RESEARCH ARTICLE

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Spatial Epidemiology of Human Papillomavirus Screening Coverage in Mexico, 2013-2019

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Abstract

Objective: We aimed to assess the coverage of a Human Papillomavirus (HPV) screening program for each of the 32 federal states of Mexico, as well as the spatial patterns for HPV infections from 2013 to 2019. **Methods:** We conducted an exploratory, ecological study on data from a national health program in Mexico during 2013-2019. Adjusted rates per 100,000 females aged 25-64 years were estimated and georeferenced at the national and state level to assess the coverage of the screening program and positive detections of HPV infections. Cluster analysis was used to identify the location, magnitude, and trends of spatial patterns (p <0.05) by year and state. **Results:** 2,529,819 screening tests for HPV detection were analyzed (2013-2019). A prevalence of HPV positivity of 11.1% (n= 228,582) was estimated. The number of HPV screening tests decreased from 2,835.4 (2013) to 0.8 (2019) per 100,000 females aged 25 to 64. HPV detection also showed a downward trend. A cluster (p <0.05) associated with a higher probability of detecting HPV infections was identified, comprised of territorially close states. **Conclusion:** A decreased coverage of the HPV screening program and geographic differences were identified, suggesting that the existing strategies to prevent and detect HPV infections to accelerate cervical cancer elimination in Mexico need to be further reconsidered.

Keywords: Human Papillomavirus (HPV)- Papillomavirus Infections- National Health Programs- Public Health

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Introduction

Human Papillomavirus (HPV) is one of the most common sexually transmitted infections worldwide. A great number of sexually active people are estimated to be infected with HPV at some point in their lives [1, 2]. HPV infection occurs sexually, as well as through skin-to-skin contact. Moreover, HPV has been identified to be transmitted via direct contact with wounds, abrasions, and infected objects [2]. There are more than 200 types of HPV and one can be infected with more than one type of HPV at the same time. This is because there are high-risk and low-risk HPVs, based on their potential to cause cancer or genital warts, respectively [1, 2].

High-risk HPV's are usually persistent and associated with nearly 5% of cancers worldwide, as they can occur among female and male individuals. HPV infection has been linked to anal, vulvar, vaginal, oral, throat, penile, and, especially, cervical cancer (CC). The latter is the most common type of cancer caused by HPV, particularly genotypes 16 and 18, which both are estimated to occur in approximately 70% of cases of CC worldwide [1-3]. Consequently, screening secondary prevention becomes relevant, since it allows timely detection of HPV to anticipate larger risk scenarios, such as the occurrence of lesions associated with CC, or worse yet, mortality rates.

Since 2020, cervical cancer has become the fourth cause of death among females worldwide [4]. The incidence and prevalence cause higher mortality rates in low- and middle-income countries [2]. Latin America has the second highest prevalence of cervical cancer worldwide (16%), only surpassed by sub-Saharan Africa (24%). Furthermore, it is the leading cause of death in females from six countries in the region [1, 2].

In Mexico, cervical cancer (CC) is the second most common cancer in females [5], with an age-standardized incidence of 7.3 to 11.5 cases per 100,000 females, while the age-standardized mortality rate has reported 9.4 cases per 100,000 females [4]. Recent investigations have reported different prevalence rates for HPV in the country. For females living in the southern region a prevalence of 54.17% was detected [6]; while in the western region, 74.5% [7]. 11.2% of females were identified to be at high risk of developing HPV in the state of Tlaxcala [8], whose magnitude was higher among females aged 35 to 39 years [9]. Likewise, genotypes 16 and 18 have been reported to

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occur more frequently in Mexican females [7, 8, 10, 11].

Studying local epidemiological data is essential to developing targeted health interventions [7], as more evidence with more territorial precision is generated to address prevention actions in places where the need is greatest or focus health services on certain territories to deal with health inequalities and inequities [12, 13]. Thus, more epidemiological studies using georeferenced data to assess the magnitude, distribution, and possible spatial patterns of priority public health concerns, such as HPV infection, because it is a preventable cancer, are further necessary.

Currently, in Latin America geographical analysis of the distribution and magnitude of HPV infection cases is not studied. In Mexico, it has particularly been suggested that the distribution of HPV infection is territorially different not only at the regional level but also for each state, though certainly no study using spatial analysis tools that show such a scenario has been conducted [5]. Therefore, this study aimed to assess the coverage of a screening program for the Human Papillomavirus (HPV) at the national and state levels, as well as the spatial patterns of HPV infections from 2013 to 2019.

Materials and Methods

An exploratory, ecological study was conducted according to the results of the Specific Action Initiative for the Prevention and Control of Cancer of the Ministry of Health of Mexico [14], which explored medical units of the National Health System located throughout the 32 federal states comprising Mexico (Figure 1).

Data source and study period

The 2013-2019 secondary data we used belong to the public domain, and were reported by the National Center for Gender Equity and Reproductive Health (CNEGSR per its Spanish acronym) of the Ministry of Health of Mexico. Given that our study analyzed secondary epidemiological data, the approval of the Research and Bioethics Committee was not obtained. However, it met current national regulations and the STROBE statement.

In the National Health System of Mexico, the Specific Action Initiative for the Prevention and Control of Cancer sets as one of its priority objectives the timely detection of cervical cancer through cervical cytology and the HPV test. The latter is detected via laboratory tests using

01	Aguascalientes	AGS	17	Morelos	MOR
02	Baja California	BC	18	Nayarit	NAY
03	Baja California Sur	BCS	19	Nuevo Leon	NL
04	Campeche	CAMP	20	Oaxaca	OAX
05	Coahuila	COAH	21	Puebla	PUE
06	Colima	COL	22	Queretaro	QRO
07	Chiapas	CHIPS	23	Quintana Roo	QROO
08	Chihuahua	CHIH	24	San Luis Potosi	SLP
09	CDMX	CDMX	25	Sinaloa	SIN
10	Durango	DGO	26	Sonora	SON
11	Guanajuato	GTO	27	Tabasco	TAB
12	Guerrero	GRO	28	Tamaulipas	TAMPS
13	Hidalgo	HGO	29	Tlaxcala	TLAX
14	Jalisco	JAL	30	Veracruz	VER
15	Mexico	MEX	31	Yucatan	YUC
16	Michoacan	MICH	32	Zacatecas	ZAC

Figure 1. Geographical Demarcation of Mexico and Location of the 32 States Comprising Mexico. Source: Prepared by the authors according to the 2013-2019 Specific Action Initiative for Prevention and Control of Cancer.

molecular biology methods, such as the Polymerase Chain Reaction (PCR) and Hybrid Capture (HC2), which are practiced among women aged 25 to 64 years. If the results are normal, then they are practiced again five years later [1, 12].

Statistical and geospatial analysis (National and state analysis)

Different analyses were performed using the variables available for each year. First, a bivariate analysis was done using the chi-squared test (Xi2) for the relationship between the affiliation type of eight health institutions and the HPV results reported by PCR or HC2 tests (positive, negative, null) during the 2013-2015 period. Furthermore, in this same period, the result of PCR tests according to genotypes 16 and 18 was reported, so the percentage distribution of positive tests was analyzed for each state.

Subsequently, adjusted rates per 100,000 females were estimated according to age group and year to analyze the program coverage nationwide, where the numerator was the total number of tests performed (negative, positive, and null) via PCR and HC2 during the study period, apart from the risk of HPV infection by federal state, which considered the total number of PCR and HC2 tests that were positive by federal state. The denominator for both rates was the women population aged 25-64 years reported in Mexico in mid-year during the period 2013-2019, which corresponded to the population projections for Mexico and the federal states (2020-2050) and the National Population Council (CONAPO per its Spanish acronym) [15].

Rate results were presented using choropleth maps to visualize the distribution and magnitude of the coverage for the Specific Action Initiative for Prevention and Control of Cancer per 100,000 women aged 25-64 years. This age range was chosen because the data used for this study were available for the same age group.

Finally, a spatial cluster analysis was used to statistically assess ($p < 0.05$) the distribution of HPV-positive detection rates according to their location [16]. As a result, the states were classified into the following categories: High-High (high values among states with high values), High-Low (high values among states with low values), Low-High (low values among states with high values), and Low-Low (low values among states with low values). Additionally, temporal changes for each state were assessed using the local spatial autocorrelation index [17], also known as local Moran's I, to identify whether the spatial clusters were located in any particular area, there were significant changes, or whether they remained in similar places during the study period. The results for each year were presented using Moran scatter plots. Pattern and map assessments were made using QGIS software version 3.22.3 (Creative Commons Corporation, Mountain View, California, United States) and GeoDa software version 1.20.0.8 (General Public License, Chicago, Illinois, United States).

Results

From 2013 to 2019 2,529,819 HPV screening tests were reported as part of the Mexican Ministry of Health's program. 2014 was the year with the highest number of diagnoses (n= 901,446) and positive cases (n= 84,117). An estimated prevalence of HPV infection was 11.1% (n= 228,582), considering the number of tests performed during the study years.

According to the positive tests reported by PCR nationwide, the percentage of HPV infection ranged between 0.3% (2014) and 13.1% (2019), while the HC2-positive tests ranged between 0.1% (2019) and 11.9% (2018). However, when considering the years in which PCR-positive tests were reported for genotype 16, the values were 0.9% (2014) and 1.1% (2015), while for genotype 18 were 0.3% (2014) and 0.4% (2015).

At the state level, PCR tests for genotypes 16 and 18 were reported by only five states, with Tlaxcala (central region) reporting the highest number of positive tests for genotype 16 in 2014: 36 positive tests (70.6%) out of 51 ($p = 0.000$); while in 2015, Jalisco (western region) reported 611 (61.2%) positive tests out of 999 ($p = 0.000$). Whereas Tlaxcala (17/19, 89.4%) and Jalisco (262/424,61.8%) were also the states with the most positive tests reported for both years ($p = 0.000$) among the five states.

When considering the eight health institutions that reported screening tests for HC2 during the three-year period 2013-2015, the Mexican Social Security Institute (IMSS per its Spanish acronym) performed the highest number of tests for each year compared to the other health institutions ($p = 0.000$). The tests conducted at IMSS that were positive showed the following percentage distribution: 7.6% (2013), 4.5% (2014), and 8.4% (2015), respectively.

Figure 2 shows a downward trend concerning the number of tests performed to detect HPV per 100,000 women aged 25-64, which accounted for a percentage change of >95% during the study period. In this context, the HPV infection rate also decreased (Figure 3), ranging from 264.6 (2013) to 0.1 (2019) per 100,000 women aged 25-64 years nationwide. Although both indicators showed a downward trend, 2014 registered the highest value and probability of detecting HPV per 100,000 females aged 25-64.

Figure 4 shows the temporal and spatial variations when conducting HPV screening tests among females nationwide. It should be noted that both the State of Mexico (central region) and Guanajuato (western region) registered the highest coverage in 2013 (230 to 281.1 HPV detection tests performed per 100,000 females aged 25-64 years) and 2019 (0.10 to 0.13 HPV detection tests performed per 100,000 females aged 25-64 years).

While in the southeastern states (Campeche, Yucatan, and Quintana Roo), the lowest coverage values were observed during the study period. In this sense, it is worth mentioning that in 2017 and 2018 there were some states located territorially close to each other in the western, Pacific, and southern areas of Mexico with lower coverage compared to other locations, that is, between 0.01 (2017) and 0.08 (2018) HPV detection tests performed per 100 thousand females aged 25-64 years.

However, states in the northern (2013-2015), western, and southern regions (2016-2017) reported a lower number

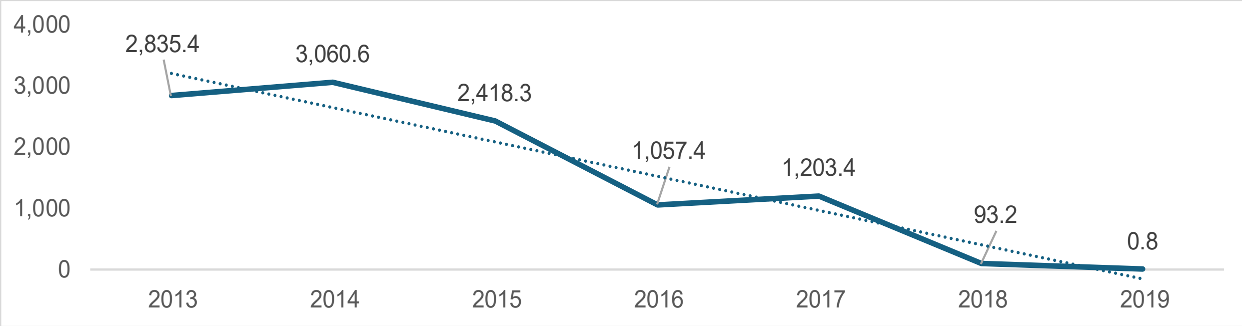

Figure 2. Trend Concerning High-Risk HPV Screening Tests among Females Aged 25 to 64 Years in Mexico, 2013-2019. Source: Prepared by the authors according to the 2013-2019 Specific Action Initiative for Prevention and Control of Cancer.

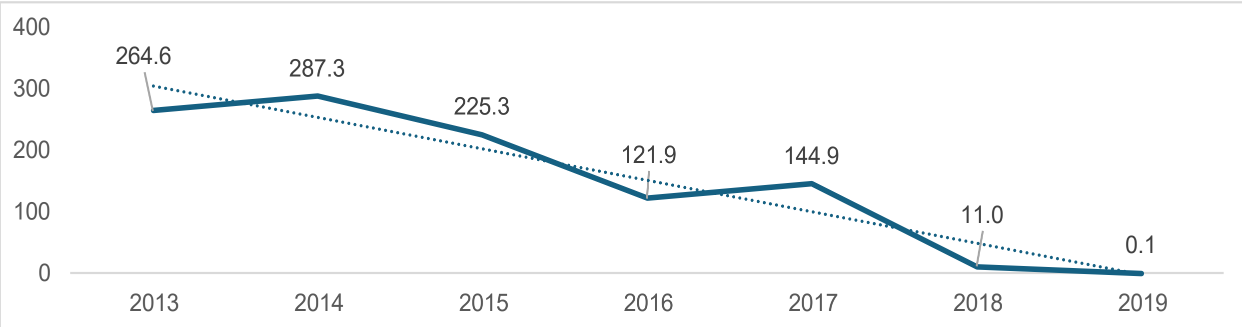

Figure 3. Trend Concerning Positive Detections of Human Papillomavirus (HPV) in Females Aged 25-64 in Mexico, 2013-2019. Source: Prepared by the authors according to the 2013-2019 Specific Action Initiative for Prevention and Control of Cancer.

of positive HPV tests reported, accounting for <3.7 per 100 thousand females aged 25-64 years.

Figure 5 shows the magnitude and changes for 2013-2019 HPV-positive detection rates. The highest values were observed in the State of Mexico (central region) and Veracruz (Gulf of Mexico region) in the study years, except in 2018, ranging to 29.4 (2014) positive detections per 100 thousand females aged 25-64 years. Instead, the northern (2013-2015), western and southern states (2016-2017) reported fewer positive HPV tests, which represented <3.7 per 100 thousand females aged 25-64 years.

Finally, in 2013 and 2019, low-high values ($p < 0.05$) for HPV-positive detections were identified in western (Michoacán), center (CDMX, Morelos, Puebla, Tlaxcala, Veracruz), and southern (Oaxaca) states (Figure 6). In the northern (Durango), east (Yucatan), western (Jalisco, Michoacan), and center (State of Mexico) states, low-low value clusters ($p < 0.05$) for HPV-positive detections were identified between 2014 and 2018. However, in the same period, federal states that adjusted to a pattern of high-high values ($p < 0.05$) were identified in the northeast (Tamaulipas), center (CDMX and Puebla), and southeast (Veracruz, Oaxaca, Chiapas, and Tabasco) regions (Figure 6).

Discussion

During 2013 - 2019 (n = 2,529,819), the total number of tests performed for HPV detection was lower than that reported during 2010 - 2017 (n = 2,737,022) [9]. Likewise, the coverage of the screening program showed a downward trend between 2013 and 2019, particularly in the southeast region (Campeche, Yucatan, Quintana Roo), ranging from 2,835.4 (2013) to 0.8 (2019) tests performed per 100 thousand females aged 25-64 years nationwide. However, in previous periods a higher average annual prevalence than other regions of Mexico has been shown [9].

At the same time, the national prevalence of HPV infection (11.1%) is higher than that reported by Hurtado-Salgado et al [9]. Furthermore, a spatial pattern was observed between 2014 and 2018, whose Moran's I increased and comprised federal states located in the northeast regions (Tamaulipas), Gulf of Mexico (Veracruz), and South Pacific (Chiapas and Tabasco).

The states with the highest coverage that we identified were Mexico City (central region) and Veracruz (southeast region). Also, these states reported the highest HPV detection rates during the study years. This may be explained because the State of Mexico is ranked among the highest quintile of the Gini index according to the 2020 National Household Income and Expenditure Survey [18]; while Veracruz reported a higher degree of marginalization compared to the other states, (National Population Council), implying poor access to education and health, inadequate housing, perception of insufficient monetary income, among others.

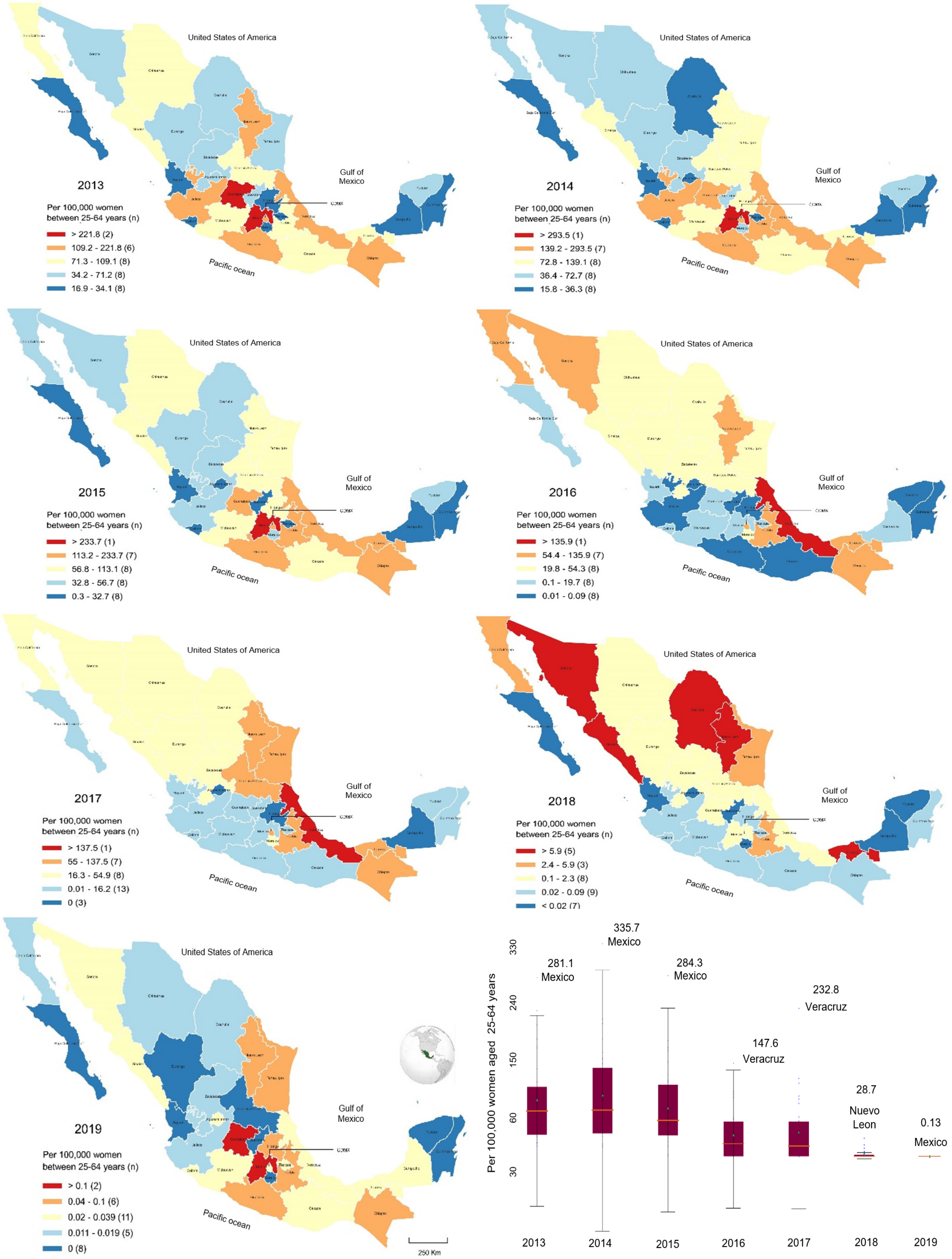

Figure 4. Coverage of the Cervical Cancer Screening Program for Females Aged 25-64 Years per State, 2013-2019. Source: Prepared by the authors according to the 2013-2019 Specific Action Initiative for Prevention and Control of Cancer.

These data note geographic differences when accessing HPV detection and prevention strategies, which may limit meeting international goals for cervical cancer elimination. In this regard, other studies have identified important geographic differences and a higher prevalence in the southern [6], center [8], and western regions [7].

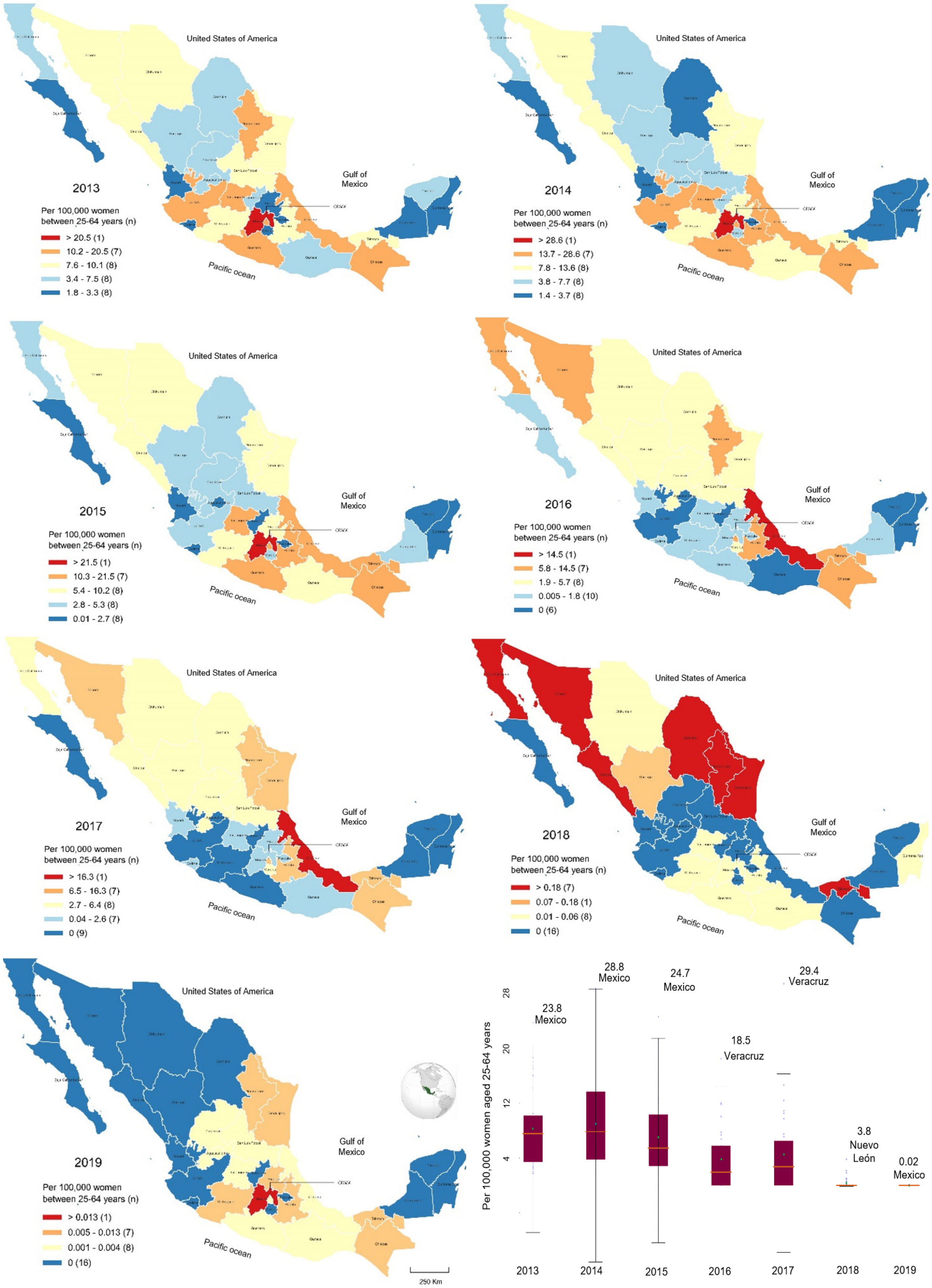

Figure 5. Human Papillomavirus Positive Detections for Women Aged 25-64 Years per State, 2013-2019. Source: Prepared by the authors according to the 2013-2019 Specific Action Initiative for Prevention and Control of Cancer.

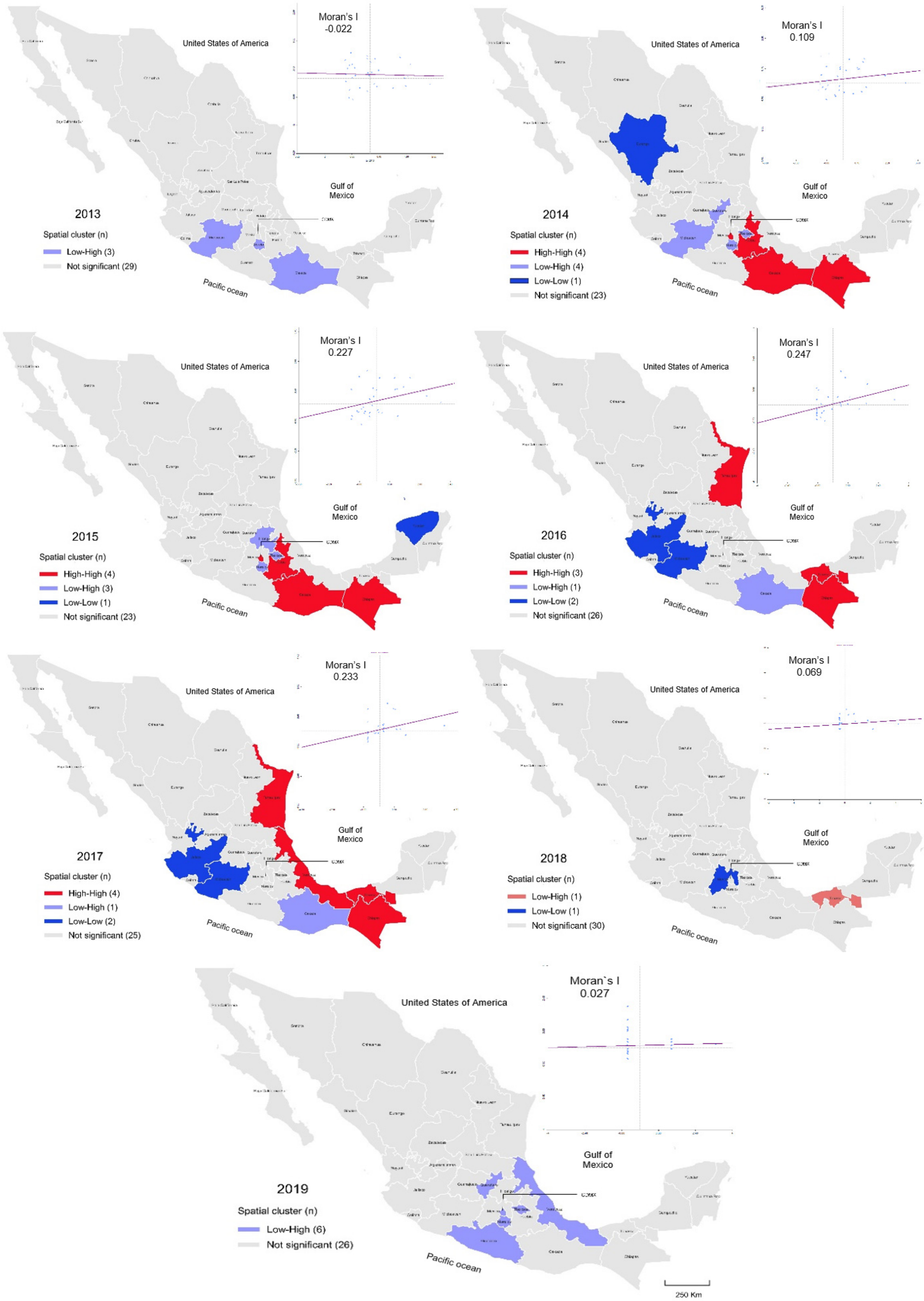

Figure 6. Spatial Clusters Associated with Human Papillomavirus (HPV) Positive Detections among Females Aged 25 to 64 Years for each State, 2013-2019. Source: Prepared by the authors according to the 2013-2019 Specific Action Initiative for Prevention and Control of Cancer.

These differences may be attributed to several factors, such as migration, sexual behavior, type of precancerous lesions, and diagnostic methods [6].

The distribution of HPV positive detection rate values per location may suggest a higher probability of positive HPV detections, mainly because Moran's I showed an upward trend with values ranging from 0.11 (2014) to 0.23 (2017). Likewise, it suggests that the larger number of tests performed per 100,000 females aged 25-64, the greater the probability of detecting HPV infection, particularly in the State of Mexico and Veracruz, since the spatial pattern was observed in similar areas for each year. In addition, it should be considered that in the south-southeast region, a higher mortality rate for cervical cancer has been reported in other areas of Mexico [19].

Thus, the results suggest that the program could have a greater impact if it were addressed to those areas with a higher risk of HPV infection to reduce cervical cancer morbidity and mortality rates. This aspect is highly relevant since achieving cervical cancer elimination requires implementing novel strategies focused on prevention, for which WHO has established the 90-70-90 targets for cervical cancer elimination by 2030 (90% of girls fully vaccinated with the HPV vaccine by age 15, 70% of females are screened with a high-performance test by 35 and 45 years of age and 90% of females diagnosed with cervical cancer receive treatment). Ensuring screening tests and epidemiological surveillance will guarantee the safety and expansion of cervical cancer care programs [4].

Thus, both at national and local levels solid epidemiological surveillance systems must continue to be complemented by detection services based on the population needs [4], so a territorial analysis may be useful. Using small territorial scales for analysis, such as municipalities, departments, and neighborhoods, among others, is a strategy contributing to accurately determining the areas where the impact may be greater and, therefore, those to which HPV prevention and care interventions should be addressed, hence reducing cervical cancer morbidity and mortality.

It should be noted that one of the most important strategies for the prevention of CC is the HPV vaccine [4]. In Mexico, since 2012 the bivalent vaccine has been given to fifth-grader girls and 11 year-girls who are not students. This vaccine confers protection against genotypes 16 and 18, which cause the majority of CC cases [20] and have been reported more frequently among females living in Mexico [21], particularly in states such as Tlaxcala [6]. Thus, the results of this study allow for precise territorial targeting of the vaccine in certain states, for instance, Tlaxcala (central region) and Jalisco (western region), where positive detections of genotypes 16 and 18 were reported. Although the national screening program conducted tests to detect these high-risk genotypes [7], it should be mentioned that these are not the only ones reported in Mexico [7, 22]; since a high prevalence of types 39, 51, 56, 59, and 66 has also been reported [7, 22]. Thus, this type of approach and data analysis on other HPV genotypes may be useful to implement more precise interventions to prevent cervical cancer, particularly more efficient approaches for HPV vaccination.

However, the epidemiological analysis of HPV infection not only considers the prevention of CC and other anogenital cancers, since HPV infection has recently been associated with other types of cancer, such as oropharynx [23], breast [24], prostate [25], and nails [26]. Similarly, there is no data on low-risk HPV genotypes, which although they are not associated with cancer causations, result in genital warts, which have a considerable impact on people's health and quality of life [2]. On the other hand, although IMSS reported the highest number of tests conducted during the study period, as well as HPV-positive detections, this may be explained because in recent years IMSS has reported the highest coverage of the beneficiary population in Mexico, meaning 4 out of 10 Mexicans when compared with the national population reported by the most recent Population and Housing Census 2020 [18].

In conclusion, our evidence notes the need to reorganize actions for the timely detection of HPV. Along with health promotion strategies and sexual education, as well as the vaccination program, cervical cancer mortality rates may be decreased, since nowadays it is one of the leading causes of death among the female population not only in Mexico but also in Latin America [1-3].

Finally, some limitations must be considered. On the one hand, given a secondary source was used, there is a possibility of underestimation or overestimation of the indicators analyzed. On the other hand, the complete record of the data corresponding to the study period was limited, as was the case of the HPV genotype detection variables, type of social security, nominal age, and type of test, among others, which certainly may have limited the results, and the epidemiological panorama described for both the national and state level. However, it should be noted that the data and indicators generated for this study corresponded to a 7-year period, which allowed us to analyze the trend and compare the coverage of HPV detection by year and federal state, resulting in states identified not only to reorganize the program objectives but also focus resources on medical treatments and HPV control in females to eventually reduce mortality.

Author Contribution Statement

Study conception, result interpretation, and discussion: Oscar Alejandro Palacios-Rodríguez, Antonio Reyna-Sevilla, Miguel Galarde-López. Study design, analysis, and data interpretation: Oscar Alejandro Palacios-Rodríguez, Antonio Reyna-Sevilla. Manuscript preparation: Oscar Alejandro Palacios-Rodríguez, Antonio Reyna-Sevilla, Miguel Galarde-López, Carlos Quezada-Sánchez.

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and dissemination of evidence.

Approval

Given our study analyzed secondary epidemiological data, the approval of the Research and Bioethics Board was not obtained. However, it complied with current regulations in Mexico.

Ethical Declaration

According to the Mexican General Health Act for health research in Mexico, this is a minimal-risk study, as it did not aim to implement any intervention or modify variables related to the health of people.

Data Availability

The data that support the findings of this study are available from the corresponding author upon request at: https://datos.gob.mx/busca/dataset/cancer-de-la-mujer-sicam-cancer-cervico-uterino.

Conflict of Interest

All authors declare that they have no conflict of interest to disclose.

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