Cervical Cancer Screening Programs in Latin America and the Caribbean

Raul Murillo[a,*], Maribel Almonte[b,c], Ana Pereira[b,d], Elena Ferrer[e], Oscar A. Gamboa[a], José Jerónimo[f,g], Eduardo Lazcano-Ponce[h]

[a] *Division of Research and Public Health, Instituto Nacional de Cancerología de Colombia, Bogotá, Colombia*
[b] *Non-communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom*
[c] *Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, London, United Kingdom*
[d] *School of Public Health, Faculty of Medicine, University of Chile, Chile*
[e] *Unit of Infections and Cancer (UNIC), Cancer Epidemiology Research Program (CERP), Institut Català d'Oncologia – Catalan Institute of Oncology (ICO), L'Hospitalet de Llobregat, Barcelona, Spain*
[f] *Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA*
[g] *PATH, Seattle, WA, USA*
[h] *Centre for Population Health Research, National Institute of Public Health, Cuernavaca, Mexico*

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A B S T R A C T

Latin America and the Caribbean (LAC) have a significant burden of cervical cancer. Prophylactic human papillomavirus (HPV) vaccines are an opportunity for primary prevention and new screening methods, such as new HPV DNA testing, are promising alternatives to cytology screening that should be analyzed in the context of regional preventive programs. Cytology-based screening programs have not fulfilled their expectations and coverage does not sufficiently explain the lack of impact on screening in LAC. While improved evaluation of screening programs is necessary to increase the impact of screening on the reduction of incidence and mortality, other programmatic aspects will need to be addressed such as follow-up of positive tests and quality control. The implementation of new technologies might enhance screening performance and reduce mortality in the region. The characteristics, performance and impact of cervical cancer screening programs in LAC are reviewed in this article.

1. Introduction

Latin America and the Caribbean (LAC) continue to bear an important burden of cervical cancer. Numerous countries in the region have attempted to implement cytology-based screening programs but without success. While the lack of impact is frequently attributed to problems associated with program performance, new screening technology and prophylactic human papillomavirus (HPV) vaccines emerge as promising alternatives for cervical cancer control. Nevertheless, to ensure success of these technological advances, public health programs will still need to be organized and structured to maximize the benefits that could be obtained with the adoption and implementation of novel methods to control cervical cancer. To that end, comprehensive analyses based upon previous regional experience with cervical cancer preventive programs will be of use.

The purpose of this paper is to review available information on basic characteristics and performance of cervical cancer screening programs in LAC.

A search in MEDLINE® (Medical Literature Analysis and Retrieval System Online) and LILACS® (Latin American and Caribbean Health Sciences Literature) databases was carried out, in addition to cross-referencing. National health and household surveys, as well as governmental reports on the performance of cytology coverage were also reviewed. Results from specific interventions to improve screening programs were excluded. Scientific papers aimed at evaluating coverage, cytology quality and follow-up of positive screening results were included only if they corresponded to reports from regular screening programs (Table 1). Specific inclusion criteria for every indicator on program performance are detailed in the corresponding tables.

In order to examine the impact of screening in the region, further analyses on the relation of performance indicators and cervical cancer mortality were done. The relation between population coverage with cytology (national data) and the reduction of age-standardized cervical cancer mortality rates in the ten-year period prior to the coverage report was examined for all countries with relevant data.

* Corresponding author. Tel.: +57 1 3341360; fax: +57 1 3341360.
E-mail address: rmurillo@cancer.gov.co (R. Murillo).

Table 1
Compendium of selected references in the review of cytology-based programs in Latin America and the Caribbean: cervical cancer screening policies, cytology coverage, quality of cytology and follow-up of positive screening results

Code	Reference
References from Table 2. ***Cervical cancer screening policies.***	
a1	Gamarra JG *et al.*, Rev Saude Publica 2005;39:270–76.
a2	Ministerio de Salud de la República Argentina. Subprograma de Detección Precoz de Cáncer de Cuello Uterino. Resolución Ministerial No. 480/98. Buenos Aires. 1998.
a3	Rocco DR. Mortalidad por cáncer de útero en Argentina: Ministerio de Salud de la Nación. No date
a4[c]	Dzuba IG *et al.*, Rev Panam Salud Publica 2005;18:53–63.
a5	Ministerio de Salud y Previsión Social Bolivia. Norma nacional, reglas, protocolos y procedimientos para la detección y control del cáncer de cuello uterino (Norma boliviana de salud NB-MSPS-07-2001). 2002.
a6[b]	Costa CRP *et al.*, Revista Brasileira de Cancerologia 2003;49:33–37.
a7	Zeferino LC, *et al.* Cad Saude Publica 2006;22:1909–14.
a8[c]	de Quadros CA *et al.*, Rev Panam Salud Publica 2004;16:223–32.
a9	D'Ottaviano-Morelli MG *et al.*, Cad Saude Publica 2004;20:153–59.
a10	Ministerio de Salud de Chile. Orientaciones para pesquisa y control del cáncer cérvico uterino. 1998.
a11[b,c]	Sepúlveda C *et al.*, Cancer Detect Prev 2005;29:405–11.
a12	Lucumi DI *et al.*, Rev Esp Salud Publica 2004;78:367–77.
a13	Ministerio de Salud de Colombia. Normas técnicas y guías de atención para las acciones de protección específica y detección temprana (Resolución 412). 2000.
a14	Diario oficial de Costa Rica. Normas y procedimientos de atención Integral a la mujer para la prevención y manejo del cáncer de cuello de útero para el I y II nivel de atención y normas de laboratorios de citología (Decreto 33119-S. Alcance 43 a La Gaceta 131). 2006.
a15[b,c]	Falcon E *et al.*, Rev Cubana Enfermer 1999;16:201–06.
a16	IARC Working Group on the Evaluation of Cancer Preventive Strategies. Cervix Cancer Screening. IARC Handbooks of Cancer Prevention Vol. 10. Lyon: IARC Press. 2005.
a17	Sociedad de lucha contra el cáncer (SOLCA). Núcleo de Quito. Programa plan vida de Cáncer de cérvix. 2007.
a18	Agurto I *et al.*, Int J Qual Health Care 2006;18:81–86.
a19[a]	López. Programa de prevención y control del cancer cérvico uterino: Ministerio de Salud Pública y Asistencia Social. El Salvador. 2002.
a20	Ministerio de Salud Pública y Asistencia Social Guatemala. Cáncer cérvico uterino: manual de referencia para la aplicación de las normas de atención. 1999.
a21	Flores Y *et al.*, Salud Publica Mex 2003;45 Suppl 3:S388–98.
a22	Hernandez-Avila M *et al.*, Int J Epidemiol. 1998;27:370–76.
a23	Lazcano-Ponce EC *et al.*, Arch Med Res 1999;30:240–50.
a24	Secretaría de Salud de México. Modificación a la norma oficial mexicana NOM-014-SSA2-1994: Prevención, detección, diagnóstico, tratamiento, control y vigilancia epidemiológica del cáncer cérvico uterino. 1998.
a25	Subsecretaría de Prevencion y Protección de la Salud de México. Programa de acción: cáncer cérvico uterino. 2002.
a26	Alvarado V *et al.* Informe Final del Programa Integral de Prevención de Cáncer Cervical colaboración ICAS y Embajada del Reino de los Países Bajos, Managua, Nicaragua, 2005.
a27	Ministerio de Salud Pública y Bienestar Social de Paraguay. Normas y procedimientos para la prevención y el control del cáncer de cuello uterino. 2002.
a28	Ministerio de Salud de Perú. Manual de normas y procedimientos para la prevención del cáncer de cuello uterino. 2004.
a29	Aguirre R. Programa Mujer y Género del Ministerio de Salud Pública. Diagnóstico de situación sobre género y salud en Uruguay. 2006.
a30	Rodriguez R *et al.*, Rev Med Uruguay 2005; 21: 200–206.
References from Table 4. ***Cytological screening coverage.***	
b1	Instituto Nacional de Estadísticas y Censos de Argentina. Primera encuesta nacional de factores de riesgo. 2005.
b2	Central Statistical Office. Belize. Family Health Survey. 1999.
b3	Instituto Nacional de Câncer, Ministério da Saúde, Secretaria de Vigilância em Saúde Inquérito Domiciliar sobre Comportamentos de Risco e Morbidade Referida de Doenças e Agravos não Transmissíveis, Capitais e Distrito Federal, 2002- 2003. Brasil. 2007.
b4	Instituto Brasileiro de Geografia e Estatística. Pesquisa nacional por amostra de domicílios. Acesso e utilização de serviços de saúde, 2003. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística; 2005.
b5	World Health Organization (WHO). World Health Survey. Brazil. 2002.
b6	Pinho A *et al.*, Cad Saude Publica 2003;19 Suppl 2:S303–13.
b7	Ministerio de Planificación MIDEPLAN, Gobierno de Chile. Encuesta de Caracterización Socioeconómica (CASEN) 2003. Santiago de Chile: 2003.
b8	Ministerio de Salud de Chile. Guía Clínica Cancer Cervicouterino 2. 1st edition. Santiago: Minsal, 2005.
b9[c]	Suarez E *et al.*, Rev Chil Obstet Ginecol 2001;66(6):480–91.
b10[b]	Capurro I *et al.*, Rev Chil Obstet Ginecol 2002;67(2):114–20.
b11	Piñeros M *et al.*, Rev Salud Publica (Bogota) 2007;9(3):327–41.
b12	Chen M *et al.* Salud Reproductiva y Migración Nicaragüense en Costa Rica 1999-2000: Resultados de una Encuesta Nacional de Salud Reproductiva. San José: Programa Centroamericano de Población. 2001.
b13	Irwin KL *et al.*, Bull Pan Am Health Organ. 1991;25(1):16–26.
b14[b]	Fernandez Garrote L *et al.*, Bull Pan Am Health Organ. 1996;30(4):387–91.
b15	Centro de Estudios de Población y Paternidad Responsable (Ecuador) and Centres for Disease Control and Prevention (US). ENDEMAIN-2004: informe preliminar. 2005.
b16	Asociación Demográfica Salvadoreña. Encuesta Nacional de Salud Familiar de 2002–2003 (FESAL-2002/03). San Salvador. 2004.
b17	Ministerio de Salud Pública de Guatemala. Encuesta Nacional de Salud Materno Infantil 2002 (Mujeres). 2002.
b18	Corrales G *et al.*, Honduras: Encuesta Nacional de Epidemiología y Salud Familiar—2001 (ENESF-01), Informe Final. Honduras: Secretaría de Salud. 2002.
b19	Monteith R *et al.*, Honduras: Encuesta Nacional de Epidemiología y Salud Familiar—1996 (ENESF–96), Informe Final. Honduras: Secretaría de Salud. 1997.
b20	Statistical Institute of Jamaica. Jamaica: Reproductive Health Survey. 1997.
b21	Subsecretaría de Prevención y Protección de la Salud. Programa de acción: cáncer cérvico uterino. Mexico. 2002.
b22	Instituto Nacional de Salud Pública de México. Encuesta Nacional de Salud. 2000
b23[c]	Rodriguez-Reyes ER *et al.*, Ginecol Obstet Mex. 2002;70:3–6.
b24	Lazcano-Ponce EC *et al.* Cancer Causes Control. 1997;8(5):698–704.
b25	Instituto Nacional de Estadísticas y Censos de Nicaragua. Encuesta nicaragüense de demografía y salud. 2001
b26	Claeys P *et al.*, Sex Transm Infect 2002;78(3):204–7.

Table 1 (*Continued*)

Code	Reference
b27	Centro Paraguayo de Estudios de Población. Encuesta nacional de demografía y salud sexual y reproductiva ENDSSR. 2004.
b28	Instituto Nacional de Estadística e Informática (INEI) de Perú. Encuesta nacional de hogares. 1998.
b29	Jeronimo J *et al.*, Rev Panam Salud Publica 2005;17(1):1–5.
b30	National Center for Chronic Disease Prevention and Health Promotion: Behavioral Risk Factor Surveillance System. Centers for Disease Control and Prevention. 2007.
References from Table 5. ***Quality of cytology.***	
c1	Pinto AP *et al.*, Diagn Cytopathol. 2005;33(4):279–83.
c2	Sebastiao APM *et al.*, Bras Patol Med Lab 2004;40(6):431–38.
c3	Guzmán S *et al.*, Rev Méd Chile 2005;133:685–92.
c4	Lazcano-Ponce EC *et al.*, Rev Inst Nal Cancerol (Mex) 1996;42(3):123–40.
c5[c]	Howe SL *et al.*, Gynecol Oncol 2005; 99(3 Suppl 1):S232–35.
References from Table 8. ***Follow-up of positive screening tests.***	
d1	Gage JC *et al.*, Cancer Detect Prev 2003;27(6):466-71.

[a] Citation in Table 4.
[b] Citation in Table 5.
[c] Citation in Table 8.

The assumption being that a gradual increase in screening coverage was achieved uniformly through the period.

To explore the effect of socio-economic variables, in addition to screening on cervical cancer mortality, an analysis with a generalized estimating equations linear model for longitudinal data was done for the period 1995–2000. This type of analysis adjusted for the autocorrelation among repeated measures over time. For the multivariate analyses only variables with significant association in the univariate analyses were included. Due to the lack of information for one or more variables during the whole period, Cuba and Puerto Rico were excluded in the multivariate analysis. The impact of cytology coverage was considered as an adjustment variable. Missing data were imputed using linear interpolation.

2. Cervical cancer: a significant public health problem in Latin America and the Caribbean

Incidence (age-standardized rate (ASR) of 29.2 per 100,000) and mortality rates (ASR of 13.6 per 100,000) of cervical cancer in LAC are high, compared to other regions in the world, except Africa [1,2]. In 2002, there were approximately 493,000 new cases of invasive cancer of the uterine cervix worldwide, 15% of them occurring in LAC where the five-year prevalence is 207,031 cases [1].

Success of cervical cancer prevention is based on the ability to detect and treat pre-cancerous cervical lesions before they become invasive cancer [3]. Pap smear screening was introduced in LAC at the beginning of the 1960s. Although there have been attempts to implement national programs, the successful reduction of cervical cancer incidence and mortality achieved in other developed countries has not been replicated in LAC. Cervical cancer mortality rates have remained almost unchanged between 1975 and 1990 in the Americas with the exceptions of Canada and the United States of America [4]. Mortality data suffer from several limitations among LAC countries such as under-registration. Current analyses show a wide variation in mortality rates, with a slight decrease overtime only in a few countries such as Mexico, Costa Rica and Chile [5].

2.1. Challenges to successful cervical cancer screening programs

The characteristics and requirements of functional and effective cytology-based screening programs have restricted successful interventions in early detection of cervical cancer, especially in developing countries ([6,7], Table 1: a23). Cytology-based screening programs require multiple visits to obtain cytology samples for screening, perform colposcopy, collect biopsies, communicate results of diagnoses, and treatment of pre-neoplasic lesions and cancer. Furthermore, necessary infrastructure must also be available for transportation of samples (sometimes from remote areas), to high quality laboratories for sample processing and interpretation, and quality control of those laboratories over time. The shortage of diagnosis and treatment centers often requires women with positive screening tests to undergo colposcopy and biopsies, and eventually cancer treatment at distant health centers that requires the patient to travel repeatedly or for extended periods of time [6,8,9].

2.2. Socio-economic status and health systems

In addition to the failure of screening programs to reduce the burden of cervical cancer, other socio-economic factors have been associated with the lack of cervical cancer control. Determinants and barriers for cervical cancer screening include women's low literacy level, cultural and religious factors, competing health needs, limited resources, poorly developed health care services and limited information on cervical cancer prevention [6,10]. Furthermore, some of these factors such as competing health needs (of other infectious diseases, reproductive health matters, and etc.) and limited resources curb public awareness and relegate cervical cancer as a small component within other public health programs such as reproductive health (Table 2). This results in the absence of centralized national programs for cervical cancer control in many countries [8,11] and deviation of screening resources from women at the highest risk (over 30 years old) to low-risk young women who usually attend family planning [12]. Besides program implementation, the abovementioned conditions introduce additional difficulties to evaluate the impact and performance of cervical screening programs.

3. Cervical cancer screening programs in Latin America and the Caribbean

Organized programs have been associated with a greater impact on cervical cancer control than opportunistic screening [13]. Nevertheless, most LAC countries have not achieved the requirements of an organized program (Table 3), and they offer opportunistic screening mainly in urban areas of the region, usually through public family planning and reproductive health care facilities or in private practices [7]. Over the last two decades, most countries in LAC have developed national cervical screening policies in an

Table 2
Cervical cancer screening policies in Latin America and the Caribbean

Country [reference code in Table 1]	Start year[a]	Screening centers	Screening age (years)	Screening scheme (years)[b]
Argentina [a1–a3]	1997	Health care centers	35–64	1-1-3
Bolivia [a4, a5]	1988 and 1998	Reproductive health service	25–49	1-1-3
Brazil [a6–a9]	1968/1996-98	Health facilities	25–59	1-1-3
Chile [a10, a11][c]	1987 and 1994	Primary health clinics	25–64	Every 3
Colombia [a12, a13]	1991 and 2000	NS	25–69	1-1-3
Costa Rica [a14]	1995	Public and private health centers	>20	Every 2
Cuba [a15][d]	1968	Primary health clinics	25–59	Every 3
Dominican Republic [a16]	1993	Family planning services	25–59	6-6-12 (months)
Ecuador [a17][e]	1996	Primary health service	35–64	Every 5
El Salvador [a18, a19]	2002	Family planning services	30–59	Every 2
Guatemala [a20]	2004	Family planning services	25–49	1-1-1-3 or 5
Haiti [a16]	Does not have a program			
Honduras [a16]	NS	Maternal health	25–59	Annually
Jamaica	Does not have a program			
Mexico [a21–a25]	1974/1994-98	Public health sector	25–64	1-1-3
Nicaragua [a26]	2003	Women's health clinics	25–59	1-1-1-3
Panama [a16]	NS	NS	>15	Every 3
Paraguay [a27]	2002[f]	Health care centers and hospitals	25–69	1-1-1-3
Peru [a16, 28]	2000[g] and 2004	Primary health care service	30–49	Every 3
Puerto Rico[d]	1960	NS	>15	NS
Trinidad and Tobago 2[d]	Development	NS	20–59	1-1-3
Uruguay [a29, a30]	Cervical screening offered by appointment since 1994			
Venezuela [a16]	1996	NS	25–64	Every 3
Caribbean Islands[d]	Cervical screening done opportunistically.			

NS: Not specified.
[a] Second date is the year of program re-launch.
[b] Screening schemes in format "1-1-3" indicate screening every 3 years after 2 consecutive annual negative smears.
[c] Systematic or opportunistic screening depending on regions.
[d] Unpublished data, based on personal reports.
[e] Started in Quito and the Manabi province and was used as a reference for the whole country.
[f] Start of program implementation.
[g] Visual inspection was incorporated as an additional screening technique into the national program.

attempt to establish well-organized screening programs (Table 2), but few have been able to implement them successfully [Table 1: a7, a9, a11, a23].

Screening policies vary widely among countries. The introduction of screening programs in the different countries spans over more than three decades in some cases. The recommended age for starting screening ranges from 15 to 35 years and for screening cessation ranges from 49 to 69 years. Most of the programs are based on cytology every three years after two negative annual Pap smears; however, some countries apply screening intervals as often as once a year with poor correlation between screening intervals and cytology coverage (Tables 2 and 4).

According to available literature, cytology-based national screening programs have been successfully implemented in Chile [Table 1: a11] and in some countries at the regional level such as Brazil [Table 1: a7, a9] and Mexico [Table 1: a23].

In Chile, cytology screening has been available since the 1960s and an organized national screening program was launched in 1994, mandating the screening of women ages 25–64 years with conventional cytology every three years [Table 1: b9]. The program has been computerized since the late 1990s, allowing for the identification, trace and proper follow-up of users. It is centrally supervised by the Ministry of Health, but managed independently by each health service and municipality. In 2005, cervical cancer was included in the free of charge GES-AUGE (Spanish acronym for "explicit guarantee model") scheme, thus ensuring the adequate evaluation and treatment of screened identified pre-cancer cervical lesions and cancers. This most recent policy may have contributed to further increased national screening coverage and program performance [14].

In Brazil, the national screening program was launched in 1998 after being piloted in five regions [Table 1: a6,a8]. The program offers free-of-charge cytological screening (including detection, diagnosis and treatment) for women ages 25–59 years every three years (after two consecutive annual negative smears) [15]. In the region of Campinas in the state of Sao Paulo, the screening program was set up in 1968, making it the first operating screening program to exist for more than 30 years in Latin America. The incidence of cervical cancer in Campinas is by far the lowest reported by a cancer registry in Brazil, and significantly lower than the national estimate, reflecting the positive effect of a well-established program [Table 1: a7, a9].

Table 3
Major issues to be considered in a national organized cervical cancer screening program

An explicit policy defining population to be covered (rights), resources and responsibilities
A defined population target including age categories and individual identification
A defined method (or methods) for screening as well as screening intervals
A management team responsible for screening implementation and monitoring
Training of health care providers
Equipment supply systems for health centers
Quality assurance structures infrastructure for screening methods including the availability of high quality laboratories
Referral pathways for treatment of patients (may involve training of people at the local level for treatment of precancerous lesions)
Development of capacity for treatment (*in situ* disease, invasive cancer and palliative care)
Monitoring systems for program performance
Methods for identifying cancer occurrence in the target population
Education of the population to ensure participation and adherence to the screening program

Source of data: [13].

Table 4
Cytological screening coverage in Latin America and the Caribbean

Target population			Women interviewed		Screening		Method of estimation	Source (see Table 1)
Country	Year	Region or city	Number of women	Age (years)	Coverage (%)	Interval (years)		
Argentina	2005	National	NS	>18	51.6	2	Survey	[b1]
Belize[a]	1999	National	4,164	13–49	13.4	1	Survey	[b2]
Brazil	2002–2005	Capital cities	13,282	25–59	63.4	1	Survey	[b3]
	2003	National	NS	>24	68.7	3	Survey	[b4]
	2002	National	2,577	18–69	64.8	3	Survey	[b5]
	2002	Pelotas	1,198	25–59	68.8	3	Survey	[a8]
	2000	Sao Paulo	1,050	15–49	77.3	3	Survey	[b6]
Chile	2003	National	27,000	>15	51.4	3	Survey	[b7]
	2003	National	–	25–64	66.0	1	SP	[b8]
	2000	National	–	25–64	64.0	3	SP	[b9]
	2000	Araucania Sur	–	25–64	56.2	3	SP	[b10]
Colombia	2005	National	34,674	25–69	50.6	1	Survey	[b11]
Costa Rica	1999–2000	National	1,612	18–44	37.0	1	Survey	[b12]
	1991	National	NS	25–58	51.3	1	Survey	[b13]
Cuba	1993–1994	National	–	>20	54.2	2	SP	[b14]
Dominican Republic	2002	National	1,389	18–69	54.4	3	Survey	[b5]
Ecuador	2004	National	10,813	15–49	31.0	2	Survey	[b15]
		Urban	5,876		35.6			
		Rural	4,938		24.9			
El Salvador	2002	National	10,689	15–49	47.0	1	Survey	[b16]
	1998	National	–	NS	19.0	3	SP	[a19]
Guatemala	2002	National	12,119	1 + 5–49	41.2	1	Survey	[b17]
Honduras	2001	National	8,362	15–49	26.0	1	Survey	[b18]
	1996	National	NS	NS	55.4	1	Survey	[b19]
Jamaica	1997	National	6,384	15–49	15.4	1	Survey	[b20]
Mexico	2000	National	–	>25	57.8	3	SP	[b21]
	2000	National	26,746	>20	27.4	1	Survey	[b22]
	1999–2000	Durango	–	15–69	27.6	1	SP	[b23]
	1994	Oaxaca (rural)	2,773	15–49	21.0	1	Survey	[b24]
		Mexico city (urban)	1,435	15–49	48.2			
Nicaragua	2001	National	14,671	14–49	23.3	1	Survey	[b25]
	1999–2000	Managua, Rivas and Matagalpa	1,185	13–72	47.0	3	Survey	[b26]
Paraguay	2004	National	7,000	15–44	73.2	2	Survey	[b27]
	2002	National	2,586	18–69	45.4	3	Survey	[b5]
Peru	1998	National	NS	15–49	22.7	1	Survey	[b28]
	1999–2000	Lima	1,921	25–50	35.0	1	Survey	[b29]
Puerto Rico	2002	National	2,692	>18	72.3	3	Survey	[b30]
Uruguay	2002	National	1,563	18–69	55.2	3	Survey	[b5]

Coverage is defined as the history of at least one Pap smear in the corresponding screening interval (1, 2, or 3 years). Only countries with data at the national level were included. Surveys from areas smaller than a city, surveys reporting only ever screened, intervention studies and methods of estimation other than surveys or screening programs were excluded. If a given country or region had several similar surveys, only the latest is shown. Data on different screening intervals (1, 2, 3 years) from the same report were limited to the shortest period.
NS: Not specified; SP: Estimated from screening program.
[a] The question on the survey is oriented to frequency of screening rather than to history of cytology in the last year.

Opportunistic cytological screening has been available since the 1970s in Costa Rica, where the national screening program started in 1995. Since then, any sexually active woman who is 20 years or older has been screened every two years. Health centers ensure that women attend screening and that proper follow-up of screened positives are maintained [Table 1: a14].

4. Performance of cytology-based screening programs

A cervical cancer screening program based on the Pap smear depends on high-quality sampling, well-trained cytologists, adequate follow-up and diagnosis of women with a positive cytology result, and broad coverage of at-risk populations among other program related factors [16]. Thus, evaluation of screening activities on a regular basis requires proper information systems. Few countries in the region have implemented these systems, making it unlikely to determine if programs are operating as expected or achieving their goals. Lack of information is closely related to the lack of organized programs hence, screening performance is frequently evaluated through secondary sources.

Several criteria for program evaluation have been proposed [17,18]. Marrett LD *et al.* considered follow-up of positive screening tests, quality of screening tests, quality of screening test results and participation in screening as core indicators for development of cer-

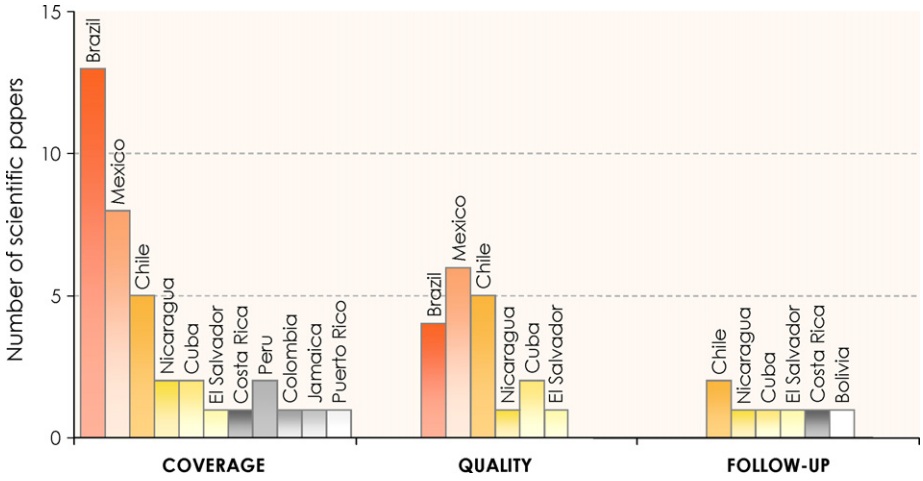


Fig. 1. Number of published studies on evaluation of cervical cancer screening programs in Latin America and the Caribbean.
The figure represents 63 scientific papers aimed at evaluating one or more core indicators of screening programs in Latin America and the Caribbean (follow-up of positive screening tests, quality of screening tests, quality of screening test results and participation in screening) [19]. 32 out of the 63 scientific publications met the inclusion criteria and were finally included in Table 1. Total amounts do not correspond to partial numbers because some studies include more than one indicator.

vical screening information systems aimed at identifying program success [19]. The short-term core indicators allow for comprehensive evaluation of screening programs and represent quality guidelines for reviewing the situation in LAC countries.

A review of 32 out of 63 publications (Fig. 1) showed that screening coverage is the most frequent indicator evaluated followed by quality of cervical cytology. Meanwhile, the follow-up of women with positive screening tests is an indicator infrequently considered. Brazil, Mexico and Chile account for the highest number of studies in the region, but differ in their scope of evaluation.

4.1. Coverage of cytology-based programs

Although coverage is associated with the largest number of published information, not all countries have national data based on probabilistic surveys (Table 4). Given the differences among screening schemes and evaluation design, the coverage period reviewed varies between one and three years. Among the countries reporting cytology coverage within the last three years, El Salvador exhibits the lowest rate (19% in 1999) [Table 1: a19] and Puerto Rico the highest (72% in 2002) [Table 1: b30]. In 2004, Ecuador held the lowest cytology coverage for a two-year period (31%) [Table 1: b15], and Paraguay the highest (73%) [Table 1: b27]. The history of cytology testing within the last year is the most common indicator used for participation in screening: Chile has the highest estimate (66% in 2003) [Table 1: b8], Belize and Jamaica the lowest (13% in 1999 and 15% in 1997, respectively) [Table 1:b2, b20]. Chile is the only country reporting one-year cytology coverage based on data from the cervical cancer screening program, which contrasts with a national population survey in the same year that reported lower cytology coverage for a three-year period (51.4%) [Table 1: b7]. These findings indicate that the data from the screening program may be overestimated in spite of the differences in ages of women interviewed.

Few countries have information comparable over time due to differences among evaluation periods or methods for coverage

Table 5
Quality of cytology in Latin America and the Caribbean

Study	Country/Region	Number of smears	Inadequate sample (%)	Histopathology positive agreement (%)	Gold standard agreement (%)	Abnormal smears (%)	Source (see Table 1)
Costa CRP *et al.*, 2003	Brazil/Passos	2,905	1.7			0.54[a]	[a6]
Pinto AP *et al.*, 2005	Brazil/Paraná	1,601		67.3		2	[c1]
Sebastiao APM *et al.* 2004	Brazil/Paraná	65,753	1.8		97.04	8.6[b]	[c2]
Sepulveda C *et al.*, 2005	Chile	2,876,074	3.5	LSIL: 70 HSIL: 79 Cancer: 93		2[b]	[a11]
Guzman S *et al.*, 2005	Chile/Valdivia	26,127	1.5[c]				[c3]
Capurro I *et al.*, 2002	Chile/Araucania	45,229	10.9[d]				[b10]
Lazcano-Ponce EC *et al.*, 1996	Mexico/Mexico DF	1,440			FN 10.4 FP 46.7	19[e]	[c4]
Howe SL *et al.*, 2005	Nicaragua/NAAR	2,132		68		3.7	[c5]
Fernandez Garrote L *et al.*, 1996	Cuba	ND	11	27		1	[b14]
Falcon E *et al.*, 1999	Cuba/Santiago	22,576	3.1				[a15]

The table includes only reports on evaluation of regular programs which included data on: (1) Quality of smear sample (exclusive of presence of endocervical cells); (2) Histopathology positive agreement (agreement of Pap smear with final local histopathology); and (3) Gold standard positive agreement (second reading by an expert). Intervention studies and external quality control programs are not included.
FN: False negative; FP: False positive; HSIL: High-grade squamous intraepithelial lesion; LSIL: Low-grade squamous intraepithelial lesion; NAAR: North Atlantic autonomous region.

[a] Epithelial cell abnormality.
[b] Positive agreement with LSIL or worse, or HSIL or worse correspondingly.
[c] Year 2003.
[d] Year 2000.
[e] Dysplasia or more.

Table 6
Results of cervical cytology proficiency testing in laboratories of the Pan American Cytology Network (RedPAC), 1998–2000

Country	Laboratories (Observers)	Year	Under diagnosis (%)	Over diagnosis (%)	Observed agreement (%)	*Kappa index*	Change in *kappa index* (%)
Mexico	15 (85)	1998	18	8	74	0.57	
	15 (83)	1999	17	4	79	0.65	(+) 14
Costa Rica	1 (5)	1998	10	13	76	0.61	
	1 (21)	1999	50	2	48	0.32	
	1 (32)	2000	2	15	83	0.65	(+) 7
Ecuador	6 (36)	1998	31	4	65	0.47	
	6 (40)	1999	20	9	71	0.51	
	6 (52)	2000	14	2	84	0.73	(+) 55
Venezuela	5 (41)	1999	17	6	77	0.61	
	5 (41)	2000	23	2	75	0.61	0
Chile	10 (48)	1999	21	1	79	0.66	
	10 (44)	2000	6	1	93	0.87	(+) 32
Perú	6 (31)	1999	23	7	69	0.50	
	6 (29)	2000	27	3	70	0.53	(+) 6
Bolivia	2 (8)	2000	6	12	81	0.64	

"Under diagnosis" represents the percentage of false negatives and "over diagnosis" the percentage of false positives. The observed agreement (%) corresponds to the simple measure of concordance between an external expert panel and the diagnostic in laboratories; this concordance is also expressed through the *Kappa index*. Change in *Kappa index* corresponds to improvements in the positive concordance after the indicated period of training. Adapted from [8].

estimation (national, regional, survey, program data, etc.). For the selected countries in Table 4, only Costa Rica and Honduras have national surveys with at least a five-year interval between them, and both cases show a decrease in cytology coverage, possibly due to differences in the interviewed population [Table 1: b12, b13, b18, b19].

Data on cytology coverage in specific regions or cities reveal an important variation in program performance within each Latin American country, such as Mexico. Coverage appears to be closely related to the level of urbanization, where rural communities have a greater difficulty in access and, consequently, to achieve high coverage [Table 1: b24].

4.2. Cytology quality

From the moment smear collection begins quality problems start. Health workers might not collect adequate samples and samples reach understaffed laboratories that lack systematic quality control and follow-up procedures ([12], Table 1: a23]). The scarce data on quality control shows a rate of inadequate samples of around 3% or lower, except for regional data from Chile (10.9%) and national data from Cuba in 1996 (11%) (Table 5). The former has achieved a decreasing trend in the mortality rate and the latter has already achieved one of the lowest cervical cancer mortality rates in the region [5]. With the exceptions of Chile and Cuba, no nationwide information on cytology quality control was found. Consequently, local and regional studies reveal significant variation on cytology positive rates as well as on histopathological and gold standard agreements (Table 5).

Mexico is the country with the largest number of studies on cytology quality in Latin America (Fig. 1). Lazcano-Ponce E *et al.* evaluated 20 cervical cytology reading centers in Mexico by distributing a panel of 220 cervical cytology specimens to be compared with the reference standard, which was assessed by an expert pathologist. Close to 67% of cervical cytology assessment centers had over 25% false negative results and four cervical cytology laboratories had over 45% false negative results including 31 false negative diagnoses of adenocarcinoma [20].

Apart from national initiatives to implement external quality control ([21], Table 1: a11), two attempts to improve the quality of cytology in LAC were implemented in the late 1990s. Under the initiative of the Pan American Health Organization (PAHO), an external quality assurance network (RedPAC (Spanish acronym for "Pan American Cytology Network")) was developed to improve cytology laboratory performance [8]. Observer agreement on cytology diagnosis within countries varied between 48% in Costa Rica (21 observers, *Kappa:* 0.32) and 79% in Mexico and Chile (83 and 48 observers, *Kappa:* 0.65 and 0.66) in 1999, and between 70% in Peru (29 observers, *Kappa:* 0.53) and 93% in Chile (44 observers, *Kappa:* 0.87) in 2000. Observed agreement improved in most countries after the introduction of RedPAC, but the increase was different among countries (Table 6).

A further proficiency test based external quality assurance exercise was carried out in Peru and Nicaragua using an adapted version of the system currently used in Scotland and Northern Ireland [22]. After two to three years of using external quality assurance, the performance of the laboratories did not improve in either Peru or Nicaragua (Table 7).

Both experiences showed that the quality of cytology can be improved up to a certain level, but maintaining that level would be difficult and the quality of techniques inevitably varies widely among laboratories. Additionally, the diagnosis for atypical

Table 7
Mean composite performance index for each year for each country and differences in performance score between years

Country	Mean composite performance index, by year			Change (mean), by year		
	2000	2001	2002	2000–2001	2001–2002	2000–2002
Peru	280.6	281.4	–	0.78	–	–
Nicaragua	273.8	282.5	271.9	9.5	−10.9	−1.0

Composite performance index = sensitivity + 2 x (specificity). The specificity is doubled to give more importance to false positives than false negatives.
The mean composite performance index represents the mean of the composite performance indexes obtained by 92 participating professionals in Peru and 67 in Nicaragua over 2 rounds of testing (40 slides per professional). Source of data: [22].

Table 8
Clinical follow-up of positive screening tests in Latin America and the Caribbean

Study (1st author, year)	Country	Year	Follow-up of positive screening results[a]		Follow-up time (months)[b]	Method of estimation	Characteristics	Source (see Table 1)
			Diagnosis (%)	Diagnosis and treatment (%)				
Dzuba IG *et al.*, 2005	Bolivia	NS	58,50		NS	SP	Data from one state in Bolivia	[a4]
Sepulveda C *et al.*, 2005	Chile	1995–1997	81,6		1	SP	National	[a11]
Suarez E *et al.*, 2001	Chile	2000	90,0		1	SP	National	[b9]
Gage JC *et al.*, 2003	Peru	1999–2000	34,0	25,1	6–21	Survey	San Martin. 18% of abnormal Pap smears on baseline received a second Pap smear as follow-up	[d1]
Falcon E *et al.*, 1999	Cuba	1990–1996	99,7		12	SP	National. Specified as positive smears attending the clinic of cervical pathology	[a15]
Rodriguez-Reyes ER *et al.*, 2002	Mexico	1999–2000	21.16		NS	SP	Durango	[b23]
Howe SL *et al.*, 2005	Nicaragua	NS		91,0	12	SP	North Atlantic autonomous region	[c5]

Intervention studies are not included.
NS: Not specified; SP: Estimated from routine evaluation of screening program.
[a] Percentage of women with positive Pap smears receiving diagnosis or diagnosis and treatment.
[b] Interval between screening and diagnosis/treatment.

squamous cells of undetermined significance (ASC-US) represents a challenge for quality control in cytology laboratories, but their impact on program performance in LAC has not been established.

4.3. Follow-up of positive screening tests

Follow-up of positive screening tests to complete diagnosis and treatment has been defined as one of the main priorities for screening programs [19]; nonetheless, this parameter yields the least information from evaluative studies in the region. Once again, only Chile and Cuba have national data for follow-up of positive screening results with a performance of over 90% (Table 8). Chile has increased the rate of women attending visits for diagnosis and treatment after a positive screening result, which may be related to improvements made to the screening program and the new regulations previously described. The rates reported from Peru (25%) and Bolivia (58.5%) contrast with data from Chile and Cuba (Table 8). This situation is consistent with trends and rates of cervical cancer mortality, suggesting that the lack of follow-up of positive screen-

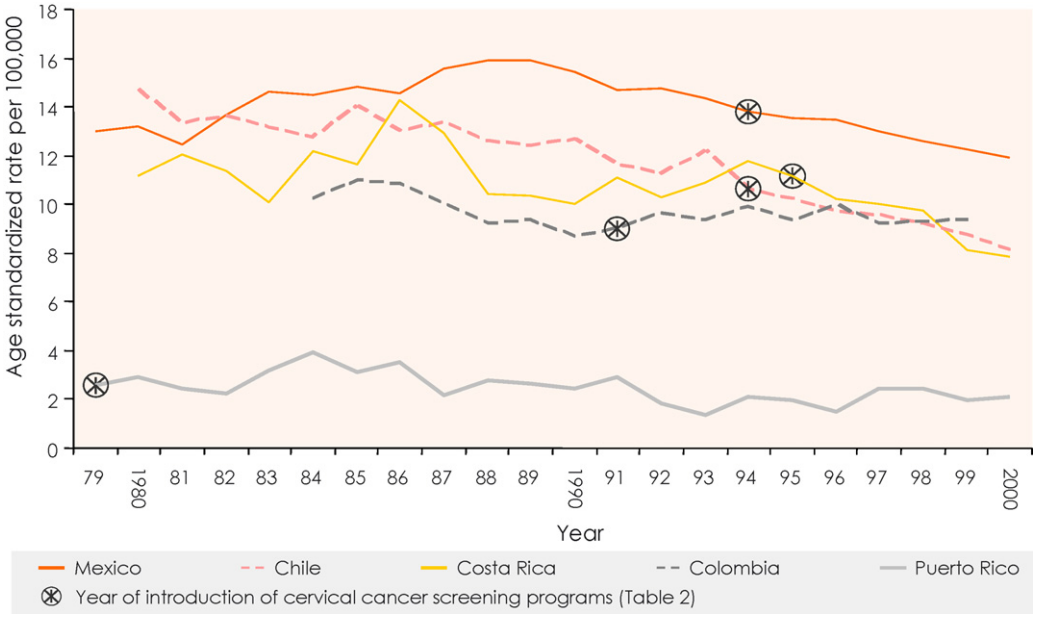


Fig. 2. Time trends of cervical cancer mortality in Latin America and the Caribbean in relation to the year of introduction of screening programs. Selected countries with decreasing trends.
Puerto Rico started screening in 1960. Source of mortality data: [25].

ing results may be one of the primary reasons for the lack of impact on the reduction of mortality rates.

5. Cervical cancer screening and mortality in Latin America and the Caribbean

Among the several factors influencing the failure of cervical cancer programs in LAC, low coverage and quality assurance of cytology have been proposed as the main reasons which screening in these countries has not impacted cervical cancer incidence and mortality ([12], Table 1: a23).

5.1. Participation rates and cervical cancer mortality

A decrease in cervical cancer mortality has been shown to be directly associated to the percentage of the population attending screening programs in developed nations [23]. The impact of screening programs in reducing mortality remains uncertain in LAC. Costa Rica reported an incidence of cervical cancer of 18.2 per 100,000 women in 2000, showing a 9% reduction since the implementation of the program five years earlier (20.1 per 100,000 in 1995–1996) [24]. Additionally, in Chile, a 38% decline in mortality from 11.1 in 1986 (before the introduction of screening) to 6.8 per 100,000 in 2001 has been linked to an increase in the average national screening participation rates, from 53% in 1996 to 65% in 2000 (Table 4) [Table 1: a11]. Moreover, the detection of invasive cervical cancers at early stages in Chile also increased from 30% to 39% in 1990 and 1996, respectively [Table 1: a11, b9]. In spite of the relation described among coverage and mortality trends, both countries showed decreasing mortality rates before the introduction of cervical cancer screening programs (Fig. 2) [25], therefore, socio-economic development might have a stronger influence on the above mentioned trends than cytology coverage.

Historical data and time series have provided the main evidence on the effect of cytology screening on mortality [23]. The results from studies in developed nations have led to the design and implementation of strategies for improving cytology coverage in LAC, although data from studies linking participation rates and mortality in industrialized countries should not be interpreted as a direct effect of cytology coverage but rather as a result of comprehensive improvements in screening programs.

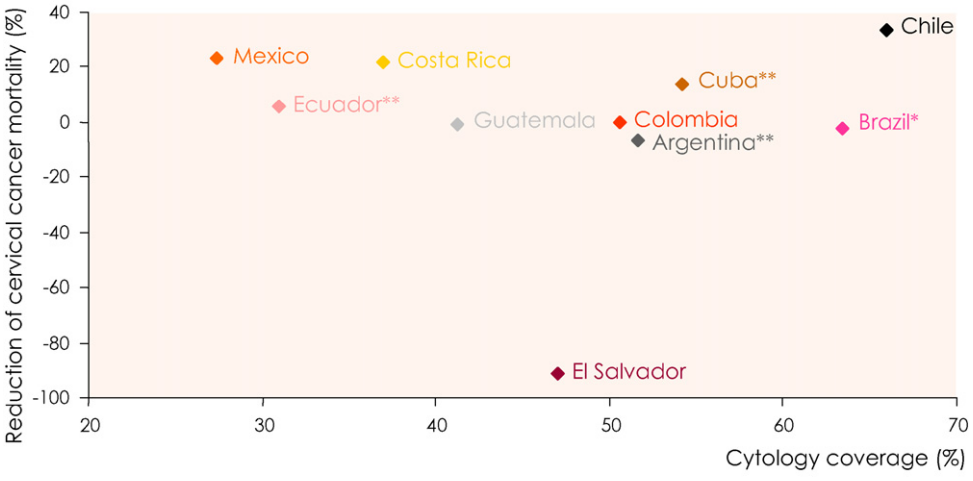
Some LAC countries have achieved cytology coverage rates similar to those observed in developed nations such as Canada [26], although LAC countries still have significantly higher cervical cancer mortality. Furthermore, coverage rates do not reflect differences in cervical cancer mortality rates and trends among LAC countries (Fig. 3), where nations with widely different levels of coverage have similar levels of reduction in cervical cancer mortality.

Existing inequalities in LAC are one of the highest in the world and may be responsible for the lack of impact of cervical cancer screening. In Brazil, the incidence of cervical cancer ranged from 14.2 per 100,000 in Campinas (1991–1995) to 64.8 per 100,000 in Belem (1989–1991) during the 1990s [27]. In Colombia, mortality in high-risk areas could be five times higher than the lowest mortality rates in the country (49.1 per 100,000 women in the Amazon and 10.3 in Boyaca) [28]. This situation might represent a high proportion of low-risk women who are repeatedly screened [29].

5.2. Cytology quality, follow-up of positive screening tests and cervical cancer mortality

In Mexico, the low detection of high-grade cervical lesions is mainly attributed to poor quality smear collection and cytological diagnosis, rather than to the screening of low-risk and the exclusion of high-risk women [20]. In addition, cost-benefit analyses from developing countries (inclusive of Colombia) have consistently shown the need for highly sensitive tests (up to 70–80%) for screening strategies to be effective [30,31].

Recent data from Colombia indicate that in a 1-1-3 cytology-based program (Table 2), follow-up for positive screening results has a greater impact on mortality than do participation rates. The follow-up of 50% of low-grade squamous cell intraepithelial lesions or worse results with 100% coverage reduces the risk of mortality by 52.7%, while follow-up of 100% of positive results with 50% coverage reduces the same risk by 74% (Fig. 4) [30]. These results corroborate with previous reports (inclusive of Peru) where cost-effectiveness ratios were sensitive to follow-up rates [32].



* Data from 18 capital cities.
** Cytology coverage (at least one Pap smear in the last 2 years). For other countries coverage corresponds to history of cytology in the last year (Table 2).

Fig. 3. Cytology coverage and reduction of cervical cancer mortality in Latin America and the Caribbean.
Reduction of cervical cancer mortality corresponds to absolute reduction in mortality rates during the period analyzed. Negative reduction of cervical cancer mortality indicates rising mortality. Source of mortality data: [25].

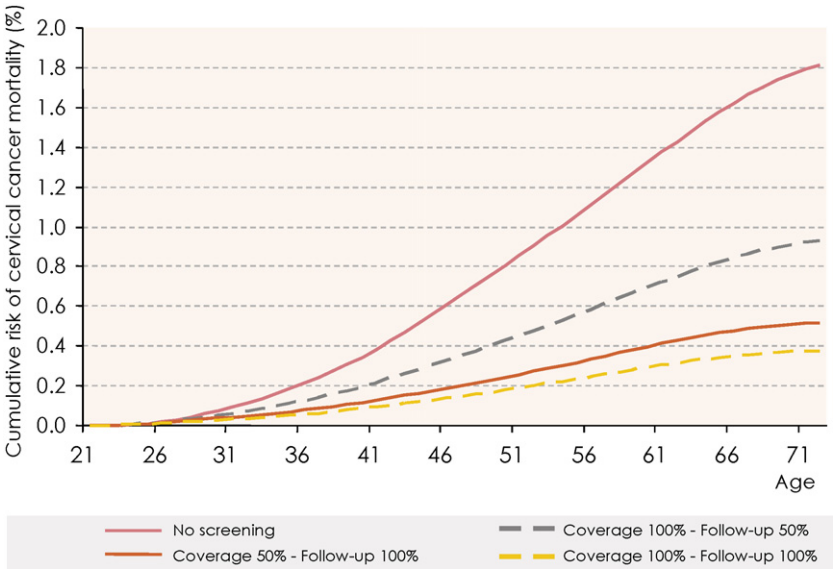


Fig. 4. Effects of screening coverage and clinical follow-up on the reduction of cervical cancer mortality.
The figure represents the cumulative risk of cervical cancer mortality without screening and with different characteristics of cytology-based screening programs (1-1-3). Adapted from [30], with permission from Salud Pública de México.

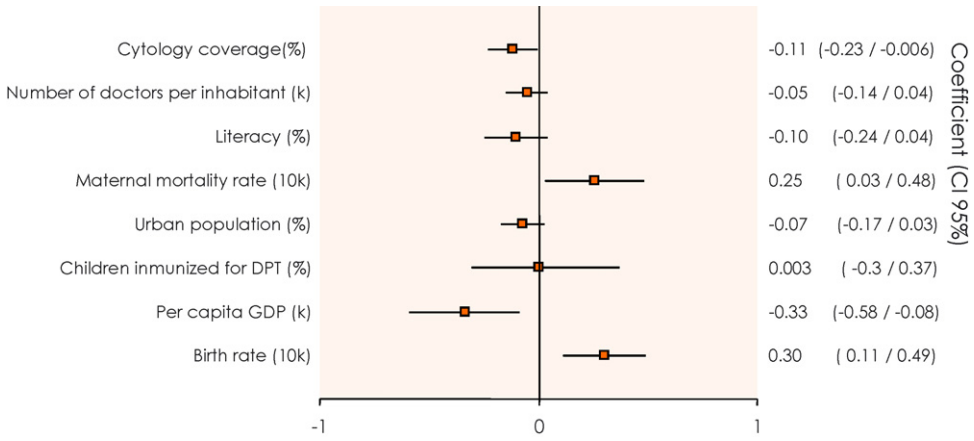


Fig. 5. Determinants of cervical cancer mortality in Latin America and the Caribbean (univariate analyses).
Generalized estimating equations linear model for longitudinal data. Coefficient values, other than zero, indicate an association between a given variable and cervical cancer mortality (ASR)
Positive values indicate direct association and negative values indicate reduction in ASR predicted by the variable.
Countries in the model include Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Guatemala, Mexico, Nicaragua, Panama, Paraguay, Puerto Rico, Uruguay, and Venezuela
Cytology coverage was included in interim analyses.
(k): units per 1,000.
Source of data: [25,33,34].

5.3. Socio-economic status and cervical cancer mortality in Latin America and the Caribbean

Several socio-economic factors have been identified as determinants of cervical cancer mortality [10]. Univariate analysis of longitudinal data from LAC countries shows a direct association of birth rates and maternal mortality and an inverse association with gross domestic product (GDP) (Fig. 5) [25,33,34]. These variables in the univariate analysis and GDP in the multivariate analysis (Coefficient [95% confidence interval (CI)]: −0.47 [−0.94 to 0.00]) were the only variables significantly associated with cervical cancer mortality. In addition, these variables have been used as indicators of social and health system development, and birth rates have been linked to cervical cancer mortality due to their relation to parity as a co-factor for disease progression [20]. When cytology coverage was included it showed a significant relation to cervical cancer mortality (Coefficient [95%CI]: −0.119 [−0.232 to −0.006]), but due to insufficient longitudinal data on coverage, this result should be carefully interpreted because the same value is repeatedly assumed when no data are available. Although the analysis has several limitations due to the lack of information and the consequent short period of evaluation, it provides more comprehensive results than cross-sectional data. These findings are consistent with previous analyses that reveal a high dependence of cervical cancer mortal-

ity on socio-economic development [10]. In this context, coverage of screening must be defined as the exposure to a comprehensive screening program (that includes coverage, quality and follow-up) where socio-economic conditions play an important role. Overall, the lower the socio-economic conditions, the higher the requirements are for a successful cytology-based program.

6. Conclusions

Conventional cytology is affected by many problems in LAC countries and, despite the investments made on cytology screening, cervical cancer remains a significant public health problem in the region. A proper understanding of cervical cancer screening program performance are essential for countries to design future interventions.

To improve the poor results currently obtained by cytology-based screening programs in the region, efforts and resources will need to be redirected. The main challenges include screening of high-risk populations (women over 30, and those who live in rural areas and/or low socio-economic levels) using a high-quality screening test, with adequate diagnosis and treatment services available for those with positive screening results.

These challenges could be addressed through the improvement of current cytology-based programs. Nevertheless, resources are scarce in most LAC countries and quality cytology-based screening programs have shown to be costly [30]. The exceptions found in Chile and Brazil, where all steps in the screening process are offered free-of-charge, may be unrealistic for the majority of countries in the region, however this may be feasible for sub-national areas in LAC.

Therefore, the opportunities opened by new emerging technologies should be carefully considered in order to maximize their benefits in the context of LAC preventive programs. HPV DNA tests have proven to have higher sensitivity than conventional cytology. Furthermore, an additional advantage is automatization and high throughput with lower human dependency and the subsequent reduction in quality control problems [35]. Furthermore, HPV DNA testing has a very high negative predictive value that permits longer screening intervals which could lead to improved follow-up and reduced costs. Accordingly, screening with HPV DNA testing followed by cytology triage of positive results [36,37] could be a more cost-effective option than frequent use of cytology alone [30,32,38].

Visual inspection is a low technology alternative for cervical cancer screening that has offered opportunities for new approaches. Sankaranarayanan R *et al.* demonstrated a 35% reduction in cervical cancer mortality in seven years and up to 66% depending on age at screening, when screening with visual inspection and treatment in one or two visits [39]. These results are consistent with analyses that indicate the importance of proper follow-up of detected abnormalities on the global impact of screening programs (Fig. 4). Follow-up related problems, particularly among the population with the highest risk, represent a formidable challenge for poor countries and regions. Similarly, the new rapid HPV DNA techniques under development provide a promising alternative to implement screen-and-treat programs suitable to LAC conditions [35]. However, to obtain better cost-effectiveness ratios when linking screening and treatment, the development of a greater capacity to treat pre-cancerous lesions at the local level is necessary.

Prophylactic HPV vaccines have the potential to significantly reduce the incidence of cervical intraepithelial lesions, leading to a significant change in the role and performance of screening programs [40]. Despite the fact that several issues, such as the duration of protection, remain unresolved, economic evaluations have shown vaccination combined with a few lifetime HPV screening visits to be the most cost-effective alternative for cervical cancer prevention [41].

Unfortunately, the factors with the greatest impact on the cost-effectiveness of vaccination are vaccine price and costs for an adolescent vaccination program [42], and both factors restrain the possibility for LAC countries to introduce HPV vaccines in the short term. Thus, the gradual implementation of new screening algorithms using a combination of screening techniques, in accordance with local infrastructure and health resources, appears to be the best option for many countries in the region [37]. However, irrespective of the screening method, quality control and follow-up of positive tests need to be improved and provided, which is the primary difficulty for current cytology-based programs in the region.

Disclosed potential conflicts of interest

None of the authors disclosed any conflict of interest.

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