12-1-2020

Gardasil Vaccine Trends within Nevada, California, and the U.S.: A Comparative Study

Karen S. Gutierrez

GARDASIL VACCINE TRENDS WITHIN NEVADA, CALIFORNIA, AND THE U.S.: A COMPARATIVE STUDY

By

Karen Samantha Gutierrez

Bachelor of Science – Biological Sciences
University of Nevada, Las Vegas
2017

A thesis submitted in partial fulfillment
of the requirements for the

Master of Public Health

Department of Environmental and Occupational Health
School of Public Health
The Graduate College

University of Nevada, Las Vegas
December 2020

UNLV | GRADUATE COLLEGE

Thesis Approval

The Graduate College
The University of Nevada, Las Vegas

November 30, 2020

This thesis prepared by

Karen Samantha Gutierrez

entitled

Gardasil Vaccine Trends within Nevada, California, and the U.S.: A Comparative Study

is approved in partial fulfillment of the requirements for the degree of

Master of Public Health
Department of Environmental and Occupational Health

Sheniz Moonie, Ph.D.
Examination Committee Co-Chair

Kathryn Hausbeck Korgan, Ph.D.
Graduate College Dean

Chad Cross, Ph.D.
Examination Committee Co-Chair

Brian Labus, Ph.D.
Examination Committee Member

Dieu-My Tran, Ph.D.
Graduate College Faculty Representative

Abstract

Despite decreasing incidence in cervical cancer in the U.S., there continues to be an increase in public health concern for cervical cancer worldwide. Recent studies report that individuals are disproportionately affected based on region, sex, and race. Additionally, the human papillomavirus (HPV) attributable cancers may be reduced between 70% and 90% through the universal use of HPV-vaccines. In order to expand current knowledge and implement intervention programs in Nevada, it is critical to examine the associations among the Gardasil vaccine, cervical cancer screening, and adverse events following immunization as well as to understand the different socio-demographic subgroups affected. To our knowledge, this study provided a novel analysis of the Gardasil vaccine usage trends within Nevada and will use an adjacent state (California) and the U.S. as comparators. This study used 2008-2018 data from TeenVaxView, Behavioral Risk Factor Surveillance System (BRFSS), and Vaccine Adverse Event Reporting System (VAERS) data reporting adverse events following an HPV vaccination. We found that California (68.4%) had the highest Gardasil vaccine usage compared to Nevada (55.9%) and the U.S. (56.4%). Chi-square trend analysis in this study showed no significant change in cervical cancer screening in Nevada ($p=0.829$); however, chi-square test for trend in California did show a significant change through time ($p<0.001$). Kolmogorov-Smirnov (KS) test with a Bonferroni adjustment examining the differences among curves representing outcome temporal rates for Nevada compared to California showed a significant difference ($p=0.031$). No association was seen between Gardasil vaccine estimates and cervical cancer screening rates. There was also no association between Gardasil estimates and adverse events through time in Nevada or the U.S.

Acknowledgements

I want to first thank my co-chairs, Dr. Chad Cross, and Dr. Sheniz Moonie. I could not have done this without the support and guidance you both provided me in the completion of my thesis. Thank you, Dr. Cross, for all those last-minute, frantic phone calls and WebEx meetings and for helping me navigate through all my SPSS troubles. Dr. Moonie, thank you for always keeping me on track with my deadlines and reminding me to breathe when I was most stressed out. It was an amazing experience to work on various projects together and thank you for helping me get through my MPH program.

I also want to thank Dr. Brian Labus and Dr. Diu-My Tran for serving on my committee. Dr. Labus, thank you for always making me laugh even through a crazy pandemic and teaching me many lessons about infectious disease, and for allowing me to get hands-on experience in the field of public health. Dr. Tran, thank you for your help in the refinement of my writing, and for all the feedback you provided me.

Last but not the least, thank you to my family and friends. I am forever grateful for the outpouring of love and support you have all provided me. Thank you to my parents for always supporting my educational journey. Thank you Mami and Papi for all the sacrifices that you have made to allow me to have the best opportunities available. I know this year has been extra rough for our family and yet both set the best example for how to overcome any situation. Carol, you always know what to say and do to help me push through in times when I struggle the most, thank you for that. Jose, thank you for listening to me and making me laugh, and believing in me even when I doubted myself. Without all of you, this milestone would not have been possible.

Table of Contents

List of Tables

List of Figures

Introduction

The human papillomavirus (HPV) is one of the most common sexually transmitted infections (STI) worldwide and results in a considerable amount of morbidity and mortality as discussed below. HPV belongs to the Papillomavirus genus and Papillomaviridae family and has more than 100 different HPV types that are the causative agents of the human HPV-related infections, cancers, precancerous or dysplastic lesions, and genital warts (Bernard et al., 2010; Kumakech, 2015; Planned Parenthood, 2015).

Most cases of HPV will resolve within 2 years of infection and many cases of infection will be asymptomatic and have no clinical manifestations (CDC, 2019a; CDC, 2019b; NIH 2020). However, according to the CDC, some possible clinical manifestations of HPV infection include anogenital warts, recurrent respiratory papillomatosis, cervical cancer precursors (cervical intraepithelial neoplasia), and cancers (CDC, 2019b).

There are four types of warts that can occur as a result of the more than 150 different HPV types including common skin warts, flat warts, plantar warts, and genital warts (Harvard Medical School, 2019; Mayo Clinic, 2019b). The most common clinical presentation of HPV is genital warts, which are typically painless growths that have a rough, cauliflower-like appearance that may cause itching or tenderness of the area (i.e., tip of penis, opening of urethra, skin around the anus, vagina, labia, vulva, or cervix) (Harvard Medical School, 2019; Mayo Clinic, 2019b).

Furthermore, certain HPV types can also lead to precancerous or dysplastic lesions and invasive cervical cancer if a persistent infection does not resolve on its own through the help of the body's immune system. The development of cervical dysplasia indicates that there are abnormal cells on the cervix that can range from mild to severe depending on histological

presentation (Mayo Clinic, 2018). Precancerous lesions attributed to HPV have abnormal cell appearance that occurs as a result of changes in the skin and mucous membrane where HPV infection occurred (Anal Cancer Foundation, n.d.). Early stages of cervical cancer are not usually detectable or show any symptoms; however, later stages of cervical cancer can cause vaginal bleeding, unusual vaginal discharge, pelvic pain, and pain during sexual intercourse (NIH, 2019 & 2020).

It is difficult to assess the case fatality rates of HPV infections. However, based on the types of cancers associated with HPV there has been extensive research done on deaths associated with cervical cancer. Approximately 311,000 women died of cervical cancer in 2018 because of an HPV infection (WHO, 2019). Of the almost 200,000 cervical precancer cases that are found in the U.S. each year, 11,000 cases were cervical cancer within approximately 4,000 of those women will die from cervical cancer attributed to an HPV infection annually (CDC, 2019d).

Background and Significance

Through the implementation of the nonvalent HPV vaccine, the potential to reduce the preventable fraction of HPV globally would be roughly 50%, hence making cervical cancer one of the most preventable cancers in the U.S. (McDougall et al., 2007; de Martel et al., 2017; Moore et al., 2018; de Sanjose et al., 2019). There are more than 12,900 newly diagnosed cases of cervical cancer and more than 4,100 annual deaths per year (McDougall et al., 2007; Yoo et al., 2017; Moore et al., 2018). When diagnosed early, the overall survival rate for cervical cancer has increased to an estimated 5-year rate of 90.8% (Churilla et al., 2016; Moore et al., 2018). There are several studies (outlined below) that show that treatment and survival from these cancers is dependent on disparities that exist within the U.S.

Although the incidence of invasive cervical cancer has declined overall in the U.S., African American and Hispanic women continue to have the highest incidence of cervical cancer (16.3/100,000 and 24.2/100,000, respectively) compared to their non-Hispanic white counterparts (10.8/100,000) (McDougall et al., 2007). Disparities in morbidity and mortality can also be found based on health insurance coverage (Churilla et al., 2016). Of the 11,714 cases that Churilla and colleagues (2016) identified, the International Federation of Gynecology and Obstetrics (FIGO) scoring methods that had late-stage presentation was found most frequently in Medicaid (40%; $p<0.001$) and uninsured patients (42%; $p<0.001$) compared to privately insured patients (28%; $p<0.001$). According to Churilla and colleagues (2016), mortality rates were higher in uninsured and Medicaid patients (OR=1.17; 95% CI [1.01-1.34] and OR=1.16; 95% CI [1.05-1.28]), respectively).

There continue to be significant health disparities associated with cervical cancer screening by race, income, education, health insurance coverage and geographic region. When

assessing cervical screening rates in the U.S. by race, Native Hawaiian/other Pacific Islanders had the lowest number of screenings (0.1%), followed by Asians (0.7%) with the highest screening rates among White non-Hispanics followed by Hispanic/Latino subgroups (Miles-Richardson, 2017). In a review conducted by Mann and colleagues (2016), they found that in Hispanic/Latin women specifically, there were many barriers to cervical cancer screenings such as socio-cultural-, system-level and lack of education. In a 2017 study, researchers found that low income level (<%24,999) had the highest screening rates compared to those all other income levels (Miles-Richardson et al., 2017). In a recent study, researchers found that women who were foreign-born and who had spent less time living the U.S. influenced whether they had a Pap test compared with U.S.-born women (Endeshaw et al., 2018). There is approximately 90% of women in the U.S. reporting having screening within 5 years. Investigators argue the need to target unscreened women to get screened versus those who are under- or over- screened, reporting that targeting these women will have a better value when the amount that can be spent improving adherence was estimated under scenarios of current practice (Castle et al., 2018).

Additionally, living in specific regions of the U.S. can positively impact screening and vaccine rates based on race subgroups (Domgue et al., 2019; Hirth 2019). Research has shown that there have been statistically significant increases in cervical cancer screening where interventions were clinic-based, used lay health advisors (i.e., cancer survivors, members of churches, community members), used behavioral theory (i.e., social influence theory, popular education and adult education theory) (Mann et al., 2015).

The best way to prevent an HPV infection would be through sex abstinence (i.e. vaginal, anal, oral sex, or any other genital contact), which is extremely difficult to do since most people will have some form of sexual contact in their lifetime (Planned Parenthood, n.d.). Therefore, the

next best thing to do for population-level control measures of HPV infections would be to get the HPV vaccine early (in children 11-12 years), preferably prior to first intimate contact (CDC, 2019c; Planned Parenthood, n.d.). Alternatively, the use of condoms and/or dental dams would provide protection any time individuals engage in sexual contact of the vagina, anus or mouth in order to decrease their risk of getting HPV (Planned Parenthood, n.d.). It is also recommended that individuals wait at least 2 weeks after genital warts have gone away prior to engaging in sex again (NY State Department of Health, 2018).

There is no cure for HPV; however, as mentioned above, most infections go away on their own within 1-2 years; however, some treatments targeting the health problems caused by the infection exist (CDC, 2019a; CDC, 2019b; NIH 2020). External genital and perianal warts caused by HPV may be treated by healthcare providers through medications (i.e., salicylic acid, imiquimod 3.75%, podofilox 0.5%, trichloroacetic acid or bichloroacetic acid 80-90%), cryotherapy (liquid nitrogen freezing of warts), electrocautery treatment (burning warts with an electrical current), excision of warts and laser surgery removal of warts (CDC, 2015b; Mayo Clinic, 2019a). Additionally, there are certain procedures that be conducted by a healthcare provider if the genital warts are not visible to the naked eye, such as the vinegar (acetic acid) solution tests, which turns the HPV infected areas white, a Pap tests, which can show cell abnormalities after a pathologist reviews the culture, and DNA tests can be conducted on the cells from the cervix to look for DNA of a variety of HPV types (Mayo Clinic, 2019a).

There are currently three HPV vaccines that have been approved by the FDA. The first vaccine approved by the U.S. Food and Drug Administrations (FDA) in 2006 was the quadrivalent HPV vaccine (Gardasil) that protects against HPV types 6, 11, 16, and 18, which are the most common HPV types to cause genital warts (6 & 11) and cervical cancer (16 & 18)

(FDA, 2018). The quadrivalent HPV vaccine was originally approved for use in women between 11-26 years; however, it was later approved for use in both males and females between the ages of 9-26 years (FDA, 2018). In 2009 the FDA approved the second HPV vaccine (Cervarix), and it was approved for use in women, between 9-26 years, only to protect them against the common HPV types (HPV types 16 and 18) that cause cervical cancer (FDA, 2019). The most recent vaccine approved by the FDA in 2014 was Gardasil 9, a nine-valent vaccine that provides protection against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 that may cause cervical, vulvar, vaginal, penile and anal cancers, as well as any precancerous or dysplastic lesions or genital warts (Merck Vaccines, 2019). The nine-valent vaccine is approved for use in males and females between 9-45 years.

The current CDC recommendations for HPV vaccination is for males and females between the ages of 9-26 years, but they highly recommend that two doses of the HPV vaccine be given to boys and girls between the ages of 11-12 (CDC, 2019c). Although there is FDA approval for the use of Gardasil 9 in older adults between the ages of 27-45 years, the HPV vaccine should ideally be administered prior to first intimate contact (vagina, anal or oral sex), which would be prior to first exposure to HPV infection in order to be most effective in preventing HPV attributable cancers (CDC, 2019c; Merck Vaccines, 2019). Hence, any HPV vaccines in the older populations may prove to be less beneficial of they have already been exposed to HPV.

Data for women who received all three doses of any of the three HPV vaccines (bivalent, quadrivalent, nine-valent) in clinical trials both demonstrated efficacy of over 90% against persistent HPV infections that were caused by HPV types 16 or 18 and they could all prevent more than 400,000 HPV-related cancers worldwide (Cutts et al., 2007; Serrano et al., 2018).

Additionally, the HPV vaccines are designed to be prophylactic and data on the efficacy, immunogenicity and safety of the vaccines in women who have already been exposed to HPV (genotypes 16 and 18) did not show a protective effect against cervical intraepithelial neoplasia (CIN) 2/3 or cervical adenocarcinoma in situ (AIS) compared to women who did not have evidence of past HPV infection (Cutts et al., 2007).

The HPV vaccines are the best public health tool for the prevention and/or eradication of many cancers; however, vaccines do not come without limitations and it is important to establish the safety of the HPV vaccines. Much of the current literature suggests similar common adverse events occurring following immunization with an HPV vaccine. In studies assessing venous thromboembolic events (VTE) following the HPV vaccine, studies have found there to be no serious concerns associated with VTE (Lui et al., 2016; Mauro et al., 2019; Naleway et al., 2016). Guillain-Barré Syndrome (GBS) findings were mixed reviews in terms of frequency of events and severity in various studies and none of the studies reported an incidence over rate 0.01/100,000 vaccine dosages (Slade et al., 2009; Gee et al., 2017; Mauro et al., 2019). Among the most common adverse events were syncope, dizziness, headaches, nausea, vomiting, autoimmune disorders, and hypersensitivity reactions are among the most common adverse events reported in various studies and differed in severity (Slade et al., 2009; Arana et al., 2018; Mauro et al., 2018; Suragh et al., 2018).

Furthermore, a study found headaches (n=152, 11.0%, 4.5/100,000 doses administered), nausea (n=125, 9.1%, 3.7/100,000 doses administered), and vomiting (n=66, 4.8%, 1.9/100,000 doses administered) to be among the most frequently reported systematic events reported in a Sao Paulo, Brazil study (Mauro et al., 2019). There were similar findings reported in U.S. studies where headaches were reported a total of 937 times, 84% were nonserious events and 16% of

headaches were considered serious adverse events based on hospitalization for neurologic evaluation after fall-related syncope (Slade et al., 2009). Additional Vaccine Adverse Event Reporting System (VAERS) data indicates that headaches were among the most frequently reported non-serious and serious AE in both females (10.5% and 29.1%, respectively) and males (8.7% and 28.0%, respectively) immunized with an HPV vaccine (Arana et al., 2018). There was also some slight variability in report severity associated with nausea. Females reported 8.6% of non-serious nausea events and males reported no non-serious nausea events, whereas both females and males reported serious events of nausea with female reports being slightly higher than males (21.6% and 20.3%, respectively) (Arana et al., 2018). Given the variation in reported adverse events in previous studies, it is important to establish clear vaccine safety in the U.S.

Purpose

The purpose of this study was to provide a first-time descriptive analysis of the use of the Gardasil vaccine within Nevada compared to California and the U.S. This study analyzed 2008-2018 CDC VaxView data, BRFSS data, and VAERS, the frequency of the use of the Gardasil vaccine and cervical cancer screening within Nevada compared to California and the U.S. Additionally, the difference in Gardasil vaccine patterns based on sociodemographic subgroups within Nevada compared to California and the U.S were assessed. In this study we determined if there was a difference between Gardasil vaccination rates and reported rates of cervical cancer screening in Nevada, California and the U.S. Lastly, an association was investigated between Gardasil adverse events by sex in Nevada, California, and the U.S.

Research Questions

Given the disparities in the use of HPV vaccines and cervical cancer screening by sociodemographic subgroups, this study will supplement current literature by explicitly

examining available subgroup data (McDougall et al., 2007; de Martel et al., 2017 & 2019; Phaswana-Maguya & Peltzer, 2017; de Sanjose et al., 2019). Additionally, there have been no previous studies assessing HPV vaccine use and cervical cancer screening studies comparing Nevada to California and the U.S. It is also critical to establish safety in the HPV vaccine and to our knowledge, there are no studies assessing how Nevada compares to the U.S. in adverse events following immunization with an HPV vaccine. Currently, only 3 U.S. states (Hawaii, Rhode Island, and Virginia) and the District of Columbia have mandated the HPV vaccine in elementary and secondary schools (Immunization Action Coalition, 2019).The U.S. is approximately 30% below the Healthy People (HP) 2020 goal for adolescents between 13 through 15 years who received 2 or more doses of the HPV vaccine (HP2020, n.d.a). Hence, there is a need to increase vaccine uptake in adolescents across the U.S. to reach HP 2030 goals of 80% from our current 48.0% baseline (HP2020, n.d.b). Lower vaccination rates and higher cervical cancer rates have been found in Nevada compared to national averages making Nevada an important target for assessment (Chen et al., 2020;(U.S. Cancer Statistics Working Group, 2020). Therefore, Nevada was also selected for this study given the state's large number of rural counties with lower healthcare access, which may be attributing to the decrease in vaccine uptake and screening. California was chosen as a comparison state in this study given its large population size and similar age and race distribution compared to Nevada (U.S. Census Bureau, n.d.). The following questions will be investigated:

1. How do Gardasil vaccination rates in Nevada compare to California and to the U.S.?
2. How do cervical cancer rate in Nevada compare to California and to the U.S.?
3. What are the sociodemographic subgroups and Gardasil vaccine patterns of those subgroups within Nevada, California, and the U.S.?

4. Are there any potential temporal associations between Gardasil vaccination rates and reported cervical cancer screening rates in Nevada, California, or the U.S.?
5. Are there any potential temporal associations between Gardasil vaccination rates and reported adverse events following HPV vaccination in Nevada, California, and the U.S.?

Objectives

The following objectives will be examined in Nevada compared to California and the U.S.

Objective 1

To determine the frequency use of Gardasil

Objective 2

To determine cervical cancer screening rates

Objective 3

To determine the difference in Gardasil vaccine patterns based on sociodemographic subgroups.

Objective 4

To determine if there is a difference between Gardasil vaccination rates and reported rates of cervical cancer screening.

Objective 5

To determine if there is an association between Gardasil vaccination rates and reported adverse events following HPV vaccination.

Hypothesis

Hypothesis 1

H_0: There will be no difference in the use of Gardasil in Nevada compared to California and the U.S.

H_a: There will be a difference in the use of Gardasil in Nevada compared to California and the U.S.

Hypothesis 2

H_0: There will be no difference in cervical cancer screening rates in Nevada compared to California and the U.S.

H_a: There will be a difference in cervical cancer screening rates in Nevada compared to California and the U.S.

Hypothesis 3

H_0: There will be no difference in Gardasil vaccine patterns based on sociodemographic subgroups in Nevada compared to California and the U.S.

H_a: There will be a difference in Gardasil vaccine patterns based on sociodemographic subgroups in Nevada compared to California and the U.S.

Hypothesis 4

H_o: There will be no association between Gardasil vaccination rates and reported rates of cervical cancer screening in Nevada, California, and the U.S.

H_a: There will be an association between Gardasil vaccination rates and reported rates of cervical cancer screening in Nevada, California, and the U.S.

Hypothesis 5

H_o: There will be no association between Gardasil vaccination rates and reported adverse events following HPV vaccination in Nevada compared to California and the U.S.

H_a: There will be an association between Gardasil Vaccination rates and reported adverse events following HPV vaccination in Nevada compared to California and the U.S.

Ethical Considerations

All data retrieved from the CDC TeenVaxView, the BRFSS, and the VAERS databases have been de-identified making this study a secondary data analysis and was deemed exempt from review by the ULNV Internal Review Board (IRB) (Appendix A).

Methods

The present study is a cross-sectional, population-based descriptive study that utilized data from the CDC TeenVaxView database, BRFSS, and VAERS database. Additionally, this study was largely descriptive a study. TeenVaxView data is collected through the National Immunization Survey-Teen (NIS-Teen), which consists of a random-digit-dialing survey of parents or guardians of adolescents between the ages of 13-17 years. The NIS-Teen telephone survey is followed-up by a questionnaire that is mailed to the adolescents' healthcare provider to obtain their vaccination history (CDC, 2017).

The data from BRFSS was retrieved for this assessment and is a cross-sectional study composed of adults over the age of 18 years (CDC, 2018). BRFSS is one of the largest health surveys in the world and on average the BRFSS completes more than 400,000 surveys annually (CDC, 2014b). Participants are surveyed nationally in all 50 states, the District of Columbia (D.C.), Puerto Rico, Guam, and the U.S. Virgin Islands (CDC, 2014). Telephone surveys are conducted by state health departments and they receive technical and methodological assistance from the CDC as needed (CDC, 2014). The landline and cell phone numbers selected for the survey are obtained through random sampling (CDC, 2018). This survey consists of a questionnaire that is composed of three components: the core component, the optional module, and the state added questions (CDC, 2014).

The VAERS database is a self-report early warning system used to detect potential safety issues in licensed vaccines in the U.S. VAERS is managed by both the Centers for Diseases Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA). VAERS uses passive surveillance where individuals are encouraged to report any adverse events (side effects) as a result of any vaccine received. Healthcare professionals and vaccine manufacturers are also

required to report all adverse events that they may encounter. Information entered into the VAERS database includes information on the patient, the vaccine type, and the adverse event reported.

Study Sample

Between 2008 -2018, there were approximately 2,328 teens who participated in the NIS-Teen survey. 132,587 participants that self-reported adverse events related to an HPV vaccine to the VAERS database between 2008-2018. Additionally, there were 82,497 participants on the BRFSS that participated in the Pap screening, where 6,8146 of those women reported having a pap test within the past 3 years.

Statistical Analysis

Data for this study was analyzed using the IBM SPSS Statistics 26.0 software. Descriptive statistics were calculated to find Gardasil vaccine frequency and cervical cancer screening rates in Nevada, California and the U.S. and to calculate differences between Gardasil vaccine patterns based on sociodemographic subgroups in Nevada compared to California and the U.S. Gardasil vaccination rates in Nevada, California, and the U.S, were calculated by dividing the number of Gardasil vaccines given between 2008-2018 and cervical cancer screening rates in Nevada, California, and the U.S. A chi-square test for trend was used to look at trends through in California and Nevada only. Lastly, a Kolmogorov-Smirnov (KS) test along with a Bonferroni adjustment was utilized to examine any differences among the curves for Nevada compared to California to represent their outcome temporal rates**.**

Results

Gardasil Usage

According to 2008-2018 TeenVax View data, 191,301 teens between the ages of 13-17 years received an HPV vaccine and of those teens, 3,025 and 3,520 were vaccinated in Nevada and California, respectively. Results below indicate that vaccine coverage estimates have been relatively stable through time and there is no significant difference in the use of Gardasil rates in Nevada compared to California and the U.S.

Frequencies for HPV vaccines administered for the US, California and Nevada can be found in Table 1. Overall, Nevada has been roughly in between the vaccine coverage estimates for California and the US with a peak in vaccine coverage estimates in 2015 that surpassed that of the U.S. and California (Figure 1). In Nevada There have also been an upwards trend in female vaccine coverage estimates through time (Figure 2). However, since the recommendation to vaccinate boys in 2011, there has been over 50% increase in vaccine coverage for boys in Nevada (55.4%), California (65.4%) and the U.S. (64.9%) (Table 1; Figure 3).

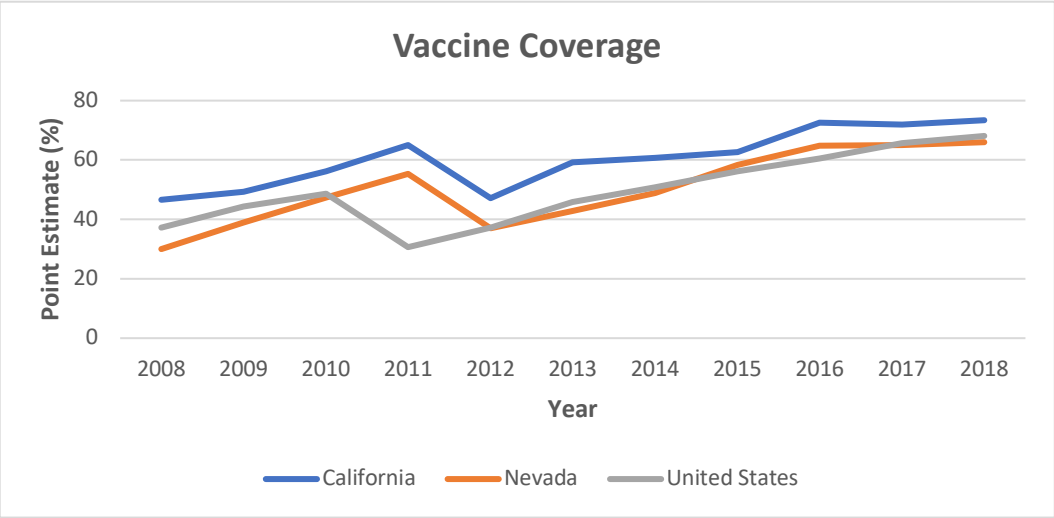


Figure 1. Vaccine coverage rates (%) through time for California, Nevada, and the US.

Nevada tends to have Gardasil vaccine usage, by gender, that lies between California and the U.S. (Figures 2 and 3). Nevada has been slightly below California gender vaccine usage in every year except for in 2015 where Nevada (72.0%) surpassed California (66.7%) vaccine usage in females (Table 1). Overall, California had the highest Gardasil usage compared to Nevada and the U.S. for both genders except for 2018 where the U.S. female vaccine usage was 1.5% higher compared to California and 3.9% in Nevada (Table 1).

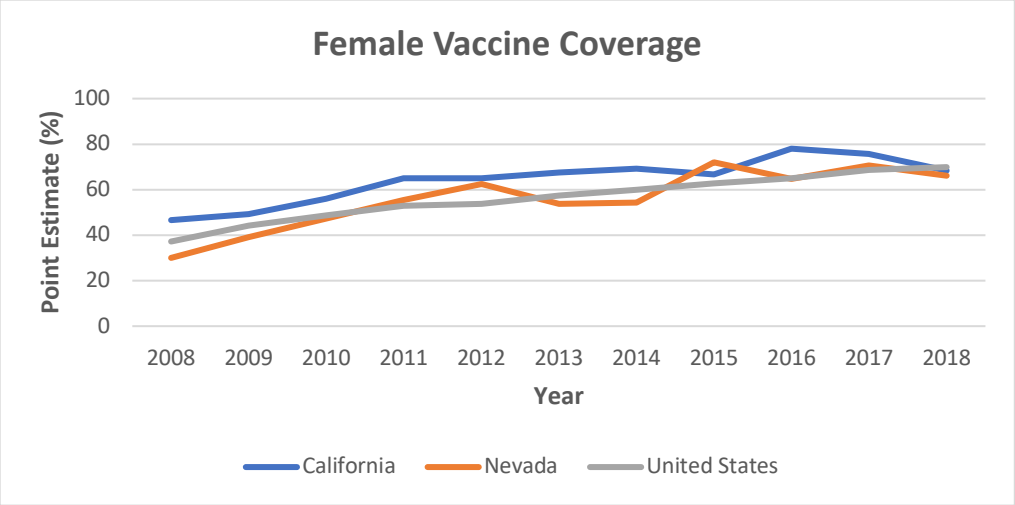


Figure 2. Female vaccine coverage rate (%) through time for California, Nevada, and the US.

Table 1. Gender vaccine frequencies through time by sex. Numbers provided as n (%).

	2008	2009	2010		2011		2012		2013	
	Female	**Female**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**
Female	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Male	150 (46.6)	190 (49.2)	163 (56.1)		270 (65.0)	313 (13.0)	202 (65.0)	228 (29.4)	148 (67.6)	161 (50.9)
Unk	117 (30.0)	159 (39.0)	165 (47.4)		189 (55.3)		159 (62.5)	170 (11.6)	150 (53.8)	185 (31.9)
	8607 (37.2)	9621 (44.3)	9220 (48.7)	10037 (1.40)	11236 (53.0)	12328 (8.30)	9058 (53.8)	10141 (20.8)	8710 (57.3)	9554 (34.6)
	2014		**2015**		**2016**		**2017**		**2018**	
Female	166 (69.2)	190 (52.1)	174 (66.7)	176 (58.5)	143 (78.0)	184 (67.3)	135 (75.6)	171 (68.2)	179 (68.4)	177 (78.4)
Male	184 (54.2)	167 (43.4)	176 (72.0)	196 (44.5)	169 (64.6)	161 (65.1)	164 (70.6)	180 (59.3)	162 (66.0)	172 (66.0)
Unk	10084 (60.0)	10743 (41.7)	10508 (62.8)	11367 (49.8)	9661 (65.1)	10814 (56.0)	9845 (68.6)	11104 (62.6)	8928 (69.9)	9772 (66.3)

Note. Male data was not available for 2008-2009.
Unk: Unknown sex.

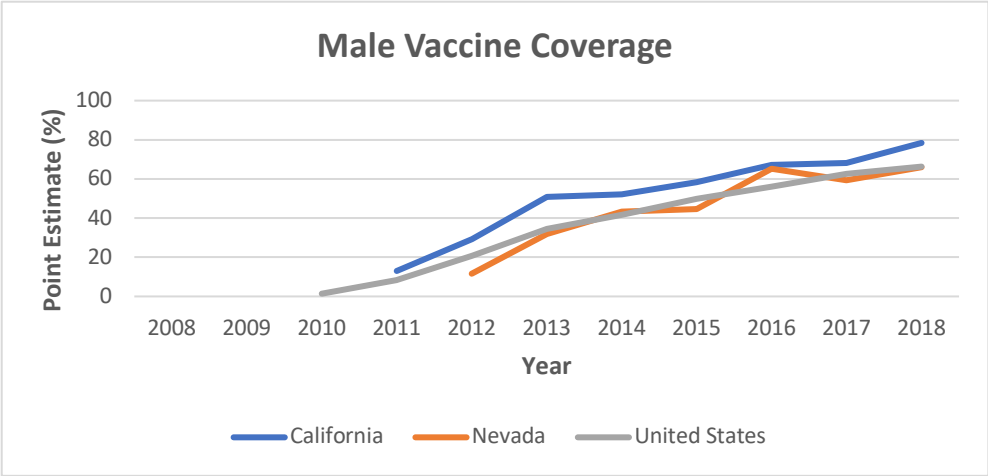


Figure 3. Male vaccine coverage rates (%) through time for California, Nevada, and the US.

Cervical Cancer Screening Rates

The chi-square test for trend of Papanicolaou (pap) testing in California indicated that there has been a change in screening proportion rates through time ($p<0.001$) (Table 2). Based on $p<0.05$ significance level, California screening proportions in 2008 (84.1%) differed from screening proportions in 2010 (81.7%), 2012 (80.7%), 2014 (76.2%) and 2018 (80.7%) (Table 2). Based on the chi-square test for trend, in Nevada, we found that the screening proportion rates do not change through time ($p=0.829$) (Table 2). However, in Nevada there was less screening in 2012 (72.8%) compared to 2008 (78.0%) and 2014 (79.5%) (Table 2). Furthermore, screening proportion rates in Nevada only differed in 2008 (78.0%) and 2012 (72.5%) with a $p<0.05$ significance level (Table 2). In the U.S., no chi-square test for trend was completed for the U.S. since only median prevalence rates were reported for all 50 states and D.C. (Table 2).

Table 2. BRFSS screening proportion rates through time. Numbers provided as n (%).

Screening	2008 n (%)	2010 n (%)	2012 n (%)	2014 n (%)	2016 n (%)	2018 n (%)	p^*	$p^{¥}$
Nevada								
Yes	1502 $(77.99)_a$	1068 $(75.75)_{a,b}$	1332 $(72.47)_b$	789 $(79.46)_a$	806 $(75.68)_{a,b}$	602 $(77.38)_{a,b}$	**0.829**	
No	424 $(22.01)_a$	342 $(24.26)_{a,b}$	506 $(27.53)_b$	204 $(20.54)_a$	259 $(24.32)_{a,b}$	176 $(22.62)_{a,b}$		**0.031**
California								
Yes	4227 $(84.12)_a$	607 $(81.68)_b$	4369 $(80.70)_b$	2147 $(76.19)_c$	2589 $(82.45)_{a,b}$	2605 $(80.73)_b$	**<0.001**	
No	796 $(15.85)_a$	1362 $(18.32)_b$	1045 $(19.30)_b$	671 $(23.81)_c$	551 $(17.55)_{a,b}$	622 $(19.27)_b$		
U.S.**								
Yes	82.9	81.3	78.0	75.2	79.8	85293 (80.2)		
No	17.1	18.7	22.0	24.8	20.2	20871 (19.8)		

Note. *Chi-square test for trend *p*-value with a $p<0.05$ significance level.
¥ Kolmogorov-Smirnov Z test proportion *p*-value at $p<0.05$ significance level.
**Median value reported with no confidence intervals for the U.S.
Subscript letter denotes a subset of Year categories whose column proportions by state do not differ significantly from each other at the $p<0.05$ level

Trend analysis for the U.S., California and Nevada showed that they all had over 70% screening rates since 2008 (Figure 4). Between 2008-2012, Nevada had approximately 6% lower screening rates compared to California and the U.S. (Table 2). The two-sample K-S test showed there was a difference between cervical cancer screening rates in Nevada compared to California (p=0.031) (Table 2). However, among pap testing there was an almost 7% increase in pap testing between 2012 and 2014 in Nevada (6.98%).

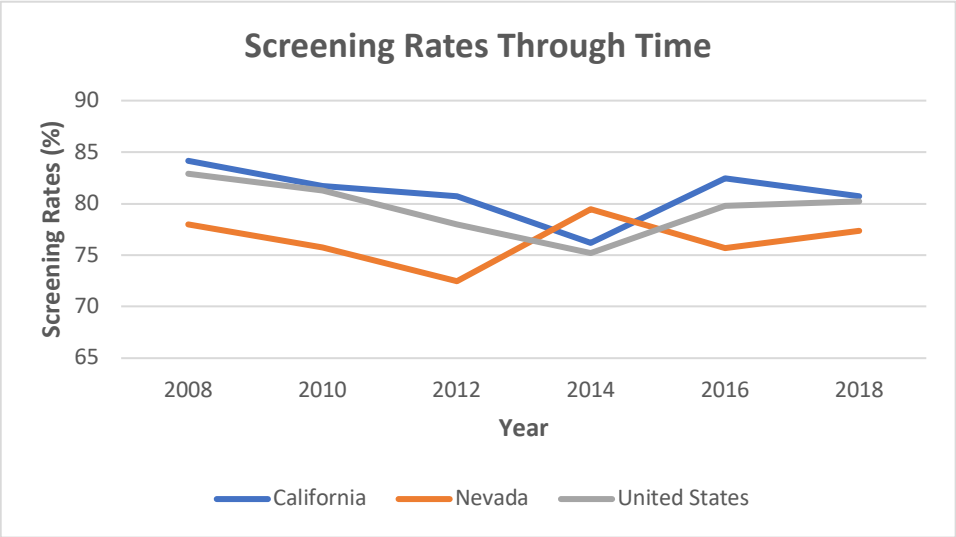


Figure 4. BRFSS screening proportion rates (%) through time for California, Nevada, and the US.

Vaccine Usage by Sociodemographic Subgroups

Results also indicate that in Nevada, California and the U.S., American Indian/American Native, Asians and Blacks were the three lowest reported race subgroups with vaccine usage (Table 3). There were 2478 American Indian/American Natives reported in the U.S.; however, estimates were not reported in Nevada in California for some race groups because data was either not collected or because the denominator for the unweighted sample size was 0.588 (Table 3). The highest reported race to get an HPV vaccine was White non-Hispanics followed by Hispanics in the U.S. (67.1% and 17.6%, respectively), and in Nevada (48.9% and 51.1%, respectively) (Table 3). Nevada and the US had over 60% vaccine coverage overtime in White teens compared to below 60% coverage in California (Table 3). The vaccine estimates for Hispanic teens living in California were much higher in recent years between 2016-2018 compared to their white counterparts (Table 3).

Table 3. Gardasil vaccine frequencies through time by sociodemographic subgroups. Numbers provided as n(%).

	2008 n (%)	2009 n (%)	2010 n (%)	2011 n (%)	2012 n (%)	2013 n (%)	2014 n (%)	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)
Race											
California											
Hispanic	56 (42.1)	82 (54.7)	63 (39.1)	239 (69.1)	164 (47.2)	113 (45.2)	158 (56.4)	122 (44.7)	112 (43.9)	129 (54.0)	151 (53.2)
White	77 (57.9)	68 (45.3)	98 (60.9)	107 (30.9)	184 (52.9)	137 (58.2)	122 (43.6)	151 (55.3)	143 (56.1)	110 (46.0)	133 (46.8)
Nevada											
Hispanic	-	35 (27.6)	42 (30.0)	47 (30.3)	34 (26.4)	106 (36.3)	112 (40.6)	109 (37.7)	105 (39.5)	96 (34.2)	102 (39.2)
White	62	92 (72.4)	98 (70.0)	108 (69.7)	95 (73.6)	186 (63.7)	164 (59.4)	180 (62.3)	161 (60.5)	185 (65.8)	158 (60.8)
United States											
AI/AN	118 (1.43)	134 (1.45)	133 (1.51)	151 (0.684)	261 (1.43)	284 (1.64)	303 (2.20)	290 (1.40)	300 (1.56)	257 (1.30)	247 (1.41)
Asian	169 (2.04)	217 (2.34)	244 (2.76)	328 (1.48)	622 (3.40)	561 (3.24)	764 (5.56)	751 (3.63)	862 (4.48)	818 (4.15)	601 (3.44)
Black	949 (11.5)	1002 (10.8)	969 (11.0)	2408 (10.9)	1928 (10.5)	1647 (9.52)	1986 (14.4)	2228 (10.8)	1990 (10.3)	1743 (8.84)	1488 (8.51)
Hispanic	953 (11.5)	1172 (12.7)	1199 (13.6)	3234 (14.6)	2552 (14.0)	2741 (15.8)	3255 (23.7)	4610 (22.3)	3223 (16.7)	3882 (19.7)	4021 (23.0)
White	6085 (73.5)	6725 (72.7)	6292 (71.2)	15970 (72.3)	12930 (70.7)	12064 (69.7)	7443 (54.1)	12835 (62.0)	12883 (66.9)	13010 (66.0)	11128 (63.6)
Poverty Status											
California											
Living at or above poverty	115 (100)	190 (57.6)	122 (77.7)	437 (76.5)	326 (78.4)	240 (87.9)	254 (74.1)	258 (77.2)	244 (75.1)	225 (77.9)	270 (79.9)
Living below poverty	-	140 (42.4)	35 (22.3)	134 (23.5)	90 (21.6)	33 (12.1)	89 (25.9)	76 (22.6)	81 (24.9)	64 (22.1)	68 (20.1)
Nevada											
Living at or above poverty	96 (100)	129 (100)	134 (100)	161 (100)	243 (88.7)	282 (78.8)	250 (73.5)	282 (78.6)	249 (78.5)	255 (76.6)	257 (86.2)
Living below poverty	-	-	-	-	31 (11.3)	76 (21.2)	90 (26.4)	77 (21.4)	68 (21.5)	78 (23.4)	41 (13.8)
United States											
Living at or above poverty	7277 (84.5)	8049 (83.7)	7513 (81.5)	19206 (81.5)	15466 (80.6)	14754 (80.8)	16404 (78.8)	16564 (75.7)	16290 (79.6)	16591 (79.2)	14716 (78.7)
Living below poverty	978 (11.4)	1208 (12.6)	1313 (14.2)	3480 (14.8)	3136 (16.3)	3078 (16.9)	3709 (17.8)	4544 (20.8)	3461 (16.9)	3579 (17.1)	3327 (17.8)
Unknown poverty	352 (0.0409)	364 (0.0379)	394 (0.0427)	878 (0.0373)	597 (0.0311)	432 (0.0237)	714 (0.0343)	767 (0.0351)	724 (0.0354)	779 (0.0372)	657 (0.0351)
Urbanicity											
California											

Living in an MSA non-principal city	66 (49.6)	106 (56.4)	84 (52.5)	134 (31.9)	228 (54.6)	165 (54.8)	173 (50.1)	180 (53.1)	160 (49.5)	151 (50.8)	168 (47.7)
Living in an MSA principal	67 (50.4)	82 (43.6)	76 (47.5)	286 (68.1)	190 (45.5)	136 (45.2)	172 (49.9)	159 (46.9)	163 (50.5)	146 (49.2)	184 (52.3)
Nevada											
Living in a non MSA	-	-	-	-	-	-	-	-	-	-	32
Living in an MSA non-principal city	-	43 (28.9)	37 (24.5)	38 (22.5)	-	-	32 (11.8)	43 (14.1)	33 (12.2)	82 (24.8)	68 (21.3)
Living in an MSA principal	73 (100)	106 (71.1)	114 (75.5)	131 (77.5)	113 (100)	236 (100)	240 (88.2)	263 (86.0)	237 (87.8)	249 (75.2)	220 (68.8)
United States	8607	9621	9220	23564	19205	18264	20827	21875	20475	20949	18700
Living in a non MSA	2169 (25.2)	2191 (22.8)	2199 (23.9)	5377 (22.8)	4225 (22.0)	4131 (22.6)	4615 (22.2)	4311 (19.7)	4248 (20.8)	4123 (19.7)	3593 (19.2)
Living in an MSA non-principal city	3268 (38.0)	3635 (37.8)	3340 (36.2)	8955 (38.0)	7552 (39.3)	7175 (39.3)	7970 (38.3)	8459 (38.7)	8248 (40.3)	8282 (39.5)	7543 (40.3)
Living in an MSA principal	3170 (36.8)	3795 (34.4)	3681 (40.0)	9232 (39.2)	7428 (39.7)	6958 (38.1)	8242 (39.6)	9105 (41.6)	7979 (39.0)	8544 (40.8)	7564 (40.4)

Note. AI/AN: American Indian/American Native. MSA: Metropolitan Statistical Area.
Estimates for American Indian/American Native, Asians, or Black adolescents were not reported in Nevada or California for some race groups because data was either not collected or because the denominator for the unweighted sample size was 0.588

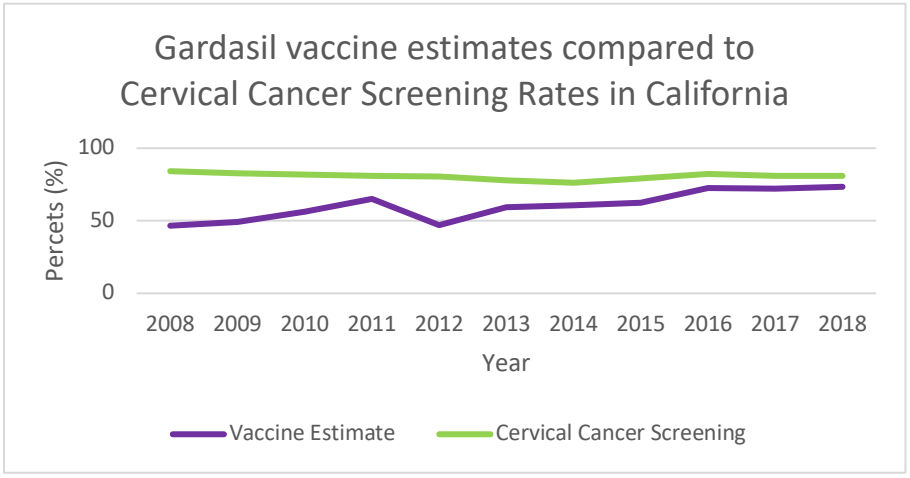
When examining poverty status in the U.S., California and Nevada, the teens that were most vaccinated were those who lived at or above poverty (Table 3). A steady vaccine usage in California, Nevada and the U.S. in teens who lived at or above poverty status (Table 3). 2009 had the highest number of teens living below poverty status who vaccinated in California (Table 3). Unknown poverty status vaccine estimates were only reported in the U.S. The US had below 1% vaccine estimates for all years in teens living in unknown poverty status (Table 3). California

and Nevada vaccine estimates were not reported for unknown poverty status because data was either not collected or because the denominator for the unweighted sample size was 0.588 (Table 3).

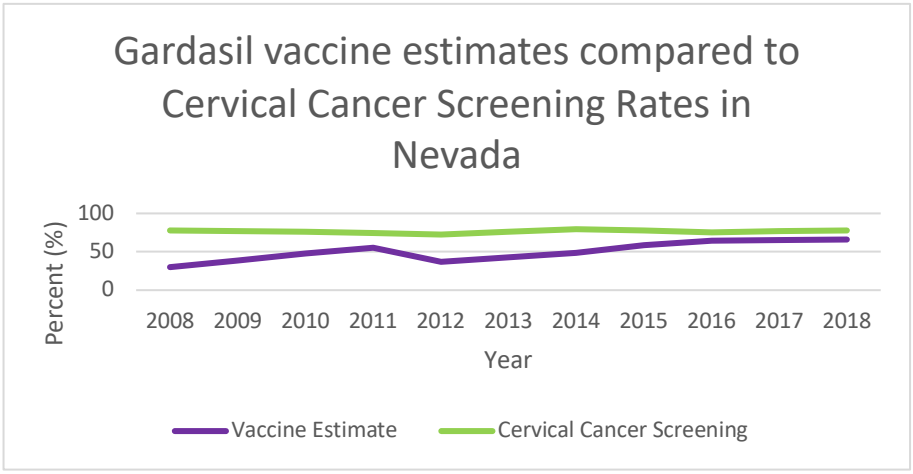
In the U.S., California, and Nevada, the majority of adolescents who received an HPV vaccine lived in a metropolitan statistical area (MSA) principal city (Table 3). Frequencies by subgroups can be seen in Table 3. Over time, California had over 50% vaccine coverage in teens living in an MSA non-principle city (Table3). The U.S. had approximately 40% vaccine estimates in teens who lived in a MSA non-principle city while Nevada had between 30 to 40% vaccine coverage over time (Table 3). Nevada had the largest number of teens living in an MSA principle city, followed by California and then the U.S. between 2008 through 2018 (Table 3). Given the reporting threshold, Nevada and California did not have vaccine estimates for teens living in a non MSA (Table 3).

Associations between Vaccines Estimates and Screening Rates

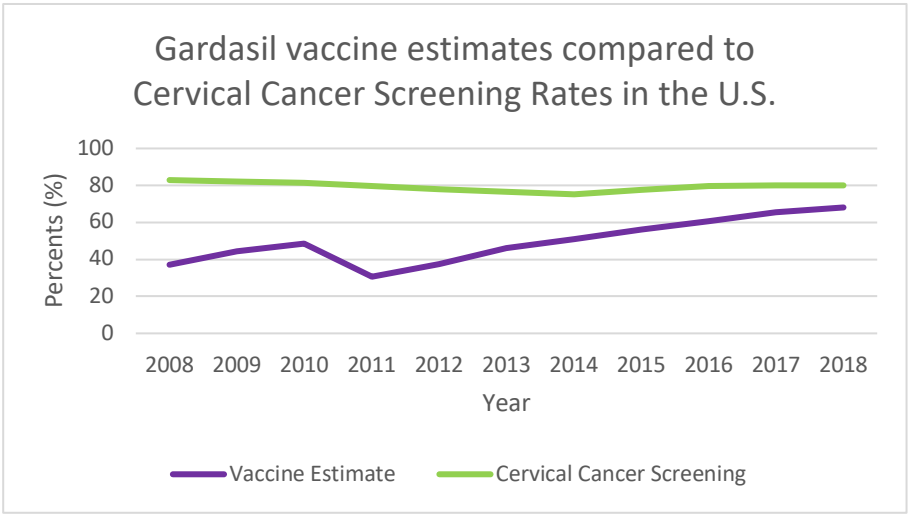
Trend analysis of screenings proportion rates with HPV vaccine coverage estimates do not show any association. No changes in cervical cancer screening rates have changed in Nevada, California or the U.S. since the introduction of the HPV vaccines in 2009 and 2014 (Figures 5a-c). Therefore, we fail to reject the fourth null hypothesis that there will be no association between Gardasil vaccination rates and reported rates of cervical cancer screening in Nevada, California, and the U.S.



a.



b.



c.

Figure 5 a-c. Associations between Gardasil estimates (%) and cervical cancer screening rates (%) through time.

Adverse Events

Frequencies of adverse events (A.E.) in California, Nevada, and the U.S. by year can be seen in Table 4. Table 7 shows the frequencies of males, females, and those with no reported gender; however, in this study, only those who had gender specified were analyzed. When comparing the top 10 adverse events in the U.S. and California had 9 out of 10 of the same adverse events compared to 8 out of 10 for Nevada (Table 4). The ninth most common adverse event reported in the last 10 years in California was pallor (1.51%), which was not one of the top 10 reported AE in the U.S. Nevada reported falls (2%) and abdominal pain (1.73%) as part of their top 10 most common AE, which were not part of the U.S. top ten AEs (Table 4).

Table 4. Top 10 adverse event reports through time. Numbers provided as n (%).

United States											
Adverse Event	**2008 n (%)**	**2009 n (%)**	**2010 n (%)**	**2011 n (%)**	**2012 n (%)**	**2013 n (%)**	**2014 n (%)**	**2015 n (%)**	**2016 n (%)**	**2017 n (%)**	**2018 n (%)**
No adverse event	41 (0.195)	12 (0.0887)	19 (0.179)	27 (0.310)	505 (5.95)	1110 (10.9)	1511 (14.1)	2484 (19.1)	2711 (17.8)	1604 (14.1)	996 (10.2)
Incorrect product storage	-	1 (0.00739)	-	-	-	-	162 (1.51)	1943 (14.9)	2241 (14.7)	608 (5.34)	-
Dizziness	722 (3.44)	430 (3.18)	353 (3.32)	325 (3.73)	275 (3.24)	301 (2.96)	299 (2.79)	299 (2.30)	365 (2.40)	289 (2.54)	250 (2.56)
Syncope	847 (5.42)	416 (4.53)	348 (4.75)	299 (5.01)	295 (5.28)	302 (4.37)	254 (3.57)	276 (3.17)	324 (3.35)	252 (3.49)	278 (4.52)
Headache	456 (2.17)	386 (2.85)	259 (2.44)	227 (2.60)	219 (2.58)	221 (2.17)	206 (1.93)	230 (1.77)	294 (1.93)	205 (1.80)	179 (1.83)
Inappropriate schedule of drug administration	232 (1.11)	48 (0.355)	23 (0.216)	7 (0.0803)	344 (4.06)	590 (5.80)	395 (3.69)	354 (2.72)	334 (2.20)	318 (2.80)	154 (1.57)
Nausea	491 (2.34)	320 (2.36)	230 (2.16)	181 (2.08)	178 (2.10)	180 (1.77)	175 (1.64)	150 (1.15)	220 (1.45)	170 (1.50)	170 (1.74)
Pyrexia	346 (1.65)	218 (1.61)	152 (1.43)	137 (1.57)	141 (1.66)	109 (1.07)	120 (1.12)	149 (1.15)	195 (1.28)	148 (1.30)	120 (1.23)
Injection site pain	378 (1.80)	163 (1.20)	150 (1.41)	128 (1.47)	86 (1.01)	117 (1.15)	109 (1.02)	140 (1.08)	179 (1.18)	170 (1.50)	131 (1.34)
Injection site erythema	219 (1.04)	108 (0.798)	126 (1.18)	148 (1.70)	168 (1.98)	135 (1.33)	130 (1.21)	151 (1.16)	173 (1.14)	169 (1.49)	121 (1.24)

Nevada											
No adverse event	-	-	-	-	-	19 (23.2)	6 (7.69)	17 (20.5)	9 (11.3)	1 (2.86)	1 (1.69)
Incorrect product storage	-	1 (0.806)	-	-	-	17 (20.7)	5 (6.41)	17 (20.5)	8 (10.0)	-	-
Injection site pain	5 (6.67)	2 (1.61)	3 (6.67)	-	6 (14.3)	2 (2.44)	8 (10.3)	6 (7.23)	4 (5.00)	8 (22.9)	-
Dizziness	4 (5.33)	2 (1.61)	2 (4.44)	2 (4.26)	2 (4.76)	2 (2.44)	1 (1.28)	3 (3.61)	4 (5.00)	3 (8.57)	4 (6.78)
Syncope	3 (4.00)	1 (0.806)	4 (8.89)	1 (2.13)	2 (4.76)	3 (3.66)	1 (1.28)	2 (2.41)	5 (6.25)	-	6 (10.2)
Headache	2 (2.67)	5 (4.03)	2 (4.44)	1 (2.13)	2 (4.76)	2 (2.56)	2 (2.56)	1 (1.20)	3 (3.75)	1 (2.86)	1 (1.69)
Fall	1 (1.33)	2 (1.61)	3 (6.67)	-	1 (2.38)	-	1 (1.28)	2 (2.41)	-	1 (2.86)	4 (6.78)
Nausea	2 (2.67)	3 (2.42)	1 (2.22)	1 (2.13)	-	3 (3.66)	1 (1.28)	1 (1.20)	1 (1.25)	1 (2.86)	1 (1.69)
Abdominal Pain	-	3 (2.42)	2 (4.44)	2 (4.26)	-	1 (1.22)	2 (2.56)	-	-	1 (2.86)	2 (3.39)
Erythema	2 (2.67)	-	-	1 (2.13)	1 (2.38)	2 (2.44)	1 (1.28)	1 (1.20)	1 (1.25)	2 (5.71)	1 (1.69)
California											
Injection site pain	83 (8.65)	22 (2.88)	19 (4.49)	26 (8.61)	105 (12.95)	4 (5.13)	72 (9.22)	31 (5.10)	37 (8.56)	27 (5.71)	27 (10.5)
Syncope	94 (9.79)	50 (6.54)	25 (5.91)	18 (5.96)	50 (6.17)	7 (8.97)	41 (5.25)	22 (3.62)	8 (1.85)	27 (5.71)	12 (4.67)
No adverse event	2 (0.208)	1 (0.131)	1 (0.23 6)	-	18 (2.22)	3 (3.85)	31 (3.97)	91 (14.97)	43 (9.95)	47 (9.94)	3 (1.17)
Incorrect site pain	3 (0.313)	-	2 (0.47 3)	-	4 (0.493)	-	40 (5.12)	91 (15.0)	50 (11.6)	46 (9.73)	1 (0.389)
Dizziness	39 (4.06)	26 (3.40)	24 (5.67)	13 (4.30)	26 (3.21)	4 (5.13)	31 (3.97)	18 (2.96)	16 (3.70)	13 (2.75)	10 (3.89)
Headache	26 (0.0271)	23 (0.0301)	5 (0.01 18)	8 (0.0265)	22 (0.0271)	2 (0.0256)	11 (0.0141)	12 (0.0197)	12 (0.0278)	8 (0.0169)	8 (0.0311)
Nausea	13 (1.35)	17 (2.22)	7 (1.65)	6 (1.99)	16 (1.97)	2 (2.56)	16 (2.05)	6 (0.987))	6 (1.39)	6 (1.27)	3 (1.17)
Pyrexia	17 (1.77)	7 (0.915)	4 (0.94 6)	6 (1.99)	18 (2.22)	1 (1.28)	13 (1.66)	10 (1.64)	4 (0.956)	12 (2.54)	2 (0.778)
Pallor	15 (1.56)	8 (1.05)	9 (2.13)	6 (1.99)	11 (1.36)	2 (2.56)	10 (1.28)	9 (1.48)	8 (1.85)	7 (1.48)	4 (1.55)
Erythema	15 (1.56)	7 (0.915)	8 (1.89)	3 (0.993)	11 (1.36)	1 (1.28)	15 (1.92)	8 (1.32)	5 (1.16)	8 (1.69)	2 (0.778)

Note. Percentages may not be equal to 100% due to rounding.

This study also found a decline in reported adverse events between 2008-2011 in the US (Table 4). We also found that there was no change overtime in reported adverse events between 2011-2014 in the US (Table 5). However, in 2014 we saw that there was a steady increase in reported adverse events nationally with the highest peak of reported adverse events in 2016

(Table 6). Nevada reported the lowest number of adverse events between 2010-2012 compared to a drop in AE in 2013 in California (Table 5). Nevada, California, and the U.S. all showed a decline in reported adverse events in 2017 (Table 5). However, Nevada reported an increase in adverse events in 2018 (7.87%) compared to 2017 (4.67%) (Table 5).

Table 5. Adverse event report frequencies through time. Numbers provided as n (%).

	2008 n (%)	2009 n (%)	2010 n (%)	2011 n (%)	2012 n (%)	2013 n (%)	2014 n (%)	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)
California	960 (16.3)	765 (13.0)	423 (7.18)	302 (5.13)	811 (13.8)	78 (1.32)	781 (13.3)	608 (10.3)	432 (7.33)	473 (8.03)	257 (4.36)
Nevada	75 (10.0)	124 (16.5)	45 (6.00)	47 (6.27)	42 (5.60)	82 (10.9)	78 (1.4)	83 (11.1)	80 (10.7)	35 (4.67)	59 (7.87)
United States	20991 (15.8)	13531 (10.2)	10634 (8.02)	8718 (6.58)	8482 (6.40)	10168 (7.67)	10700 (8.07)	12999 (9.80)	15215 (11.5)	11369 (8.57)	9780 (7.38)
Note. Row percentages may not add up to 100% due to rounding.											

Among sex, female adverse event reporting (AER) is approximately 30% higher than that of male AER between 2015 through 2018 (Table 6). In Nevada, female vaccine estimates are below California and US estimates, but male vaccine estimates are above California, and the U.S. vaccine estimates (Table 6).

Table 6. Adverse event reports through time by sex. Numbers provided as n (%).

	2008 n (%)	2009 n (%)	2010 n (%)	2011 n (%)	2012 n (%)	2013 n (%)	2014 n (%)	2015 n (%)	2016 n (%)	2017 n (%)	2018 n (%)
California											
Female	950 (99.0)	762 (99.6)	391 (92.4)	235 (77.8)	503 (62.0)	47 (60.3)	464 (59.4)	216 (35.5)	229 (53.0)	243 (51.4)	200 (77.8)
Male	6 (0.625)	-	23 (5.44)	62 (20.5)	284 (35.0)	28 (35.9)	250 (32.0)	197 (32.4)	121 (28.0)	133 (28.1)	55 (21.4)
Unk	4 (0.417)	3 (0.392)	9 (2.13)	5 (1.66)	24 (2.96)	3 (8.58)	67 (8.58)	195 (32.1)	82 (19.0)	97 (20.5)	2 (0.778)
Nevada											

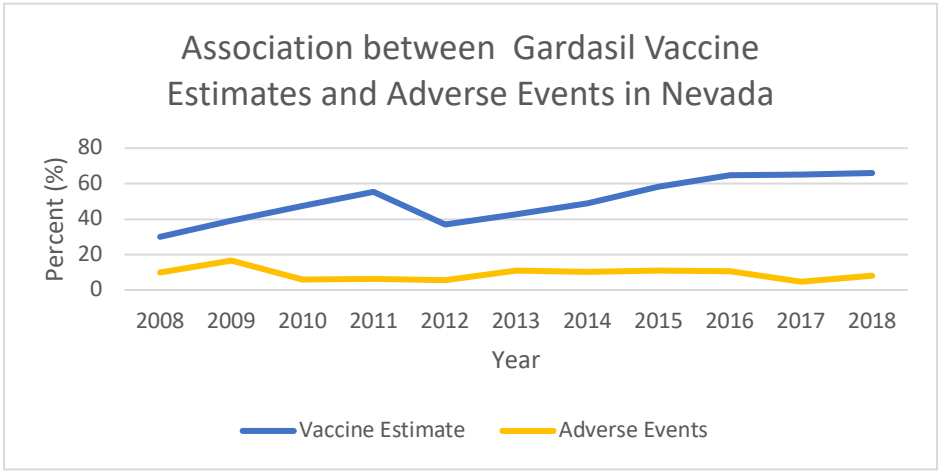
Female	75 (100)	124 (100)	45 (100)	26 (55.3)	17 (40.5)	31 (37.8)	41 (52.6)	20 (24.1)	3 (46.3)	17 (48.6)	26 (44.1)
Male	-	-	-	21 (44.7)	15 (35.7)	16 (19.5)	27 (34.6)	24 (28.9)	25 (31.3)	18 (51.4)	31 (52.5)
Unk	-	-	-	-	10 (23.8)	35 (42.7)	10 (12.8)	39 (47.0)	18 (22.5)	-	2 (3.39)
United States											
Female	20694 (98.6)	13369 (98.8)	9856 (92.7)	7126 (81.7)	5667 (66.8)	6100 (60.0)	5675 (53.0)	5434 (41.8)	6463 (42.5)	5585 (49.1)	5153 (52.7)
Male	83 (0.395)	31 (0.229)	677 (6.37)	1504 (17.3)	2191 (25.8)	2527 (24.9)	2532 (23.7)	2907 (22.4)	3550 (23.3)	2834 (24.9)	2874 (29.4)
Unk	214 (1.02)	131 (0.968)	101 (0.950)	88 (1.01)	624 (7.36)	1541 (15.2)	2493 (23.3)	4658 (35.8)	5202 (34.2)	2950 (26.0)	1753 (17.9)
Total	**22026**	**14420**	**11102**	**9067**	**9335**	**10328**	**11559**	**13690**	**15727**	**11877**	**10096**

Note. Unk: Unknown gender.

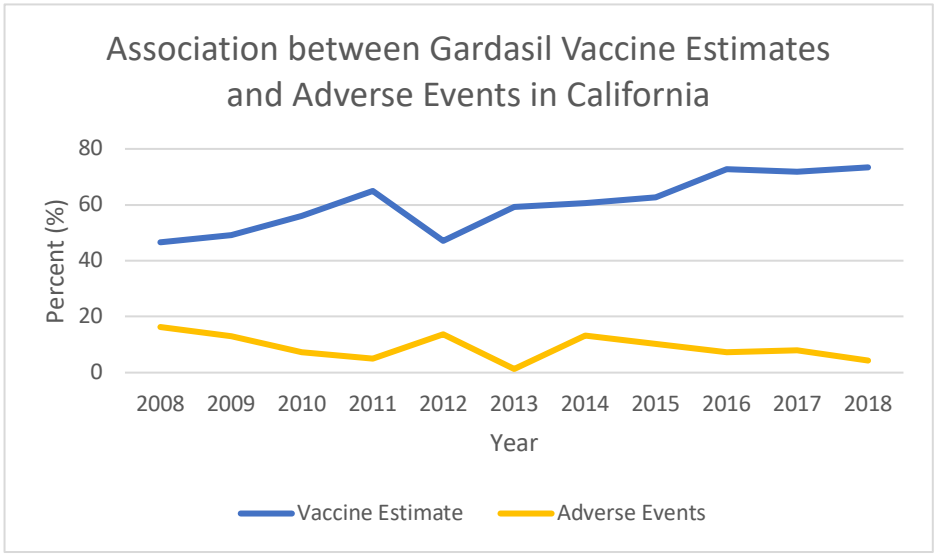
Associations between Adverse Events and Gardasil Vaccine Estimates

Adverse event reporting increases correlate with vaccine coverage estimates by gender. There was a higher reported adverse event in males following introduction of a new vaccine after 2009 and after 2014 (Table 6). The U.S. and Nevada had an almost 20% increase in vaccine coverage between 2014 and 2018 compared to an approximately 13% increase in California (Table 6). In Nevada, we found a slight correlation between the increase in vaccine estimates was following by an increase in adverse events only between 2008-2009 (Figure 6a). Our study found that an increase or decrease in vaccine estimates was followed by an increase or decrease, respectively the following year in California (Figure 6b). In the U.S., there were no correlations seen between vaccine estimates and adverse events (Figure 6c).

a.



b.



c.

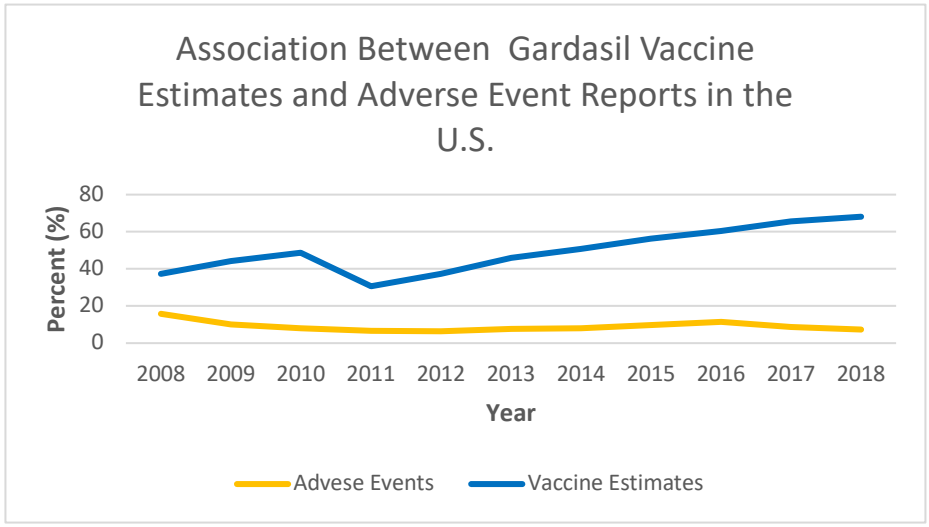


Figure 6 a-c. Associations between adverse event reports (%) and Gardasil estimates (%) through time.

Discussion

Gardasil usage

Overall, there has been a 30.2% increase in vaccine coverage for females in Nevada, California and the U.S. combined since 2008. In 2017 California had almost 10% decrease in vaccine coverage, where Nevada had an approximately 5% decrease. However, males have seen over 50% increase in vaccine coverage since the Advisory Committee on Immunization Practices (ACIP) allowed boys to be vaccinated in 2009. The results of this study are consistent with other research findings. In 2011, there was high HPV vaccine coverage for at least one dose (53%) in females; however, there was a lower vaccine coverage (35%) for dose completion (3 doses) in the same year (Saraiya et al., 2013).

This study only retrieved data for teens between the ages of 13-17 years; however, it is important to note the age distribution for vaccine uptake in the U.S. When considering the vaccine age distribution in the U.S. in 2018, a total of 18.5% of children 12 and younger, were vaccinated, 25.6% of adolescents between 13-14 years were vaccinated, 34.5% of adolescents between 15-17 years and 21.4% of adults 18-26 were vaccinated (Boersma & Black, 2020). With only 21.4% of adults getting the HPV vaccine and 78.6% of teens getting vaccinated, parental consent does not appear to be an obstacle for all underage persons (Boersma & Black, 2020). However, only 18.5% of those vaccinated in 2018 were 12 years or younger, indicating that there may be some barriers such as lack of parental knowledge, or misconceptions of the vaccine, which may cause parents to think their children will engage in risk sexual behavior (Boersma & Black, 2020).

Cervical cancer screening proportions

In this study, 76.1% of women in Nevada were screened for cervical cancer in the last 10 years, while 81.3% and 79.6% were screened in California and the U.S., respectively. Overall,

there has not been a change through time with regard to cervical cancer screening after the implementation of the HPV vaccines. Saraiya and colleagues (2013) confirmed that screening levels may remain consistent since most providers use HPV testing with the Pap test annually. The large increase in cervical cancer screening in 2014 for Nevada was likely due to the change in the BRFSS questionnaire. In 2012, the BRFSS survey included women aged 18 and older and in 2014, questionnaire only including women aged 21-65 years who had a pap test in the past three years. There is a need to increase screening among younger women, various studies show that women aged 45 to 74 years and older are more likely to be screened than those who are 18-44 years and 75 years and older (Miles-Richardson et al., 2017). Interventions that showed a notable increase in cervical cancer screening included those that were clinic-based, used lay health advisors (i.e., cancer survivors, members of churches, community members), and used behavioral theory (i.e., social influence theory, popular education and adult education theory) (Mann et al., 2015).

The reason for increase in pap screening is not entirely understood. However, the increase in screening in Nevada may be due to the change in the BRFSS question for cervical cancer screening in 2014. The question previously included women aged 18 years or older who got a pap test within the past 3 years and as of 2014, it only included women 21-65 years. No change in cervical cancer screening rates are likely due to the lag time between HPV vaccine age and the age (≥21 years) at which women begin having cervical cancer screenings.

Gardasil vaccine coverage by sociodemographic subgroups

This study continues to support research that there are health disparities among race, urbanicity and poverty status of teens who are vaccinated. American Indian/American Native (AI/AN) subgroup is the lowest subgroup in the U.S. to become vaccinated with HPV. In the

U.S., AI/AN make up only 1.4% of teens who have been vaccinated with an HPV vaccine in the last 10 years, followed by Asians (3.4%). White non-Hispanics continue to be the largest race subgroup who receives an HPV vaccine, followed by Hispanics (67.1% and 17.6%, respectively). Previous studies have assessed possibilities for the disparities in vaccine coverages. Issues with HPV vaccine coverage by race are affected by how parents perceive the vaccine. Research findings found that barriers for HPV vaccine administration was related to the concern that it would lead to premarital sexual activity (Galbraith et al., 2016). It is critical for health care providers to provide parents and adolescents with HPV vaccine education. Several studies reported that the recommendation from a health care provider to receive the HPV vaccine was a common reason for HPV vaccine administration among parents and adolescents (Alexander et al., 2014; Galbraith et al., 2016).

It is no surprise that those who are living at or above poverty have the highest vaccine coverage of adolescents. In California, Nevada, and the U.S., over 75% of teens vaccinated live at or above poverty, while approximately 20% of teens who have gotten an HPV vaccine live below poverty. Similar findings were reported that children with an employed parent, healthcare coverage and/or higher income were more likely to be vaccinated compared to children who did not have the above scenarios (Liddon et al., 2012; Shapiro et al., 2018). A study by Bhattacharya and colleagues (2019) found that a higher income level was highest among all women regardless of nativity status (being US- versus foreign-born). Higher estimates of vaccine in teens of higher SES are likely due to higher healthcare coverage, parent education, and overall ease of access to healthcare facilities. However, in a study done by Grandahl and colleagues (2017), they found that neither mother's and father's education status or occupation had a significant impact on males or female vaccine uptake in Sweden. The difference in vaccine update by SES status

between Sweden and the US may be due to Sweden's national vaccine program where eleven vaccines (including the HPV vaccine) are given free of charge to children (Public Health Agency of Sweden, n.d.).

Overall, California is doing very well in terms of vaccine uptake for teens. This study indicates that in the last 3 years, California has been able to increase the vaccine rates for Hispanic adolescents above those of White adolescents. The large vaccine uptake in Hispanic adolescents may have related to decreased language barriers between physicians and patients given that the Hispanic population makes up 40% of their population (U.S. Census Bureau, n.d.). Additionally, California has implemented the use of the VFC program and the California Health & Wellness program, which allows adults (19 years or older) and their families to get vaccinated for free (California Health & Wellness, n.d.). Both of these programs cover the HPV vaccine for free at any pharmacy which broadens its availability for children, mid- to late-adolescents and adults. Nevada could start to make more tailored programs for each race/ethnic subgroup to attempt to bridge any language gaps so that each subgroup could make their own informed health decisions.

This study indicated that Nevada falls behind California's vaccine and screening rates despite similarities in age and race/ethnic group proportions. One reason may be because Nevada has three urban and rural counties and 11 frontier counties, which demonstrates the highly underserved communities in the state. The sparsity of many of the hospitals and community health centers in Nevada's rural and frontier countries causes longer travel times and distances to centers with specialized medical facilities. Hence, this may be the cause for less vaccine uptake in children that do not live in a principle city.

Adverse Events

This study showed that the highest number of adverse events that have occurred in all the U.S., California and Nevada were non-serious events due to reasons such as incorrect vaccine given or a vaccine given to a male prior to accepted guidelines. Despite studies reporting high VTE adverse events, this study did not reveal VTE to be one of the top 10 AEs in the U.S., California, or Nevada (Lui et al., 2016; Mauro et al., 2019; Naleway et al., 2016). This study also did not find any AEs related to GBS in the top 10 reported AEs despite other research studies (Slade et al., 2009; Gee et al., 2017; Mauro et al., 2019). This study supports other research findings syncope, dizziness, headaches, nausea, vomiting, among the most common adverse events (Slade et al., 2009; Arana et al., 2018; Mauro et al., 2018; Suragh et al., 2018).

Gardasil's manufacturing company reports that the most common side effects included injection site pain, swelling, erythema, itching, bruising and reports of fever(pyrexia), abdominal pain, diarrhea, sore throat, tiredness and nausea (Merck & Co., Inc., 2020). The top three injection site reactions, for males and females receiving Gardasil (quadrivalent vaccine), were pain (61.4% and 83.9%, respectively), swelling (13.9% and 25.4%, respectively) and erythema (16.7% and 24.7%, respectively) (CDC, 2014a). This study maintains that the leading adverse events are non-serious. Arana and colleagues (2018) confirm that 94.2% of adverse event reports were non-serious supporting that the use of these vaccines is not in maleficence.

Vaccine Perceptions

There has been much controversy related to the HPV vaccine. Some of the misconceptions may be due to the age that was selected for girls to be vaccinated. The Advisory Committee on Immunization Practices (ACIP) recommended routine vaccines for girls as young as 9 years to allow for the vaccine to be administered prior to first sexual encounter (Saraiya et

al., 2013). There are parents with the perception of the vaccine creating the path of risky sexual behaviors for their children (Leidner et al., 2020).

Canada has an HPV vaccine program that targets school-age children, resulting in high vaccine coverage (Saraiya et al., 2013). The ACIP has included HPV vaccines for the Vaccines for Children Program since October 2009, which covers the cost of the HPV vaccine for children younger than 18 years, who are uninsured, Medicaid-eligible, or who are American Indian/Alaska Native (CDC, 2020). Health insurances typically cover vaccines that are routinely recommended by ACIP, which can further assist increasing HPV vaccine coverages.

California Planned Parenthood Education Fund was established to help expand access, availability and affordability of the HPV vaccine (CPPEF, 2016). The AB 499 in California expands current legislation to include the HPV vaccine, and other STD prevention. AB 499 allows teens 12 years and older to consent to receiving the vaccine in order to protect themselves against sexually transmitted diseases whereby the child's parent or guardian is not liable to pay for medical care received by the minor (AB No. 499; CPPEF, 2016). There are also various organizations (i.e., California Medical Association, California Family Health Council, California Primary care Association, American Congress of Obstetricians and Gynecologists, District IX) making strides to try to increase HPV vaccine uptake (CPPEF, 2016).

Nevada has not implemented any statewide legislation for the requirement of the HPV vaccine in adolescents. There has been recent pushback in the Nevada Legislature Legislative Committee on Health Care. During the third meeting of the Legislative Committee on Health Care for the 2019-2020 Interim, several public comments reporting severe adverse events opposing the use of the HPV vaccine (LCHC, 2020).

Overall, the U.S. is making strides in making the HPV vaccines accessible to adolescents. Washington D.C., Puerto and 48 U.S. states allow pharmacists to administer the HPV vaccine in children (NCSL, 2020). However, there continues to be only 3 states (RI, HI, VA), Washington D.C. and Puerto Rica that require the HPV vaccine for school attendance. There is a need for better education that targets specific subgroups and cultural differences. (NCSL, 2020).

Limitations

As is to be expected, there are limitations found in this study. All TeenVaxView data are self-reported increasing the likelihood of recall bias because parents may not remember all of their child's vaccine record history. It is also likely that this study contains selection bias since some parents may not report vaccine history due to a lack of trust, knowledge, or cultural beliefs about HPV. Additionally, differences in sociodemographic data, lifestyle, and medical practices may exist in parents who choose to vaccinate their child with Gardasil versus parents who opt-out.

Furthermore, given that there was a follow-up questionnaire sent to physicians in the NIS-Teen, there is the potential for losses to follow-up. Losses to follow-up could be due to differences in referral criteria, improper procedures for cases, or sociodemographic information, which could lead to misclassification bias. Another limitation of this study is the possibility of underreporting or sample bias in those who file an adverse event report compared to those that do not. There is also the limitation that may be caused by unevaluated dosing effects from HPV vaccine administration given missing or unreported data.

We also expect to see limitations due to self-reporting data obtained from BRFSS. Respondents may not report accurate information. Question wording may lead to measurement error or time lapse between survey and a particular event may lead to response error in BRFSS.

However, given the complexity of sampling through random-digit dialing, the BRSS offers several advantages such as obtaining generalizable population.

Additionally, the use of VAERS data presents limitations due to VAERS' passive reporting system. Since VAERS relies on individuals to report any adverse events associated with a vaccine, it's use is not to determine if a vaccine caused a health problem, but rather for detecting any unusual patterns of adverse events. Hence, limitations associated with VAERS includes reporting bias and sampling bias. Severity of an adverse event is subjective and can result in measurement error. Additionally, sampling bias could result since those who report to VAERS may not be the same as those who do not report adverse events thus leading to less generalizability. Our study was not able to assess incidence of adverse events given that VAERS lacks information on the total number of people who are vaccinated and those people who experience an AE.

Lastly, given that correlation will be used to test for potential temporal associations for hypotheses three and four, this data should be interpreted cautiously given this data is strictly correlational and will be used for the basis of future hypothesis-generating results. Although this study assessed Gardasil vaccine rates and screening rates together, we expect there to be a lag time between when we can see more accurate screening rates given that the lag time between vaccine age and screening age do not align.

Future Public Health Policy and Research Recommendations

The present study illustrates the ongoing disparities among adolescents based on SES, race/ethnicities, and urbanicity that has been seen in previous years in the U.S. As of 2020 policies requiring HPV vaccination in school-aged children has not reached by all U.S. states. With only three states and Washington D.C. requiring HPV vaccination to enter secondary

school, there is a need to consider statewide school mandates that will increase vaccine uptake in school-aged children prior to their first HPV exposure (Immunization Action Coalition, 2019). There has been increase in the analysis of effective policy efforts to try to increase vaccinate coverage across the U.S. Saulsberry and colleagues (2019), found that parents preferred a physician mandate, which would require physicians to offer the HPV vaccine ($p<0.01$) compared to middle school mandates, which would require students to get vaccinated in school. Policy makers should ensure that federally funding vaccine programs be provided to all school-aged children nationwide. Existing currently is the Vaccines for Children Program (VFC), which provides the vaccine at no cost to American Indian/Alaskan Native, uninsured, Medicaid-eligible, or underinsured children (less than 18 years). Despite the VFC program, states vary in their supply of the vaccine and determination of vaccine eligibility. However, Dorell and colleagues (2013) determined that when comparing VFC program funding, states that provided universal vaccine coverage had higher HPV initiation rates. Some states are only able to supply eligible children through VFC criteria only (noted above). There are other states who use state and local funds to supply the VFC program making uninsured children and those who meet VFC criteria eligible, and other states have universal (VFC-eligible, underinsured, and privately insured children) coverage through the use of state and local funds to supplement the VFC program (Dorell et al., 2013). Mandated education in schools has not shown any significant increase in vaccine coverage for girls before or after the mandate (Pierre-Victor et al., 2017). While it is important to education parents and children on the benefits of the HPV vaccine, mandated education should be supplemented with physician mandates to discuss HPV vaccine benefits. Discussions about HPV vaccine eligibility, social stigma and parent preferences are three factors that influence this decision-making process.

Mortality in cervical cancer has gone down in the last couple of years (Sawaya & Huchko, 2017). The decrease in morality may be due to better treatment of cervical cancer, early screening before the cancer is in the late stage. It is also possible that we will see more decrease in morality of cervical cancer through vaccine uptake. Despite the importance that all those factors play in the decrease of cervical cancer mortality, we did not look at morbidity/mortality in this study because that data was not available for us to use. However, future studies need to be done to assess the change in mortality of cervical cancer in Nevada once all vaccinated girls have reached screening ages (i.e., in the year 2021 and further or an approximate time lag of 10 years between 9-21years).

To the author's knowledge, there have no previously published studies that analyze state-specific data on Gardasil vaccine coverage, adverse events and screening that compares Nevada, to California and the U.S.

Conclusion

The data used in this study supplemented current research with the most recent data available for Nevada, California, and U.S. This study found that screening rates have not decreased; however, future studies should assess screening rates in 2021 and further to capture all girls vaccinated with the HPV vaccine. Of the three locations analyzed, California showed to have the highest vaccine estimates through time compared to Nevada and the U.S., which is likely due to variations in state demographics. It would be interesting to assess each state by demographics along with the current vaccine programs in place. No association was seen between Gardasil vaccine estimates and cervical cancer screening rates in this study. This study showed a temporal association between adverse events and Gardasil vaccine estimates in California only. Furthermore, this project provides information on adverse events that could further support legislation to create a vaccine program nationally that better targets subgroups. This project also shows the need to target American Indian/American Native subgroups given their extremely low vaccine rates despite current child vaccine programs. Finally, given the largely descriptive nature of this study, the main outcomes provided hypothesis generating results for future studies.

Appendix

Appendix A: Internal Review Board Exclusion

UNLV

UNLV Biomedical IRB - Administrative Review
Notice of Excluded Activity

DATE:	July 22, 2020
TO:	Sheniz Moonie, PhD, MS
FROM:	UNLV Biomedical IRB
PROTOCOL TITLE:	[1636038-1] Gardasil vaccine usage trends within Nevada; a comparative study
SUBMISSION TYPE:	New Project
ACTION:	EXCLUDED - NOT HUMAN SUBJECTS RESEARCH
REVIEW DATE:	July 22, 2020
REVIEW TYPE:	Administrative Review

Thank you for your submission of New Project materials for this protocol. This memorandum is notification that the protocol referenced above has been reviewed as indicated in Federal regulatory statutes 45CFR46.

The UNLV Biomedical IRB has determined this protocol does not meet the definition of human subjects research under the purview of the IRB according to federal regulations. It is not in need of further review or approval by the IRB.

We will retain a copy of this correspondence with our records.

Any changes to the excluded activity may cause this protocol to require a different level of IRB review. Should any changes need to be made, please submit a Modification Form.

If you have questions, please contact the Office of Research Integrity - Human Subjects at IRB@unlv.edu or call 702-895-2794. Please include your protocol title and IRBNet ID in all correspondence.

Office of Research Integrity - Human Subjects
4505 Maryland Parkway . Box 451047 . Las Vegas, Nevada 89154-1047
(702) 895-2794 . FAX: (702) 895-0805 . IRB@unlv.edu

References

Alexander, A. B., Stupiansky, N. W., Ott, M. A., Herbenick D., Reece, M., Zimet G. D. (2014). *Health Psychology, 33*(5), 448-456. http://dx.doi.org/10.1037/a0033863

American Cancer Society. (2017, 13 November). Can anal cancer be found early? https://www.cancer.org/cancer/anal-cancer/detection-diagnosis-staging/detection.html

American Cancer Society. (2018a, 25 June). Can penile cancer be found early? https://www.cancer.org/cancer/penile-cancer/detection-diagnosis-staging/detection.html

American Cancer Society. (2018b, 9 March). Can oral cavity and oropharyngeal cancers be found early? https://www.cancer.org/cancer/oral-cavity-and-oropharyngeal-cancer/detection-diagnosis-staging/detection.html

American Cancer Society. (n.d., a). Treating anal cancer. https://www.cancer.org/cancer/anal-cancer/treating.html

American Cancer Society. (n.d., b). Treating penile cancer. https://www.cancer.org/cancer/penile-cancer/treating.html

American Cancer Society. (n.d., c). Treating oral cavity and oropharyngeal cancer. https://www.cancer.org/cancer/oral-cavity-and-oropharyngeal-cancer/treating.html

Anal Cancer Foundation (ACF). (no date, n.d.). About HPV/Treatment/Precancer. https://www.analcancerfoundation.org/about-hpv/treatment/pre-cancer/?geoip=US

Arana, J. E., Harrington, T., Cano, M., Lewis, P., Mba-Jonas, A., Rongxia, L., Stewart B., Markowitz, L. E., and Shimabukuro, T. T. (2018). Post-licensure safety monitoring of quadrivalent human papillomavirus vaccine in the Vaccine Adverse Event Reporting System (VAERS), 2009-2015. *Vaccine, 36,* 1781-1788.

Assembly Bill No. 499. Minors: Medical care: Consent. Chapter 652: An act to amend Section 6926 of the family code, relating to minors. Retrieved November 7, 2020. https://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201120120AB499

Beavis, A. L., Gravitt, P. E., Rositche A. F. (2017). Hysterectomy-corrected cervical cancer mortality rates reveal a larger racial disparity in the United States. *Cancer, 123,* 1044-1050. https://dx.doi.org/10.1002/cncr.30507

Benard VB, Thomas CC, King J, et al. Vital signs: cervical cancer incidence, mortality, and screening - United States, 2007–2012. MMWR Morb Mortal Wkly Rep 2014;63(44):1004–9. [PubMed: 25375072]

Bernard, H. U., Burk, R. D., Chen, Z., van Doorslaer, K., zur Hausen, H., de Villiers, E. M. (2010). Classification of papillomaviruses (PVs) based on 189 PV and proposal of taxonomic amendments. Virology, 401(1), 70-79. https://doi.org/10.1016/j.virol.2010.02.002

Bhattacharya, M., Reiter, P. L., & McRee, A. L. (2019). Nativity status and genital HPV infection among adults in the U.S. *Human Vaccines & Immunotherapeutics, 15,* 1897-1903. https://doi.org/10.1080/21645515.2019.1578592

California Health & Wellness. (n.d.). *Vaccinations*: *Why vaccinate.* https://www.cahealthwellness.com/members/medicaid/benefits-services/pharmacy/Vaccinations.html

California Planned Parenthood Education Fund. (2016). HPV Vaccine. Retrieved November 7, 2020. http://www.cppef.org/our-issues/hpv-vaccine/

Castle, P. E., Wheeler, C. M., Campos, N. G., Stephen S., Burger, E. A., Kim, J. J., on behalf of the New Mexico HPV Pap Registry Steering Committee. *Preventive Medicine, 111*, 177-179. https://doi.org/10.1016/j.ypmed.2018.03.011.

Centers for Disease Control and Prevention (CDC). (2014a). *Human Papillomavirus Vaccination: Recommendations of the advisory committee on Immunization Pracices (ACIP).* Morbidity and Mortality Weekly Report (MMWR). https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6305a1.htm#tab7s

Centers for Disease Control and Prevention (CDC). (2017). TeenVaxView. Retrieved March 18. 2020, from https://www.cdc.gov/vaccines/imz-managers/coverage/teenvaxview/data-sources.html

Centers for Disease Control and Prevention (CDC). (2014b). Behavioral risk factor surveillance

Centers for Disease Control and Prevention. (2015a). 2015 Sexually transmitted disease treatment guidelines: Human papillomavirus (HPV) infection. Retrieved May 3, 2020 from https://www.cdc.gov/std/tg2015/hpv.htm

Centers for Disease Control and Prevention. (2015b). Sexually transmitted diseases: Summary of 2015 CDC treatment guidelines. Retrieved on May 1, 2020 from https://www.cdc.gov/std/tg2015/2015-wall-chart.pdf

Centers for Disease Control and Prevention. (2016b). Human papillomavirus (HPV): Treatment and care. Retrieved on May 3, 2020 from https://www.cdc.gov/std/hpv/treatment.htm

Centers for Disease Control and Prevention. (2018a). Behavioral risk factor surveillance

Centers for Disease Control and Prevention. (2019a). About HPV. Retrieved on April 7, 2020 from https://www.cdc.gov/hpv/parents/about-hpv.html

Centers for Disease Control and Prevention. (2019b). Chapter 11: Human Papillomavirus. Retrieved on May 1, 2020 from https://www.cdc.gov/vaccines/pubs/pinkbook/hpv.html

Centers for Disease Control and Prevention. (2019c). Human papillomavirus (HPV): Vaccinating boys and girls. Retrieved on May 3, 2020 from https://www.cdc.gov/hpv/parents/vaccine.html

Centers for Disease Control and Prevention. (2019d). Human papillomavirus (HPV): HPV Disease and Cancer. https://www.cdc.gov/hpv/parents/cancer.html

Centers for Disease Control and Prevention. (2020). Paying for HPV vaccine. https://www.cdc.gov/vaccines/vpd/hpv/hcp/payment.html#:~:text=Paying%20for%20HPV%20Vaccine,-Related%20Pages&text=The%20Vaccines%20for%20Children%20(VFC,or%20American%20Indian%2FAlaska%20Native. Accessed November 11, 2020.

Churilla, T., Egleston, B., Dong, Y., Shaikh, T., Murphy, C., Mantia-Smaldon, G., Chu, C., Rubin, S., Anderson, P. (2016). Disparities in the management and outcome of cervical cancer in the United States according to the health insurance status. *Gynecologic Oncology, 141,* 516-523. http://dx.doi.org/10.1016/j.ygyno.2016.03.025

Cutts, F. T., Franceschi, S., Goldie, S., Castellsague, X., de Sanjose, S., Garnett, G., et al. (2007). Human papillomavirus and HPV vaccines a review. World Health Organization. https://www.who.int/bulletin/volumes/85/9/06-038414/en/

de Martel, C., Plummer, M., Vignat, J., Franceschi, S. (2017). Worldwide burden of cancer attributable to HPV by site, country and HPV type. *International Journal of Cancer, 141,* 664-670.

de Sanjose, S. Serrano, B., Tous, S., Alejo, M., Lloveras, B., Quiros B., et al. (2019). Burden of Human Papillomavirus (HPV)-Related Cancers Attributable to HPVs 6/11/16/18/31/33/45/52 and 58. *JNCI Cancer Spectrum, 2*(4), pky045.

Domgue, J. F., Chido-Amajuoyi, O. G., Yu, R. K., Shete, S. (2019). Beliefs about HPV vaccine's success at cervical cancer prevention among adult US women. *JNCI Cancer Spectrum, 3*(4), pkz064. http://dx.doi.org/10.1093/jncics/pkz064

Dorell, C. G., Markowitz, L. E., Hariri, S., Stokley, S., Yankey, D. (2013). Role of HPV Financing and Policy. [Abstract]. *52*, S21-S113.

Duggan, M. A., Anderson W. F., Altekruse S., Penberthy, L., Sherman, M. E. (2016). The surveillance, epidemiology and end results (SEER) program and pathology: Towards strengthening the critical relationship. *American Journal of Surgical Pathology, 40*(12), e94-e102. https://dx.doi.org/10.1097/PAS.0000000000000749.

Endeshaw, M., Clarke, T., Senkomago, V., & Saraiya M. (2018). Cervical cancer screening among women by birthplace and percent of lifetime living in the United States. *Journal of Lower Genital Tract Disease, 22*(4), 280-287. doi:10.1097/LGT.0000000000000422.

Galbraith, K. V., Lechuga, J., Jenerette C. M., Moore, A. D., Palmer, M. H., & Hamilton J. B. (2016). Parental acceptance and uptake of the HPV vaccine among African-Americans and Latinos in the United States: A literature review. *Social Science & Medicine, 159*, 116-126. http://dx.doi.org/10.1016/j.socscimed.2016.04.028

Gee, J., Sukumaran, L., Weintraub, E., & the Vaccine Safety Datalink Team. (2017). Risk of Guillain-Barré Syndrome following quadrivalent human papillomavirus vaccine in the Vaccine Safety Datalink. *Vaccine, 35*, 5756-5758).

Globocan 2018 (2019, May). *900 World fact sheet*. Retrieved March 23, 2020, from http://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf

Grandahl, M., Larsson, M., Dalianis, T., Stenhammar, C., Tyden, T., Westerling, R., Neveus T. (2017). Catch-up HPV vaccination status of adolescents in relation to socioeconomic factors, individual beliefs and sexual behavior. *PLOS one, 12*(11), e0187139. https://doi.org/10.1371/journal.pone.0187193

Harvard Medical School. (2019, July). Human Papilloma Virus (HPV). Harvard Health Publishing. https://www.health.harvard.edu/a_to_z/human-papilloma-virus-hpv-a-to-z

Healthy People 2020. (n.d.a) *Washington, DC: U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion: Immunization and Infectious Diseases.* https://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases/objectives

Healthy People 2020. (n.d.b). *Washington, DC: U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion: Increase the proportion of adolescents who get recommended doses of the HPV vaccine—IID-08.* https://health.gov/healthypeople/objectives-and-data/browse-objectives/vaccination/increase-proportion-adolescents-who-get-recommended-doses-hpv-vaccine-iid-08

Hirth, J. (2019). Disparities in HPV vaccination rates and HPV prevalence in the United States: A review of the literature. *Human Vaccines & Immunotherapeutics, 15*(1), 146-155. https://doi.org/10.1080/21645515.2018.1512453

Immunization Action Coalition. (2019, December). State Information: HPV Vaccine Mandates for Elementary and Secondary Schools. https://www.immunize.org/laws/hpv.asp

Kumakech, E. (2015). Human immunodeficiency virus (HIV), human papillomavirus (HPV) and cervical cancer prevention in Uganda: prevalence, risk factors, benefits and challenges of post-exposure prophylaxis, screening integration and vaccination. (Publication No. 1652-4062) [Dissertation, Orebro University]. Orebro University 2015. http://oru.diva-portal.org/smash/get/diva2:809485/INSIDE01.pdf

Leidner, A. J., Chesson, H. W., & Talih, M.

Liddon, N. C., Leichliter, J. S., & Markowitz, L. E. (2014). Human papillomavirus vaccine and sexual behavior among adolescent and young women. *American Journal of Preventative Medicine, 42*(1), 44-52. doi: 10.1016/j.amepre.2011.09.024

Longworth, M. S., and Laimins, L. A. (2004). Pathogenesis of human papillomaviruses in differentiating epithelia. Microbiology and Molecular Biology Reviews, 362-372.

Lui, X. C., Bell, C. A., Simmonds, K. A., Svenson, L. W., Russell, M. L. (2016). Adverse events following HPV vaccination, Alberta 2006-2014. *Vaccine, 34*, 1800-1805.

Mann, L., Foley, K. L., Tanner, A. E., Sun, C. J., Rhodes, S. D. (2015). *Journal of Cancer Education, 30*(2), 374-387. doi:10.1007/s13187-014-0716-9

Mauro, A. B., Fernandes, E. G., Miyaji, K. T., Arantes, B. A., et al. (2019). Adverse events following Quadrivalent HPV vaccination reported in Sao Paulo, Brazil, in the fisrt three years after introducing the vaccine for routine immunization (March 2014 to December 2016). *Journal of the São Paulo Institute of Tropical Medicine, 61,* e43.

Mayo Clinic (2019a, August 30). HPV Infection: Diagnosis and Treatment. https://www.mayoclinic.org/diseases-conditions/hpv-infection/diagnosis-treatment/drc-20351602

Mayo Clinic. (2018, November 2). Cervical dysplasia: Is it cancer? https://www.mayoclinic.org/diseases-conditions/cervical-cancer/expert-answers/cervical-dysplasia/faq-20058142

Mayo Clinic. (2019b, August 30). HPV Infection: Symptoms and Causes. https://www.mayoclinic.org/diseases-conditions/hpv-infection/symptoms-causes/syc-20351596

McDougall, J. A., Madeleine, M. M., Daling J. R., Li C. I. (2007). Racial and ethnic disparities in cervical cancer incidence rates in the United States, 1992-2003. *Cancer Causes & Control, 18*, 1175-1186.

Merck Vaccines. 2019. Gardasil 9 Human Papillomavirus 9-valent Vaccine, Recombinant. Retrieved on April 13, 2020 from https://www.merckvaccines.com/gardasil9/

Merck & Co., Inc. (2020, June). *Patient information about GARDASIL®9 (pronounced "gard-Ah-sill nīn") (Human Papillomavirus 9-valent Vaccine, Recombinant).* https://www.merck.com/product/usa/pi_circulars/g/gardasil_9/gardasil_9_ppi.pdf

Miles-Richardson, S., Allen, S., Claridy, M. D., Booker, E. A., Gerbi, G. (2017). Factors associated with self-reported cervical cancer screening among women aged 18 years and older in the United States. *Journal of Community Health, 42,* 72-77.

Moore, J. X., Royston K. J., Langston, M. E., Griffin, R., Hidalgo, B., Wang, H. E., Colditz, G., Akinyemiju, T. (2018). Mapping hot spots of breast cancer mortality in the United States: place matters for Blacks and Hispanics. *Cancer Causes & Control, 29* 737-750.

Morales-Campos, D. Y., Villarreal, E. K., Crocker, L. C., Guerrero, A., Fernandez, M. E. (2018) Cervical cancer, human papillomavirus (HPV), and HPV vaccination: exploring gendered

perspectives, knowledge, attitudes, and cultural taboos among Mexican American adults. *Ethnicity & Health,* 1-19. https://doi.org/10.1080/13557858.2018.1494821

Naleway, A. L., Crane, B., Smith, N., Daley M. F., Donahue, J., et al. (2016). Absence of venous thromboembolism risk following quadrivalent human papillavirus vaccination, Vaccine Safety Datalink, 2008-2011.

National Cancer Institute (NIH). (2019). Cervical cancer treatment (PDQ) - Patient Version. https://www.cancer.gov/types/cervical/patient/cervical-treatment-pdq

National Cancer Institute (NIH). (2020). HPV and cancer. https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-and-cancer#cancers-caused

Nevada Legislature Legislative Committee on Health Care. Nevada Revised States 439B.200. The third meeting of the Legislative Committee on Health Care for the 2019–2020 Interim was held on Wednesday, January 15, 2020, at 9 a.m. Retrieved on November 7, 2020. https://www.leg.state.nv.us/App/InterimCommittee/REL/Document/15047

New York State Department of Health. (2018, December). Genital warts (venereal warts, HPV). Retrieved from https://www.health.ny.gov/publications/3837/

Peterson, S. S., Doe, S., Buekers, T. (2018). *Gynecologic Oncology Reports, 25,* 102-105. https://doi.org/10.1016/j.gore.2018.06.010

Phaswana-Mafuya, N., and Peltzer, K. (2017). Breast and cervical cancer screening prevalence and associated factors among women in the South African general population. *Asian Pacific Journal of Cancer Prevention, 19*(6), 1465-1470.

Pierre-Victor, D., Trepka, M. J., Page, T. F., Li, T., Stephen, D. P., & Madhivanan, P. (2017). Impact of Louisiana's HPV vaccine awareness policy on HPV vaccination among 13- to 17-year-old females. *Health Education & Behavior, 44*(4), 548-558.

Planned Parenthood. (2015, June). HPV -- The most common sexually transmitted virus. Retrieved from https://www.plannedparenthood.org/uploads/filer_public/76/a1/76a15bc6-4317-4cb9-b6cc-765a1bef0f06/pp_hpv_factsheet.pdf

Planned Parenthood. No date (n.d.). How can I make sure I don't get or spread HPV? https://www.plannedparenthood.org/learn/stds-hiv-safer-sex/hpv/how-can-i-make-sure-i-dont-get-or-spread-hpv

Plummer. M., de Martel, C., Vignat, J., Ferlay, J., Bray, F., Franceschi, S. (2016). Global burden of cancers attributable to infections in 2012: A synthetic analysis. *Lancet Global Health, 4*, e609-e616.

Public Health Agency of Sweden. (n.d.). Vaccine programmes: Vaccine programme for children. https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/vaccinations/vaccination-programmes/

Rauh, L. A., Saks, E. J., Nakad-Rodriguez, D., Showalter, T. N., Duska, L. R. (2018). Cervical cancer care in rural Virginia: The impact of distance from an academic medical center on outcomes & the role of non-specialized radiation centers. *Gynecologic Oncology, 150*(2), 338-342.

Saraiya, M., Steben, M., Watson, M., & Markowitz, L. (2013). Evolution of cervical cancer screening and prevention in United States and Canada: Implications for public health practitioners and clinicians. *Preventative Medicine*, *57(*5), 426-433. https://doi.org/10.1016/j.ypmed.2013.01.020

Saulsberry, L., Fowler, E. F., Nagler, R. H., and Gollust S. E. (2019). Perceptions of politicization and HPV vaccine policy support. *Vaccine, 37,* 5121-5128. https://doi.org/10.1016/j.vaccine.2019.05.062

Sawaya, G. F. & Huchko M. J. (2017). Cervical cancer screening. *Medical Clinics of North America, 101*(4), 743-753. https://doi.org/10.1016/j.mcna.2017.03.006.

Serrano, B., Brotons, M., Bosch, F. B., and Bruni, L. (2018). Best Practices and Research Clinical Obstetrics and Gynaecology, 47, 14-26. http://dx.doi.org/10.1016/j.bpobgyn.2017.08.006

Shapiro, G. K., Tatar, O., Amsel, R., Prue, G., Zimet, G. D., Knauper, B., Rosberger, Z. (2018). Using an integrated conceptual framework to investigate parents' HPV vaccine decision for their daughters and sons. *Preventative Medicine, 116,* 203-2010. https://doi.org/10.1016/j.ypmed.2018.09.017

Slade, B. A., Leidel, L., Vellozzi, C., Woo, E. J., Hua W., et al. (2009). Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA*, *302*(7), 750-757.

Suragh, T. A., Lewis, P., Arana, J., Mba-Jonas, A., Li, R., et al. (2018). *British Journal of Clinical Pharmacology, 84,* 2928-2932.

system overview: About BRFSS. Retrieved from https://www.cdc.gov/brfss/about/htm

system overview: BRFSS frequently asked questions (FAQs). Retrieved from https://www.cdc.gov/brfss/about/brfss_faq.htm

U.S. Cancer Statistics Working Group. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. *U.S. Cancer Statistics Data Visualizations Tool, based on 2019 submission data (1999-2017).* www.cdc.gov/cancer/dataviz, released in June 2020.

U.S. Census Bureau. (2020). *Quick Facts: California; Nevada.* U.S. Census. https://www.census.gov/quickfacts/fact/table/CA,NV/AGE295219

U.S. Food and Drug Administration (FDA). (2018). Gardasil vaccine safety. Retrieved on April 20, 2020 from https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/gardasil-vaccine-safety

U.S. Food and Drug Administration (FDA). (2019, 25 October). Cervarix. Retrieved on April 20, 2020 from https://www.fda.gov/vaccines-blood-biologics/vaccines/cervarix

World Health Organization (WHO). (2019, 24 January). Human papillomavirus (HPV) and cervical cancer. Retrieved from https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer

Yoo, W., Kim, S., Huh, W. K., Dilley, S., Coughlin, S. S., Patridge, E. E., Chung, Y., Dicks, V., Lee, J. K., Bae, S. (2017). Recent trends in racial and regional disparities in cervical cancer incidence and mortality in United States. *PLoS One, 12*(2), e0172548. https://dx.doi.org/doi:10.1371/journal.pone.0172548.

Curriculum Vitae

Karen Gutierrez
ks.gutierrez2@gmail.com

EDUCATION

M.P.H.	University of Nevada, Las Vegas | School of Public Health	December 2020
B.S.	University of Nevada, Las Vegas | College of Sciences	July 2017

PUBLICATIONS

De Leon, J., Moonie, S., Cross, C., Shen, J., Gutierrez, K. (2020). Opioid-Related Hospitalizations and Intravenous Drug Users: Socio-Demographic, Spatial, and Comorbid Associations among Hospital Inpatients and Community-Based Harm Reduction Organization Participants. *Journal of Opioid Management*. https://doi.org/10.5055/jom.2020.0000

Ganta, V., Moonie, S., Labus, B., Gutierrez, K., Goodman, X. (2020) Barriers for Cervical Cancer Screening in Women Living with HIV: A Systematic Review. Journal of Health Disparities Research and Practice. http://digitalscholarship.unlv.edu/jhdrp/

Goertz, A., Moonie, S., Anderson, J., Gutierrez, K., Bungum, T. (2019). The economic recession on the health of adult Nevadans. *Nevada Journal of Public Health*. 1-8. http://www.npha.wildapricot.org/resources/Documents/NJPHDocs/NJPH%20Moonie_Goertz%202019.pdf

Johnson, H., Anderson, J., Moonie, S., Gutierrez, K., Hogan MB. (2020). Factors and Cost Associated with Atopic Dermatitis in Nevada. *Journal of Postgraduate Medicine (IPGM). 132*(7), 629-635. https://doi.org/10.1080/00325481.2020.1764263

Keeley, J., Flatt, J., Sy, F., Gutierrez, K. S., Bungum, T., Cross, C., Moonie, S. (2020). Mental Health Disparities among Sexual Monitories. 10-17. *Nevada Journal of Public Health*. http://www.nphaonline.org/resources/Documents/NJPHDocs/NJPH%20Keeley%202020.pdf

OTHER REPORTS

Moonie, S., Gutierrez, K., Anderson, J. (2019). 2019 Health for Nevada—Top Health Indicators for Nevada and the U.S.

Cross, C., Kumar, P., Gutierrez, K., Moonie, S. (2019). The impact of sociodemographic factors in breast, prostate and lung cancer in the patterns of care related to the availability of radiation therapy (RT) in a rural mountain west state.

UNIVERSTIY RESEARCH EXPERIENCE

Graduate Research Assistant | University of Nevada, Las Vegas
August 20, 2018 – August 14, 2020

- Collected, coded, and or analyzed data
- Conducted literature reviews or library research
- Prepared materials for submission to funding agencies and foundations
- Wrote reports
- Prepared materials for IRB review
- Utilized SPSS, Excel
- CITI Program- Research Ethics and Compliance Trained and Certified

UNLV Undergraduate Student Researcher | Las Vegas, NV
October 2012 – January 2015

- Fruit Fly Research
    - Assisted graduate assistant in demonstrating laboratory procedures
    - Aided in setting up lab equipment prior to data analysis
    - Aided in preparing food for *Drosophila melanogaster*
    - Aided in transfer of *Drosophila melanogaster*
    - Assisted in data recording

PROFESSIONAL EXPERIENCE

Graduate Research Assistant – Contact Tracing Team Supervisor | University of Nevada, Las Vegas
August 17, 2020 – Present

- Coursera - COVID-19 Contact Tracing certified.
- Astho – Making Contact: A training for COVID-19 Contact Tracers certified.
- Supervise Contact tracers.
- Ensure that new cases of COVID-19 are contacted within 24-hours of receipt of laboratory confirmation.

- Conduct training, orientation, and scheduling for employees.
- Submit reports as needed
- Data entry and analysis

Healthy Food Access Project Intern | Southern Nevada Health District
May 21, 2019 – August 9, 2019

- Completed Emergency Evacuation Training, Hazard Communication Training, HIPPA Training
- Conducted needs assessments related to healthy food access under the supervision of SNHD staff
- Conducted basic analysis of needs assessment data and prepared summary reports of findings
- Researched nutrition standards policies for specific locations and/or populations
- Assisted with focus groups
- Conducted outreach and participated in selecting community events and tracking efforts as required
- Provided basic nutrition, health and wellness-related education
- Worked with community and grant partners, stakeholders and priority populations
- Participated in coalition meetings as appropriate
- Advocated for increasing access to healthy foods
- Prepared and submitted monthly progress summaries towards internship deliverables to SNHD supervisor
- Engaged with priority populations in culturally appropriate, respectful and effective manner
- Maintained confidentiality

PROFESSIONAL MEMBERSHIPS

Delta Omega Public Health Honor Society Delta Theta Chapter of UNLV

- Member since December 2020