DOI: https://doi.org/10.11144/Javeriana.umed63-4.foll

Follow-up on Women with Abnormal Findings of Cervical Cancer Screening in "The Americas" Region: A Systematic Review Protocol

Seguimiento a mujeres con hallazgos anormales en el tamizaje de cáncer de cuello uterino en la región de las Américas: protocolo de una revisión sistemática

Received: 27 April 2022 | Accepted: 08 september 2022

Ginna Fernández-Deaza
Centro Javeriano de Oncología, Hospital Universitario San Ignacio, Bogotá, Colombia
ORCID: https://orcid.org/0000-0002-0080-4071

María Zuluaga
Centro Javeriano de Oncología, Hospital Universitario San Ignacio, Bogotá, Colombia
ORCID: https://orcid.org/0000-0002-4656-6064

Mauricio Maza
Pan American Health Organization, Washington DC, United States of America
ORCID: https://orcid.org/0000-0003-2027-4431

Silvana Luciani
Pan American Health Organization, Washington DC, United States of America
ORCID: https://orcid.org/0000-0002-3122-1258

Raúl Murillo [a]
Centro Javeriano de Oncología, Hospital Universitario San Ignacio, Bogotá, Colombia. Facultad de Medicina, Pontificia Universidad Javeriana, Bogotá, Colombia
ORCID: https://orcid.org/0000-0001-7187-9946

[a] Corresponding author: rmurillo@husi.org.co

How to cite: Fernández-Deaza G, Zuluaga M, Maza M, Luciani S, Murillo R. Follow-up of women with abnormal findings of cervical cancer screening in the Americas region: a systematic review protocol. Univ. Med. 2022;63(4). https://doi.org/10.11144/Javeriana.umed63-4.foll

ABSTRACT

Background: The Americas region ranks third in the world in incidence and mortality from cervical cancer among World Health Organization (WHO) regions. Several studies analyze screening coverage and accuracy of screening tests as the main reasons for lack of effectiveness; however, reports on follow-up of positive-screened women are scarce. **Aim:** To synthesize the existing knowledge about compliance with follow-up recommendations after an abnormal result of cervical cancer screening. **Methods:** We will search the PubMed via Medline and LILACS databases, with additional searches of grey literature. Inclusion criteria comprise studies on adult women from the Pan American Health Organization (PAHO) affiliated countries, with full text available and with specified data on follow-up outcomes. There are no language or publication date restrictions. Studies on special populations or including only women under age 25 will be excluded. Two reviewers will screen titles and abstracts independently, and two researchers will assess the methodological quality and risk of bias by using validated tools according to type of study. Disagreements will be solved by consensus. **Discussion:** This systematic review will provide information on differences and determinants of effective follow-up of positive-screened women in cervical cancer screening. The use of a Latin American database, the review of grey literature, and the inclusion of studies in all languages will allow us to identify more reports that might be relevant for low and middle income countries (LMIC) accounting with a high burden of disease.

Keywords
Americas; uterine cervical neoplasms; cervical intraepithelial neoplasia; mass screening; lost to follow-up; follow-up studies.

RESUMEN
Introducción: La región de las Américas se encuentra en tercer lugar a nivel mundial en incidencia y mortalidad por cáncer de cuello uterino. Un gran número de estudios han analizado el comportamiento de la cobertura y la precisión de las pruebas como factores determinantes de la efectividad del tamizaje; sin embargo, son escasos los reportes sobre el seguimiento de las mujeres con pruebas positivas. **Objetivo:** Sintetizar la evidencia disponible en las Américas sobre adherencia al seguimiento de las recomendaciones posterior a pruebas anormales. **Métodos:** Búsqueda en Medline y LILACS, complementada con literatura gris. Los criterios de inclusión comprenden mujeres adultas de estados miembro de la Organización Panamericana de la Salud, texto completo e información específica de los desenlaces estipulados. Sin restricción de idioma o fecha de publicación; se excluirán los estudios de poblaciones especiales y que incluyan solo mujeres menores de 25 años. Dos investigadores revisarán títulos y resúmenes de manera independiente; además, evaluarán la calidad metodológica y el riesgo de sesgo usando instrumentos validados. Las discordancias se definirán por consenso. **Discusión:** Esta revisión brindará información de factores determinantes en el seguimiento de mujeres positivas al tamizaje. La búsqueda en literatura gris y en LILACS permitirá la identificación de una mayor cantidad de reportes relevantes en la región.

Palabras clave
Américas; neoplasias del cuello uterino; neoplasia intraepitelial cervical; tamizaje masivo; pérdida de seguimiento; estudios de seguimiento.

Introduction

The Americas region ranks third in the world in incidence and mortality from cervical cancer among World Health Organization (WHO) regions with approximately 74,000 women diagnosed with invasive cancer and 37,000 deaths every year. There are significant disparities within the region, with incidence and mortality rates over three times higher in Latin America and the Caribbean than in North America (1).

Cervical cancer screening has reduced cervical cancer mortality in high- and some high-middle income countries (2,3); however, most low- and middle-income countries (LMIC) have not been successful in cervical cancer control. Several factors are associated with the lack of screening effectiveness in these settings, including low screening coverage, low screening quality, and deficient follow-up of positive-screened women (4). Accordingly, the WHO's initiative for cervical cancer elimination aims to reach, by the year 2030, 90% Human Papilloma Virus (HPV) vaccination coverage for girls under 15 years of age, 70% screening coverage between ages 35 to 45, and 90% treatment of identified precancerous lesions.

Several studies address the status of screening coverage and associated factors and evaluate alternatives to increase women's participation in cervical cancer screening (5–8). Similarly, multiple reviews analyze the accuracy of screening tests (cytology, HPV, visual inspection) as a measure of screening quality (9). In contrast, there are fewer reports on follow-up of women with a positive screening test, which may be a more decisive determinant of cervical cancer mortality in some settings (4), and, to our knowledge, no systematic review regarding this subject has been carried out for countries in the Americas region. Hence, we developed this protocol to summarize the available data regarding follow-up of women screened for cervical cancer in Pan American Health Organization (PAHO) Member States (10). We consider this systematic review relevant, taking into account not only the recently launched WHO global strategy for cervical cancer elimination, but also the regional plans for cervical cancer control (11,12).

Methods

The protocol is registered in the PROSPERO database (ID: CRD42021281055).

Aim and objectives

This systematic review aims to synthesize and report the existing knowledge about compliance with follow-up recommendations after an abnormal result of cervical cancer screening in the Americas region.

This will be achieved by systematically searching, selecting, and synthesizing the existing knowledge to answer our research question. So, the specific objectives are:

1. To summarize data on compliance with triage testing after positive HPV in the Americas region.
2. To summarize data on compliance with diagnostic work-up (colposcopy/biopsy) as indicated after primary screening or after triage testing in the Americas region.
3. To summarize data on compliance with treatment of cervical pre-cancerous lesions in the Americas region.
4. To summarize data on compliance with subsequent screening rounds after negative screening results in the Americas.

Study design

We designed the protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) (Figure 1).

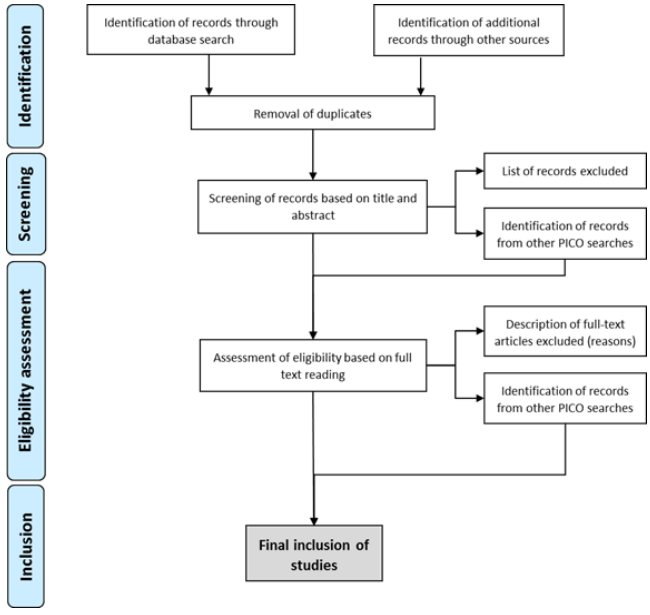

Figure 1
Flowchart of methods according to the PRISMA protocol (13)
Source: Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Dec 4;339(jul21 1):b2700–b2700

Search strategy

We will systematically search in PubMed via the Medline and LILACS databases, and, after that, we will conduct updates and searches for grey literature via the TRIP-database and Google Scholar. Cross-referencing will be used to find additional articles for review.

The Participants, Interventions, Comparators, Outcomes (PICO) question was defined to carry out a structured search as indicated in Table 1. Compliance is defined as the percentage of women undergoing the corresponding procedure within the screening algorithm: triage testing, colposcopy/biopsy, ablative or excisional treatment of precancerous lesions, ablative or excisional treatment after positive screening results in screen-and-treat approaches, new screening round after negative screening results.

We will remove duplicates and publications will be independently screened based on title and abstract by two members of the research team, and all disagreements will be solved by consensus.

Table 1.
PICO question for the systematic review

P	Adult women from the Americas region undergoing cervical cancer screening
I	Follow-up of positive screening results
C	Default
O	Follow-up compliance rate

Search terms

1. Population Adult women AND

"Antigua and Barbuda"[Mesh] OR "Argentina"[Mesh] OR "Bahamas"[Mesh] OR "Barbados"[Mesh] OR "Belize"[Mesh] OR "Bolivia"[Mesh] OR "Brazil"[Mesh] OR "Canada"[Mesh] OR "Chile"[Mesh] OR "Colombia"[Mesh] OR "Costa Rica"[Mesh] OR "Cuba"[Mesh] OR "Dominica"[Mesh] OR "Dominican Republic"[Mesh] OR "Ecuador"[Mesh] OR "El Salvador"[Mesh] OR "Grenada"[Mesh] OR "Guatemala"[Mesh] OR "Guyana"[Mesh] OR "Haiti"[Mesh] OR "Honduras"[Mesh] OR "Jamaica"[Mesh] OR "Mexico"[Mesh] OR "Nicaragua"[Mesh] OR "Panama"[Mesh] OR "Paraguay"[Mesh] OR "Peru"[Mesh] OR "Saint Lucia"[Mesh] OR "Saint Vincent and the Grenadines"[Mesh] OR "Saint Kitts and Nevis"[Mesh] OR "Suriname"[Mesh] OR "Trinidad and Tobago"[Mesh] OR "United States"[Mesh] OR "Uruguay"[Mesh] OR "Venezuela"[Mesh] OR “Latin America”[Mesh] OR “South America”[Mesh] OR “North America”[Mesh] OR “Central America”[Mesh] OR "Caribbean Region"[Mesh] OR "West Indies"[Mesh] OR America OR America’s region OR Americas

2. Intervention

("Mass Screening"[Mesh] OR "Early Detection of Cancer"[Mesh] OR "Early Diagnosis"[Mesh] OR "Diagnostic Screening Programs"[Mesh] OR "Papanicolaou Test"[Mesh] OR "Vaginal Smears"[Mesh] OR Cytodiagnosis[Mesh] OR "Human Papillomavirus DNA Tests"[Mesh] OR "HPV tests" OR "Direct visual inspection" OR "VIA" OR "VILI" OR "Visual Inspection with Acetic Acid" OR "Visual Inspection with Lugol Iodine" OR Colposcopy[Mesh] OR screening)

AND

("Uterine Cervical Neoplasms"[Mesh] OR "Uterine Cervical Dysplasia"[Mesh] OR "Cervical Intraepithelial Neoplasia"[Mesh] OR "Cervical cancer" OR "Cervical pre-cancer" OR "Squamous Intraepithelial Lesions of the Cervix"[Mesh]) NOT (metastatic OR "Neoplasm Metastasis"[Mesh] OR "Lymphatic Metastasis"[Mesh] OR "Breast Neoplasms"[Mesh] OR "Colorectal Neoplasms"[Mesh])

3. Outcome

("Follow-up" OR "Follow-up Studies"[Mesh] OR "Lost to Follow-up"[Mesh] OR "Diagnostic work-up" OR "Treatment compliance" OR " Further assessment rate" OR "Patient Compliance"[Mesh] OR “Colposcopy compliance” OR "Treatment Adherence and Compliance"[Mesh])

Eligibility criteria

We will select papers based on the following criteria:

1. No language restrictions.
2. No publication date range defined
3. Full text availability.

4. Studies including adult women. Studies only on adolescents or upper age limit below 25 years old will be excluded.
5. Studies conducted in populations from PAHO affiliated countries.
6. Outcome specified and data on outcomes available as defined in the PICO question.
7. Studies conducted in the general target population. Studies in special populations will be excluded.
8. Type of study.
    - 8.1. Cross-sectional surveys based on self-report.
    - 8.2. Cross-sectional surveys based on secondary sources (medical records or information systems).
    - 8.3. Cohort studies
    - 8.4. Intervention studies (randomized and non-randomized). Qualitative studies will be excluded.

Quality appraisal

For all included studies, two independent reviewers will assess the methodological quality and risk of bias. For cross-sectional, descriptive and population-based studies, we will use the 20-item appraisal tool for cross-sectional studies (AXIS) (14). Cohort studies will be assessed using the checklist developed by the Scottish Intercollegiate Guidelines Network (SIGN) (15). We are not looking for the efficacy of interventions to improve follow-up rates—rather, we search data on follow-up rates on regular basis of screening programs; therefore, we will assess intervention studies (randomized and not randomized) with the SIGN tool for cohort studies, which would be more suitable for the objectives of the review.

We will include original research; thus, if a review is found as initial source of information, we will search the data in the original papers. However, we will also retrieve data, if available in the review but not in the original paper, and, in such case, we will assess the review quality with the AMSTAR2 instrument.

Data management

Studies retrieved from the search will be listed in Zotero® to identify duplicates. If a given study is published in different journals but having differences in sub-group analyses or presenting updated data, we will extract data from all reports but only the latest data available will be included in the analysis. If related publications presenting different information are found, they will be included in the analysis indicating that they correspond to a group of reports with the same origin (clustered studies).

We will prepare three data extraction sheets in Microsoft Excel®: the first one to register eligibility criteria for all studies selected for full text review; the second one for detailed data extraction from studies finally included in the review; and the third one to register the quality appraisal in detail.

From each study included, we will extract general information (author, title, year of publication, observation period, database source, type of study, and country). We will also extract data on the methods, including sample size, follow-up (cohort studies), eligibility criteria for the study population, age (range, median, mean), and statistics used for significance analysis. Finally, the outcomes will be extracted as absolute numbers, when available, in addition to the corresponding indicator (prevalence rate, percentage, etc.). Odds ratio and relative risks will be collected only if the comparator is the regular care or no-intervention.

Data analysis

Compliance with follow-up will be estimated as the percentage of women undergoing the corresponding procedure (triage, diagnosis, treatment, new screening round) among those with indication of the procedure (referral) within the screening algorithm. The main outcome will be the global compliance (follow-up) rate

summarizing all steps, and additional outcomes will be compliance with triage, compliance with diagnostic workup, compliance with treatment, and compliance with subsequent screening rounds among negative screened women. Depending on availability of information, a composite index will be estimated by adding the women undergoing the procedures in every step until treatment in the numerator and the women referred for the procedures in every step until treatment in the denominator. If detailed data were not available, we will collect data on the global compliance as reported, categorizing the results based on the compliance definition provided. No compliance analysis after treatment will be done and data regarding compliance with subsequent screening rounds after negative screening results will be analyzed separately.

For intervention studies, only data from baseline (for before and after designs) or data from the control arm (for controlled studies) will be included in the general compliance estimates. A sensitive analysis will be carried out with and without data from intervention studies. Data after any intervention under evaluation will be collected and reported separately, and these data will be summarized by type of intervention (health system, provider, patient).

Depending on the results, we will also conduct meta-analysis. We will use Revman5 (Cochrane Collaboration, London, United Kingdom) to prepare our review and possible meta-analysis. For this, we will review heterogeneity and quality of studies in addition to availability of detailed information. We will apply a fixed effects model if the heterogeneity is small and a random effects model if the heterogeneity is high. Variation in values by geographic area (North America, Central America, South America, Caribbean) and type of study are expected. We will use funnel plots (Christmas tree and "trim and fill") to assess possible publication bias. Since these methods are unreliable if the number of studies is less than ten, we will only apply it if there are more than ten studies available.

We will present data considering quality of studies and geographic representation, including differences in outcomes and variability in studies. Other subgroup analyses will be carried out by type of study (cross-sectional, cohort, intervention), program approach (screen-and-treat, screen-diagnose-treat, screen-triage-diagnose-treat), primary screening test (cytology, HPV, visual inspection), treatment modality (ablative, excisional). Other analyses might be possible depending on specific findings.

Discussion

We anticipate finding valuable information for policy makers in the Americas as we aim to provide new data to support actions to accelerate the elimination of cervical cancer in the region.

A reduced incidence and mortality from invasive cancer is the essential objective of cervical cancer screening. However, the impact of screening depends on program organization, and several intrinsic and contextual factors may influence program performance (16). The large variability in successful screening determinants makes difficult to properly analize the association between program performance and cervical cancer incidence and mortality, particularly when no organizaed program is in place and, consequently, no routine program data are available.

Access to diagnostic workup and treatment of precancerous lesions has been proposed as a key factor for reduced screening effectiveness in Latin America and the Caribbean (4). Most LMIC lack organized population-based screening, and screening algorithms requiring several visits challenge women's follow-up and adherence in such settings. Thus, to achieve the WHO target goals for cervical cancer elimination, LMIC should overcome barriers to proper access to screening, diagnosis, and treatment of cervical precancer. The requirement of such effort is common to underserved populations in high-income countries.

Our search is targeted to identify publications on compliance with follow-up algorithms and related factors in the Americas. In this review, the use of a Latin American search engine (LILACS), the review of grey literature, and

the inclusion of studies in all languages will allow us to identify more reports that might be relevant for LMIC with a high burden of disease. We aim to identify differences in follow-up rates according to income level, sub-region of the Americas continent, screening test, and programmatic approach. We also aim at exploring how the study of the subject evolved over time and to summarize the latest evidence on the topic.

We follow an standard methodology (PRISMA-P) (13) and assess the quality of studies to reduce the risk of bias. We believe that the methodological approach guarantees our conclusions to be based on the best available evidence. To our knowledge, despite the significant amount of literature on the subject, no systematic review has been conducted to synthesize the available information in the Americas region. It is paramount to carry out this review to set baseline values for regional indicators facing the challenges of the WHO cervical cancer elimination strategy (17). In addition, we consider that, by improving the knowledge on the current situation regarding the status of women's follow-up as a key component of cervical cancer screening programs we will contribute to enhance regional and country specific plans for cervical cancer control.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/Pan American Health Organization/ World Health Organization, the authors alone are responsible for the views expressed in this document, and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/Pan American Health Organization/ World Health Organization.

Ethical Considerations

This study will not include human or animal participants; therefore, it does not require ethical approval.

Conflict of interests

No competing interests are declared by the authors.

Funding

This study will be funded by the Pan American Health Organization under a contract with Hospital Universitario San Ignacio in Bogotá, Colombia.

References

1. International Agency for Research on Cancer. Global Cancer Observatory. Cancer today [Internet]. 2020 [cited 2021 Jan 29]. Available from: https://gco.iarc.fr/today/home

2. Murillo R, Herrero R, Sierra MS, Forman D. Cervical cancer in Central and South America: burden of disease and status of disease control. Cancer Epidemiol. 2016 Sep;44:S121–30. https://doi.org/10.1016/j.canep.2016.07.015

3. Singh G. Global inequalities in cervical cancer incidence and mortality are linked to deprivation, low socioeconomic status, and human development. Int J MCH AIDS. 2012;1(1).

4. Murillo R, Almonte M, Pereira A, Ferrer E, Gamboa OA, Jerónimo J, et al. Cervical cancer screening programs in Latin America and the Caribbean. Vaccine. 2008 Aug 19;26 Suppl 11:L37-48.

5. Devarapalli P, Labani S, Nagarjuna N, Panchal P, Asthana S. Barriers affecting uptake of cervical cancer screening in low and middle income countries: a systematic review. Indian J Cancer. 2018;55(4):318. https://doi.org/10.4103/ijc.IJC_253_18

6. Majid U, Kandasamy S, Farrah K, Vanstone M. Women's preferences and experiences of cervical cancer screening in rural and remote areas: a systematic review and qualitative meta-synthesis. Rural Remote Health. 2019;19(4):5190. https://doi.org/10.22605/RRH5190

7. Rees I, Jones D, Chen H, Macleod U. Interventions to improve the uptake of cervical cancer screening among lower socioeconomic groups: a systematic review. Prev Med. 2018 Jun;111:323–35. https://doi.org/10.1016/j.ypmed.2017.11.019

8. Mann L, Foley KL, Tanner AE, Sun CJ, Rhodes SD. Increasing cervical cancer screening among US Hispanics/Latinas: a qualitative systematic review. J Cancer Educ. 2015 Jun;30(2):374–87. https://doi.org/10.1007/s13187-014-0716-9

9. Mustafa RA, Santesso N, Khatib R, Mustafa AA, Wiercioch W, Kehar R, et al. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. Int J Gynecol Obstet. 2016 Mar;132(3):259–65. https://doi.org/10.1016/j.ijgo.2015.07.024

10. Pan American Health Organization. Pan American Health Orgnization: Member States [Internet]. [Cited 2021 Sep 16]. Available from: https://www.paho.org/hq/index.php?option=com_content&view=article&id=103:member-states&Itemid=1110&lang=fr

11. Pan American Health Organization. Plan of Action for the prevention and control of HIV and sexually transmitted infections 2016-2021. WHO; 2016. [Internet]. [Cited 2021 Sept 16]. Available from: https://iris.paho.org/handle/10665.2/34081.

12. Pan American Health Organization. Plan of action for cervical cancer prevention and control 2018-2030 [Internet]. PAHO; 2018 [cited 2021 Sept 16]. Available from: https://www.paho.org/hq/index.php?option=com_docman&view=download&category_slug=mandates-strategies-3448&alias=47584-plan-cervical-cancer-2018-2030&Itemid=270&lang=en

13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Dec 4;339(jul21 1):b2700–b2700. https://doi.org/10.1136/bmj.b2700

14. Downes MJ, Brennan ML, Williams HC, Dean RS. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). BMJ Open. 2016 Dec;6(12):e011458. https://doi.org/10.1136/bmjopen-2016-011458

15. Scottish Intercollegiate Guidelines Network. Critical appraisal notes and checklists [Internet]. [Cited 2021 Sept 16]. Available from: https://www.sign.ac.uk/checklists-and-notes

16. de Sanjose S, Holme F. What is needed now for successful scale-up of screening? Papillomavirus Res. 2019 Jun;7:173–5. https://doi.org/10.1016/j.pvr.2019.04.011

17. World Health Organization. Draft: Global Strategy Towards the Elimination of Cervical Cancer as a Public Health

Program. [Internet]. 2020. Available from: https://www.who.int/publications/m/item/draft-global-strategy-towards-eliminating-cervical-cancer-as-a-public-health-problem