Vaccine 26S (2008) L88–L95

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

ICO Monograph Series on HPV and Cervical Cancer: Latin America and the Caribbean Regional Report

Integration of Human Papillomavirus Vaccination and Cervical Cancer Screening in Latin America and the Caribbean

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ARTICLE INFO

Keywords:
HPV
Vaccination
Latin America
Caribbean
Cervical cancer
Screening
HPV DNA testing

ABSTRACT

Despite substantial efforts to control cervical cancer by screening, most Latin American and Caribbean countries continue to experience incidence rates of this disease that are much higher than those of other Western countries. The implementation of universal human papillomavirus (HPV) vaccination for young adolescent women is the best prospect for changing this situation. Even though there are financial challenges to overcome to implement such a policy, there is broad political support in the region for adopting universal HPV vaccination. The costs of implementing this policy could be largely alleviated by changing cervical cancer control practices that rely on inefficient use of resources presently allocated to cytology screening. In view of the strong evidence base concerning cervical cancer prevention technologies in the region and the expected impact of vaccination on the performance of cytology, we propose a reformulation of cervical cancer screening policies to be based on HPV testing using validated methods followed by cytologic triage. This approach would serve as the central component of a system that plays the dual role of providing screening and surveillance as integrated and complementary activities sharing centralized resources and coordination.

1. Introduction

The recognition that infection with certain human papillomavirus (HPV) types is a necessary cause of cervical cancer has opened new fronts for the prevention of this disease. Primary prevention is now possible through immunization with highly efficacious prophylactic HPV vaccines and secondary prevention has gained momentum with the introduction of sensitive HPV DNA testing to improve traditional Papanicolaou (Pap) cytology screening programs. There has been strong endorsement by the Pan American Health Organization (PAHO) for the implementation of HPV vaccination in the Latin America and the Caribbean (LAC) region [1]. It is clear, however, that cervical cancer screening will have to continue after vaccination but as summarized in this chapter, screening programs in the region must be urgently revisited, not only from a structural and delivery standpoint but also from the perspective of the adequacy of the current testing paradigm of Pap cytology.

2. Burden of disease beyond statistics

The LAC regions include some of the highest risk areas for cervical cancer in the world. Haiti was listed in the GLOBOCAN 2002 compilation of cancer incidence as the highest recorded rate at 87.3 new cases per 100,000 women annually, age-adjusted to the world population standard of 1960 [2,3]. Ranges of age-adjusted incidence rates were 8.8–87.3 for the Caribbean, 21.6–52.4 for Central America, and 18.8–55.0 for South America (per 100,000 women annually) [2,3]. Bahamas, Puerto Rico (a USA protectorate), and Uruguay were the only three countries among the 28 represented in the LAC region that had rates lower than 20 per 100,000 women, a threshold that is frequently used to reveal higher risk areas worldwide in which cytology screening must be implemented or reassessed if already implemented. Expectedly, there is also a strong correlation between incidence and mortality rates for LAC countries.

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0264-410X/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2008.05.026

Screening has had less than the expected impact in reducing cervical cancer rates in most LAC countries despite substantial efforts and healthcare investments. As described elsewhere in this issue [4,5], reductions in morbidity and mortality have occurred in some countries but it is unknown the extent to which such reductions resulted from the actual impact of screening or from the decreased fertility rates following economic development, access to family planning services and education, and the empowerment of women in society. A screening program has been publicly funded in Mexico for over 20 years but with little impact on incidence and mortality rates. In Cuba, where a screening program has been in operation since 1968, there have been no downward trends in incidence or mortality. In Colombia, Brazil, Peru, and Venezuela mortality rates have remained stable and high. In El Salvador, cervical cancer mortality has increased in the 1996–2001 period [6].

Epidemiology statistics do not completely describe the direct and indirect burden of cervical cancer. An important caveat must be recognized when considering cervical cancer rates in the region. The average incidence for each country is estimated primarily on the basis of data that population-based cancer registries report to the International Agency for Research on Cancer (IARC). Registry coverage is incomplete or nonexistent in developing countries and, when available, it provides an over-representation of cancer occurrence in urban areas or large cities and capitals [2], which are more likely to have specialized cancer screening and care services. Because of the typical risk factor profile of cervical cancer, being more common in multiparous women in resource-poor regions and rural areas not reached by screening or by cancer registration, it is likely that the average incidence rates in many resource-poor countries in the LAC region [3] may underestimate their true cervical cancer burden [7]. This fact further underscores the importance of combined primary and secondary prevention efforts for the LAC region. If properly implemented they are likely to exert an impact that will reach beyond the burden of illness measured through official statistics.

Finally, one must also consider the importance of the potential years of life lost due to cervical cancer, which is relatively high compared with other neoplasms. The most recent PAHO mortality data indicated that 74,855 women had died from cervical cancer in 1996–2001 in 13 Latin American countries. Of these, 50,032 women were in the 25–64 years age range, which translated into more than 1.56 million years of potential life lost, due to their premature deaths [6]. Not uncommonly, women with cervical cancer die before the age of 45 years and they have a proportionally higher number of children than other women of the same age. The untoward public health and social consequences of the loss of these mothers are not captured by any health indicator and likely contribute to the high rates of marginalization of children and adolescents in the region.

Childhood immunizations have always been considered a high priority. Without dismissing the tangible potential impact of other vaccinations (e.g., rotavirus, currently considered for adoption in the LAC region), implementing HPV vaccination and appropriate screening programs must be considered in light of the fact that we will be protecting the mothers of infants who will be at risk for a variety of infectious diseases. Preventing their premature deaths will go a long way towards improving the health and the quality of life of LAC populations.

3. Adequacy of the health care infrastructure in the region and perceived deficiencies

Before considering the opportunities for an integrated system that combines primary (HPV vaccination) with secondary (screening) prevention for cervical cancer, we must examine the experience of LAC countries in deploying these two preventive approaches independently. While HPV vaccination is a novel technology yet to be tested for large-scale implementation, cervical cancer screening has existed for decades as a separate cancer control activity. Immunization practices have also had a long history in LAC countries. As independent disease prevention activities, however, cervical cancer screening and immunization against vaccine-preventable infectious diseases have had remarkably different track records in the LAC region. While the latter has been generally successful, screening has not reached its stated goal of reducing cervical cancer incidence to acceptable standards.

3.1. Status of cervical cancer screening

The Pap test is undoubtedly the first cancer screening test with the best record of accomplishments in contemporary medical practice. Pap test screening targets mainly the detection of cervical cancer precursors, thereby allowing close monitoring of equivocal or low-grade abnormalities on repeat tests or immediate referral for colposcopy, biopsy and treatment of high grade or more severe lesions. Preventing cervical cancer is thus accomplished by arresting neoplastic development within the cervical epithelium before it becomes invasive (i.e., when lesions break through the basement membrane and invade connective tissue, which worsens the prognosis considerably).

There are two types of cervical cancer screening programs: opportunistic and organized. Opportunistic screening is carried out by suggestion from a health care provider when a woman presents for consultation for reasons other than cervical disease. Organized screening requires a system with mechanisms to identify the target population and invite all of its members to participate. Treatment and management protocols must be in effect and facilities must exist with sustained quality control procedures to ensure the overall effectiveness of a programme. The World Health Organization (WHO) has established guidelines for organized cervical cancer screening [8,9]. There is consensus that organized screening is superior to opportunistic screening in terms of cost-effectiveness and equitable distribution of benefits to all women [9,10].

The history of implementing screening programmes in the LAC region is described elsewhere in this issue [5]. WHO and PAHO guidelines, augmented by local ministerial or professional initiatives, have been instrumental in the implementation of cytology-based screening programmes and clinical practices for frequency and coverage. A WHO survey conducted in 2001 assessed national capacities for cervical cancer prevention and control [6]. Strictly speaking, no LAC country has fulfilled all the criteria for a functional organized screening programme; Chile is perhaps the one coming closest to meeting this definition. In fairness, few countries in the world have succeeded at implementing a fully organized programme with an information system to permit universal invitation to screen and management of abnormalities. Scandinavian countries, the United Kingdom, and a few Canadian provinces serve as examples of efficient organized screening. Most of the industrialized world relies on opportunistic screening.

Coverage is used as an indicator of the potential impact of a screening programme, however, this statistic alone does not gauge the success of a screening program or is it the only variable to impact on cervical cancer morbidity in the region. As shown in Table 1 [6,11–16], nine LAC countries have attained coverage levels that are consistent with most women of screening age having received at least one smear in the past 12 months. For some countries (e.g., Jamaica, Nicaragua, and Trinidad and Tobago) coverage is much too low to have any impact. On the other hand, the levels of Pap smear coverage attained by many LAC countries are comparable with, if

Table 1
Cervical cancer screening coverage in selected countries in Latin America and the Caribbean and in Canada measured as the proportion of women reporting having had a Pap smear within the last 12 months

Country	Year	Coverage (%)
Brazil, Campinas	2001	79.4[a]
Brazil, Rio de Janeiro	2005	90.0[a]
Chile, Valdivia	1994	31.0
Chile, Valdivia	2003	79.0
Colombia	2005	50.6
Costa Rica	1986	70.5
Costa Rica	1993	66.9
Ecuador	1987	27.8
Ecuador	1994	72.2
El Salvador	1993	79.2
Guatemala	1987	76.0
Honduras	1996	55.4
Jamaica	1997	15.3
Mexico, Mexico City	1997	48.2
Mexico, Oaxaca	1997	22.5
Nicaragua	1992	61.1
Nicaragua	1998	20.5
Paraguay	1996	49.1
Peru	1996	42.9
Dominican Republic	1996	44.8
Trinidad & Tobago	1987	35.4
Canada (range for all 10 provinces)	1999	45.4–55.2

Sources of data: [6,11–16].
[a] Proportion reporting at least one smear in the last 3 years.

not higher than, those of Canada, a country that has a long-standing history of successful cervical cancer screening as part of universal healthcare practices, much like the experience of Scandinavian countries. Rates of cervical cancer in Canadian provinces are among the lowest in the Western world and are less than half that of the LAC country with the lowest cervical cancer incidence (Bahamas at 16.7 per 100,000) and less than one-tenth of the incidence in Haiti, the highest risk LAC country [2,3].

Coverage statistics based on self-reported use of Pap tests collected in population surveys are known to overestimate the outreach of a screening programme. Furthermore, assessment of screening coverage may reflect primarily the population segment that has access to health care because of ability to pay or availability of insurance (e.g., upper middle-class women in urban settings in LAC countries). These women also benefit from health promotion messages, family planning services and other conditions that would ultimately place them at a low-risk of cervical cancer (e.g., delayed childbearing because of the need to maintain a career could lead to nulliparity or low parity, conditions that are inversely associated with cervical cancer risk).

It is clear, therefore, that besides coverage other variables along the entire continuum of care are required for effective cervical cancer screening. Paramount among them are the quality of cytology services provided and proper treatment, management and follow-up of all patients with precancerous and cancerous cervical lesions. Few LAC countries have been able to implement the necessary comprehensive infrastructure to provide wide coverage with high quality diagnostic and treatment services that is sustainable enough to achieve the levels of reduction in cervical cancer burden that resource-rich countries have experienced.

Part of the reason for the perceived failure of screening programmes in the LAC region may stem from the limitations of Pap cytology. This screening tool is based on the subjective interpretation of morphologic alterations present in cervical samples that must be collected with proper attention to sampling cells of the transformation zone. Also, the highly repetitive nature of the work of screening smears leads to fatigue, which invariably causes errors in interpretation. The average sensitivity of Pap cytology to detect high-grade cervical intraepithelial neoplasia of grade 2 or worse (CIN2+) or invasive cervical cancer has been reported as 53% and its average specificity as 97%. In addition there is large heterogeneity in sensitivity from about 30% to 75% [17]. The most critical limitation, however, is the Pap test's high false-negative rate. The use of liquid-based cytology has improved the efficiency in sample processing but because liquid-based cytology has comparable sensitivity to the conventional Pap smear [18] the limitations of cytology remain the same.

To compensate for the low sensitivity of the Pap test, the common requirement for women entering screening with an initially negative smear is to repeat their tests at least twice over the next 2-3 years before they can be safely followed as part of an extended screening schedule. In reality, this stipulation is rarely relaxed by clinicians because of fear of missing lesions by cytology and thus the frequency of Pap screening typically remains as an annual schedule throughout life. HPV DNA testing in cervical cancer screening largely circumvents the above problems [17,19]. HPV DNA testing has very high sensitivity and robustness for large-scale implementation, in addition this method reduces the dependence on human interpretation. The application of this testing method could potentially lengthen the screening intervals and quality control procedures. This would result in more affordable and sustainable screening in LAC countries. These desirable features of HPV DNA testing form the central argument for our proposal, subsequently in this chapter, of an integrated surveillance system that combines vaccination with screening.

3.2. Status of immunization practices

Contrary to the modest progress achieved with cervical cancer screening in LAC countries, there has been a remarkably successful history of vaccination against childhood diseases in the region in spite of challenges. The WHO's Expanded Program on Immunization (EPI) was started in the late 1970s, in which vaccination coverage in most countries was less than 20% and systems for delivering immunization services were dysfunctional or even nonexistent in some countries. Vaccine supply was unstable and countries faced frequent stockouts. However, EPI addressed these difficulties using a concerted national and regional approach that was supported by high-level political commitment from all countries [20]. This approach also engaged strategies to ensure high-quality technical assistance as well as programmatic and financial sustainability. As a consequence, countries have attained very high levels of vaccination coverage (Table 2) for most common diseases preventable by immunization [21]. Consistent with the WHO's and PAHO's strategies of global immunization to reach the Millennium Development Goals, PAHO's Revolving Fund has been able to assist member countries with bulk purchase of new vaccines.

Vaccination coverage of children aged <3 years is reported as remarkably high (>90%) in the vast majority of LAC countries for three of the main childhood vaccines: polio, diphtheria-tetanus-pertussis (DTP), and measles-mumps-rubella (MMR) (Table 2), similar to the USA and Canada. Much progress has been made towards the elimination of rubella and congenital rubella syndrome; all LAC countries include MMR in their childhood schedules. Rubella vaccination campaigns targeting adolescents and adults have reached over 116 million people [21]. Rates of immunization coverage against *Haemophilus influenzae* type B and hepatitis type B have also been high. The initial challenge was to overcome the problems mentioned above, and then to sustain the effort. There are multiple obstacles to sustain high vaccination coverage, but a key one is complacency.

Should we be concerned that delivery of an adolescent HPV vaccine may fall short of the successful coverage statistics for childhood

Table 2
Immunization coverage (percentage of target population) for selected vaccines in countries in Latin America and the Caribbean[a]

LAC Region	Country	Polio[a] (<1 year of age)	DTP3[a] (<1 year of age)	MMR[a] (1 year of age)
South America	Argentina	92	91	97
	Bolivia	82	83	88
	Brazil	99	99	99
	Chile	94	94	91
	Ecuador	97	98	97
	Guyana	92	93	90
	Paraguay	85	85	88
	Peru	95	94	99
	Suriname	84	84	83
	Uruguay	95	95	94
	Venezuela	73	71	95
Central America	Belize	98	98	99
	Costa Rica	89	89	90
	El Salvador	96	96	98
	Guatemala	92	91	95
	Honduras	87	87	91
	Mexico	98	98	96
	Nicaragua	88	87	98
	Panama	98	99	94
Caribbean	Anguilla	93	99	93
	Aruba	NA	NA	NA
	Bahamas	94	95	88
	Cuba	99	89	96
	Dominica	96	95	99
	Grenada	91	91	99
	Haiti	75	80	66
	Jamaica	86	85	87
	Montserrat	99	99	99
	Netherlands Antilles	88	88	93
	Dominican Republic	88	89	99
	St.Kitts & Nevis	99	99	99
	St. Lucia	85	85	94
	St. Vincent & Grenadines	99	99	99
	Trinidad & Tobago	89	92	89

DTP: Diphtheria-tetanus-pertussis; MMR: Measles-mumps-rubella.
Adapted from [21].
For explanatory notes refer to original source.
[a] For third doses of DTP and polio, and for first dose of MMR vaccines.

immunizations that are sustained year to year? Thus far, there is no evidence to indicate that the technical, programmatic, and financial challenges overcome by EPI in LAC countries over the past 30 years and the daily performance necessary to sustain high coverage will not also be achievable by efforts to introduce HPV vaccination of adolescents. Thus far, the experience with vaccination campaigns in the LAC region that reached older age groups (e.g., hepatitis B, influenza, and rubella) has been as successful as the infant programs [21].

Yet, much work remains to be done; up to one-third of children in LAC countries live in municipalities or districts with low immunization coverage. PAHO aims at raising coverage rates above 95% in all countries. Moreover, the need to extend coverage to rotavirus and pneumococcal vaccines highlights the necessity of considering HPV vaccination in the context of other important public health priorities, without pitting one life-saving intervention against another [1]. These challenges notwithstanding, it seems that LAC countries will successfully implement universal HPV vaccination as already endorsed by PAHO member countries [1].

4. Status of regulatory approval and availability of HPV vaccines and HPV testing in LAC countries

4.1. HPV vaccination

The first prophylactic HPV vaccine (Gardasil®, Merck & Co., Inc., Whitehouse Station, NJ USA) to pass regulatory approval and reach the market in most LAC countries targets four HPV types: −6 and 11, which cause most cases of genital and oral condylomata, and −16 and 18, which are the two most important oncogenic types in terms of etiologic fraction in cervical cancer. A second vaccine (Cervarix™, GlaxoSmithKline Biologicals, Rixensart, Belgium), targets the latter two types only and has just recently become available in selected LAC countries. At the time this overview was written Gardasil® had been registered in all LAC countries except Venezuela, Bolivia and Guyana. Mexico was the first LAC country to approve it (June 1, 2006). Likewise, Cervarix™ had reached the same stage of approval and availability in Argentina, Chile, Colombia, Uruguay, and Mexico as of January 31, 2008. Manufacturers' local branches have begun to stockpile the vaccines, indicating that they are positioning themselves for more rapid uptake. The ministerial decisions concerning public implementation of universal HPV vaccination are yet to be taken. Where available, the two HPV vaccines have been delivered on an opportunistic basis as part of the healthcare provided by private paediatricians and general practitioners.

Through socio-cultural research and a health system capacity assessment undertaken in Peru, the Ministry of Health identified feasible delivery mechanisms for HPV vaccines that could reach a high proportion of young adolescent girls. In a study carried out in 2007 more than 2,100 girls in primary grade 5 were vaccinated with Gardasil® in selected schools in three regions. Acceptance and completion of the 3-dose series were high [22]. The national immunization program is expanding this initiative to other schools in one of the regions in 2008 and will use the experience to project the coverage and costs of such a program on a national scale.

PAHO ministers have recently agreed that universal HPV vaccination of young adolescent women should be made a priority in the LAC region [1]. To that end, the agency will include HPV vaccines in its Revolving Fund to assist with centralized procurement so as to reduce costs and emphasize equity in access to the benefit of all areas. To date, no country in the region has implemented an official policy of universal HPV vaccination but high-level consultations are ongoing both within countries and with PAHO.

4.2. HPV testing

The reader is referred to in-depth reviews of the evidence concerning HPV DNA testing as a cervical cancer screening tool [17,19,23,24]. In brief, HPV DNA testing is the most promising among all the new technologies considered for this purpose, but at present, financial considerations related to the cost of testing and available healthcare infrastructure have prevented its wide-scale implementation as part of screening programmes. On the other hand, substantial experience is available since the LAC region has played a key role in conducting prominent studies concerning the applicability of this technology in cervical cancer screening.

Few countries in the LAC region have in place regulatory approval processes for diagnostics. HPV DNA testing is available from two manufacturers: Qiagen Gaithersburg, Inc., MD, USA (previously Digene Corp.) and Roche Molecular Systems Inc., Branchburg, NJ, USA. Qiagen commercializes the Hybrid Capture® 2 (HC2) test, the most extensively clinically validated HPV DNA test and the only one to obtain regulatory approval from the FDA for two clinical applications (triage of equivocal smears and screening in conjunction with cytology). Roche commercializes the AMPLICOR® and Linear Array® systems; the former is a probe-cocktail test for oncogenic HPV types (comparable to HC2 except for the type of assay) and the latter is for HPV typing [23]. A few countries in the region have begun to formulate policies concerning implementation of this technology for two main uses: triage of equivocal Pap smears and primary screening (the latter as an adjunct test to Pap cytology). Mexico and Colombia are probably the countries that have gone the farthest in terms of Ministerial policies that attempt to regulate and implement use of HPV testing. In other countries (e.g., Argentina, Barbados, Brazil, Costa Rica, Dominican Republic, El Salvador, Guatemala, Nicaragua, Panama, Peru, Trinidad and Tobago, and Venezuela), HPV testing has been used as opportunistic triage or screening tool, but only as a reflection of the local preference by general practitioners and gynaecologists. There are no reliable statistics for the "penetrance" of HPV testing in LAC countries but market data from manufacturers indicate that availability of HPV testing is increasing as a result of the growing body of evidence in favour of this technology.

5. Proposal for integrated vaccination and screening programs

A strategy that fulfills the dual mission of primary and secondary cervical cancer prevention encompasses the following arguments: 1) HPV vaccination is more effective and equitable when deployed as universal policy; 2) over time, HPV vaccination will have a negative impact on the performance of cytology, thus further straining the credibility of this test if it continues to be the cancer screening paradigm in the LAC region; 3) HPV DNA testing has the performance characteristics that make it a more efficacious and robust primary screening test than cytology, especially in the post-vaccination era; and 4) a new paradigm of HPV testing followed by cytologic triage would fulfill the role of a screening approach while also serving as a surveillance system to monitor the effectiveness of HPV vaccination. Such an integrated approach could also permit more realistic implementation of screening as universal policy thus circumventing today's problems of low and inequitable coverage.

5.1. Importance of universal HPV vaccination

The challenges of HPV vaccine implementation in LAC countries are primarily financial. Lack of political will is likely to last for as long as the cost of HPV vaccination remains at current levels (i.e., 10- to 20-fold higher than what is affordable by these countries' healthcare budgets). The cruel logic that stems from having to defer policy decisions due to the high costs of vaccination is that this may increase the existing socio-economic inequity in cervical cancer burden in the region. Without a publicly-funded programme, HPV vaccination may initially exist only as an opportunistic, fee-based health service available privately. Women targeted by commercial vaccine promotion messages already afford health care and the benefits of having annual Pap smears. These women have a low-risk to develop cervical cancer because they are diligent clients of screening offered to them on an opportunistic basis by their physicians. While they are not candidates for vaccination because of their age, they will learn that their daughters can benefit from receiving it. Like their mothers, however, these young women, even without vaccination, would not be at high-risk for cervical cancer later in life because they would probably become clients of the intensive, elitist screening that benefited their mothers. On the other hand, women without access to health promotion who cannot afford private health care and thus have to depend on the public system (which has low quality, inconsistent, or nonexistent screening) are not being screened adequately or at all. Without a public programme, they will not learn about HPV vaccines and thus their daughters will not be offered vaccination. "Like mothers, like daughters. . ."; the latter, unvaccinated and unprotected by screening, may sadly end up contributing to the cruel statistics of cervical cancer 10–20 years later, like their mothers do today. Therefore, it is plausible to assume that increased inequity in cervical cancer risk may follow HPV vaccination that is exclusively opportunistic. Publicly-funded HPV vaccination will prevent this from occurring but will not come without substantially straining LAC countries' healthcare budgets. The solution is to redirect some of the resources, presently wasted in inefficient screening, to vaccination and to seek more favourable prices through negotiated large purchases.

5.2. Expected impact of HPV vaccination on cytology screening practices

As the successive cohorts of vaccinated young women reach screening age, the reduction in cervical lesions will lead to a decrease in rates of colposcopic referral to about 40%–60% or less of the existing case loads in most Western countries, judging from attributable proportion estimates [25] and preliminary findings from the vaccination trials [26]. Such reductions are likely to translate into initial savings to the health care system or to individuals but the vaccine-induced decrease in cervical lesions will lead to a degradation of performance characteristics of Pap cytology (because of a decreased expectation of abnormalities on a day's smear workload) with consequent concerns related to the need for heightened quality assurance. The positive predictive value (PPV) of Pap cytology will decline paralleling high vaccine uptake because clinically relevant lesions will become less common. This will lead to a decline in the performance of cytology because of a decrease in the signal (squamous abnormalities) to noise (inflammation and reactive atypias) ratio that characterizes the subjective and tedious work of reading and interpreting smears. In other words, a low lesion rate will lead to losses in sensitivity by causing

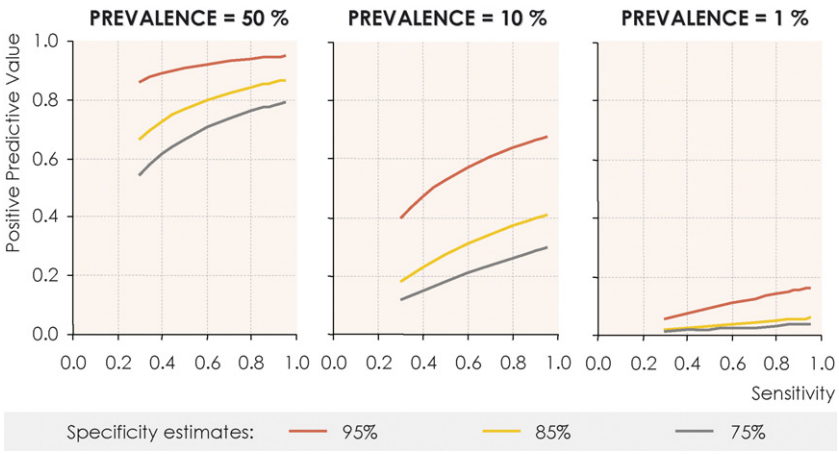

Fig. 1. Expected impact of the reduction in disease prevalence induced by HPV vaccination on the screening performance of Pap cytology.
The graphs show the joint influence of changes in sensitivity, specificity and lesion prevalence on the positive predictive value (PPV) of Pap cytology.
The three curves in each graph represent different specificity estimates: red: 95%, yellow: 85% and grey: 75%. The combinations of lesion prevalence reflect hypothetical Pap cytology screening conditions in different settings and post-vaccination. In unscreened or high-risk populations prevalence of cervical lesions of any grade is around 10% (middle graph). Post-vaccination lesion rates may be as low as 1% (third graph). The 50% prevalence graph (first graph) is a scenario to represent the situation expected in Pap smear triage, following an initially screen positive HPV test. As lesion prevalence decreases due to vaccination the PPV will decrease even for equivalent conditions of sensitivity and specificity. However, to compound the problem there may be losses in sensitivity (shifting estimates from right to left in the x axis) and in specificity (shifting estimates from the red to the grey curve). It can be seen that cytology will have its highest PPV and thus greatest clinical utility if lesion prevalence can be maintained at a high level, a situation that is artificially created if women are screened first with the HPV test and then triaged by cytology.
Adapted from [27] Copyright 2006, with permission from Elsevier.

a decrease in familiarity for recognizing abnormal cells as well as specificity, because fear of missing disease leads to more overcalls of benign abnormalities [27]. Fig. 1 illustrates the impact of combined changes in lesion prevalence and Pap performance on the PPV of cytology screening.

The above reductions in case loads will be a function primarily of two factors: 1) the overall uptake of HPV vaccination by the successive cohorts of adolescents and young women targeted by vaccination; and 2) the time it will take for protected women to reach the age when they become eligible for screening [27]. Vaccinated adolescents will reach the recommended age of cervical cancer screening within three years after the onset of sexual activity, as is commonly practiced. Therefore, the impact on screening and management case loads will be initially minimal for women vaccinated between the ages of 10 and 18 years.

Even with high HPV vaccination uptake, a statistically noticeable reduction in cervical cancer incidence is unlikely to be observed for at least 10–20 years because vaccination below age 20 will take some time for the averted high-grade cervical intraepithelial neoplasia (CIN) lesions to have had the time to progress to invasive cancer. A paradoxical situation may arise if high vaccine uptake occurs primarily among women who will eventually be adherent with screening recommendations (i.e., if publicly-funded HPV vaccination is deferred for many years). If adolescents and young women who are more likely to be vaccinated are also more likely to attend screening, the reduction in cervical lesions will be seen nearly exclusively among such women. On the other hand, unvaccinated women may be less likely to be screened and their undetected precancerous lesions will progress until invasion occurs, when the overt symptoms will then prompt the need for diagnosis [27].

5.3. *The "HPV testing followed by Pap triage" paradigm*

In light of the pitfalls of existing cervical cancer screening programmes in LAC countries and the promise of alternative screening technologies, we propose a strategy for a re-formulated screening approach that serves the additional role of a mechanism for post-vaccination surveillance. The overriding concern is how to achieve a cost-effective policy that implements universal pre-exposure HPV vaccination and reformulates screening practices to make them more efficient in detecting the cervical precancerous lesions that may occur in women who were not vaccinated and in those who were vaccinated but were not protected (e.g., vaccine failures and lesions caused by HPV types other than 16 and 18) as soon as they enter screening age and must thus be monitored. Integration of vaccination and screening databases is necessary to achieve synergy between primary and secondary prevention and to monitor long-term vaccine protection. Fig. 2 shows the potential synergy to be derived by employing shared public health resources and infrastructures in combining surveillance activities needed for monitoring HPV vaccine effectiveness and screening for cervical cancer.

As documented elsewhere [17,19,24], testing for oncogenic HPV DNA has been shown to circumvent the high false-negative rate of Pap cytology in detecting cervical pre-cancer. The perceived downside is its relatively higher positivity rate compared with cytology, since it detects viral infection in cervical cells before they begin to show abnormalities recognizable on cytology. Cytologic triage of such HPV-positive women on screening will reveal the ones that should undergo colposcopic examination and biopsy and will largely obviate the concerns related to false-positives. With the improved sensitivity to detect existing lesions and the more "upstream" focus on cervical carcinogenesis this strategy could be implemented via longer screening intervals than are currently possible with cytology alone, and thus be cost-saving. The "HPV testing followed by Pap triage" screening model has gained favour in recent years as a more cogent approach that may become cost-effective once HPV testing is deployed as a screening tool and is no longer seen as a niche market for triaging equivocal or mild abnormalities [27–29]. However, it is in the post-vaccination era when the cohorts of women vaccinated in their teens enter screening age that this approach may prove most valuable by permitting a surveillance system that can serve two roles simultaneously: monitoring duration of vaccine protection (with HPV typing for those who are positive) and screening for cervical cancer [27,29].

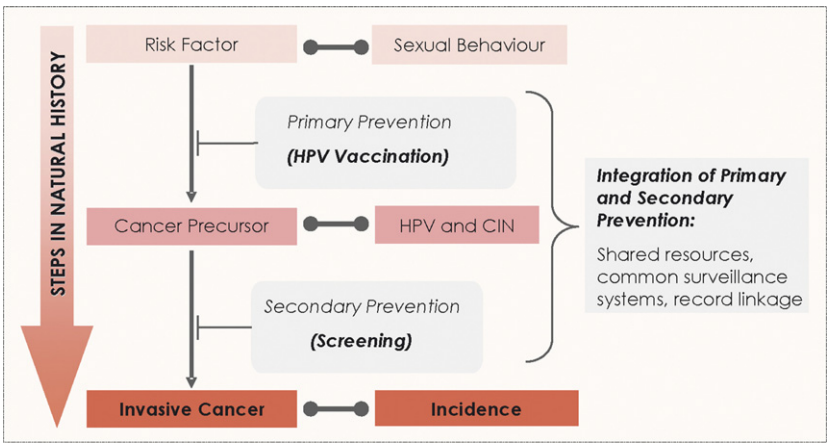

Fig. 2. Opportunities for primary (HPV vaccination) and secondary (screening) cancer control interventions to interrupt the progression of the natural history of cervical cancer.
Surveillance of the effectiveness of the primary prevention strategy implies continued monitoring for the occurrence of cervical HPV infection in vaccinated women. Screening for cervical cancer precursors (cervical intraepithelial neoplasia (CIN) will continue to be necessary as secondary prevention strategy but the existing cytology screening paradigm does not permit an early monitoring system for virological endpoints following vaccination and is likely to have degraded performance under low lesion prevalence conditions. HPV testing as the primary cervical cancer screening tool has the advantage of permitting post-vaccination surveillance via record linkage of screening and vaccination registries, thus allowing an efficient and low-cost strategy to monitor long-term protection among vaccinated women while providing a cervical cancer screening service to the population.

Simply making cytology screening less frequent may not be a viable strategy to achieve a cost-effective combination of vaccination and screening in light of the aforementioned potential problems that may plague Pap cytology performance in conditions of low lesion prevalence (illustrated in Fig. 1). Although the "quantitative" effect shown in Fig. 1 will also negatively affect the PPV of HPV testing, the latter is unlikely to be affected by the "qualitative" effects on sensitivity and specificity due to readers' lack of experience in identifying true lesions. HPV testing has the screening performance characteristics that would make it an ideal primary cervical cancer screening test in such conditions. Pap cytology should be reserved for triage settings, i.e., in assisting management of HPV positive cases because it is more likely to perform with sufficient accuracy in conditions in which lesion prevalence is high, a situation that is artificially created when the workload includes only smears from women harbouring HPV infection (Fig. 1) [27,29]. Placing such a high clinical value on cytology by restricting it to a more diagnostic role in triage will also help protect its credibility as an important cervical cancer control tool. In LAC countries, this approach will also help maintain the niche of professional expertise in cytopathology with ongoing training and maintenance of quality control activities.

As a bonus, another key advantage of using HPV testing as the primary screening tool in prevention programs is the opportunity to create HPV infection registries with the provision to link test results from the same women over time. This strategy would permit an efficient and low-cost strategy to monitor long-term protection among vaccinated women, particularly after the advent of low-cost HPV typing in the future [27,29].

5.4. Economies of scale and market forces may lower costs of HPV testing in screening

At present, the main obstacle for the adoption of the above policy is the high cost of HPV testing. The fact that the market is dominated by only one or two manufacturers of clinically approved HPV assays is certainly a deterrent for achieving lower prices for HPV testing. Another problem comes from the current practice guidelines which at most approve HPV testing for the triage of equivocal abnormalities, an admittedly restricted niche market that represents at most 5% of the total population being screened. It is expected that once HPV testing is deployed in the high volume of primary screening there will be a reduction in the cost of individual tests because of the market expansion following an economy of scale. Low-cost, rapid HPV tests with acceptable performance may also become a reality in the near future [19,23]. Governments and non-government organizations may be able to negotiate with the manufacturers for lower prices conditional on high-volume purchasing, much like the central procurement programs for bulk vaccine purchases. Furthermore, a change in market potential from simple triage to wide-scale primary screening will inevitably bring other biotechnology companies to compete by having their own molecular HPV tests undergoing validation and regulatory approval. Taken together, the combination of shifting trends in screening practices, economies of scale, and perception of new market opportunities for companies will further contribute to a reduction in the overall cost of the "HPV followed by Pap" screening approach. The potential already exists for the unit cost of a validated HPV test to be eventually set a lower level than that of Pap cytology.

6. Conclusions

A disproportionately high burden of cervical cancer consequent to the failure of multiple components of cervical cancer screening makes the case for universal HPV vaccination of young adolescent women a priority for the LAC region. We argued that implementation of the latter requires a critical rethinking of existing cervical cancer control policies to correct the historical shortcomings of cytology screening and to take advantage of the opportunity to adopt a strategy that synergistically combines primary (HPV vaccination) and secondary (screening) activities as mutually complementary activities with shared resources and central coordination for maximal cost-effectiveness. In our view, the central piece of a surveillance system that fulfills these two roles is the adoption of HPV testing as a primary screening test followed by triage with Pap cytology. This strategy has the added benefit of providing epidemiological surveillance of vaccinated populations. Demonstration projects should be implemented to test the effectiveness, feasibility, and long-term sustainability of this approach

in areas that are selected for early implementation of universal HPV vaccination.

Disclosed potential conflicts of interest

EF: Advisory Board (GenProbe Inc., GlaxoSmithKline, Roche); Research Grants (Merck & Co., Inc).

AH: Research Grants (GlaxoSmithKline).

NM: Advisory Board (Merck & Co., Inc. and Sanofi-Pasteur MSD); Speakers Bureau (Sanofi-Pasteur MSD); Steering Committee (Merck & Co., Inc.).

Acknowledgements

The authors are indebted to Irma Alfaro (Qiagen) and Kathleen Menzel (Roche) for market and regulatory information on HPV tests, and to Hugues Bogaerts and Dirk Campens (GlaxoSmithKline Biologicals) and James Mansi (Merck & Co.) for the same information on HPV vaccines in LAC countries.

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