SYMPOSIUM CANCER OF THE CERVIX UTERI

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Is it time for Peru to adopt the nine-valent vaccine?

¿Es momento de pasar a la vacuna nonavalente en Perú?

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ABSTRACT

Cervical cancer remains a challenge worldwide, especially in middle- and low-resource countries. HPV vaccination is one of the most important weapons included in the WHO's goals for 2030. The need to use a single dose is increasingly accepted in various national programs. The comparison of one, two, and three doses of HPV vaccines is very important to understand the changes occurring in the national policies of different countries. In Peru, the national vaccination program uses a single dose of the tetravalent vaccine from 9-18 years of age, gender-neutral.

Key words: Uterine cervical neoplasms, Vaccines, Human papilloma virus, Papillomavirus vaccines, Nonavalent vaccine, Peru

RESUMEN

El cáncer de cuello uterino sigue siendo un reto en el mundo, especialmente en países de recursos medianos y bajos. La vacunación contra el VPH es una de las armas más importantes incluida en las metas de la OMS para el 2030. La necesidad de usar una sola dosis es cada vez más aceptada en los diferentes programas nacionales. La comparación de una, dos y tres dosis de las vacunas contra el VPH es muy importante para entender los cambios que se están dando en las políticas nacionales de diferentes países. En el Perú, el programa nacional de vacunación utiliza una sola dosis de la vacuna tetravalente desde los 9 hasta los 18 años de edad, género neutro.

Palabras clave: Neoplasias del cuello uterino, Vacunas, Virus del papiloma humano, Vacuna contra Papilomavirus, Vacuna nonavalente, Perú

Introduction

Cervical cancer generates 604,127 new cases each year worldwide, ranks fourth in mortality, and is the second leading cause of cancer in women aged 15-44[1].

It is estimated that in Peru there are 4,809 new cases of invasive cervical cancer per year, according to the Global Cancer Observatory - Globocan[2], with an incidence of 23.9 and a mortality rate of 12.1 per 100,000 women.

In November 2020, the World Health Organization - WHO proposed a global strategy for the elimination of cervical cancer, aiming to reach 4 cases per 100,000 women and proposing 3 fundamental pillars for 2030[3]:

1. 90% of women aged 9-14 must be vaccinated against the human papillomavirus (HPV).

2. 70% of women should be screened with high-precision tests.

3. 90% of women with high-grade premalignant lesions and cancer cases must be treated.

Despite all the efforts made, in Peru 80% of cervical cancer cases continue to be identified at advanced stages, stages that require systemic treatment with chemotherapy and radiotherapy, with limitations at the public level for access. The Ministry of Health -MINSA- of Peru has 10 healthcare facilities that provide radiotherapy services, 4 with their

own services [Goyeneche Hospital in Arequipa, Regional Institute of Neoplastic Diseases - IREN SUR in Arequipa (southern coast of Peru), IREN Centro (Junín, central Peru), and the National Institute of Neoplastic Diseases – INEN (Lima)] and 6 with outsourced services [IREN Norte (northern coast of Peru), Regional Hospital of Lambayeque (northern coast), and María Auxiliadora Hospital, Loayza Hospital, Dos de Mayo Hospital, and National Children's Institute of San Borja (the 4 located in Lima)] (Table 1). This equipment scenario does not make it possible to treat all diagnosed women.

HPV vaccines

The HPV vaccine was introduced into the Peruvian vaccination schedule in 2011, starting with the bivalent vaccine for girls aged 10-15 with 3 doses. In 2014, the quadrivalent vaccine was introduced for girls aged 10-13 with 3 doses, switching to two doses in 2016. In 2023, gender-neutral vaccination was introduced for girls and boys aged 9-13 with a single dose, in line with the recommendation proposed by the WHO[4]. And, due to the effect of the COVID pandemic, vaccination coverage dropped from 78% in 2019 to 20% in 2020. In 2024, it was proposed to update the vaccination for men and women up to 18 years old with a single dose. Based on schools, the current coverage under the nominal population has been close to 100% (figure 1)[6-7].

The first evidence of the efficacy of the single dose in the prevention of HPV infection was in 2011 with the CVT (Costa Rica Vaccine Trial) study, which used the bivalent vaccine (*Cervarix*) comparing three doses versus a control group in

Table 1. Equipment and resources. Radiotherapy equipment, location, and assigned population.

Region	Health facilities	Service	Service location	Assigned population
Arequipa	Hospital Goyeneche	P		Southern macro region: Arequipa: 1'177,200 Cusco: 460,325 Puno: 1'172,697 Moquegua: 187,941 Tacna: 332,273 Madre de Dios: 141,070
Arequipa	Instituto Regional de Enfermedades Neoplásicas – IREN SUR	P		
Junín	Instituto Regional de Enfermedades Neoplásicas	P		Center macro region: Ancash: 1'083,519 Ucayali: 496,459 Junín: 1'246,038 Huánuco: 847,714 Pasco: 271,950 Huancavelica: 509,117
La Libertad	Instituto Regional de Enfermedades Neoplásicas – INRE NORTE	T	Inside the hospital	Northern macro region: Tumbes: 224,863 Piura: 1'856,809 Lambayeque: 1'020,000 La Libertad: 1'778,080 Cajamarca: 1'341,012 Amazonas: 332,975 San Martin: 840,790
Lambayeque	Hospital Regional de Lambayeque	T	Out of the hospital	
Lima	Hospital María Auxiliadora	T	Out of the hospital	Integrated Health Network Directions - DIRIS Lima South 2'498,264 At the national level
Lima	Hospital Nacional Arzobispo Loayza	T	Out of the hospital	DIRIS Lima Center: 2'602,377 At the national level
Lima	Hospital Nacional Dos de Mayo	T	Out of the hospital	DIRIS Lima Center: 2'602,377 At the national level
Lima	Instituto Nacional de Enfermedades Neoplásicas - INEN	P	Inside the hospital	DIRIS Lima Center: 2'602,377 At the national level
Lima	Instituto Nacional de Niño de San Borja	T	Out of the hospital	DIRIS Lima Center: 2'602,377 At the national level

7,153 women. Vaccine efficacy was determined using HPV infection and persistent HPV infection as endpoints. 5.4% (196/3,575 women) received only one dose of vaccine for reasons unrelated to the vaccine. After 4 years of follow-up, efficacy was found to be similar when comparing three doses, two doses, and the single-dose vaccine group[8]. This study was not designed to evaluate this comparison, one dose versus three doses of HPV vaccine. However, the incidental finding was cause for great attention. On the other hand, after one dose, antibodies remain above 9-fold of natural infection, although at a lower level than with the three doses. However, we do not know what is the minimum level of antibodies necessary for permanent protection

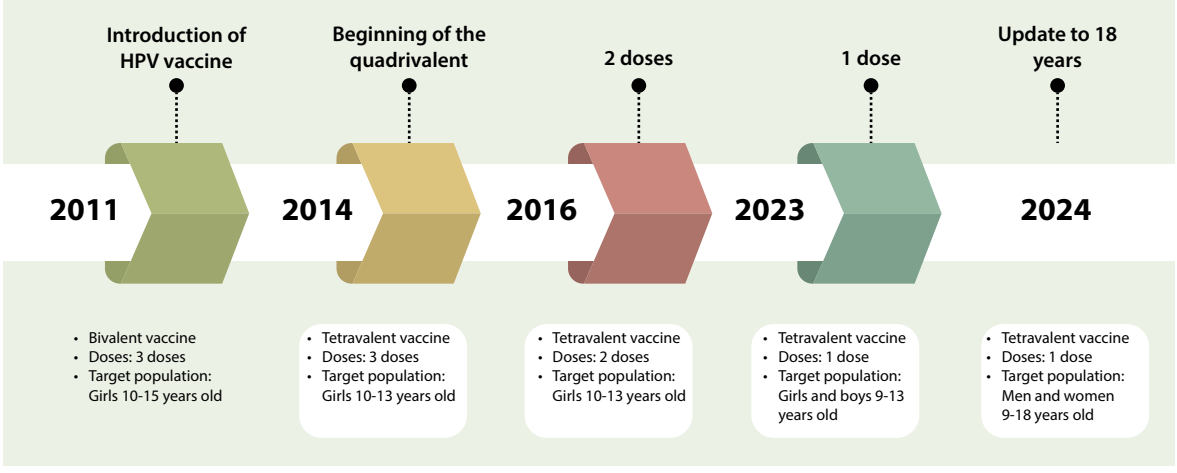
Additionally, it has been found that the protection has persisted even up to 16 years of follow-up. This was presented in 2023 at the 35th International Papillomavirus Conference, which reinforces the value of the finding, as the study population has had greater exposure to HPV with more years of follow-up[9].

In 2009, the International Agency for Research on Cancer (IARC) initiated a multicenter national study in India with the quadrivalent vaccine (*Gardasil*). The initial design of the study was to compare two versus three doses of the vaccine. However, having started the study, the government of India suspended its continuation, leaving patients with one, two, and three doses who were followed for more than 10 years. The protection found against persistent infection with HPV 16/18 with one, two, and three doses of the quadrivalent vaccine was similar[10].

The third study regarding the use of a single dose of the HPV vaccine began in 2017 in Tanzania and is known as DoRIS. (Dose Reduction Immunobridging and Safety). The bivalent vaccine (*Cervarix*) and the nonavalent vaccine (*Gardasil*) were used, comparing one versus two and three doses in a population of 1,002 schoolchildren aged 9-14, with the final comparison point being the levels of antibodies against HPV 16/18. The result at 24 months -which is a short time- showed positive seroconversion in 99% and 98% for HPV 16 and HPV 18, respectively, with a single dose compared to two and three doses in both vaccines. The non-inferiority criterion was met in such a short time for HPV 16, but not for HPV 18. It is important to note that the antibody levels were as high as those observed in the CVT and IARC studies. These results suggest the high efficacy of a single dose of these vaccines[11].

The most recent published study began in 2018 in Kenya and is known as KEN SHE (KENya Single-dose HPV vaccine Efficacy). It is a multicenter, randomized, double-blind study. A dose of the nonavalent vaccine (*Gardasil*-9), the bivalent vaccine (*Cervarix*), and in a third group the meningococcal vaccine were used (control group). The number of incident and persistent cases infected with HPV 16/18 and HPV 16/18/31/33/45/52/58 was compared. 2,275 women aged 15-20 were included. The protection against HPV 16/18 was 98.8% with the nonavalent vaccine and 97.5% with the bivalent vaccine. On the other hand, the protection against HPV 16/18/31/33/45/52/58 with the nonavalent vaccine was 95.5% with three years of follow-up[12].

Figure 1. Evolution of the indication for HPV vaccines to a single dose against HPV[6,7].



The single dose versus two or three doses of the HPV vaccine is ideal for simplifying its administration, increasing coverage, and reducing costs. This vaccine is a virus-like particle (VLP) that does not contain DNA, self-assembles after application, generates strong immunity with a single dose, a stimulus similar to that achieved with whole virus vaccines, highly immunogenic instead of a subunit vaccine. This supports a biological mechanism for the efficacy of the single dose[13].

These studies have led to the WHO recommending one or two doses of HPV vaccines for children, adolescents, and young adults aged 9-20 in April 2022. However, data on the long-term durability of single-dose HPV vaccination is still awaited. Four HPV vaccines have been approved by the WHO (*Cervarix, Cecolin, Gardasil and Gardasil-9*). At least 15 countries have established the use of 'a single dose' in their national HPV vaccination program, including Peru. In 2023, the national vaccination program of MINSA standardized gender-neutral vaccination with a single dose of the quadrivalent vaccine for ages 9-13, extending it for both women and men up to 18 years old. Administering a single dose of the vaccine will help us get closer to the WHO's goal, which includes achieving 90% coverage in the population under 15 years of age by 2030. Moreover, it will have a greater impact on public health than continuing with two or three doses. Given these results and perspectives, it is important to transition to a nonavalent vaccination in a single dose with a public health vision to reach a larger population.

Screening

According to the Demographic and Family Health Survey (ENDES, for its initials in Spanish) the coverage of cervical cytology screening (Pap smear - PAP) in the last 3 years has been 47.5% of the population[14]. The data from the ESTAMPA study define that the sensitivity for the identification of CIN 3+ is 48.5% (95% CI: 44-53)[15]. In the 2017-2021 cervical diagnosis and treatment guidelines, the HPV molecular test is proposed as the ideal test for women aged 30-49, and the incorporation of this strategy would be gradual[16]. This proposal has been reinforced with successive regulatory documents. By September 2024, the MINSA has incorporated 25 HPV processing centers at the primary care level (Table 2), and the strategy under opportunistic screening is inviting women to take the test either by a healthcare provider or self-collection, finding that 82% of women accept using self-collection, and that the findings for self-collection and provider collection have not shown significant differences in the first 45,708 women evaluated. The prevalence found for HPV is 15.2% with 1.1% of invalid (test's inability to identify HPV infection) results[17].

The systematic review of 111,000 HPV-positive women in cervical cancer cases in the global literature has found that the attributable fraction (AF) of HPV16 for cancer is 61.7%, the cumulative rate of HPV 16 -HPV18 is 77.0%, and the cumulative rate of the eight genotypes HPV 16, 18, 31, 33, 35, 45, 52, and 58 is 94.7%[18]. These data are key to predicting the potential impact of the benefit of incorporating the nonavalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) into the immunization strategy.

Table 2. Laboratories for processing HPV tests. There are 22 real-time PCR machines available for the detection of HPV DNA.

Ayacucho	Reference laboratory of Ayacucho
Cajamarca	Reference laboratory of Cajamarca
Callao	Rehabilitation hospital of Callao
Cusco	Reference laboratory of Cusco
Huancavelica	Reference laboratory of Huancavelica
Huánuco	Reference laboratory of Huánuco
Ica	Reference laboratory of Ica
Junin	Hospital of Chanchamayo "Julio César Dimarini Caro"
Lambayeque	Reference laboratory of Lambayeque
Libertad	Hospital I distrital Vista Alegre – La Libertad
Lima	DIRIS Lima center
Lima	DIRIS Lima east
Lima	DIRIS Lima north
Lima	DIRIS Lima south
Lima Region	Health Center base Huaral
Loreto	Laboratory of molecular biology – Loreto
Madre de Dios	Reference laboratory of Madre de Dios
San Martín	Reference laboratory of San Martín
Piura	Reference laboratory of Piura
Tacna	Reference laboratory of Tacna
Tumbes	Reference laboratory of Tumbes
Ucayali	Reference laboratory of Ucayali

Source: LP16-2024-CENARES-MINSA

New proposals

The HPV-FASTER strategy proposes[19]:

1. Continue the vaccination of women aged 9-14.

2. Catch up with women up to at least 25-30 years old.

3. Offer vaccination to women aged 30-45.

Additionally, women aged 25-30 and older will be offered HPV screening with concurrent follow-up (triennial and diagnostic) for women affected by HPV and, if necessary, treatment for pre-cancerous lesions.

The advantages of HPV FASTER are that the anticipated subsequent needs for screening can be drastically reduced to one or two lifetime visits, increasing sustainability and compliance, as well as alleviating the burden and workload in healthcare centers, which are typically already overloaded with patient care[15].

HPV-FASTER protocols could be used as geographically adapted cross-sectional campaigns that would greatly reduce repeated screening visits for women, which has proven to be a barrier to sustainability in low- and middle-income countries (LMIC).

Another concept is EVEN FASTER, which is based on[20]:

1. Use the HPV reproduction rate (or related measures) to determine the optimal age groups to target with a FASTER vaccination and screening campaign.

2. Use specific screening campaigns, instead of programs that require long-term infrastructure. Here it is suggested that the optimal maximum age for HPV vaccination be defined first by considering the contribution of each age group to the circulation of HPV infection in the population.

The main objective of secondary prevention is to achieve high treatment rates. Here we find our most important barrier. The geographical characteristics, access, idiosyncrasy, the gap in human resources and equipment make it so that we still cannot ensure the treatment of suspected or positive cases. According to the Directorate of Cancer Prevention and Control, we have 153 colposcopes, 62 LEEP units, 160 cryotherapy units, and 265 thermocoagulation units. These equipments are insufficient for the disease burden we have, not to mention that the list of equipment used in secondary prevention described has a short lifespan (Table 3).

Additionally, the need for follow-up of the treated patient must be reinforced. In the Bogani study, it was determined that, out of 2,966 women treated with LLETZ or LEEP conization, approximately 8.1% experienced recurrence at 5 years[21,22].

In the study by Torres et al., cervical cancer deaths were obtained from the World Health Organization's mortality database. They estimated age-standardized mortality rates per 100,000 woman-years in women aged 20-44 using the world standard population for 16 countries (and territories) in Latin America and the Caribbean (LAC) from 1997 to 2017. The average mortality rates over 4 years (2014-2017) were estimated, finding that, in relation to the mortality of young women by the year 2030, Argentina, Brazil, Paraguay, and Venezuela showed an upward trend for 2030, while Nicaragua, Panama, and Peru showed a downward trend. Other factors that could increase cervical cancer mortality in LAC are social inequalities, low-income environments, and the difficulty in accessing prompt and adequate healthcare[23].

Finally, since we do not have the equipment to treat advanced cases, the strategies used have had no impact, and the equipment for secondary prevention is very limited. We should consider modifying the strategy by directing it towards the creation of units for managing premalignant lesions at the primary care level with HPV tests and ensuring the treatment of positive cases. Vaccination coverage must be maintained and, given that it is the best result achieved, improved by incorporating nonavalent vaccination in a public health vision with a single dose in a wider vaccination

Table 3. Equipments in MINSA for the treatment of premalignant lesions.

Equipments	Number of equipments
Colposcopes	153
LEEP equipments	62
Cryotherapy equipments	160
Thermocoagulation equipments	265

range (9-26 years), to achieve herd effect in the population. Likewise, incorporate new screening campaign strategies associated with vaccination, to reduce the number of interventions as a potential tool to be used in specific areas.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49. https://doi.org/10.3322/caac.21660
2. World Health Organization. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention, second edition: use of mRNA tests for human papillomavirus (HPV): web annex: evidence-to-decision framework for mRNA testing for HPV [Internet]. World Health Organization; 2021 [cited 29 March 2022]. iii, 11 p. https://apps.who.int/iris/handle/10665/350557
3. Wilailak S, Kengsakul M, Kehoe S. Worldwide initiatives to eliminate cervical cancer. Int J Gynecol Obstet. 2021;155(S1):102-6. doi: 10.1002/ijgo.13879
4. Santé WHO. O mondiale de la Weekly Epidemiological Record. 2022;97:50 [full issue]. Wkly Epidemiol Rec Relevé Épidémiologique Hebd. 16 December 2022;97(50):645-72. https://iris.who.int/handle/10665/365350
5. Repositorio único nacional de información en salud. https://www.minsa.gob.pe/reunis/data/Indicadores_Inmunizaciones.asp
6. Venegas Rodríguez G, Jorges Nimer A, Galdos Kajatt O. Vacuna del papilomavirus en el Perú. Rev peru ginecol obstet. [Internet]. 3 December 2020 [cited 29 March 2022];66(4). DOI: 10.31403/rpgo.v66i2286
7. Norma técnica N.° 196-MINSA/DGIESP-2022 [Internet]. [cited 17 October 2024]. https://www.gob.pe/institucion/rishuamalies/normas-legales/4249834-196-minsa-dgiesp-2022
8. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine - PubMed [Internet]. [cited 17 October 2024]. https://pubmed.ncbi.nlm.nih.gov/21908768/
9. Bénard É, Drolet M, Laprise JF, Gingras G, Jit M, Boily MC, et al. Potential population-level effectiveness of one-dose HPV vaccination in low-income and middle-income countries: a mathematical modelling analysis. Lancet Public Health. 1 October 2023;8(10):e788-99. doi. 10.1016/S2468-2667(23)00180-9
10. Basu P, Malvi SG, Joshi S, Bhatla N, Muwonge R, Lucas E, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. Lancet Oncol. November 2021;22(11):1518-29. DOI: 10.1016/S1470-2045(21)00453-8
11. Watson-Jones D, Changalucha J, Whitworth H, Pinto L, Mutani P, Indangasi J, et al. Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls (DoRIS): an open-label, randomised, non-inferiority trial. Lancet Glob Health. October 2022;10(10):e1473-84. DOI: 10.1016/S2214-109X(22)00309-6
12. Barnabas RV, Brown ER, Onono MA, Bukusi EA, Njoroge B, Winer RL, et al. Durability of single-dose HPV vaccination in young Kenyan women: randomized controlled trial 3-year results. Nat Med. 4 December 2023;29(12):3224. DOI: 10.1038/s41591-023-02658-0
13. Lowy DR. HPV vaccination to prevent cervical cancer and other HPV-associated disease: from basic science to effective interventions. J Clin Invest. 4 January 2016;126(1):5. doi: 10.1172/JCI85446
14. Encuesta Demográfica y de Salud Familiar (ENDES) 2017 - [Instituto Nacional de Estadística e Informática - INEI] | Plataforma Nacional de Datos Abiertos [Internet]. [cited 27 October 2024]. https://www.datosabiertos.gob.pe/dataset/encuesta-demogr%C3%A1fica-y-de-salud-familiar-endes-2017-instituto-nacional-de-estad%C3%ADstica-e
15. Ramírez AT, Valls J, Baena A, Rojas FD, Ramírez K, Álvarez R, et al. Performance of cervical cytology and HPV testing for primary cervical cancer screening in Latin America: an analysis within the ESTAMPA study. Lancet Reg Health – Am [Internet]. 1 October 2023 [cited 17 October 2024];26. DOI: 10.1016/j.lana.2023.100593
16. Guía de práctica clínica para la prevención y manejo del cáncer de cuello uterino. Guía técnica [Internet]. [cited 17 October 2024]. https://www.gob.pe/institucion/minsa/informes-publicaciones/284801-guia-de-practica-clinica-para-la-prevencion-y-manejo-del-cancer-de-cuello-uterino-guia-tecnica
17. Venegas C, Matos Orbegozo A, Palacios V, Benites V, Baena, Rolando Herrero A, Almonte M, et al.. Implementation of a Primary Screening Program with DNA HPV Testing in Lima, Junin and Loreto (Peru): Self-Sampling Experience. PDF Flip [Internet]. [cited 29 October 2024]. https://info.kenes.com/Flip/IPVC23_IPVC%202023%20-%20Abstracts%20E-Book/
18. Schiffman M, de Sanjose S. The rational design of cervical cancer prevention strategies. Lancet Lond Engl. 3 August 2024;404(10451):406-7. DOI: 10.1016/S0140-6736(24)01547-2
19. Bosch FX, Robles C, Bosch FX, Robles C. HPV-FASTER: Combined strategies of HPV vaccination and HPV screening towards a one visit for cervical cancer preventive campaigns. Salud Pública México. December 2018;60(6):612-6. DOI: https://doi.org/10.21149/10171
20. The EVEN FASTER concept for cervical cancer elimination [Internet]. [cited 22 October 2024]. https://www.hpvworld.com/articles/the-even-faster-concept-for-cervical-cancer-elimination/
21. Bogani G, DI Donato V, Sopracordevole F, Ciavattini A, Ghelardi A, Lopez S, et al. Recurrence rate after loop electrosurgical excision procedure (LEEP) and laser Conization: A 5-year follow-up study. Gynecol Oncol. December 2020;159(3):636-41. DOI: 10.1016/j.ygyno.2020.08.025
22. Venegas-Rodríguez G, Cardoza-Jiménez K, Alvarez M, Santos C, Mariátegui JC, Velarde C, et al. Recurrencia/persistencia de neoplasia intraepitelial cervical posterior a cono LEEP en el Instituto Nacional de Enfermedades Neoplásicas. Horiz Méd Lima. January 2017;17(1):6-10. http://www.scielo.org.pe/scielo.php?script=sci_arttext&pid=S1727-558X2017000100002&lng=es
23. Torres-Roman JS, Ronceros-Cardenas L, Valcarcel B, Bazalar-Palacios J, Ybaseta-Medina J, Carioli G, et al. Cervical cancer mortality among young women in Latin America and the Caribbean: trend analysis from 1997 to 2030. BMC Public Health. 16 January 2022;22(1):113. doi:10.1186/s12889-021-12413-0