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Eliminating Andean Region Health Disparities via Human Papilloma Virus Vaccination Administration Programs Implementation

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Abstract

This study explores human papilloma virus (HPV) disease epidemiology, successful school-based and combined clinic- and school-based HPV vaccination programs, and the applicability thereof to Andean low- and middle-income countries (LMIC). Only 17% of incident cervical cancer cases occur in the Latin American Countries (LAC) of the Caribbean, Central and South America. But, the LAC have a 38% cervical cancer mortality. School-based HPV vaccination programs in LMIC have achieved three-dose vaccination rates greater than 80%. School-based vaccination programs are cost effective, deserving expansion. Three-dose HPV vaccination in LMIC schools satisfy the World Health Organization vaccination program requirements. Sustainable HPV vaccination campaigns require media campaigns including Internet components for health care providers, parents, and students. Campaigns cosponsored by Ministries of Education, Health, and Finance will increase national HPV vaccination awareness, program acceptance, and school-based program use.

Keywords: Andean Region; Disease Prevention; Human Papilloma Virus Vaccination; Immunization Programs; Vaccination Cost

Abbreviations: CC: Cervical Cancer; CIN: Cervical Intraepithelial Neoplasia; EGL: External Genital Lesions Include External Genital Warts (EGW), Vaginal Intraepithelial Neoplasia (VIN), and Vulvar Intraepithelial Neoplasia (VaIN); FSW: Female Sex Worker; GAVI: Global Alliance for Vaccines And Immunization; HPV: Human Papilloma Virus; HPV2: Bivalent HPV Vaccine; HPV4: Quadrivalent HPV Vaccine; HPV9: Nonavalent HPV Vaccine; HR: High Risk; ICER: Incremental Cost-Effectiveness Ratio; LAC: Latin America And The Caribbean; MCV4: Neisseria Meningitidis Serotypes A/C/Y/W-135 Vaccine; NGO: Non-Government Organization; PAHO: Pan American Health Organization; PC-GDP: Per Capita Gross Domestic Product; QALYs: Quality Added Life Years; RRP: Recurrent Respiratory Papillomatosis; Tdap: Tetanus, Diphtheria and Acellular Pertussis Vaccine; US$: United States Dollars; YLL: Years of Life Lost; YLS: Years of Life Saved; +: Positive.

Introduction

Bolivia, Chile, Colombia, Ecuador, and Peru are part of the Latin American Andean region of South America. Globally, human papilloma virus (HPV) is responsible for over 500,000 incident cases of cervical cancer (CC), 86,000 (17%) of which occur in the Latin American

Countries (LAC) of the Caribbean, Central and South America [1,2]. This amounts to about 7.8 million female years of life lost (YLL), limiting women's socioeconomic contribution as grandmothers, mothers, daughters, sisters, and wives [3]. CC is the most frequent female cancer in Bolivia, the second most frequent female cancer in Colombia, Ecuador, and Peru, and the third most frequent female cancer in Chile [4]. Globally, about 274,000 die from CC annually, representing the fourth cause of global female deaths, but 241,120 (88%) of CC deaths occur in low- and middle-income countries (LMIC) [3-7]. Both LAC and LMIC comprise the Andean region. Cervical cancer is attributed with at least 33,000 (12%) deaths in LAC [8,9]. In 2002 Colombia had 5,500 incident CC cases and 2,045 deaths [10]. In Peru CC has an estimated annual mortality rate of 24.6 per 100,000 translating to 2,098 deaths annually [2,11-13]. CC is the leading female cancer mortality cause in Bolivia, Colombia, Ecuador, and Peru [2,10,12]. Consistent with this, increased case-fatality associated with decreased national income has been demonstrated for CC [14]. Between 1987 and 2003, Chile achieved a 48% reduction in CC mortality following improved CC screening [15,16]. The outcome, a CC mortality rate of 8.4 per 100,000 women represents 677 deaths, the second leading female cancer mortality cause, and 129 YLL per 100,000 women in 2003 [16]. Subsequently, the CC mortality rate dropped to 7.3 per 100,000, reducing CC to the sixth cause of female cancer mortality in Chile for 2003 to 2007 [4].

The heat-labile bivalent (HPV2), quadrivalent (HPV4) and nonavalent (HPV9) vaccinations provide prophylactic primary prevention against the 70-82% of CC due to high risk (HR) HPV-16 and -18 [8,12,17,18]. Long-term efficacy of HPV4 was confirmed with 6.26 years follow-up in Colombia [19]. An additional 9-15% prevention of CC from HR HPV-31, -33, -35, -45, -52, and -58 is provided by HPV9 [18]. Vaccination-based primary prevention of CC is the leading method for LAC and LMIC to forestall impending unaffordable long term health care associated costs [14]. Peru approved HPV4 in 2008, the same year that hepatitis B virus vaccination (HepBV; the only other vaccine for primary prevention of cancer) was incorporated into the Peruvian National Vaccine Schedule [2]. HepBV implementation in low-income countries can take 20 years [13]. It may be unrealistic to expect HPV vaccination program implementation completion in less than 20 years from HPV vaccination marketing (2006). Colombia began a 3-dose school-based HPV vaccination program for 9 year old and older girls in 2011 [4]. Conversely, Chile started a 2-dose school-based HPV vaccination program for 9 year old and older girls in 2014 [4]. In 2011 Peru began a 3-dose school-based HPV vaccination program for 10 year old girls [4]. Bolivia and Ecuador lack HPV vaccination programs [4].

HPV is etiological in anal, oropharyngeal, penile, vaginal, and vulvar cancers [5,20]. HPV types 6 and 11 contribute to 4.3 cases of incompletely curable recurrent respiratory papillomatosis (RRP) per 100,000 children [21]. HPV4 administered post incidence of RRP may reduce frequency of subsequent bouts of RRP [21]. External genital warts (EGW) may have a prevalence of 1%, with a total lifetime risk of 10% [22]. HPV types 6 and 11 are responsible for 90% of EGW [5]. HPV4 and HPV9 protect against EGW and RPP [18,21]. Treatment of recurrent EGW has significant human and financial costs in Central and South America [1]. Low HPV vaccination rates mean that the incidence of anal, cervical, oropharyngeal, penile, vaginal, and vulvar cancers, EGW, and RRP will not decline as rapidly as possible.

The Ministers of Health of LAC agreed in 2006 to introduce the HPV vaccination [9]. Yet, the Chilean Working Group on HPV requested additional information prior to HPV vaccination implementation leading to cost-effectiveness studies of HPV in Chile, which are reviewed below [23]. Despite proven efficacy, calculated cost-effectiveness, and a measure of political will, nine years later the Andean region lacks universal HPV vaccination programs. Attitudes towards HPV, vaccine supply costs, and vaccination implementation needs contribute to low vaccination rates. Attitudinal determinants of HPV vaccination acceptability will be the topic of a separate paper. Acceptable vaccination cost may be linked to both personal and national income, referred to in terms of gross domestic product (GDP). Vaccination acceptability only leads to immunization if affordable vaccine is available. Early detection and treatment may cure CC [14]. Given that LAC and LMIC may only have sufficient resources for a CC screen and treat program or an HPV vaccination program, means of reducing HPV vaccination program cost will be identified. It will be shown that there are resources available to provide HPV vaccination in the Andean region. Two Peruvian concurrent screen and treat and HPV vaccination trials will be presented. The selected approach to introduction of HPV vaccination in a nation may

predetermine successful attainment of adequate vaccination rates.

Methods

The PubMed database was searched using the terms "HPV vaccine" or "HPV vaccination" and Bolivia, Chile, Colombia, South America, Ecuador, or Peru as shown in Figure 1 yielding 58 English and 16 Spanish language articles. Articles were eliminated for duplication or redundancy, topic mismatch including sociocultural focus, repetitive phase 3 trials, repetitive discourse on the history of HPV-attributable disease and HPV vaccination. Spanish language articles were excluded, resulting in 29 included articles from the PubMed database searches. For coverage of the HPV9 vaccine, 1 article was added. For adequate background and discussion, 6 articles from the author's prior research were added as shown in Figure 1 and Table 1.

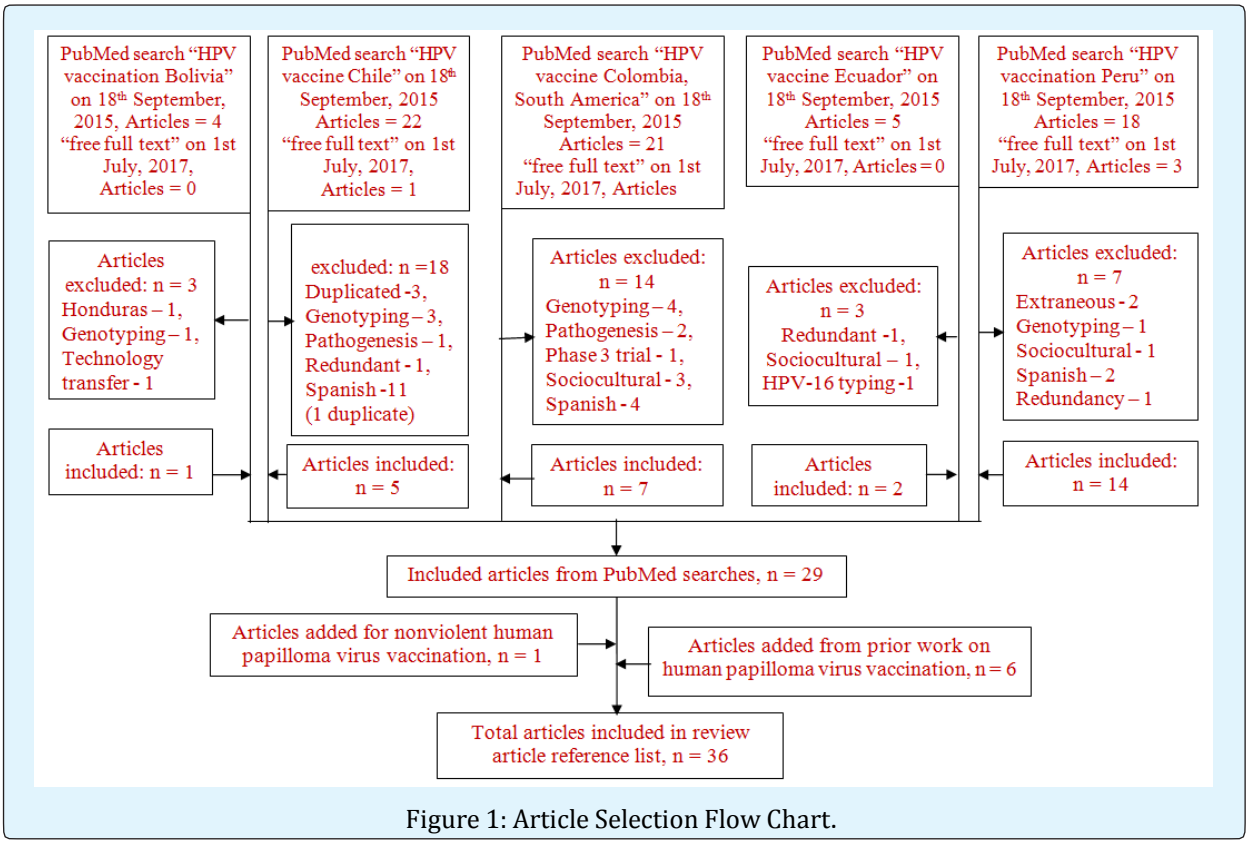

Figure 1: Article Selection Flow Chart.

Ref, Author	Setting	Relevance	Patient Population	Methodology	Outcomes	Results
Perez G, et al. [1]	Peru -1	HPV4 efficacy in Colombia and Peru.	6,004 females aged 9-24 years in Brazil, Colombia, Costa Rica, Guatemala, Mexico and Peru, without prior	Randomized, blinded, placebo-controlled trial of 3-dose HPV4 vaccine	Cervical intraepithelial neoplasia and external genital lesion occurring 30 or more days after the 3rd HPV dose	92.8% efficacy in CIN prevention. 100% efficacy in EGL prevention.

			abnormal Papanicolaou tests, and with 4 or less sexual partners.			
Brown B, et al. [2]	Peru -2	HPV awareness. HPV vaccine acceptability.	319 FSW aged 18-29 years in Lima, Peru	Purposive sampling, mixed-methods study.	HPV awareness. HPV vaccine acceptability.	9.9% knew of HPV vaccine for CC prevention. 99% would accept 3-dose HPV vaccine. Average acceptable vaccine cost was US $27.70. HPV knowledge was associated with having a STI within 1 year (p =.01), education, higher income, and not drinking alcohol before work (p =.033).
Forman D, et al. [3]	Context -1	Global HPV epidemiology.	Global men and women.	GLOBOCAN 2008 data.	HPV-related cancer and non-cancer diseases	Adjusted female HPV prevalence with normal cervical cytology ranges from 1.7% in western Asia to 35.4% in the Caribbean.
Soohoo M, et al. [5]	Peru -3	HPV prevalence in FSW.	286 FSW in Lima, Peru	Review article.	HPV prevalence	HPV prevalence ranged from 50.6-66.8%.
Levinson KL, et al. [6]	Peru -4	Intervention ability to achieve 85% or higher 3-dose HPV vaccination rate.	Co-registering, 352 non-pregnant girls aged 10-13 years non previously vaccinated against HPV, and 323 non-pregnant women aged 30-45 years	Community health worker led community-based participatory research.	Subject participation, retention, and satisfaction.	86% girls got 3-doses HPV vaccine. 92% girls got 2-doses HPV vaccine. 95% girls got 1-dose HPV vaccine. 94% HPV+ women were treated. 90% HPV+ women had 6-month follow-up. 96% participants were highly satisfied.
Ladner J, et al. [7]	Bolivia -1	NGO-led GAP supported vaccination program.	30,900 girls aged 9-13 years in a mixed school and clinic-based HP vaccine program, and 3,480 girls aged 9-13 years in a school-based HPV vaccine program.	GAP provided free 3-dose HPV vaccine per participant. NGOs covered cold-chain, promotion and administration.	Program vaccination coverage based on census data. Vaccination adherence (3-dose completion).	The school-based program was over subscribed with 3,739 participants (107%) receiving 3-doses HPV vaccine. The mixed school and clinic-based program achieved an 89% 3-dose HPV vaccination rate. Both programs had a 96% vaccination adherence rate

Bartolini RM, et al. [8]	Peru -5	Groundwork for HPV vaccine introduction	Children, parents, community leaders, health and education officials, and policymakers.	Mixed-methods formative research, including focus groups and in-depth interviews.	-	All respondents supported HPV vaccine introduction, cancer prevention. Community-level service safety and quality concerns exist.
Andrus JK, et al. [9]	Context -2	Review of LAC HPV vaccine policy and delivery.	-	-	-	Use PAHO's ProVac initiative for support. Provide HPV vaccine at US$5 or less, per dose. Use school-based vaccination programs.
Aponte-González J, et al. [10]	Columbia -1	CC epidemiology in Colombia. Comparative cost-effectiveness of 2vHPV and 4vHPV in Colombia.	CC incidence of 5,500. Annually, 2,045 CC deaths. 70% CC screening coverage.	Markov model simulation of cervical cancer and EGW natural history, CC screening, 2vHPV vaccination and screening, and 4vHPV vaccination and screening.	2vHPV should cost US$ 17-47 to be very cost-effective or cost-effective. 4vHPV should cost US$19-49 to be very cost-effective or cost-effective.	Cost-effective HPV vaccine in Colombia should cost at most US$141-147 per vaccinated girl. Due to reduction of EGW, 4vHPV is more cost-effective than 2vHPV.
Lee FH, et al. [11]	Peru -6	Brief educational intervention effectiveness.	511 women aged 25-65 years inhabiting Puente Pidera, Los Olivos, and Comas, 3 low-income districts in Lima, Peru.	Convenience sampling, half from health centers, half from the market, pretest, posttest mixed methods survey with a 10-minute educational intervention	Knowledge of and attitudes towards HPV and CC. Knowledge that HPV vaccine prevents CC, and HPV vaccine acceptability.	33% knowledge of HPV, CC, and HPV vaccine. 51% willingness to pay US$15 for HPV vaccination. 90% HPV vaccine acceptability.
Penny M, et al. [12]	Peru -7	Identified facilitators of and barriers to HPV vaccinatio	12 health facilities with affiliated schools and communities	Mixed-method, cross-sectional, purposive, case-study of	Feasibility of HPV vaccine addition to existing Peruvian Ministry of	95% school-based HPV vaccination. 80% 1-dose or higher HPV vaccination rate. Unaffected routine vaccination schedules.

		n implementation.	, health personnel, teachers, female 5th graders, aged 9 years or older, mothers, and civil authorities.	school-based HPV vaccination programs.	Health vaccine delivery.	PATH financial and technical support essential for program success.
Bartolini RM, et al. [13]	Peru -8	Identification of determinants of parental acceptance of HPV vaccine.	Parents of girls participating in a 2008 Piura region school-based HPV vaccine demonstration project.	Purposive sampling, qualitative study with in-depth interviews.	Parental HPV vaccine decision-making conceptual model. Differences in factors favoring HPV vaccine acceptance and refusal.	Nonlinear HPV decision-making process changes with time from HPV vaccine introduction. Prevention, cost, availability, and credibility favor acceptance. Health system distrust favors refusal.
Farmer P, et al. [14]	Colombia -2	National health insurance program.	(Mandatory cancer treatment since 1994).	-	-	(Vested interest in cost-effective cancer prevention to prevent potentially unaffordable national health insurance program outlays for cancer treatment).
Gomez JA, et al. [15]	Chile -1	Decision support for possible Chilean HPV vaccination program.	Model cohort was 123,581 girls aged 11 years, 58% CC screening onset at 25 years, 95% vaccination coverage, 80% prevalence of HPV 16/18, EGW incidence of 4,685	Static Markov model simulation of CC screening with 2vHPV or 4vHPV vaccination	Cost-effectiveness of 2vHPV and 4vHPV, both costing US$ 20 per dose.	2vHPV ICER was US$ 116 per QALY gained or US$ 147 per YLS. 4vHPV ICER was US$ 541 per QALY gained or US$ 726 per YLS. All are less than the PC-GDP US$ 14,278.
Suarez E, Prieto M [16]	Chile -2	Effect of CC in Chile.	Incidence 1,350. Annual mortality 677 representing 129 YLL per 100,000 women.	(1997 Free radiotherapy in PHI. 2001 Free chemotherapy in PHI).	(2005 Chileans can sue if PHI does not provide covered CC services).	(Chilean PC-GDP US$ 4,747).

			68.3% of Chileans have public health insurance (PHI).			
Goldie SJ, et al. [17]	Peru -9		School-based female 5th grade aged 9 years or older in the Ayacucho, Piura, and Ucayali demonstration project.	Empirically calibrated computer-based simulation of childhood HPV vaccination and 3-5 lifetime adult HPV DNA screenings.	Benefits, cost-effectiveness, and affordability of HPV vaccination in Peru.	Childhood HPV vaccination and 5 adult HPV DNA screenings may prevent 2/3 of CC deaths. Per dose HPV vaccine cost needs to be $20 or less, for an ICER of $1,200/YLS, which is less than half Peru's 2005 PC- GDP of US$ 2,852.
Riethmuller D, et al. [18]	9vHPV trials	Comparison of simulated 9vHPV efficacy to 4vHPV efficacy.	HPV genotype distributions analyzed against HPV-related diseases and low-and high-efficacy 9vHPV estimates	Posthoc analysis of 6 multicenter retrospective studies.	9vHPV effect on anogenital and oropharyngeal HPV-related disease in France	9vHPV additional effect ranges from 9.9-15% for CC, 24.7-33.3% for CIN2-3, 12.3-22.7% for CIN1, 2.1-5.4% for EGW, 8.5-10.4% for anal cancer, 0-1.6% for oropharyngeal cancers. 9vHPV affords protection from almost 90% of CIN, CC, EGW, and anal cancer.
Luna J, et al. [19]	Colombia -3	6.26-year post-4vHPV vaccination efficacy in Colombia	804 women aged 24-49 years in the early vaccination group, 703 women aged 29-50 years in the catch-up vaccination group, and 103 women aged 29-50 years in the placebo group.	-	-	At 6.26 years post-4vHPV vaccination no cases of HPV 6/11/16/18 – related CIN, EGW, or HPV 16/18-related CIN2 or worse occurred.
Alemany L, et al. [20]	Ecuador -1	HPV contribution to VAIN and vaginal cancer.	80 Latin American VAIN and 191 American vaginal	Retrospective, cross-sectional study using hospital pathology	HPV DNA genotyping via DNA Enzyme Immunoassay.	Latin American VAIN samples had a 93% HPV prevalence. American vaginal cancer samples had a 78% HPV prevalence. HPV 31 has the greatest relative contribution cancer:VAIN ratio at 9.56, 95%

			cancer samples, with sources including Chile, Colombia, and Ecuador.	archives.		Confidence Interval 1.28-71.47.
Sanchez GI, et al. [21]	Colombia -4	RRP epidemiology in Colombia.	129 confirmed histologic RRP primary cases with available paraffin blocks, amplifiable DNA.	5 laboratory retrospective cohort.	HPV genotype detection by DNA enzyme immunoassay.	HPV 6 was present in 69% of cases. HPV 11 was present in 27.1% of cases. HPV 16 was present in 7.8% of cases. HPV 6 and 11 were present in 6% of cases.
Piñeros M, et al. [22]	Colombia -5	Knowledge and sources of knowledge of HPV-attributable disease and HPV vaccine.	106 men and 155 women aged 18-44 years, with histologically confirmed EGW at a private outpatient clinic in Bogotá, Colombia.	Cross-sectional study.	HPV knowledge in patients with EGW.	25% of men and 48% of women were aware of the HPV vaccine. About 50% of men and women were aware of HPV. The media was the source of 82% of participants HPV knowledge and 60% of participants HPV vaccine knowledge.
Marquez-Calderon S et al. [23]	Chile -3	Chilean HPV vaccination policy.	(Chilean working group on HPV noted conflicts of interest with HPV vaccination).	-	-	Policy level recommendation against HPV vaccination program pending additional information led to an independent HPV vaccination in Chile cost-effectiveness study.
Murillo R, et al. [24]	Colombia -6	Global efficacy of 4vHPV versus 9vHPV. HPV epidemiology.	217 cases of histologically confirmed CC.	18 clinical centers retrospective cohort.	HPV prevalence in low-high risk regions of Colombia.	63% overall HPV 16 and HPV 18 prevalence. HPV-18 less prevalent in high risk populations in whom HPV 31, 45, and 58 may have up to 19% prevalence
Mejía L, et al. [25]	Ecuador -2	HPV-type prevalence	164 women aged 19-77 years with CIN 2-3 or CC.	Cross-sectional study of colposcopic biopsies at Sociedad de Lucha contra	HPV genotype distribution in CIN 2-3 or CC.	Prevalence HPV 16/58/52/66/31/18 was 41.8%/30.5%12.1%/7.8%/10%/2.8% respectively. In Ecuador, 9vHPV should be more cost-effective than 2vHPV or 4vHPV.

				el Cáncer Hospital, Quito, Ecuador from May 2012 to June 2013.		
Velicer C, et al. [26]	Colombia -7	HPV 6/11/16/18 prevalence.	1,583 women aged 24-45 years, enrolled via primary care providers, academic and community health centers.	International 4vHPV efficacy trial, epidemiologic analysis.	HPV prevalence. Serum and anogenital swabs at day 1, months 7, 12, 24, 36, and 48. Anogenital swabs at months 18, 30, and 42.	HPV 16/18 prevalence - baseline 18.5% HPV 6/11 prevalence – baseline 17% Risk factors for HPV infection – prior Chlamydia or gonorrhea infection, 2 or more lifetime sex partners, 1 or more new sex partners in the last 6 months, marital status other than first marriage.
Colantonio L, et al. [27]	Chile -4	HPV vaccine cost-effectiveness in Peru and Chile.	Estimated oncogenic HPV prevalence of 9.2% in Chile, 13.2% in Peru, resulting in 917 and 4,860 CC cases respectively, and 532 and 3,155 CC deaths respectively	Markov cohort model.	Does universal HPV vaccination cost less than twice the PC-GDP in Chile (3x US$26,594) and in Peru (3x US$ 9,863).	Vaccination plus current screening has an ICER per QALYs gained ranges from US$ 4,576 in Peru to US$ 17,666 in Chile. As a middle-income nation Chile does not have access to the same funding array that Peru may have access to.
LaMontagne DS, et al. [28]	Peru -10	HPV vaccine acceptability.	8,092 5th grade girls in Piura region, who had participated in a PATH collaborated, school-based project, encompassing 264 schools and 161 health facilities.	Cross-sectional, 2-stage cluster sample design, using census districts.	HPV vaccination rates. HPV acceptance or refusal rationale.	82.6% HPV vaccination coverage in Peru. HPV vaccine was accepted for CC protection, disease prevention, and pro-vaccination belief. HPV refusal was programmatic, such as school absenteeism and lack of make-up vaccination chances, or due to experimentation fears, allergies, and being advised against vaccination.
PATH, et al. [29]	Peru -11	Peruvian HPV	5th grade girls, aged 9	School-based HPV	School-based HPV	>80% 3-dose HPV vaccination rate. Multi-dose vaccination

		vaccine pilot study.	years or older.	vaccination.	vaccination rate.	schedule requires co-ordination from education and health sectors. Health centers can be used for catch-up doses. Use consistent parental consent for all childhood vaccines.
Levin CE, et al. [30]	Peru -12	Fiscal analysis of Peruvian HPV vaccine pilot study [27, 28].	8,092 5th grade girls, aged 9 years or older, Piura region, involving 264 schools and 161 health centers, from which 12 facilities were selected for in-depth analysis.	Mixed-methods fiscal analysis of school-based HPV vaccination.	Delivery cost school-based adolescent HPV vaccination.	US$ 3.88 per dose, for 82.6% 3-dose HPV vaccination rate. Project start-up and recurrent personnel costs are largest portion of budget. HPV delivery cost can be reduced if delivery is combined with existing health services.
Abuelo CE, et al. [31]	Peru -13	Community-based CC screen, treat, and vaccinate program	Mothers and daughters/ grand-daughters, nieces, or female children of the community, aged 10-13 years.	Prospective cohort	Completion of 3-doses HPV vaccine. Treatment of HPV+ women. 6-month follow-up of treated HPV+ women	56% girls got 3-doses HPV vaccine. 86% girls got 2-doses HPV vaccine. 98% girls got 1-dose HPV vaccine. 81% HPV+ women were treated. 57% HPV+ women had 6-month follow-up. 99.7% were highly satisfied
Vicari A, et al. [32]	Context -3	HPV vaccination program planning.	-	-	-	CC incidence of 4,400, with 2,100 deaths annually in Peru. Plan vaccinate 287,000 girls aged 10 years annually.
Schilling A, et al. [33]	Peru -14	9vHPV with routinely scheduled pediatric vaccines	Boys and girl aged 11-15 years in Chile (*n* = 100), Colombia (*n* = 140), and Peru (*n* = 100).	Non-blinded, randomized, multicenter, comparative study with 1:1 gender and intervention stratification	Anti-HPV titers on day 1 and month 7. Antibody titers for diphtheria, Neisseria meningitidis, pertussis, and tetanus on day 1, month 1, and month 7 for intervention,	Equivalent antibody titers when 9vHPV was given with MCV4 and Tdap, or when 9vHPV was given 1 month prior to MCV4 and Tdap.

					or month 1, month 2, and month 7 for controls.	
Andrus JK, et al. [34]	Context -4	LAC vaccine program financing.	-	-	-	(PAHO Revolving Fund. PAHO technical advisory group. HPV vaccine cost in Mexico).
Goldie SJ, et al. [35]	Context -5	LAC CC prevention simulation. GAVI eligible nations	Population, country, and region specific data. HPV 16/18 CC prevalence – in Bolivia 39%, in Chile 69%,	Individual-based stochastic model	CC reduction, ICER, YLS	CC screening at ages 35, 40, and 45, and vaccinating 70% girls aged 9-12 years, costs US$360 per girl: In Chile – 60% CC reduction at US$ 3,400 ICER/YLS. In Colombia – 67.1% CC reduction, at US$ 3,170 ICER/YLS. In Peru – 55% CC reduction, at US$ 7,070 ICER/YLS.
Lowy DR, Schiller JT [36]	Context -6	Prevention HPV-related cancers.	Early global HPV vaccination programs' theoretical and actual effectiveness	Review article.	-	Recommend HPV vaccination programs simultaneously for adult women and adolescent girls.

Table 1: Selected Articles on Human Papilloma Virus and Human Papilloma Virus Vaccination.

Cost-effectiveness of HPV Vaccination Programs in the Andean Region

Cost per vaccinated person, and vaccine efficacy for reduction of CC and EGW incidence are major determinants of HPV vaccine cost-effectiveness [24]. HPV2 or HPV4 administered pre-coitarche may reduce CC by 65% in Central and South America [24]. The Pan American Health Organization (PAHO) has led HPV cost-effectiveness analysis workshops for all LAC [9].

One of 5 blinded, placebo-controlled 3-dose international clinical trials of HPV4 included 725 female Colombians and 393 female Peruvians aged 9-24-years-old who received HPV4 [1]. Placebo adjuvant aluminum vaccine was received by 637 female Colombians and 374 female Peruvians [1]. At 7 months post vaccination series, the per protocol efficacy population (PPE) achieved 92.8% efficacy against cervical intraepithelial neoplasia grade 1 (CIN1) or worse, 95.3% efficacy against cervical intraepithelial neoplasia grade 2 (CIN2) or worse, 92.5% efficacy against CIN3, and 100% efficacy against EGW [1]. Forty-three Colombians out of 6,004 total participants received HPV-16 monovalent vaccine. Pain, swelling, and erythema were the three most common adverse events [1,9].

While HPV2 and HPV4 have similar efficacy for HPV-16 and -18 etiologic CC and CIN1-3, HPV2 has twice the effectiveness of HPV4 against other HPV-type etiologic CC and CIN1-3 [15]. As HPV-18 occurs in only 2.8% of female Ecuadorian HPV-positive specimens, and HPV-6, -11, 16 and -18 occur .52-.67 times less often in Colombia than in the United States, HPV2 with double the non-HPV-16 and -18

effectiveness, may be more cost-effective in Colombia and Ecuador than HPV4 [25,26].

Mathematical Cost-Effectiveness Models

The Chilean National Health System Universal Access with Explicit Guarantees Plan (AUGE) ensures treatment of cervical cancer [27]. Using a $210 overall cost of HPV vaccination (or $70 per dose in 2006 U.S.$), which is less than the Chilean per capita GDP of $8,865, the undiscounted cost of HPV vaccination for one birth cohort of 12-years-old Chilean females would be $21 million. When applied to Peru, this model gives an undiscounted HPV vaccination cost for one birth cohort of $45 million [27]. In Chile, the projected incremental cost-utility ratio (ICUR)/incremental cost-effectiveness ratio (ICER) per quality-adjusted life years (QALY) for HPV2:HPV4 is 1:4.7 (116:541) and for life-years saved (LYS) 1:4.9 (147:726) [15]. Therefore, in Chile, HPV2 would be the economically expedient HPV vaccine choice for addition to the existing CC screening program [14]. However, in Colombia, where 37-61% of women age 18-25 years has annual CC screening, HPV4 is cost-effective at US$ 49 or less per dose, whereas HPV2 must cost $2 less [10]. Modeling with HPV9 may yield a different outcome given intentional coverage of five additional HPV types.

Pre-coitarche HPV2 vaccination of 82% of Peruvian females would reduce the lifetime risk of cervical cancer by more than 50%, preventing 5,500 cases of cervical cancer, saving over 80,000 life years for one birth cohort [17]. At US$ 5 - 20 per dose, annual HPV vaccination would cost $5 million-$16 million, or from less than $300-$1,300 per year of life saved (YLS), which is less than the 2005 Peruvian per capita GDP of $2,852 in 2009 US$ [17].

School-based HPV Vaccination Programs

Two Bolivian non-governmental organizations (NGOs) successfully applied for donated HPV4 from the Gardasil Access Program (GAP) from 2009 to 2011 [7]. All other support for GAP approved programs comes from the applying nation [7]. The 2009 Bolivian program covered 57 schools, targeting 3,480 9- to 13-years-old females, but achieved 107.4% program coverage by prolonging the vaccination period by two weeks to include unintended school sites, vaccinating 3,739 females at a 96.1% three-dose vaccination rate [7]. The 2010 Bolivian program was both clinic- and school-based, with 258 sites, targeting 30,900 9- to 13-years-old females, achieving 89.3% program coverage, by vaccinating 27,597 females with a 96.2% three-dose vaccination rate [7]. For successful school-based vaccination programs GAP recommends advanced coordination and logistical support, and planned completion of vaccination within the academic year limiting loss to follow-up [7]. Mixed clinic- and school-based vaccination programs are better able to vaccinate persons absent from school on vaccination days, but require greater coordination and logistic support, and more cold chain capacity than do solely school-based vaccination programs [7].

Peru undertook a pilot study of HPV vaccination of fifth grade females 9-years or older with the Program for Appropriate Technology in Health (PATH) in 2007. PATH, working within World Health Organization (WHO) guidelines, selected school based outreach for the Expanded Program on Immunization (EPI) delivery of HPV vaccination in Peru. This was a donated HPV4 school-based vaccination program targeting 8,092 females attending 527 schools and 105 health centers in the Piura region of northwestern Peru in 2008 [12,28]. Peru simultaneously promoted HepBV for 2-11-years-old children, and upgraded the cold chain [12].

Cascade training of vaccination program staff included effective communication [12]. Regional planning meetings were held [12]. Radio stations, television, and the print media concurrently advertised each of the three doses of the HPV4 vaccination [13]. Program success depended on health system capacity comprising personnel, physical structures, cold chain, immunization supplies, training, and reporting, without negatively affecting existing vaccination programs [12]. In part due to single dose vial HPV packaging, cold chain capacity was to be increased by up to 103% in Ayacucho, 117% in Piura, and 167% Ucayali [8]. 82.6% of eligible females were vaccinated (95% CI 79.3-85.6), with 95% of vaccinations being school-based [12,13,28]. Support of educators accounted for 100% vaccination rates in some schools [29]. In other schools where educators were uninvolved vaccination rates could be as low as 50% [29]. As the consenting process for HPV was different than for HepBV some parents questioned the program legitimacy [29].

However, school-based outreach can cost more than twice health-center based or integrated outreach [30]. The lowest delivery cost per dose of HPV vaccine was

$1.44 for Ugandan integrated outreach, contrasted with $3.88 for Peruvian school based outreach [30]. Integrated outreach costs are dependent upon existing program capacity especially for storage and transportation, and simultaneous introduction of other new vaccines [30].

PATH estimates that HPV vaccine introduction costs 5-13% of a national immunization budget, which may be greater than currently provisioned for EPI vaccines. Other program limitations are difficulties tracking receipt of all vaccination doses per person, training cost and time, logistics and expense of vaccination at isolated schools or in homes when doses were missed at school [12]. Following the success of this school-based program, in April 2011 HPV was included in the Peruvian national vaccination schedule [12,28].

Health Center-Based HPV Vaccination Programs

The Peru CC prevention study (PERCAPS) intended for mothers and daughters, comprised of self-sampling for HPV, and treatment of HPV with cryotherapy for 30- to 45-years-old mothers accompanied by 10- to 14-years-old daughters who received three doses of HPV4 in Manchay (a shanty town outside Lima) and in the Iquitos region of Peru (Table 2) [6].

Trial Variables	Manchay [5]	Iquitos Region [21]
30- to 45-years old mothers, grandmothers, aunts		
Recruited	323	320
Submitted HPV specimen	312	320
High risk HPV positive	31	37
High risk HPV negative	281	283
High risk HPV prevalence rate	9.9%	11.5%
Received cryotherapy	29	28
Received cervical biopsy	0	2
Adherent with 6-month follow-up	26	16
High risk HPV initial treatment rate	93.5%	81.1%
10- to 14-years old female relatives		
Recruited	352	318
Initiated HPV vaccination (trial- or school-based)	332	309
Received two doses of HPV (trial- or school-based)	323	282
Completed three doses of HPV (trial- or school-based)	300	200
Declined	22	4
Pregnant	0	4
Absent	?	22
Inaccessible	?	14
Not located	4	32
Moved outside area	2	32
Initiators' 3-dose completion rate	90.4%	64.7%
Responding participant willingness to participate in a future study	96.4%	99.7%

Table 2: Comparison of Peru cervical cancer screening study (PERCAPS) trials at Manchay, Peru and the Iquitos region, Peru.

Data tabulated from text of [6,22].

In Manchay trial PERCAPS achieved a 90.6% three dose HPV4 vaccination rate [6]. The second HPV4 dose arrived onsite one month late by which time some study subjects were lost to follow-up [6]. At completion 96.4% of PERCAPS subjects were willing to participate in another study [6]. School-based vaccination was suggested to reduce logistical loss to follow-up from cold chain and other supply issues including delayed vaccine delivery [6]. In the Iquitos region rural and urban trial of clinic-based HPV4 (and school-based HPV2) vaccination, a 64.7% three dose vaccination rate was achieved [31]. The lower completion rate was attributed to flooding of roads and bridges, impaired travel, delayed vaccine delivery, and loss of 64 subjects to follow-up [31].

Tools to improve HPV Vaccination Program Implementation

In Chile, Colombia, and Peru public health insurance can be a mechanism for HPV vaccination. Bolivia's and Ecuador's public health systems could consider HPV vaccination as part of system modernizations. Increased public awareness of HPV-associated diseases and the prevention thereof by HPV vaccination through health promotion advocacy programs can improve public reception of HPV vaccination programs [8]. HPV2 vaccination of 82% of one birth cohort of Peruvian females would reduce the lifetime risk of cervical cancer by more than 50%, preventing 5,500 cases of cervical cancer, saving about 2,625 lives [17]. In 2011 the Peruvian Ministry of Health planned to purchase HPV2 for the national vaccination program targeting sequential birth cohorts of 10-years-old females at one-quarter the market price via the PAHO Revolving Fund [32].

Means for Improving HPV Vaccination Rates

Immunization encounter reduction by simultaneous administration of HPV vaccine with either influenza vaccine or with tetanus, diphtheria, acellular pertussis vaccine (Tdap) and meningococcal vaccine (MCV4) eases the logistics of HPV vaccination program implementation while potentially increasing first and second dose HPV vaccine administration rates [33]. Co-administration of HPV9 vaccine, Tdap, and MCV4 achieves equivalent immunogenicity as separate vaccination schedules, with a statistically significant increase in injection site swelling, $p = 0.007$ [33].

None of the Andean region countries are currently eligible for support from the Global Alliance for Vaccines and Immunizations (GAVI), which works with the United Nations Children's Fund (UNICEF), the WHO, the World Bank, and other organizations to assist in vaccination delivery in developing countries. The HPV4 vaccine is prequalified by the WHO and available to GAVI at $5 per dose [28]. This price is less than both the $34 per dose cost negotiated by Mexico, and the $120 per dose price in the USA [34]. At $5 per dose, translating to $25 per vaccinated person, HPV vaccination cost is equivalent to other vaccination series and is also less than per capita GDP for all LAC, making further cost-effectiveness redundant [34]. HPV vaccination is further subsidized by GAVI in the most economically disadvantaged nations [35,36]. Boliva, a low-income country, was previously the only Andean nation qualified for GAVI new vaccine program introduction [9]. Chile is a middle-income country and would not normally qualify for GAVI, which supports the perceived need for Chilean cost-effectiveness studies prior to HPV vaccination program implementation [23,27].

HPV vaccine is also available for $10-15 per dose via the PAHO Revolving Fund of the WHO established in 1977 for LMIC LAC [30,34]. Due to PAHO Revolving Fund $40 million working capital LMIC LAC may prepay or reimburse PAHO within 60 days of receipt of vaccine [34]. Of note, PAHO adopted a Regional Strategy and Plan of Action for Cervical Cancer Prevention and Control, within the ProVac Initiative in 2008 [8]. ProVac allows for rapid start HPV vaccination programs [8]. Since 2004 ProVac has worked to improve LAC public health infrastructure, assure availability of appropriate data and analysis thereof for policy formation, promote new vaccination implementation programs, and foster partnerships for attainment of health care goals [9]. Peru has ordered 600,000 doses of HPV vaccine from PAHO [17]. The Peruvian immunization budget was increased by 500% from 2006 to 2010 for the 2011 launch of HPV vaccination [30].

Discussion

Comparative study of national vaccination programs or mathematical models thereof would be facilitated if identical types of data were published. For instance, some authors use discounted and undiscounted costs, total quality-adjusted life years, QALYs gained, and incremental cost-effectiveness ratio (ICER) per QALY gained, whereas other authors use cost per YLS or YLL [17,27]. Given differing efficacy against non-HPV 16/18 genotypes, in

Colombia and Ecuador, and other nations with comparatively low HPV 18 prevalence, HPV2 and HPV9 may be more cost-effective than HPV4 [15].

Given documented pregnancies at 10-years-old, it is recommended that national guidelines permit initiation of HPV vaccination at 9-years-old, which is consistent with manufacturers' guidelines [31]. Many LAC and LMIC are in regions with drastic seasonal climate and other geophysical variables (earthquake, tornado, monsoon). To preclude interruption of vaccination programs by uncontrollable climate and geophysical variables, vaccination programs should be held in the most stable season. For instance, in Peru the goal should be to start annual vaccination drives simultaneously with the onset of the dry season. If all doses cannot be accommodated within one dry season, the plan should be to give the remaining dose(s) in the following year when the first dose is administered to the next birth cohort. Consideration of multidose vials may reduce demands on cold chain infrastructure.

Reduction of HPV background prevalence could be approached in a similar manner to elimination of rubella [9] First, attain high vaccination rates for male and female birth cohorts at 9-years-old, primarily via school based vaccination programs [9] Second, vaccinate those 10- to 26-years-old who were not vaccinated as part of a birth cohort. Third, improve secondary prevention screen and treat programs for cervical cancer that will also serve as vaccination program effectiveness surveillance.

Increasing HPV awareness via media campaigns and health care worker promotion emphasizing CC primary prevention, increasing the volume of trained community health workers (CHWs) and health leaders (HLs), coupled with increased cold chain capacity to preclude delays in vaccine delivery at administration sites form part of a health systems strengthening diagonal approach [14,28].

This requires collaboration with national Ministries of Health who may also participate in the PAHO Directing Council of Ministers of Health [9]. Consistent nationwide use of school-based or integrated clinic- and school-based programs requires collaboration with national Ministries of Education [9]. Funding for the above may be more available if Ministers of Finance are also involved [9]. Consistent consenting processes for all adolescent vaccines will promote the legitimacy of vaccination programs in the community [28]. Consenting may begin in the prior academic year so that signed consents are available at the start of the vaccination academic year [28].

Conclusion

Consistent with scientific literature, varied HPV vaccination cost-effectiveness study methodology precludes direct study comparison. Moreover, increasing acceptance of more affordable 2-dose instead of costlier 3-dose HPV vaccination schedules reduces the direct applicability of much of the existing HPV vaccination cost-effectiveness studies. Nonetheless, irrespective of whether a 2- or 3-dose HPV vaccination program is chosen, the framework for vaccination program implementation remains constant: Program maintenance costs should be reduced. Vaccination program models and supportive international agencies are in place to assist national vaccination program implementation. Political will driving the necessary policy enactment and cooperation between Ministries of Education, Health, and Finance, are crucial for successful implementation and maintenance of Andean nation HPV vaccination programs.

Conflicts of Interest

Potential conflicts of interest. O. B. Nwanodi has ownership of less than $5,000 common stock outside of mutual funds in GlaxoSmithKline (Brentford, United Kingdom) and Merck (Kenilworth, United States).

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