Review

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Review

HPV Vaccine Uptake in Tennessee: Implications for Improving HPV Vaccine Coverage with the Inclusion of Mid-Adults

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Abstract: Human papillomavirus (HPV) is the most common sexually transmitted infection in the US and the world. Infection with high-risk oncogenic HPV strains have been shown to induce cellular transformation leading to anogenital and oropharyngeal cancers. The HPV vaccine first developed in 2006 for females aged 9-26 years has been demonstrated to be safe and effective in preventing 90% of all HPV associated cancers. However, vaccine hesitancy, misinformation, and barriers to vaccine access has resulted in suboptimal vaccination rates among adolescent populations, especially in rural communities in the South. HPV vaccine coverage in Tennessee is currently below the national average and below the Healthy People 2030 goal of an 80% vaccination rate for individuals 13-17 years old based on recommendation guidelines for up-to-date HPV vaccination status as of 2022. HPV vaccination rates for Tennesseans with private insurance in 2022 was 68% and 38% for those that were insured. Up-to-date HPV vaccination rates for Tennesseans living in urban communities was 58% in 2022 and 46% for those living in rural communities. Overall, HPV associated cancers rates are higher in Tennessee at 12.9/100,000 compared to the overall rate in the US of 11.8/100,000 persons in 2022. Interventions to improve HPV vaccine awareness, education, and access could improve vaccine confidence and uptake especially among rural and uninsured populations in Tennessee. Most recently, the Advisory Committee on Immunization Practices (ACIP) has expanded recommendations for the HPV vaccinations for some individuals 27-45 years who were not vaccinated at a younger age with shared clinical decision-making. The impact of this recommendation on Tennesseans should be examined.

Keywords: Human papilloma virus; HPV; Tennessee; vaccine; vaccine hesitancy; vaccination rate; mid- adults

1. Introduction

Human papillomavirus is the most commonly sexually transmitted infection in the US and world. There are more than 150 strains of HPV including high-risk strains that can induce cellular transformation that can lead to cancer [1]. The HPV virion was first observed by Strass et al., in 1949 [2] via electron microscopy but it was Harold Zur Hausen in 1976 that proposed HPV as the etiological cause of cervical cancer that lead to the isolation of HPV 16 and 18 from cancerous cervical tissue [3]. HPV is readily transmitted via sex and skin- to-skin contact with virus gaining access to mucosal surfaces via micro lesions in cervical epithelium basement membrane leading to virus uptake by endocytosis and subsequent initiation of nuclear replication [4]. HPV is ubiquitous in the

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general population with more than 80% of sexually active individuals being exposed within a lifetime. Spontaneous viral clearance usually occurs within two years after infection however, persistent infections with HPV can lead to benign lesions such as genital warts as well malignancies of the cervix, penis, anus, vagina, vulva, and esophagus [5]. Individuals with HIV/AIDS or who are iatrogenically immunosuppressed are less likely to achieve viral clearance and are susceptible to HPV associated disease and HPV associated malignancies [6]. HPV vaccine hesitancy and vaccine uptake in the state of Tennessee and the Southern US have been challenging. Tennessee HPV vaccination rate for 13-17-year olds as of 2022 is 74% compared to the national average of 76% in 2022. [7]. Although vaccine coverage of greater than or equal to one dose (1</=) has increased in Tennessee by 19% since 2016, and UTD (up to date) coverage has increased by 28%, HPV vaccine coverage in Tennessee is currently below the national average and below the Healthy People 2030 goal of 80% UTD [7]. UTD vaccination rates among Tennesseans 13-17 years of age was lowest, 38% among uninsured teens compared to 58% of teens with Medicaid insurance and 52% of teens with private insurance [7]. Even more, rates of cervical and oropharyngeal cancer that are the most common HPV associated cancers were higher in Tennessee 5.7 and 6.6/100,000 persons respectively and for the US 5.0 and 6.5/100,000 persons respectively. Vaccine education, awareness, and access could improve uptake among medically underserved populations in Tennessee especially in rural communities and among uninsured populations that would move Tennessee closer to the Healthy People 2030 goal of 80% UTD. Overall, HPV associated cancers rates are higher in Tennessee at 12.9/100,000 compared to the overall rate in the US of 11.8/100,000 persons [7]. Most recently, the ACIP committee has expanded recommendation for the HPV vaccinations for some individuals 27-45 years who were not vaccinated at a younger age with shared clinical decision-making [8]. Here we examine the ACIP recommendation on Tennesseans and its potential impact on the medically underserved. We also present a brief overview of HPV biology and associated cancers, the HPV vaccine and vaccination rates in the US, HPV disease burden and vaccination rates in Tennessee, HPV vaccination rates by race/ethnicity, insurance coverage, and urbanicity in Tennessee, HPV vaccination rates for individuals 27-45 years old (mid-adults) and the implications for mid-adults in Tennessee, disparities in HPV vaccine health literacy, and strategies that could be implemented to improve HPV vaccine confidence and uptake in Tennessee.

2. Materials and Methods

County-wide HPV vaccination data for the year 2023 was obtained from the Tennessee Department of Health's Immunization Statistics. This data measures the HPV vaccination rate for the West, Middle, and East Tennessee regions. The 21 counties within the West Tennessee Region are Benton, Carroll, Chester, Crockett, Decatur, Dyer, Fayette, Gibson, Hardeman, Hardin, Haywood, Henderson, Henry, Lake, Lauderdale, Madison, McNairy, Obion, Shelby, Tipton, and Weakley counties. The Middle Tennessee region consists of 41 counties. These counties are Bedford, Cannon, Cheatham, Clay, Coffee, Davidson, Dekalb, Dickson, Fentress, Franklin, Giles, Grundy, Hickman, Huston, Humphreys, Jackson, Lawrence, Lewis, Lincoln, Macon, Marshall, Maury, Montgomery, Moore, Overton, Perry, Pickett, Putnam, Robertson, Rutherford, Sequatchie, Smith, Stewart, Sumner, Trousdale, Van Buren, Warren, Wayne, White, Williamson, and Wilson. The 33 counties Anderson, Bledsoe, Blount, Bradley, Campbell, Carter, Claiborne, Cocke, Cumberland, Grainger, Greene, Hamblen, Hamilton, Hancock, Hawkins, Jefferson, Johnson, Knox, Loudon, Marion, McMinn, Meigs, Monroe, Morgan, Polk, Rhea, Roane, Scott, Sevier, Sullivan, Unicoi, Union, and Washington counties form the East Tennessee Region.

Descriptive, exploratory, and graphical data analyses were performed on HPV vaccination rates for 11-17 and 18-26 age groups by region, and county. Differences in the means of the HPV vaccination rate were compared between the two age groups using the independent t-test. For each age group a one-way ANOVA was performed to examine the differences in the vaccination rates among the three Tennessee regions. Pairwise comparisons were made using Bonferroni post-hoc test. In addition to the regional analysis, a county-wide comparative analysis was performed.

Human Papilloma virus and associated cancers

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(HPV) is a member of the Papillomaviridae family of small non-enveloped viruses with a double-stranded circular DNA genome [9]. Infections can be persistent and are usually self-limiting. HPVs represents a large family of viruses that are divided into five different genera namely the Alpha, Beta, Gamma, Mu, and Nupapillomaviruses [10]. The Alpha, Mu, and Nupapillomaviruses are clinically associated with benign lesions in the form of warts while the Beta and Gamma genera are associated cutaneous asymptomatic infections. The Alpha genera HPVs are also known to cause infections of oral and anogenital mucosal epithelial cells and a subset of these HPVs have oncogenic potential leading to cancers. The HPV genome is 7- 8 kb in length and encodes eight viral proteins that includes six early proteins E1, E2, E4, E5, E6, and E7 that are required for genome replication and protection against host immune defenses [9]. There are two additional late proteins, L1 and L2 that encode the viral capsid proteins that facilitate genome packing that are designated as important for viral entry and initiation of infection in permissive cells [Graham 2010]. The L2 protein is essential in facilitating L1 assembly into viral-like particles (VLPs) and viral genome encapsidation [11]. Upon viral entry the E6 and E7 oncoproteins target tumor suppressor proteins p53 and Rb respectively for suppression and dysfunction [12]. Integration of high-risk HPV genomes into permissive cells can lead to over-expression of E6/E7 protein that can drive tumorigenesis. Infections with low risk HPVs rarely result in genomic integration often resulting in benign low-grade lesions [13]. HPV is known to be associated with a majority of 6 different types of cancer in humans. HPV has been shown to be associated >91% of cervical cancers, 91% of anal cancers, 70% of oropharyngeal cancers, 75 % of vaginal cancers, 69% of vulvar cancers, and 63% of penile cancers [Figure 1]. In 2019, there were 48,416 HPV associated cancer cases in the US or 12.2 cases per 100,000 persons. Among these cases there 12,175 cases of cervical cancer (7.2%/100,000), 7,902 cases of colorectal cancer (2.0 cases/100,000), 21,567 cases of oropharyngeal cancer (5.2 per 100,000), 824 cases of vaginal cancer (0.4/100,000), 4,459 cases of vulvar cancer (0.4/100,000), and 1389 cases of penile cancer (0.8/100,000) [Figure 2].

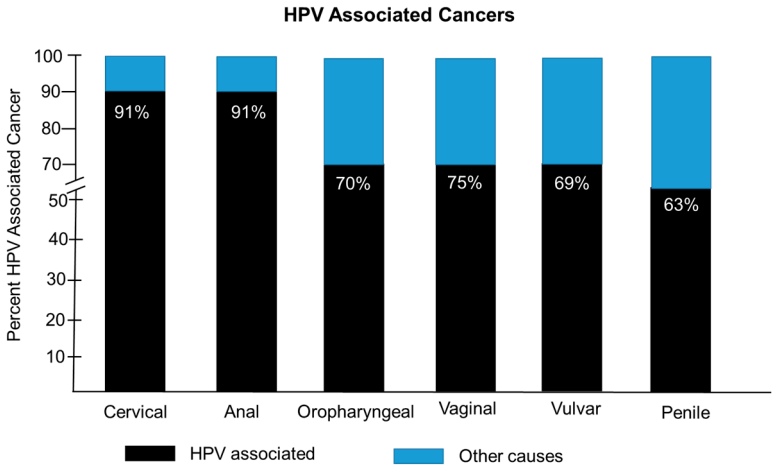

Figure 1. The percentages of HPV associated cancers. The percentages of HPV associated cancers shown as black bars and other causes shown by blue bars include cervical, anal, oropharyngeal, vaginal, vulvar, and penile cancer linked to HPV.

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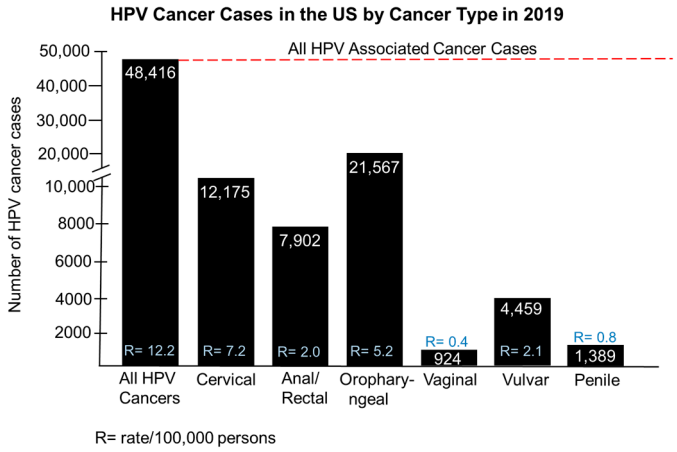

Figure 2. HPV cancer cases in the US by cancer types in 2019. The black bars represent all HPV cancers (represented by the red dotted line) as well as the respective case number breakdown by cancer type. R= cancer rate which is the number of cancer cases /100,000 persons.

HPV vaccine and vaccination rates in the US

There are three preventive HPV vaccines licensed for use in the US including Cervarix a bivalent vaccine or 2vHPV (GlaxoSmithKline), Gardasil, (Merck), quadrivalent vaccine or 4vHPV and most the recently 9valent/9vHPV vaccine known as Gardasil 9, (Merck). Most recently, two additional bivalent (HPV 16 and 18) HPV have been approved in China for HPV associated cervical cancers [14, 15]. The greatest HPV cancer burden is cause by HPV 16 and 18 and these two types are targeted by all three HPV vaccines (2vHPV, 4vHPV and 9vHPV) licensed in the US however v4HPV and 9vHPV protects against HPV types 6, and 11 that causes anogenital warts. Most notably v9HPV also protects against 5 other high-risk types that include HPV 31, 33, 45, 52, and 58 [16]. However, since 2016 Gardasil 9 is the only HPV vaccine available in the US, which protects against 9 different HPV types and 6 different human cancers [17]. All three HPV vaccines employ recombinant DNA technology that involves purified L1 capsid protein that undergoes self-assembly to form a virion shell or virus-like particles or VLPs as the antigen. The most recent FDA approved HPV vaccine the 9vHPV vaccine is noninfectious virus-like particle vaccine (VLP) first approved by the FDA in December of 2014, for use in females aged 9 through 26 years and males aged 9 through 15 years. Safety and efficacy data for v9HPV to date has not been determined for children under 9 years of age. Upon review of clinical trial data for 4vHPV in women age 24 to 45 years old along with bridging of safety and immunogenic profiles observed women and men for 4vHPV, the FDA in 2018, expanded the age range for 9vHPV from 9 through 26 years old to 9 through 45 years old for both men and women [16]. In 2019, the ACIP then approved shared clinical decision-making for mid-adults that lack vaccine protection and were at risk of novel HPV type acquisition. HPV vaccination rates vary in the US by region and Southern states consistently have some of the lowest vaccination rates in the country [Figure 3] [17]. In 2019, vaccination rates among adolescents 13-17 years old with the Up-To-Date vaccination series are shown in Figure 3. Only the states Rhode Island (78.9%) North Dakota (76.9%), Massachusetts (74.3%), Maryland (68.9%) and Hawaii (66.0%) had vaccination rates >/= 64% (shown in orange) [Figure 3] [18]. Only seven states had vaccination rates > or = to 46.7% which included Utah (44.6%), Idaho (44.1%), Tennessee (43.0%), Oklahoma (41.89%), Wyoming (41.5%), Indiana (41.2%), and lowest HPV vaccination rate was found in Mississippi at 30.5%. [Figure 3] [18]. The HPV vaccine is required for girls to enter sixth grade in Virginia and Washington DC. However, parents can opt out for medical, religious, or moral reasons. However all students entering the seventh grade in Rhode Island must be vaccinated for HPV. Laws that govern mandatory HPV vaccinations in the US have been controversial because of the concern that HPV vaccination could encourage sexual activity among teens. However, studies have refuted these concerns and have shown that HPV vaccine initiation is not associated with unwarranted sexual activity among teens. [19].

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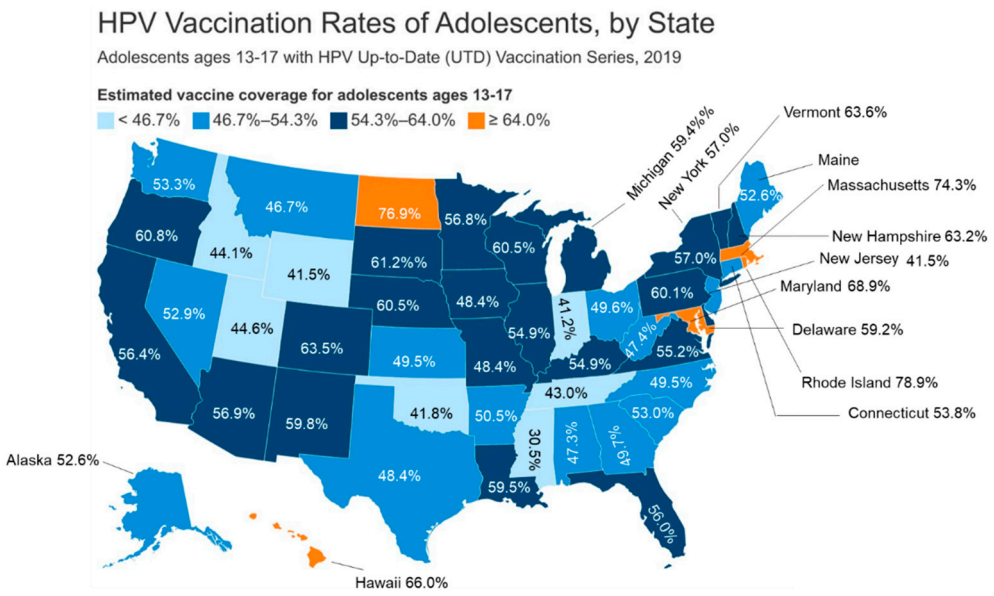

Figure 3. HPV vaccination rates in the US of adolescents, by state in 2019. The numbers for each state represent estimated coverage of adolescents aged 13-17 years that had received an HPV Up-To- Date (UTD) vaccination series. State colors represent HPV vaccination levels for the different states in the US with light blue representing UTD vaccination rates <46.7% and orange states with UDT HPV vaccination rates >/= 64.0%.

HPV disease burden and vaccinations in Tennessee

Tennessee vaccination rates consistently fall short of public health goals outlined by the Healthy People 2030 initiative of an 80% vaccination rate for individuals 13-17 years [20]. Vaccination rates for HPV in Tennessee are consistently at the bottom fifth of states in the US [20]. There is a high incidence of cervical cancer and cervical cancer mortality in Tennessee, which warrants increasing HPV vaccination coverage in Tennessee that could prevent more than 90% of these cancers. The two most common HPV associated cancers in Tennessee are oropharyngeal cancer and cervical cancer [Table 1]. In 2022, the oropharyngeal cancer rate in Tennessee was higher than the national average of 5.0%/100,000 compared to 5.7%/100,000 in Tennessee. The cervical cancer rate in 2022 in Tennessee is 6.6%/100,000 compared to 6.5%/100,000 in the US overall [Table 1]. Overall Tennessee has a higher cancer rate for all HPV associated cancers at 12.9%/100,000 compared to a national average 11.8%/100,000 [Table 1] [21]. There were also gender differences observed with oropharyngeal cancers in Tennessee compared to the national average [Table 1]. In Tennessee, males accounted for 9.9%/100,000 of oropharyngeal cancers compared to 1.9%/100,000 for females compared to a US average of 8.8%/100,000 for males and 1.6%/100,000 for females [Table 1] [21].

Table 1.

Two Most Common HPV Related Cancer in Tennessee

	All HPV Cancers	Oropharyngeal Cancer	Cervical Cancer
United States Overall	11.8%	5.0%	6.5%
Tennessee Overall	12.9%	5.7%	6.6%
Gender Differences			
United States Overall	Male 10.9% Female 12.9%	Male 8.8% Female 1.6%	TN is ranked in the Top 30 nationally in cervical Cancer rates
Tennessee Overall	Male 11.9% Female 14.0%	Male 9.9% Female 1.9%	

Incidence rates shown in cases per 100,000

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Ways to improve vaccine uptake is essential for reducing the incidence of HPV associated cancers in Tennessee. Currently the HPV vaccine is not recommended for school attendance in Tennessee only four jurisdictions in the US require HPV vaccinations for school attendance that includes Hawaii, Virginia, Rhode Island, and District of Columbia (DC) [22]. In April of 2023, laws were passed in Tennessee that prohibit primary care providers from vaccinating anyone under 18 years old without informed consent from a parent or legal guardian [23]. The law requires that medical providers maintain vaccination records on all children and failure to comply could result in their license being revoked [23]. The current HPV vaccination recommendations based on age dose and dose intervals are outlined in Table 2 [24]. The HPV vaccine is recommended for males and females ages 9 to 45 years old [Table 2]. Ages 9 to14 years old require a two dose regimen that is 6 to 12 months apart. Ages 15 to 45 years require a three-dose regimen. For ages 15 to 26 years old require a second dose that should be given 1-2 months after first and third dose 1-6 months after first dose [Table 2]. For individuals ages 27 to 45 years old, they should consult with their primary care physician (shared clinical decision making) to determine if they would benefit from HPV vaccinations [Table 2] [24].

Table 2.

HPV Vaccination Recommendation

	On Time	Late	Extra Dose	Consultation
Age	9-12 years	13-14 years	15-26 years	27-45 years
Doses #	2 Doses	2 Doses	3 Doses	3 Doses
Dosing interval	Each dose 6-12 months apart	Each dose 6-12 months apart	Second Dose 1-2 months after first; Third dose 1-6 months after first dose	Consult with your primary care physician to determine if they recommend an HPV vaccination

We examined HPV vaccination rates in Tennessee by region in the year 2023 for ages 11-17 and 18-26 [Figures 4A and 4B]. [25, 26]. An analysis of regional vaccination rate for 11-17-year-olds shows that the East region of Tennessee had a mean HPV vaccination rate of 36.44% [SD = 7.01, 95% CI = (33.95, 38.92)] [Figure 4A]. The minimum HPV vaccination rate for the East region was 19.80%, which belonged to Claiborne County; and the maximum HPV vaccination rate was 52.00%, which belonged to Cocke County. The Middle Tennessee region had a mean HPV vaccination rate of 29.18% [SD = 9.26, 95% CI = (26.26, 32.11)] [Figure 4A]. The lowest HPV vaccination rate for Middle Tennessee belonged to Lewis County (13.00%) and the highest rate was 51.30%, which belonged to Davidson County. The West Tennessee region had a mean HPV vaccination rate of 29.09% [SD = 7.13, 95% CI = (25.84, 32.33)]. Decatur County had the lowest HPV vaccination rate in the West region (18.00%), while Lake County had the highest rate of 49.6%. For 11-17-year-old age group, there was no significant difference among the three Tennessee regions with respect to mean HPV vaccination rates (p-value < 0.001) [Figure 4A]. The Bonferroni pairwise comparison revealed a significant difference in the mean HPV vaccination rate between West and East regions (p-value = 0.005). In addition, there was a significant difference in the mean HPV vaccination rate for 11-17-year-olds between Middle Tennessee and East Tennessee regions (p-value < 0.001).

Similarly, the regional analysis for 18-26-year-olds for East Tennessee [26] had a mean HPV vaccination rate of 34.49% [SD = 7.25, 95% CI = (32.42, 37.56)] [Figure 4B]. Claiborne County had the lowest HPV vaccination rate (21.00%) and Meigs County had the highest rate of 52.7%. In the Middle Tennessee region, the mean HPV vaccination rate for 18-26-year-olds was 26.74% [SD = 6.29, 95% CI = (24.26, 28.22)] [Figure 4B]. Moore County in Middle Tennessee had the lowest HPV vaccination rate of 15.1% for 18-26-year-olds and a maximum rate of 44.1%, which belonged to Van Buren. For 18-26-year-olds, the mean HPV vaccination rate for the West Tennessee region was 30.82% [SD = 7.37,

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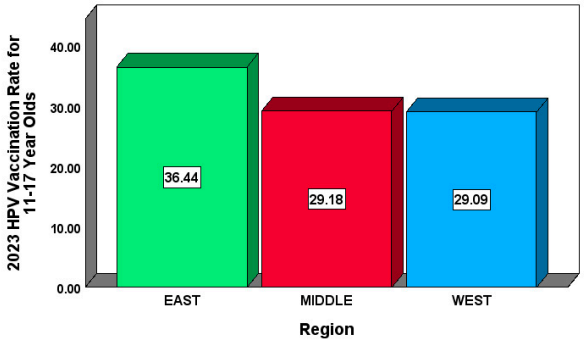
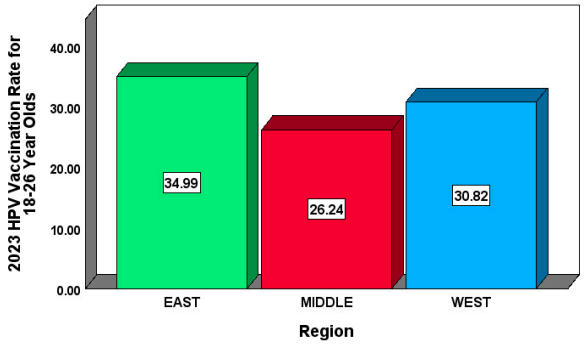
95% CI = (27.47, 34.18)]. Chester County in West Tennessee had the lowest HPV vaccination rate of 15%, while Benton County had the highest HPV vaccination rate of 44.7%. For the 18-26-year-old age group, there was a significant regional difference in the mean HPV vaccination rate (p-value < 0.001) [Figure 4B]. A pairwise comparison indicated a significant difference between mean HPV vaccination rate of Middle Tennessee and East Tennessee (p-value < 0.001). There was also a significant difference in HPV rate between West Tennessee and Middle Tennessee for the 18-26 age group (p-value = 0.044).

[Figure 4A] illustrates the East, Middle, and West regional mean HPV vaccination rate for year 2023 for age group 11-17. The highest mean HPV vaccination rate belonged to East Tennessee region (36.44%) and the lowest mean rate was from the Middle Tennessee region (29.18%). Similarly, for the age group 18-26, the East Tennessee region maintains the highest mean HPV vaccination rate (34.99%), while the Middle Tennessee region had the lowest rate (26.24%) as shown in [Figure 4B].

We also examined HPV vaccination rates for 11-17 and 18-26-year-olds in Tennessee by county as reported by TennIIs in 2023 [Figure 5]. Among 11-17-year-olds, Lewis County had the lowest HPV vaccination rate of 13% and Cocke County had the highest rate of 52%. Among 18-26-year-olds, Chester County had the lowest HPV vaccination rate of 15%, while Meigs County had the highest rate of 52.7%. There was no significant difference between the mean HPV vaccination rate between 11-17 and 18-26-year-olds (p-value = 0.249). In 2023, the mean HPV vaccination rate for 11-17-year-olds in Tennessee was 31.68% with a standard deviation of 8.73%. Similarly, the mean HPV vaccination rate in 2023 for 18-26-year-olds in Tennessee was 30.29% with a standard deviation of 7.82% [Figure 5].



4A. HPV Vaccine Uptake in Tennessee by Region for Ages 11-17 Years.



4B. HPV Vaccine Uptake in Tennessee by Region for Ages 18-26 Years.

Figure 4. HPV vaccination rates in Tennessee by region in the year 2023 for ages 11-17 (4A) and 18-26 (4B). Mean vaccination rate values are shown inside the colored bars for East, Middle, and West Tennessee regions.

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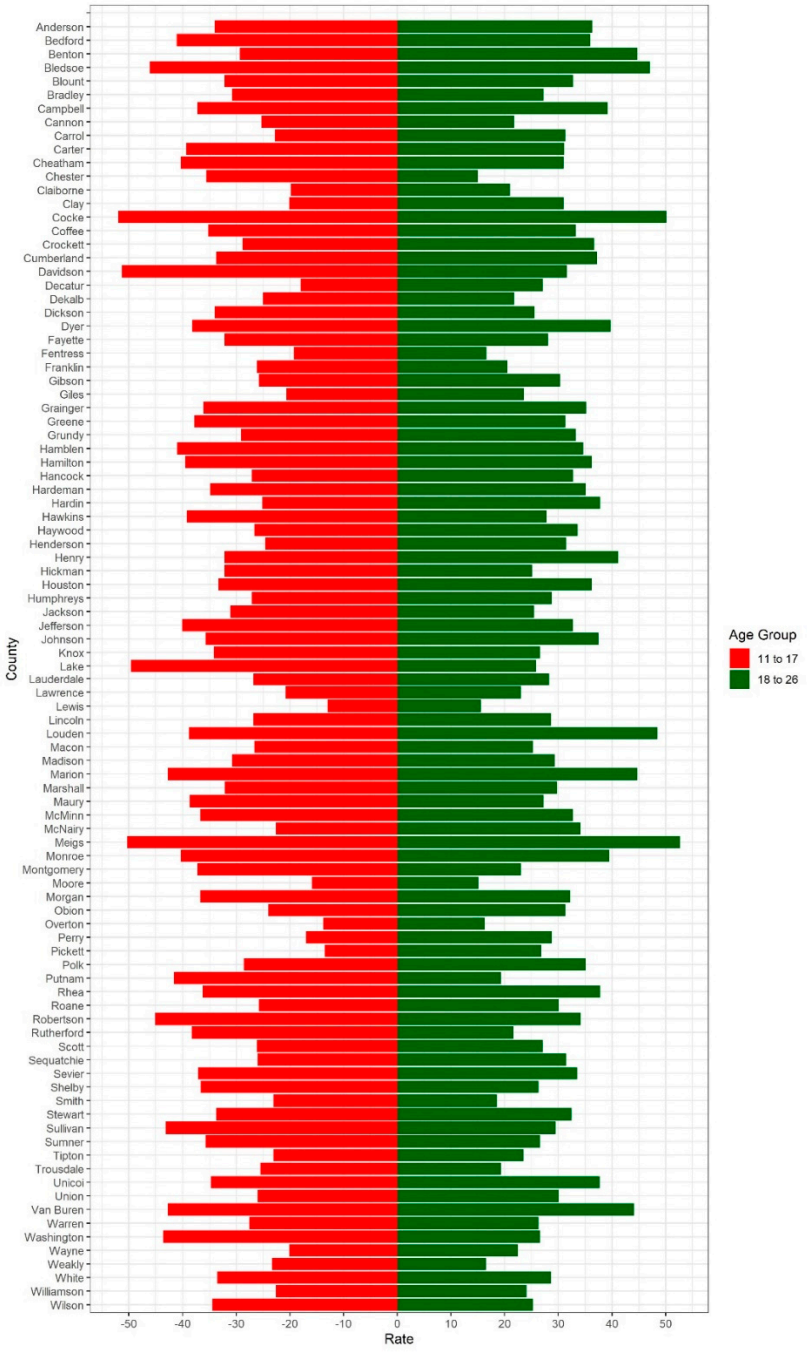

County HPV Vaccination Rates in 2023 Stratified by Age Group.

Figure 5. HPV vaccination rates for 11-17 and 18-26-year-olds in Tennessee by county as reported by TennIIs in 2023.

HPV vaccination rates by race/ethnicity, insurance coverage, and urbanicity in Tennessee.

We examined the HPV vaccination rate for Tennessee by race/ethnicity, insurance coverage, and urbanicity for 13-17-year olds in 2022 [Figure 6A]. Based on the Healthy People 2030 goal of an 80% vaccination rate for 13-17-year olds in US that received >/= to 1 dose of the HPV vaccine and those that completed the dosing regimen and were up-to-date (UTD) [26]. Tennessee fell short of these goals with the exception of Blacks that achieved an HPV vaccination rate of 82% [Figure 6A] compared White (65%), Hispanic/Latinx (58%), and others (69%) for populations receiving </= to 1 dose [27]. For populations of 13-17years that were to be up-to-date, no race or ethnic group in

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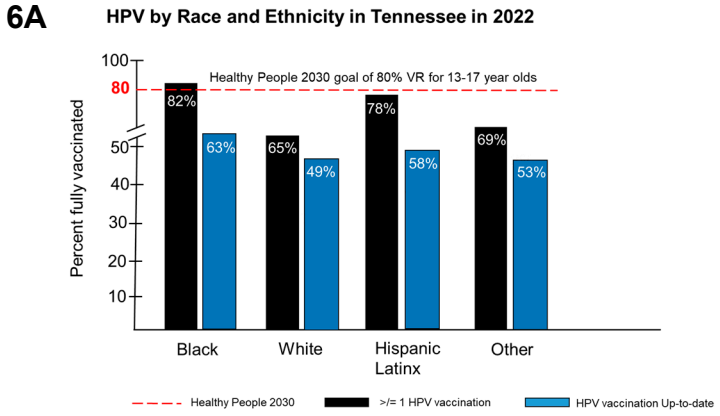
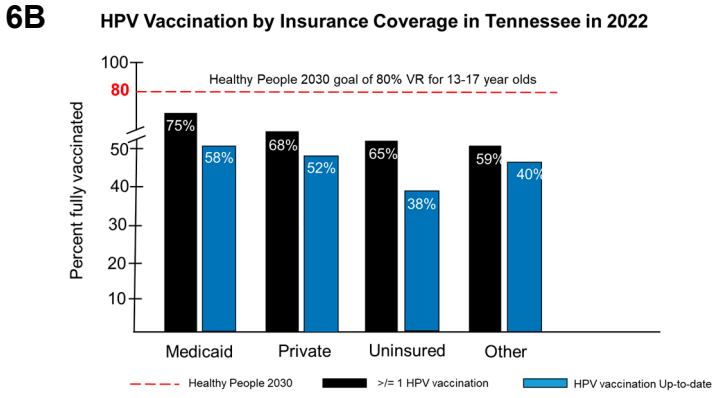
Tennessee reached a rate of 80%. The rates observed for all races and ethnicities including Blacks at 63% followed by Hispanic/Latinx populations at 58%, other at 53% and Whites at 49% [Figure 6A] [27]. Analysis of HPV vaccination rates based on insurance coverage showed that a high level of vaccine initiation was observed among 13-17-year olds that received >/= 1 dose compared to those that were UTD for their HPV vaccinations [Figure 6B]. Those individuals insured by Medicaid had the highest level (75%) of vaccine initiation for all racial and ethnic groups that received >/= 1 dose followed by private insurance, the uninsured and other forms of insurance [Figure 6B]. Among 13-17-year olds that were UTD for their HPV vaccinations, populations insured by Medicaid has the highest of UTD vaccination with 58% followed by private insurance (52%), other (40%) and the uninsured has the lowest UTD vaccination rate of 38% [Figure 6B]. None of the insured or uninsured populations reached the Health People 2030 goal of the 80% vaccination rate for either incomplete or UTD HPV vaccinations [27]. Finally, we examined the HPV vaccination rates in Tennessee for 13-17-year olds in 2022. No racial or ethnic group in Tennessee reached the Health People 2030 goal of an 80% vaccination rate for those receiving >/= 1 dose or for those that were UTD for their HPV vaccinations [Figure 6C]. Populations living in MSA Principal City locations had the highest level of vaccine initiation (>/=1 dose) at 74% compared to those living in non-MSA Principal City locations (65%) and the vaccination initiation rate observed among those populations living in non-MSA rural communities was the lowest vaccination rate of 64% [Figure 6C] [27].





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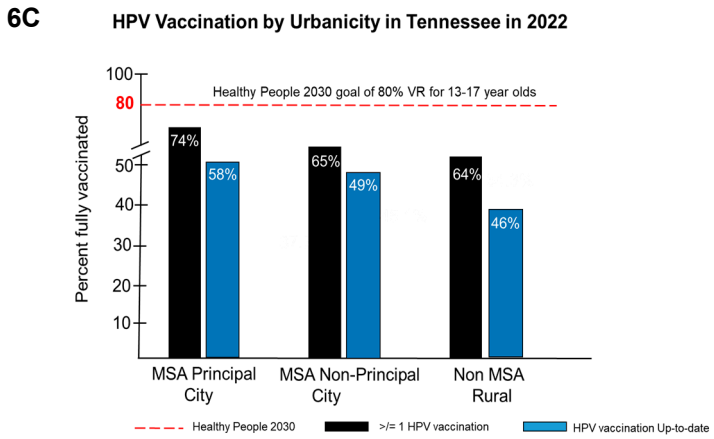

Figure 6. HPV vaccination rates by race/ethnicity, insurance coverage, and urbanicity in Tennessee in 2022. HPV vaccination rate by race and ethnicity for 13 to 17 year olds in 2022 (**6A**). HPV vaccination rates in Tennessee based on insurance coverage, for 13 to 17 year olds in 2022 (**6B**). HPV vaccination rates in Tennessee based on urbanicity, for 13 to 17 year olds in 2022 (**6C**). All rates were compared to the Healthy People 2030 goal of an 80% vaccination (shown by the red dotted line) rate for 13-17-year olds in the US that received >/= to 1 dose of the HPV vaccine and those that completed the dosing regimen and were up-to-date (UTD). Rates are shown for Black, Whites, Hispanic/Latinx, and Others.

HPV vaccination rates for individuals 27-45 years old (mid-adults)

In 2018, the FDA approved HPV vaccinations for individuals 27-45 years old (mid-adults) and is supported by the Advisory Committee on Immunization Practices (ACIP) recommendations of shared clinical decision-making rather than routine vaccination of mid-adults [28]. This decision by ACIP and is based on individuals who are not adequately vaccinated and could be at risk for new HPV infections and might benefit from HPV vaccinations as mid-adults. FDA approval of the HPV vaccine for individuals 27-47 years was based on reported safety and efficacy data. A study by Munoz et al., demonstrated 90.5% efficacy in reducing HPV infections in women 24 to 45 years old [29]. In a HPV vaccine clinical trial study by Castellsagu´e et al., they observed efficacies of 88.7% and 79.9% protection against cervical intraepithelial neoplasia (CIN) and external genital lesions in women 24-45 years old [30]. However, the HPV vaccine has been shown to be most effective in individuals with no prior exposure to HPV [31,32]. There have been very few studies performed on HPV uptake among mid adults in the US. However, in a cross-sectional study performed by Kasting et al., employing data from the 2017 National Health Interview Survey showed that up to 47.2% of 27-to-45-year-olds had initiated vaccination at age 19 or older [33–35]. In addition, the survey showed that participants with higher education such as a bachelor's degree or higher, having insurance, and of female gender were more likely to receive HPV vaccinations as mid-adults. The ACIP recommendations of shared clinical decision-making for HPV vaccination of mid-adults will require medical provider consultations, which could improve education and awareness of HPV and HPV associated diseases. This strategy would also allow timely diagnosis and treatment of HPV associated clinical disease as well as support up-to-date HPV vaccinations. However, for medically underserved populations who are uninsured or underinsured and may not have a primary care provider, they are more likely to be less educated about HPV and HPV associated diseases and less likely to initiate HPV vaccination. Studies by Reiter et al; show that recommendations by medical providers and the perceived importance of preventing HPV associated disease was a significant factor in initiating HPV vaccination in a study with women 18 to 45 years old [36]. Even more, in a study by Weldon et al., in mid-adults, showed that 80% of participants wanted more information about the vaccine prior to decision-making and 87.8% reported that medical providers were the primary source of information about the HPV vaccine [37]. In a recent study by Akpan et al., that employed a national sample of 27-45-year-olds using the Andersen's Behavioral Model of Health

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Services Use, showed that persons of female gender, person designated as being from other racial/ethnic groups, and person with higher education attainment were more likely to initiate HPV vaccinations for this age group [38]. In addition, the study showed that participants in relationships, those identifying as non-Hispanic Asian persons, and Hispanic/latinx participants were less likely to have ever received the HPV vaccine as mid-adults [38]. They also found that persons that identified as female gender, Hispanic, non-Hispanic Black, and non-Hispanic Asian race/ethnicity were more likely to initiate HPV vaccination after age 26 [38]. The study by Akpan et al., employed the analysis of data from the 2019 National Health Interview Survey. The study involved 8556 individuals classified as mid-adults aged 27-45 and a separate group of 7307 mid-adults that self-reported to have been vaccinated for HPV along with individuals who were unvaccinated for HPV. The overall outcomes of the study were HPV vaccination and vaccination initiation. Independent variables were aligned with Andersen's Behavioral Model of Health Services Use. The study compared HPV vaccine initiation reported among individuals 9-26 and 27-45 years. Vaccination initiation among individuals 9-26 years was highest among whites at 65% and 13% and 12.6% among Hispanic/Latinx and Black participants respectively [Figure 7A]. Asian and Other participants had the lowest level of vaccine initiation with both at 4.7% [Figure 7A]. They also examined HPV vaccine initiation among mid-adults aged 27-45 and found a significant difference between vaccine initiation among whites from 65% among 9-26 years to 33.6% for 27-45 years [Figure 7B] [38]. However, they observed a significant increase in HPV vaccine initiation among Blacks and Hispanic/Latinx participants from 13% and 12.6% among 9-26 years to 26.2% and 26.6% when compared to mid-adults respectively [Figure 7B]. They also observed a significant increase in HPV vaccine initiation among Asian participants from 4.7% to 8.9% when they compared 9-26-year olds to mid-adults however, they found no significant increase in participants identified as Other [Figure 7B] [38].

The collection of data for HPV vaccination initiation for individuals 27-45 years (mid-adults) to our knowledge has not been reported for Tennessee. HPV vaccination rates among adolescents are suboptimal which suggest that there is a pool of unvaccinated adults that are eligible and could benefit from vaccination [39]. HPV vaccinations would benefit mid-adults that develop new sexual partnerships with exposure to sexually transmitted infections that would increase their risk of acquiring new strains of HPV [40]. Lewis et al., reported that 15-35% of sexually active women and 23-33% of sexually active men 25 to 49 years old in the US are infected with at least one or more high-risk HPV types [41]. These findings suggest that there is ongoing transmission of high-risk HPV types among mid-adults that would warrant HPV vaccination in this at-risk population. Even more, the humoral response to HPV infection were found to be more robust when employing the 9vHPV vaccine compared to natural immunity to protect against reinfection [42, 43]. As reviewed by the ACIP committee for their recommendation of HPV vaccination of mid-adults, multiple models demonstrated a significant cost saving and reduction in disease burden when implementing 9vHPV vaccinations for all eligible mid-adults [44-47]. Regardless, of exposure to an infection with ≥1 HPV type over their life-course, few mid-adults have immunity to all HPV types covered by 9vHPV vaccine [41]. Even more, physicians will also need training regarding shared clinical-decision making when recommending the HPV vaccine to mid adults. In a study by Hurley et al., showed that 42% of primary care providers recommended the HPV vaccine for their mid-adult patients. In the same study, 57% of providers did not know what information to share with their mid-adult patients [48]. However, mid-adult populations that are medically underserved and are less likely to engage primary care physicians for their health needs, may not have an opportunity to participate in shared clinical decision-making for facilitate HPV vaccine initiation.

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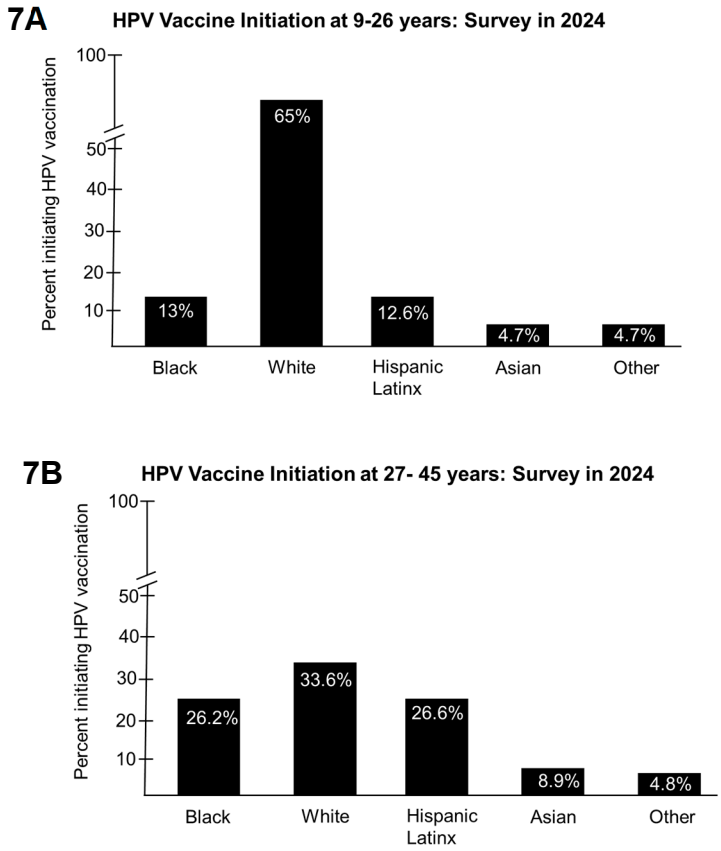

Figure 7. Vaccine initiation rates for ages 9-26 and 27- 45 based on data from the 2019 National Health Interview Survey and reported in 2024. Shown are the percentage of HPV vaccine initiation for ages 9-26 years in black bars for Blacks, Whites, Hispanic/Latinx, and Others (7A). The percentage of HPV vaccine initiation for ages 27-45 years in black bars for Blacks, Whites, Hispanic/Latinx, and Others (7B).

Disparities in HPV vaccine health literacy

Studies have shown disparities in HPV associated cancers that disproportionately affect medically underserved populations [49-52]. Disparities in HPV vaccine health literacy can contribute to disparities vaccine access and uptake. Racial and ethnic disparities for HPV vaccine access and uptake. Recent studies have shown that HPV health literacy is significantly lower among Black and other racial/ethnic minorities regarding HPV awareness, the vaccine and HPV associated malignancies [53]. Studies by Adjei et al., have identified disparities in HPV vaccine awareness and uptake among adolescents and young adults [54]. In the study, Blacks were 33% (95% CI: 0.47 – and 44% (95% CI: 0.39 – 0.81) less likely than non-Hispanic Whites to have heard of HPV and the HPV vaccine, respectively. Hispanics were 27% (95% CI: 0.52 – 1.02) and 53% (95% CI: 0.34 – 0.64) less likely than non-Hispanic Whites to have heard of HPV and the HPV vaccine, respectively, [54]. In a study by King et al., gaps in knowledge regarding HPV vaccinations in mid-adult populations was observed in both patients and providers [55]. It is essential to develop interventions to improve HPV vaccine health literacy in medically underserved communities.

Strategies that could be implemented to improve HPV vaccine confidence and uptake in Tennessee

In Tennessee, there are 95 counties and 78 of these counties are designated as rural counties. These rural counties have less health care infrastructure, fewer primary care physicians, poor Social Determinant of Health (SDOH), less educational attainment, less health literacy, distrustful of the government and medical establishment, are highly exposed to misinformation about vaccines, and are more likely to be vaccine hesitant when compared to urban communities in Tennessee [56-58]. Improving health literacy among populations who have less educational attainment especially in

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rural communities in Tennessee could reduce vaccine hesitancy and improve HPV vaccine confidence and uptake [59]. In general, HPV vaccine coverage in rural communities is low and the incidence of HPV associated disease burden and cancer remains high [60]. Transportation to engage medical providers may represent an access barrier for rural communities in Tennessee. The deployment of mobile medical units staffed with physicians, nurses, and community health care workers could support the shared clinical decision-making recommended by ACIP for HPV vaccinations among mid-adult in Tennessee [61]. Health fairs, Town halls, faith-based community events, wellness visits by medical providers, and Telehealth education programs can expand HPV vaccine access and related services to medically underserved communities in Tennessee. Expansion of Medicaid services in Tennessee and in the South would increase the number of medical insured communities which would provide greater access to HPV education and related services including vaccines. HPV vaccination outreach and interventions should not be focused on females only, suggesting that HPV affects only females but should include males to achieve equity in reducing HPV infection and associated disease burden in the general population. HPV should be designated as a gender-neutral vaccination due to known HPV induced malignancies in males (penile, anal, oropharyngeal cancers).

3. Conclusion

Each year in the US approximately 48,000 HPV associated cancers occur and approximately 80% of these cancers could have been prevented with an HPV vaccination [62]. HPV associated cancer rates in Tennessee are consistently higher than the national average. Specific interventions to reduce HPV vaccine hesitancy and improve vaccine initiation and completion of the HPV dosing series is essential for Tennessee to achieve the Healthy People 2030 goal of an 80% vaccination rate for respective age groups. HPV vaccine uptake in Tennessee has shown to be greatly influenced by age, race, insurance status, and urbanicity. Strategies to achieve HPV vaccine equity should improve HPV vaccine initiation in Tennessee to achieve the Health People 2030 goals. Even more, HPV vaccinations of mid-adults are currently not being captured in Tennessee to our current knowledge that will require ACIP recommendations of shared clinical decision-making to support vaccine initiation and completion of HPV vaccine dosing in this population. Finally, disparities in vaccine literacy and vaccine hesitancy especially in rural communities in Tennessee must be addressed by focusing on the efficacy of cancer prevention provided by the HPV vaccine.

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