boys can be protected by vaccination and achieve lifetime immunity. Adult population can be incorporated to a catch-up vaccination program and also achieve immunity. Cervical intraepithelial neoplasia (CIN) can develop in females and progress though several histological grades (1, 2, 3 and persistent) prior to cervical cancer. CIN can spontaneously regress to normal with or without infection, or can be diagnosed by screening and treated. Infected females and males can progress to other anogenital and oropharyngeal carcinomas, as well as develop genital warts or recurrent respiratory papillomatosis in those infected with HPV 6/11. Individuals can also leave compartments because of a specific-cause or all-cause death.

cancer at 25 years, and to 79% (SD: 9.9%) at 50 years. On the other hand, isolated current female vaccination without a screening program would need around 100 years to eliminate cervical cancer from the local population.

Figure 3 shows the annual number of new cases of cervical cancer throughout time, according to different scenarios of exclusive female vaccination coverage. Results from dynamic simulations suggested that all these scenarios would eliminate cervical cancer after 50 years, as long as the current cervical screening program remained constant. It should be noted that a two-dose vaccination coverage of 50% of the female population, without one-dose coverage or catch-up vaccination cohorts did not eliminate cervical cancer in the long term. In short, the sensitivity analysis demonstrates that a program covering over time at least 60% of girls aged 11 years with a two-dose coverage could significantly reduce cervical cancer in 25 years and virtually eliminate it in 50 years.

Extending vaccination to boys was proposed to enhance herd immunity and allows a further reduction of female HPV-related cancers. Figure 4 shows the annual number of cervical cancers when considering a vacci-

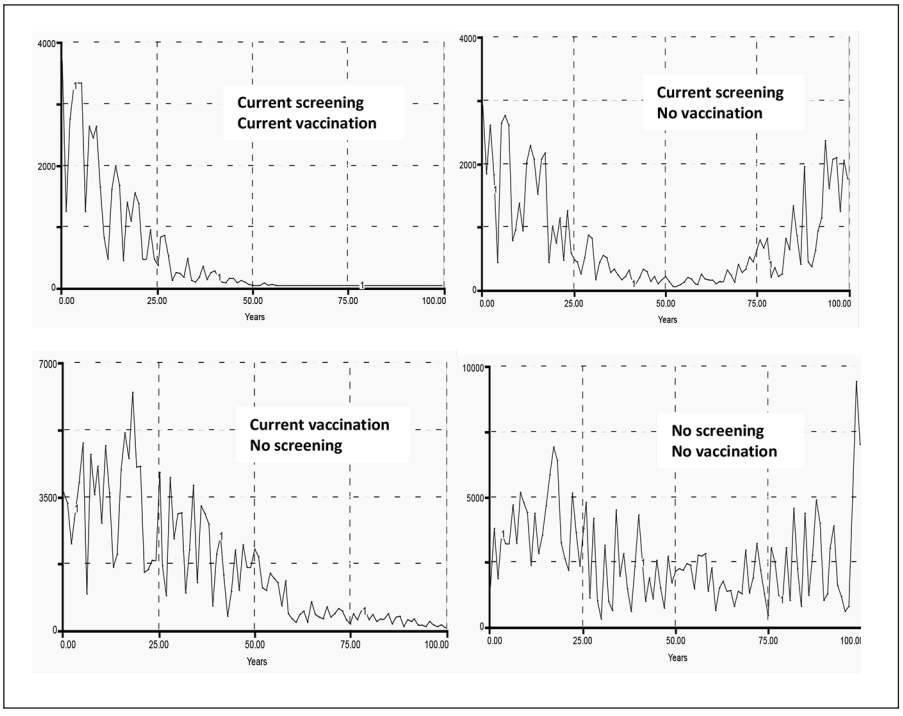

Fig. 2.– Long-term stochastic dynamic simulation of the annual number of new cases of cervical cancer (y-axis) according to different scenarios. Plots show that current cervical cancer screening plus current female vaccination would eliminate cervical cancer in 50 years (saw waves were generated because of the stochastic component of simulations).

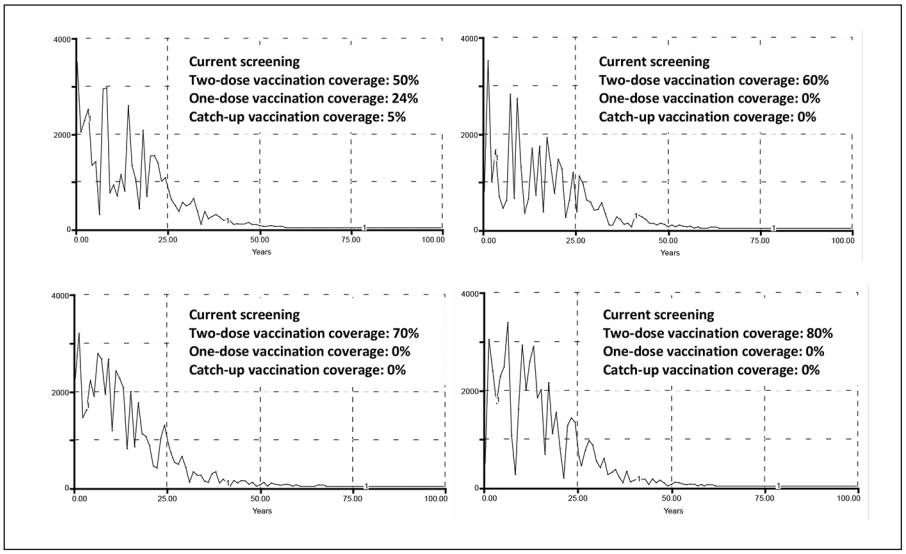

Fig. 3.– Sensitivity analysis of the annual number of new cases of cervical cancer (y-axis) throughout time, according to different scenarios of female vaccination coverage. Plots generated from stochastic dynamic simulations show that all these scenarios eliminate cervical cancer after 50 years. A two-dose vaccination coverage of 50% without one-dose coverage or catch-up vaccination cohorts does not manage to eliminate cervical cancer (plot not shown). All these strategies included the current cervical screening program (saw waves were generated because of the stochastic component of simulations).

nation strategy of boys and girls aged 11 years versus girls-only vaccination, within two scenarios of 50% and 70% two-dose vaccine coverage for all cohorts after 25 years. Simulations suggested that, independently of vaccine coverage, the inclusion of boys' vaccination did not manage to reduce the annual number of cervical cancer

at 25 years. When vaccine coverage in girls was under 50%, the model suggested that the optimal combination of boys and girls vaccination required to eliminate cervical cancer follows a near negative linear relationship (Fig. 5). For instance, a vaccination rate in girls of only 40% would require vaccinating of at least 30% of boys to meet the goal of eliminating cervical cancer at 50 years.

The hypothetical influence of vaccination on vulvar, vaginal, anal, penile, and oropharyngeal cancers, both in women and men, is shown in Figure 6. Long-term simulations demonstrated that current female vaccination without male vaccination would virtually eliminate the fraction of these cancers associated to HPV in about 40 years in women, and 35 years in the male population. The images in the right column of the figure show that under this vaccination program, the long-term growth of these cancers is based on non HPV-related forms. Considering HPV- and non HPV-related cancers collectively, the cur-

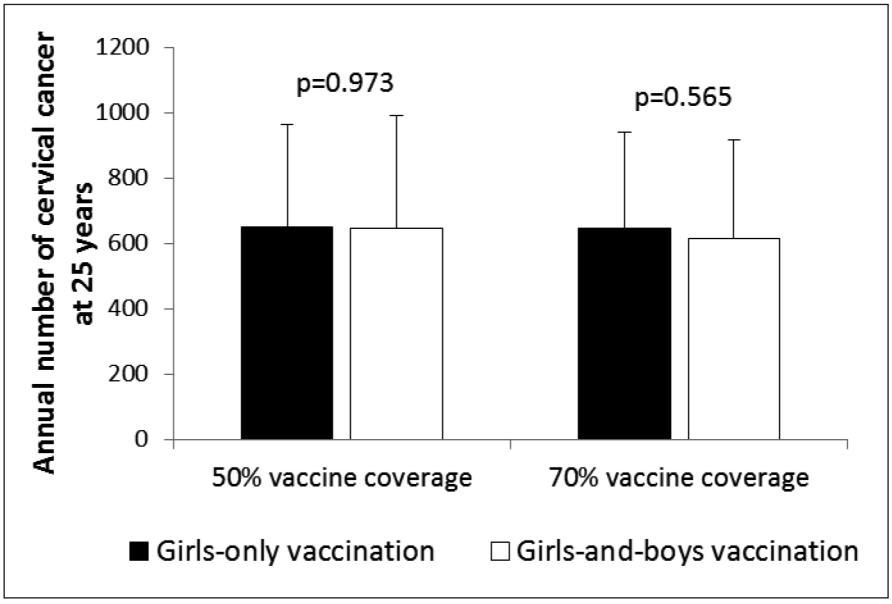

Fig. 4– Annual number of cervical cancers when considering a vaccination strategy of boys and girls aged 11 years versus girls-only vaccination, within two scenarios of 50% and 70% two-dose vaccine coverage for all cohorts after 25 years (values were expressed as mean and standard deviation; data were obtained from 50 simulations).

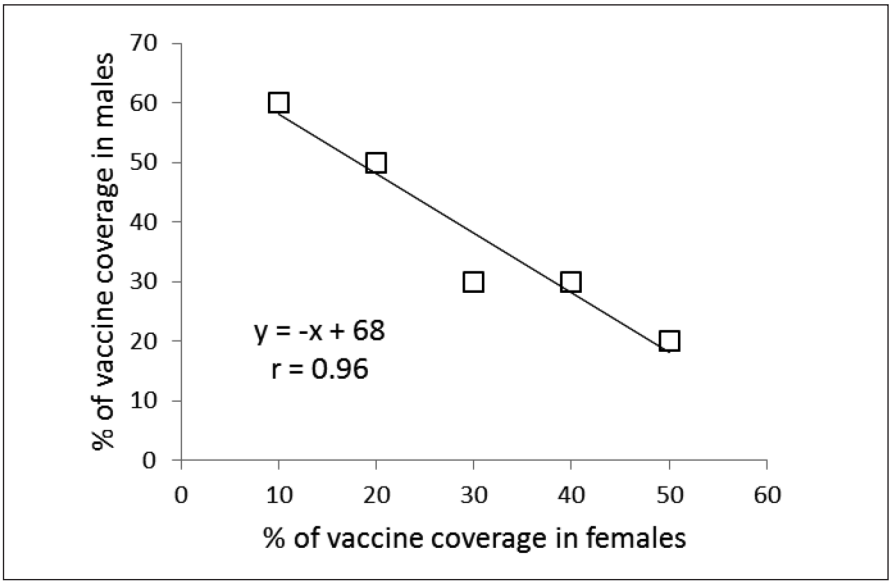

Fig. 5.– Combination of boys and girls vaccination needed to eliminate cervical cancer, when vaccine coverage in girls was under 50%.

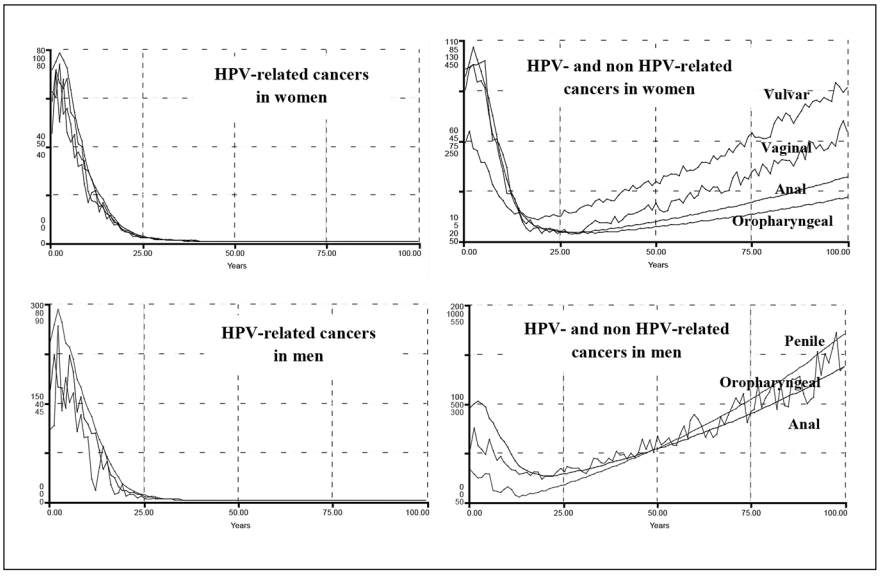

Fig. 6.– Long-term stochastic dynamic simulations of the annual number of new cases of vulvar, vaginal, anal, and oropharyngeal human papillomavirus (HPV)-related cancers in women (top plots), and penile, anal, and oropharyngeal HPV-related cancers in men (bottom plots). The left column plots show that current female vaccination (without male vaccination) would virtually eliminate the proportion of these cancers associated to HPV in 35-40 years, both in women and men. The right column plots show the evolution of all types of HPV- and non HPV-related vulvar, vaginal, anal, penile, and oropharyngeal (only tongue, tonsils and oropharynx) cancers. When the evolution of the different types of cancer were similar, each plot was not individualized. For comparative purposes, note that Y-axis scales are different (saw waves were generated because of the stochastic component of simulations).

rent coverage rate would lead to 59% (SD: 2.0%) reduction in the global incidence of vulvar cancer, 76% (SD: 1.8%) for vaginal cancer, 85% (SD: 0.9%) for female versus 70% (SD: 1.1%) for male anal cancer ($p < 0.0001$), 34% (SD: 14.5%) for penile cancer, and 87% (SD: 1.6%) for female versus 44% (SD: 12.5%) for male oropharyngeal cancer ($p < 0.0001$), all reductions estimated over a 25-year time prospect. Extending the vaccination program to boys significantly changed the cancer reduction rates in males but not in women, probably due to the effect of the fraction of males who have sex with males (Table 1).

Figure 7 shows the percent reduction in the incidence of anogenital warts in females and males at a 25-year simulation, according to girls-only and boys-and-girls vaccination strategies. The current girls-only vaccination program would lead to a higher reduction of anogenital warts in females than in males; nevertheless, males could achieve a similar reduction by adding a 70% two-dose immunization coverage rate in boys. Finally, RRP occurring in children below 11 years and in the adult population could be virtually eliminated at 25 years with the current girls-only immunization program. No benefit was observed when boys' vaccination was added to the model.

Discussion

Cervical cancer peaks in women aged 45 years and above; consequently, most of population health gains for cervical cancer prevention are likely to be observed several decades after HPV vaccination implementation. Therefore, mathematical models play a key role in evaluating long-term predictions of health benefits for policy decision-making, especially in developing countries with limited resources. In most countries, HPV vaccination rates are low compared with rates for other recommended vaccines. In Argentina, vaccine coverage increased from negligible levels before 2011 to a national average of 87.9% for the first dose, 71.6% for the second dose, and 52.2% for the third dose in 2013; nevertheless, there is a large variance in coverage across provinces[17, 51]. In the present study, we developed an epidemiological dynamic model able to explore HPV vaccination strategies within the local context. Globally, the present long-term stochastic simulation revealed that maintaining a mean two-dose vaccine coverage of $\geq$60% only for girls aged 11, cervical cancer could be drastically reduced or virtually eliminated in a 50-year term, as long as the current screening rate were maintained.

TABLE 1.– *Reduction rates (%) in the global incidence of HPV/non HPV-related cancers in women and men, comparing current girls-only vaccination coverage versus girls-and-boys vaccination strategy. A 70% two-dose immunization coverage rate was assumed in boys. Dynamic simulations were done over a 25-year horizon (values were expressed as mean percent reduction and standard deviation). Data show that adding vaccination to boys was only beneficial for the male but not for the female population*

	Girls-only vaccination % (SD)	Girls-and-boys vaccination % (SD)	Difference	P-value
Female cancers				
Vulvar	59 (2.0)	57 (3.0)	+2%	0.040
Vaginal	76 (1.8)	76 (2.4)	0%	0.928
Anal	85 (0.9)	85 (0.7)	0%	0.737
Oropharyngeal	87 (1.6)	86 (2.2)	+0.7%	0.229
Male cancers				
Penile	34 (14.5)	56 (12.4)	-22%	< 0.0001
Anal	69 (1.1)	79 (0.7)	-10%	< 0.0001
Oropharyngeal	44 (12.5)	63 (8.2)	-19%	< 0.0001

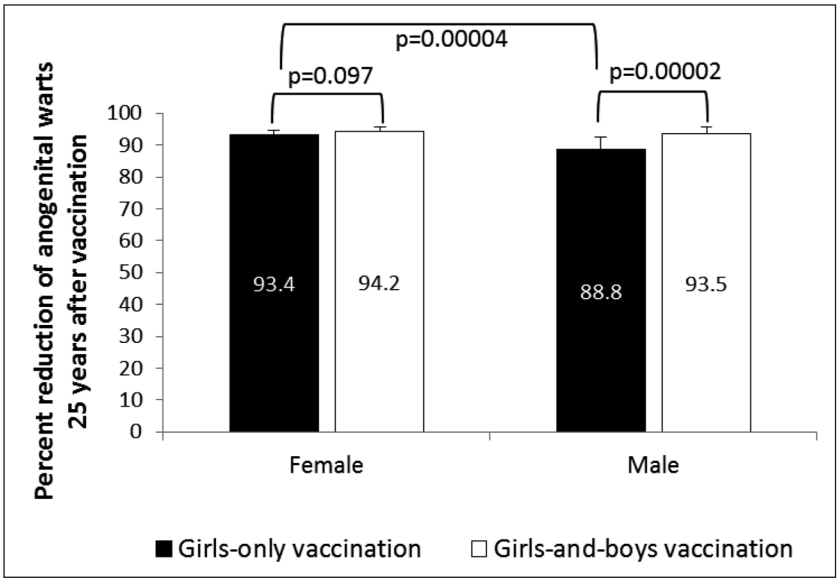

Fig. 7.– Percent reduction in the incidence of anogenital warts in females and males at 25 years, considering a strategy for girls-only vaccination (coverage rate of 70% for two-dose application, 24% for one-dose, and 5% for catch-up vaccination), versus girls-and-boys vaccination strategy (boys' coverage rate of 70% for two-dose application). Additional boys' immunization accounted for a significant but marginal reduction in the number of anogenital warts cases.

Recent evidence-based guidelines of the American Society of Clinical Oncology recommended two doses of HPV vaccine for girls aged 9 to 14 years, and if more than 50% coverage in the female population were achieved, then boys could be vaccinated to prevent other non-cervical HPV-related cancers and diseases[52]. Furthermore, a third dose of HPV vaccine is unlikely to be cost-effective if duration of two-dose protection is longer than 30 years[53].

Updated studies suggest that vaccination of pre-adolescent males may be cost-effective if vaccination coverage in females cannot be increased above ~50%. However, the present analysis found that, assuming overall vaccination coverage of 50% or 70%, the vaccination of both girls and boys was not associated with reduction of cervical cancer versus a strategy of girls-only vaccination. Furthermore, these findings are in coincidence with other

modeling studies, which concluded that the incremental impact of vaccinating boys was limited[54-57]. Only the study by Marty el al.[57] indicated that vaccination of both girls and boys was associated with notable incremental clinical benefits; however, this last study may be partially biased by the authors' competing interests.

The present study also recognized the value of older female catch-up vaccination for two-dose borderline coverage. Likewise, a recent research based on a Markov model concluded that extending vaccination to older girls and females (catch-up vaccination), instead of adding boys' immunization would maximize the number of cervical cancer cases prevented[58].

The scope of the present study was not limited to cervical cancer but also accounted for other HPV-related neoplasms. Although those other cancers are less commonly related to HPV than cervical carcinomas, vulvar, vaginal, penile, anal, and oropharyngeal types were drastically reduced with the current girls-only vaccination coverage, as simulated over a 35-40-year time horizon. Extra vaccination on the boys' cohort modified reduction rates of these cancers in men but not in women.

A model developed by Elbasha et al.[59] showed that by vaccinating girls alone, an 83% reduction in the incidence of anogenital warts was expected, but this reduction increased to 97% if boys were also vaccinated. A random network model assuming a vaccine coverage of 73% in girls-only and catch-up coverage rates decreasing with age to 52% for 20-26 year-olds, calculated a 59% reduction in anogenital wart cases[47]. Another research concluded that focusing on attaining high HPV vaccination coverage of girls, rather than including boys in a vaccination program, may be a more efficient strategy to reduce anogenital warts in low-resource settings[60]. The current model showed a drastic reduction in the incidence of anogenital warts both in females and males at 25 years, by vaccinating girls alone; it also indicated that an extra vaccination in boys would provide a significant but marginal reduction of nearly 5% in the male incidence of warts.

Recurrent respiratory papillomatosis is a condition characterized by the repeated growth of benign exophytic papillomata in the larynx. In the juvenile-onset form of this disease, perinatal transmission of HPV is thought to occur intrapartum from infected mother to child, and must be differentiated from the adult form[49]. The current model ran two separate simulations for children and adult cohorts. At 25 years, both simulations showed virtual disappearance of RRP with the current girls-only vaccination strategy, and no benefits were observed when incorporating immunization to boys.

Future modeling applications should explore how cervical cancer screening strategies might evolve over time following the onset of HPV vaccination in Argentina, particularly for underserved women. In this research line, the present study suggests the possibility of virtually eliminating cervical cancer with a rational vaccination strategy after a 100-year period, even in the absence of any type of cervical cancer screening program. However, since about 18% of cervical cancer would not be covered by the current quadrivalent vaccine, cervical screening programs should remain as the best known prevention practice for early diagnosis and treatment.

Even though HPV vaccine seems to have been firmly established, the evaluation of HPV vaccination programs around the world is still an active research area[61-66]. It has been recognized that once a national vaccination program is initiated, it is difficult to influence the design and impose a monitoring mechanism to gather information[1]. However, and specially for developing countries, to construct a pilot model of vaccination coverage could be used to improve the understanding of the dynamic effects of vaccination and to recalculate regional long-term health goals. Other classical dynamic models have been published to date[67-70]. Two models focused on HPV infection only, and not on subsequent HPV diseases[66, 69]. Barnabas et al.[69] modeled the potential epidemiologic impact of an HPV vaccine in an unscreened developing-world population; Taira et al.[68] combined a cohort model with a transmission model into an hybrid system.

This study has some limitations. First, these dynamic models explored only HPV-related cancer; other etiological presentations of vulvar, vaginal, anal, penile and oropharyngeal carcinomas were marginally modeled and included in the outcomes. Second, all simulations were done considering a homogeneous mean coverage vaccination rate over time throughout the whole country. Therefore, models did not consider the fact that there are local populations where both women and men are protected because of the high vaccination coverage rate; whereas in populations with low vaccination coverage that would potentially benefit from vaccination of males (herd protection), the vaccine does not reach either group. Additional regional simulations should be performed to compensate for local heterogeneities. Third, the model did not offer a cost-effectiveness evaluation; nevertheless, if there were reliable costs, they could be easily incorporated into the model in future research. Fourth, cohorts were not divided into age-specific or sexual activity class reflecting a different risk for acquiring the infection; conversely, the population was analyzed as a whole. Some recent research in Argentina found a low degree of knowledge about HPV infection and its prevention in the population[71], and a low rate of vaccination acceptance in other selected communities[72]. These key points should be included in future models. Much of the current consensus on how anal dysplasia evolves is derived directly from cervical cancer evolution[12]; nevertheless, as there is no universal accepted algorithm for anal cancer screening, early detec-

tion programs were not included in the model. Finally, all the outcomes should be considered in the context of widely accepted rational assumptions, and based on the accuracy of the model parameter set obtained from the literature.

In conclusion, this study intends to be a translational academic paper for health policy application. A mathematical dynamic model focusing on both the infection and the disease process was developed to explore the population-level impact of the Argentine HPV vaccination program on the incidence of HPV-related cancers. This model analyzed the effect of different levels of vaccination coverage, both in females and males, to propose rational epidemiological and policy-making strategies to reduce HPV-related diseases in Argentina in the long term. Female HPV vaccination within the context of current cervical cancer screening should reach a minimum long-term mean coverage of 60% of girls aged 11 years, receiving at least a two-dose vaccine schedule, to significantly reduce or virtually eliminate cervical cancer at 50 years. Different combinations of one- and two-dose protection plus catch-up vaccination programs in older females also showed to be beneficial options. Including vaccination to boys aged 11 to improve herd immunity did not influence the incidence of cervical cancer over time, as long as the female coverage did not fall below 50%. Regarding vulvar, vaginal, anal, penile, and some oropharyngeal cancers, current girls-only based vaccination could virtually eliminate these cancer types after 35-40 years, both in women and men, with extra benefits only in males when adding simultaneously boys' vaccination. A similar outcome is expected for anogenital warts and RRP at a 25 year horizon, but the benefit for males when adding boys' immunization was marginal for warts and nil for RRP. Results from the current model can be instrumental for evaluating HPV vaccination policies in Argentina.

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Appendix

Model input data

A comprehensive search of the literature was conducted to obtain baseline values for model parametrization. They are summarized in Table S1 for cervical cancer, Table S2 for anogenital cancer, and Table S3 for oropharyngeal cancer. The analysis incorporated female-specific conditions including HPV-related cervical, vulvar and vaginal carcinomas, penile carcinoma in males, and anal carcinoma, genital warts, recurrent respiratory papillomatosis (RRP), and head and neck cancers in both males and females. Epidemiologic input data concerning the incidence of HPV-related diseases in Argentina were derived from previously published epidemiologic studies. Regarding cervical cancer, the model incorporated both HPV vaccination and screening programs. Specific progression rate of HPV-16 and HPV-18 to different stages of cervical dysplasia and cancer were estimated from the literature. Current estimates regarding Pap screening, lesion treatment, cancer progression and mortality were also considered. Sexual behavior was introduced in the model by including average age at first marriage, mean number of partners, condom use rate, and the fraction of males who have sex with males. Finally, the impact of non-vaccinated adult people migrating to the country was taken into account by adding an annual fixed number of infected and non-infected migrants to the model. Calibration for all types of cancers was done to adjust the model outcomes to their annual incidences reported for Argentina. To validate the model, the incidence of cancer cases and deaths predicted by the model was compared with those reported by the National Ministry of Health[1-16]. The annual rates of cancer cases of the current model matched accurately local data after calibration.

Assumptions

For modeling purposes, the following assumptions were considered: HPV is carried and sexually transmitted by both females and males; routine HPV vaccination is considered to be effective in pre-adolescent or early adolescent girls or boys prior to sexual debut (HPV DNA negative); catch-up vaccination cohorts are more likely to have prior exposure to HPV infection; and preventable HPV-related cancers in males are considerably lower than those in females, but vaccination of males can potentially affect transmission to females and other males. The vaccine (both for girls-only and boys-and-girls vaccination programs) was assumed to be administered to 11-year olds. Initially, a vaccine coverage of 70% was assumed for girls receiving at least two vaccination doses, and a vaccine coverage of 24% for those receiving one vaccination dose. One-dose coverage was taken into account as an imperfect adherence to the scheduled vaccination course, and decreased vaccine efficacy was also assumed for those having received one dose in comparison with those who were fully vaccinated (two doses).These figures represent the data for Argentina reported in 2013[17].

A four-year transition period was assumed from vaccination to first sexual contact, and the duration of vaccine protection was considered to be that of the patient's lifetime. Finally, low-risk HPV types 6 and 11 were assumed to account for nearly all cases of anogenital warts and RRP.

TABLE S1.– *Initial model parameters and assumptions for cervical cancer*

Variable	Value (probabilities)	Data source/Ref.
Initial population		
Female population over 10-year-old	17 500 000 women	14
Fraction of 11-year-old female population	0.01	14
Fraction of female population between 13 and 26-year-old	0.24	14
Birth rate	0.0175	15
Annual immigration of non-vaccinated adult population	75 000 women	Assumption
Population mortality rate	0.0076	15
Fraction of susceptible population	0.693	16
Fraction of HPV infected population	0.133	16
HPV 16-18 infected with normal cytology	0.087	16
HPV 31 infected with normal cytology	0.035	16
HPV 45 infected with normal cytology	0.011	16
Fraction of population with CIN*	0.0089	16
Initial population with cervical cancer	18 000 women	15
Average annual number of deaths from cervical cancer	980	26
Fraction of naturally-immune population	0.138	
Sexual intercourse data (number of partners)	1.5	Assumption
Average age at first marriage	23.3-year-old	16
Prevalence of condom use	0.329	16
Condom-use HPV protection	0.7	16
Cervical cancer not covered by quadrivalent vaccine	0.183	28
Prevalence of HPV types		
HPV 16	0.595	3, 19, 20
HPV 18	0.155	3, 19, 20
HPV 31	0.046	3, 19, 20
HPV 45	0.031	3, 19, 20
Vaccination		
Target age for routine vaccination	11-year-old	17
Age at "catch-up" vaccination	13 to 26-year-old	Assumption
Vaccine coverage (one dose)	0.24	17
Vaccine coverage (two doses)	0.7	17
"Catch-up" vaccine coverage	0.05	Assumption
HPV 16-18 type vaccine effectiveness	0.95	3
HPV 31 type vaccine effectiveness	0.6	3
HPV 45 type vaccine effectiveness	0.78	3
"Catch-up" vaccine global effectiveness	0.3	3
Vaccine-acquired immunity loss	0.0	Assumption
Naturally acquired immunity loss	0.0	
Assumption		
Transition probabilities of HPV-related diseases		
Progression		
Normal to HPV (effective contact rate)	0.6 to 0.8	24-25
Infection to CIN1	0.0575 to 0.1023	18
CIN1 to CIN2-3	0.0022 to 0.0467	18
CIN2-3 to persistent CIN2-3	0.11	21-23
Persistent CIN2-3 to cervical cancer	0.0006 to 0.0722	18
Cervical cancer annual mortality rate	0.06	27
Regression		
HPV to normal	0.29 to 0.55	18
CIN1 to normal	0.372	18
CIN2-3 to normal	0.0118 to 0.0424	18
Cervical cancer to cancer cured	0.084	29
TABLE S1.- (continued)		
Variable	Value (probabilities)	Data source/Ref.
Cancer screening and treatment		
Regular screening coverage	0.3	3, 30
Irregular screening coverage	0.4	3, 30
Interval between regular screening	3 years	3
Sensitivity to detect CIN1	0.5	3
Sensitivity to detect CIN2-3	0.6	3
CIN1 treatment effectiveness	0.64	3
CIN1 treatment effectiveness	0.77	3

**CIN: cervical intraepithelial neoplasia*

TABLE S2.– *Initial model parameters and assumptions for anogenital cancer*

Variable	Value (probability)	Data source/Ref.
Anogenital cancer (including vulvar, vaginal, penis, anus)		
Vulvar cancer		
Annual number of new cases of vulvar cancer	≈284 cases	16
Basaloid/warty type vulvar cancer	0.349 to 0.455	31
HPV-related basaloid/warty type vulvar cancer	0.75 to 1.0	16
Probability of developing vulvar cancer	0.0000162	16
Prevalence of HPV type 16	0.253	31
Prevalence of HPV type 18	0.028	31
Prevalence of HPV type 45	0.025	31
Prevalence of HPV type 33	0.022	31
Probability of developing non HPV-related vulvar cancer	0.000014 to 0.000016	16
Vulvar cancer annual mortality rate	0.06	32
Vaginal cancer		
Annual number of new cases of vaginal cancer	≈102 cases	16
HPV-related vaginal cancer	0.7 to 0.91	33, 34
Probability of developing vaginal cancer	0.000006	16
Prevalence of HPV type 16	0.424	35
Prevalence of HPV type 18	0.042	35
Prevalence of HPV type 31	0.058	35
Prevalence of HPV type 33	0.042	35
Prevalence of HPV type 52	0.031	35
Probability of developing non HPV-related vaginal cancer	0.000003 to 0.0000037	16
Vaginal cancer annual mortality rate	0.12	36
Female anal cancer		
Annual number of new cases of anal cancer	≈91 cases	16
HPV-related anal cancer	0.88	33
Probability of developing anal cancer	0.0000052	16
Prevalence of HPV type 16	0.73	33
Prevalence of HPV type 18	0.05	33
Probability of developing non HPV-related anal cancer	0.0000017	16
Anal cancer annual mortality rate	0.06	37
Male anal cancer		
Male population over 10 years old	16 600 000 men	16
Fraction of 11-year-old male population	0.01	14
Fraction of male population between 13 and 21years old	0.16	14
"Catch-up" vaccine coverage	0.05	Assumption, 38
Age at "catch-up" vaccination	13 to 21-year-old	38
Fraction of male who has sex with male (last year)	0.01 to 0.08	39
Annual number of new cases of anal cancer	≈100 cases	16
HPV-related anal cancer	0.88	33
Probability of developing anal cancer	0.000006	16
Prevalence of HPV type 16	0.73	33
Prevalence of HPV type 18	0.05	33
Probability of developing non HPV-related anal cancer	0.0000019	16
Anal cancer annual mortality rate	0.06	37
Penile cancer		
Annual number of new cases of penile cancer	≈219 cases	16
Probability of developing penile cancer in the population	0.0000132	16
Prevalence of HPV in penile cancer	0.552 to 0.83	16
Prevalence of HPV type 16	0.211	40
Prevalence of HPV type 18	0.289	40
Probability of developing non HPV-related penile cancer	0.0000008 to 0.0000095	16
Penile cancer annual mortality rate	0.06	41

TABLE S3.– *Initial model parameters and assumptions for oropharyngeal cancer, anogenital warts and recurrent respiratory papillomatosis*

Variable	Value (probabilities)	Data source/Ref.
Oropharyngeal cancer (including tongue, tonsils, oropharynx)		
Female oropharyngeal cancer		
Annual number of new cases of oropharyngeal cancer	≈63 cases	16
Probability of developing oropharyngeal cancer in the population	0.0000036	16
Prevalence of HPV in oropharyngeal cancer	0.389 to 0.766	42-45
Prevalence of HPV type 16	0.48	42, 45
Prevalence of HPV type 18	0.04	42, 45
Probability of developing non HPV-related oropharyngeal cancer	0.0000009	16
Oropharyngeal cancer annual mortality rate	0.12	46
Male oropharyngeal cancer		
Annual number of new cases of oropharyngeal cancer	≈315 cases	16
Probability of developing oropharyngeal cancer in the population	0.000019	16
Prevalence of HPV in oropharyngeal cancer	0.389 to 0.766	42-45
Prevalence of HPV type 16	0.48	42, 45
Prevalence of HPV type 18	0.04	42, 45
Probability of developing non HPV-related oropharyngeal cancer	0.0000079 to 0.000013	16
Oropharyngeal cancer annual mortality rate	0.12	46
Female and male anogenital warts		
Probability of developing anogenital warts in the population	0.008	4
HPV-related anogenital warts	0.9 to 1.0	47
HPV 6-11 type vaccine effectiveness	0.971	4
Fraction of treated anogenital warts	0.5	Assumption
Female and male recurrent respiratory papillomatosis (RRP)		
Probability of developing RRP in the adult population	0.00016 to 0.00018	48, 49
Probability of developing RRP in children	0.00016 to 0.00134	48, 49
Prevalence of HPV in RRP	0.85	48
Prevalence of HPV type 6	0.638	50
Prevalence of HPV type 11	0.212	50
Median age of diagnosis in the adult population	31 to 44 years	48, 49
Median age of diagnosis in children	3.2 to 5.6 years	48
Prevalence of RRP in the adult population	0.00038	48
Prevalence of RRP in children	0.00388	48