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A Comparison of HPV Vaccination Coverage Estimates Among U.S. Adolescents and Adults using Birth Cohorts for Long-Term Evaluation

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Abstract

A Comparison of HPV Vaccination Coverage Estimates Among U.S. Adolescents and Adults using Birth Cohorts for Long-Term Evaluation

By Rachael G. Lewis

To our knowledge, this is the first analysis which utilizes a birth cohort approach to directly compare projections of HPV vaccination coverage from adolescent vaccination assessments to actual coverage estimates from adult vaccination assessments. Our analysis identifies discrepancies between adolescent and adult HPV vaccination estimates using two national immunization surveillance systems, NIS-Teen and NHIS. To achieve our research aims, we constructed each birth cohort using data from the NHIS (2013-2018) and the NIS-Teen (2008-2017) datasets. Coverage projections were generated using a survey-weighted Poisson regression analysis of adolescent data from NIS-Teen. Survey-weighted point estimates of adult vaccination coverage were calculated from NHIS data. Birth cohorts were selected if they had HPV vaccination data for all adolescent years (13-17) and at least one year of adult data (19+). HPV vaccination coverage was measured through either parental-report or self-report of having received at least one dose of the HPV vaccine.

Our analysis found that the projected HPV vaccination coverage estimates for young adults are higher than the actual coverage estimates, thereby indicating a plateau in the rate of vaccine uptake after mid-adolescence (13-17 years). Our findings also draw attention to potential reporting issues between NIS-Teen and NHIS, as the estimated vaccination coverage in young adults is lower than the estimated coverage of the same birth cohort in adolescence. Our project highlights the need for further investigation into the impact of the HPV vaccine uptake plateau seen in young adult populations in the United States.

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Chapter 1: Introduction

The problem

Human Papilloma Virus (HPV) infects millions of people in the United States each year. Transmission of HPV occurs in many ways, with the most common mode of transmission being through sexual contact. Although in 91% of cases the human body can naturally clear an HPV infection within 2 years, in some instances HPV can causes severe and even life-threatening health outcomes (1,2). Although there is a safe and effective vaccine to prevent against infection with HPV, coverage still consistently lags behind that of other routine adolescent vaccines (3). There is a need to document and understand how patterns in HPV vaccine coverage within specific birth cohorts span into young adulthood to assess vaccine coverage measurements and understand the landscape of HPV catch-up vaccinations.

Background

In 2006, the United States Food and Drug Administration (FDA) approved the first HPV vaccine, HPV4, for use in females ages 9-26 (4). In 2011, the HPV4 routine recommendation was subsequently expanded to include males ages 9-21 and men who have sex with men (MSM) up to age 26 (5). In 2014, the US FDA also approved HPV9 for routine use in males and females aged 9-26 (6). HPV9 expanded upon HPV4 by providing protection against five additional oncogenic strains. Vaccination with HPV9 enables high rates of seroconversion to prevent persistent infection with strains known to cause cervical, vulvar, and vaginal disease. Despite the demonstrated safety and efficacy of the HPV vaccine, coverage is consistently lower than that of other routine adolescent vaccines, such as Tdap and MenACWY.

Ramifications

It is ideal for the HPV vaccination series to be initiated in early adolescence. The ACIP recommend series initiation at age 11-12 (7), whereas the American Academy of Pediatrics and American Cancer Society recommend beginning at age 9 (8,9). Although vaccination coverage increased drastically following the original FDA approvals, in the period from 2011-2018, HPV up-to-date (UTD) rates only rose by 6.6% among girls ages 9-12 (10). Recent coverage increases were modest compared with previous years, and most were primarily observed in boys (11). If HPV vaccination coverage in the United States continues to trend towards an eventual plateau, the burden of HPV infection will continue increasing in the population. HPV infections burden the US healthcare system approximately $775 million dollars in direct medical costs per year, with over 40 million people in the United States living with HPV (12). It is vital that HPV vaccination coverage continues to increase among both males and females to diminish the health and economic burden of genital warts and cervical cancer in the United States.

Theoretical and practical significance

To date, there has not been a comprehensive study to evaluate trends in HPV vaccine coverage as adolescent birth cohorts span into young adulthood. There are no studies which compare the statistical measurements of these birth cohorts between the NIS-Teen and NHIS datasets and identify the differences between them. NIS-Teen monitors vaccination coverage among US adolescents ages 13-17 (13). NHIS collects data on a wide range of health outcomes and behaviors among children, adolescents, and adults in the US (14). It is important that we utilize these databases to document and analyze trends in HPV vaccination coverage to understand the landscape of catch-up vaccination among birth cohorts in the United States.

Problem Statement

Accurate and precise estimates of HPV vaccination coverage in the US allow us to understand the vaccination landscape and propose potential changes to immunization programs and policies. If national databases, such as NIS-Teen and NHIS, provide drastically different estimates of HPV vaccination coverage among identical birth cohorts, our understanding of HPV vaccination coverage in the population will vary widely. Appropriate, timely, and effective public health interventions require guidance from robust and evidence-based recommendations. It is vital that the evidence which guides our recommendations is accurate and dependable. Without a robust understanding of how HPV vaccination coverage evolves among birth cohorts in the population, we cannot maintain utmost confidence that our public health interventions are effectively tailored to address the needs of the population. Our analysis will further support our foundational understanding of the distribution of HPV vaccination uptake in the United States.

Purpose Statement

Do projections in HPV vaccination coverage among birth cohorts from NIS-Teen match actual adult HPV vaccination coverage estimates from NHIS? How do trends in HPV vaccination coverage within birth cohorts differ between the NIS-Teen and NHIS national databases?

This research project aims to directly compare projections of HPV vaccination coverage from NIS-Teen adolescent vaccine assessments to actual coverage estimates from NHIS adult vaccine assessments. We plan to investigate temporal trends in HPV vaccination coverage by analyzing rates of HPV vaccination in specific birth cohorts over time. Additionally, we aim to identify patterns and trends among birth cohorts as HPV vaccination coverage changes each year.

The results of our analysis will allow us to identify the discrepancies in HPV vaccination coverage estimates between the NIS-Teen and NHIS national databases. Our analysis will also enable us to identify if sampling bias contributes to coverage discrepancies between the databases. There is a need to ascertain how vaccine coverage may be expanding beyond the routinely studied 13-17 adolescent years to better understand the landscape of HPV catch-up vaccination. Highlighting missed opportunities in catch-up vaccination and identifying demographic trends in vaccine initiation and uptake will better inform our understanding of HPV vaccination in the United States.

Research Questions/Objectives

1. Do projections in HPV vaccination coverage among birth cohorts from NIS-Teen match actual adult HPV vaccination coverage estimates from NHIS?
2. How do trends in HPV vaccination coverage within birth cohorts differ between the NIS-Teen and NHIS national databases?

Significance Statement

Our research projects aims to generate greater understanding into HPV coverage estimates among birth cohorts from different national databases. We intend to identify demographic patterns and trends in HPV vaccination coverage as adolescents progress into adulthood. The understanding generated from this research project will allow us to maximize catch-up vaccination initiatives and identify groups that are consistently susceptible to HPV infection and HPV-related cancers.

Definition of Terms

HPV*: Human Papilloma Virus*

NIS-Teen*:* National Immunization Survey-Teen. A survey sponsored and conducted by the National Center for Immunization and Respiratory Diseases (NCIRD) of the Centers for Disease Control and Prevention (CDC) (13)

NHIS*:* National Health Interview Survey.

Birth cohort*:* US citizens born in the same calendar year (ie: people in the 1995 cohort were all born in the same calendar year.)

Catch-up vaccination: Vaccination which occurs outside of the recommended time frame. For HPV, catch-up vaccinations include when vaccination was initiated after age 12.

Routine adolescent vaccine: Immunizations that the ACIP recommends to be initiated between ages 11 and 18 (7).

ACIP: Advisory Committee for Immunization Practices of the US Centers for Disease Control and Prevention.

Chapter 2: Literature Review

Background of HPV

Human Papilloma Virus (HPV) infection is a major factor in the development of genital warts, anogenital, oropharyngeal and cervical cancers in the United States. Transmission of HPV primarily occurs via skin-to-skin or skin-to-mucosa contact during sexual activity, and can occur even if the infected individual does not show any signs or symptoms of HPV infection (2). Although sexual contact is the most frequent mode of transmission, non-sexual transmission has also been documented (15). As of January 2021, the Centers for Disease Control and Prevention (CDC) reported 42.5 million people in the United States living with HPV, making it the most prevalent sexually transmitted infection in the United States. The high burden of HPV-related disease costs the US healthcare system approximately $775 million per year (12).

After 24 months, the human body can naturally clear approximately 91% of HPV infections (1). However, when the immune system does not naturally clear the infection, HPV can cause more severe or even life-threatening health outcomes (2). According to the CDC, “about 45,300 HPV-associated cancers occur in the United States each year: about 25,400 among women, and about 19,900 among men,” (16). Although there are over 100 types of HPV, only fourteen are classified as “high-risk types” which have been shown to cause cervical and anogenital cancers (17). HPV 16/18 account for 70% cervical cancer cases, while HPV 6/11 cause 90% of genital warts (18). Fortunately, the nonvalent HPV vaccine (HPV9) contains specific antigens for nine oncogenic strains, including 16/18/6/11. According to the CDC, “more than 98% of [vaccine] recipients develop an antibody response to HPV types included in the respective vaccines one

month after completing a full vaccination series," (19). HPV9 has immense potential to reduce the burden of HPV infections in communities across the United States.

HPV vaccination was first recommended for use in the United States for females in 2006 and for males in 2009 (17,18). There are three types of HPV vaccines, but only one—HPV9— is currently approved in the United States. HPV9 protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (20). Despite having full FDA approval, HPV vaccination coverage with HPV9 still lags behind that of other common routine adolescent vaccines, such as tetanus, diphtheria, and acellular pertussis (Tdap) and quadrivalent meningococcal conjugate vaccine (MenACWY), which are recommended for use in the same age groups (21). The percentage of adolescents aged 13-17 who were up-to-date with their HPV vaccination series in 2020 was 58.6%. These estimates stand in stark contrast to the 90.1% coverage for Tdap and the 89.3% coverage for MenACWY (3). HPV coverage estimates are even lower among adults and young adults. Studies report HPV vaccine coverage in young adults (approximately 18-29 years old) to range from 29-48% (22–24). Coverage estimates further decrease among those in older age categories as well. One study from 2017 reports only 9.7% of 27-45 year olds to have received one or more doses of the HPV vaccine (23). Given these estimates, there is a need to understand patterns in HPV vaccination coverage to increase vaccine uptake among all eligible age groups in the United States.

HPV Vaccination Policies & Programs in the United States

The United States Food and Drug Administration (FDA) approved the first HPV vaccine, HPV4, for females in 2006. This first generation HPV vaccine prevents against infection from HPV 6, 11, 16, and 18 (4). Although HPV4 is no longer used in the United States, a study by Ferris et al (2017) indicates that 89%-96% of study participants who received HPV4 remained seropositive for HPV types 6, 11, and 16 through 10-years after vaccination. Additionally, no cases of disease from any of the strains included in the vaccine were observed. These study results, among others, indicate that the original HPV4 vaccine is highly immunogenic, clinically effective, and generally well tolerated for at least 10 years post-vaccination (25). Although HPV4 has since been replaced by HPV9, those who were vaccinated with HPV4 still exhibit robust protection against infection from HPV 6, 11, 16, and 18.

Three years after approving HPV4 for females, in 2009 the FDA permitted its use in males ages 9-21 as well as men who have sex with men (MSM) up to age 26. This original licensure was a permissive recommendation-- HPV4 *could* be used to prevent genital warts in males, but it was not yet a *routine* recommendation (5). Two years later, in 2011, the CDC's Advisory Committee for Immunization Practices (ACIP) supported the FDA's permissive recommendation, citing efficacy data on high levels of protection against infection and high seroconversion rates. Henceforth, HPV4 was recommended for routine administration in male adolescents. Series initiation was recommended for 11-12 year olds, but could begin as early as age 9 or as late as age 21, with MSM being eligible until age 26. Subsequent research suggests that males vaccinated at ages 9-15 have higher antibody titers than those vaccinated at ages 16-26, further supporting HPV vaccine series initiation early in adolescence. Although those in the latter age

group exhibited lower levels of antibody titers, they still received significant benefits in immune protection from HPV4 (26). Therefore, it is pertinent that males of all eligible age groups have ample opportunities receive the currently recommended HPV vaccine to protect against infection with and transmission of HPV.

In 2014, the US FDA approved HPV9 which prevents against infection with five additional oncogenic strains previously excluded from HPV4 (6). HPV9 enables high rates of seroconversion for antibodies to HPV 6, 11, 16, and 18 -- while also preventing cervical, vulvar, and vaginal disease and persistent infection from the five additional oncogenic strains (27). According to Journa et al (2015), HPV9 has the potential to prevent up to 90% of cervical cancer. Compared to an estimated 70% prevention from HPV4, HPV9 offers considerably greater levels of immune protection against cervical cancer. Furthermore, Damme et al (2015) reports, "99% of girls, boys, and young women seroconverted for each vaccine HPV type [in HPV9]," (28). Regardless of sex, participants exemplified high immunogenicity and antibody persistence resulting from HPV9. HPV9 should be widely used to reduce the burden of cervical and anogenital cancers in the United States because it is safe, effective, and highly immunogenic.

The current ACIP-recommended HPV vaccination schedule in the United States recommends that all male and female adolescents receive their first dose of HPV vaccine between ages 11 and 12. However, the HPV vaccine may be given as early as age 9 (6). The goal of initiating HPV vaccination early in adolescence is to elicit a robust immune response *prior* to HPV exposure. In

most cases, exposure to HPV occurs during sexual activity. Therefore, there are multiple benefits to initiating the vaccination series in adolescents and pre-adolescents prior to their first sexual experience. One study revealed that 28.5% of females will become infected with human papilloma virus within one year of their sexual debut (29). According to the National Survey for Family Growth conducted by the CDC, the mean age at first intercourse is 17.0 and 17.3 years for males and females, respectively (30). Given that sexual activity is rare before age 12, it is crucial for HPV vaccination to occur within the 9-12 year old window of adolescence (31). Initiating vaccination within the preadolescent period produces robust antibody responses to HPV which are sustained for many years after the vaccine series is completed (25). HPV vaccine induced immune responses are stronger than those from natural infection, providing further support for encouraging vaccine induced immunity as opposed to naturally acquired immunity (32). Likewise, if the HPV vaccine series is initiated prior to age 15, only two doses are required to complete the series (33). As discussed by Johnson Jones et al (2020), vaccines with fewer required doses simplify national vaccination programs and increase the likelihood of series completion (34). Therefore, initiating HPV vaccination in early adolescence is advantageous from both an immunologic and operational perspective.

Initiating the HPV vaccine series at ages 11-12 directly aligns with the vaccine scheduling recommendations for Tdap and MenACWY (7). Harmonizing the HPV vaccination schedule with two other routinely recommended adolescent vaccines serves to increase uptake rates of all three vaccines. High coverage estimates of Tdap and MenACWY indicate that adolescents are receiving medical care where vaccines are available. Therefore, as Bednarczyk (2019) postulates,

concomitant administration of HPV, Tdap, and MenACWY vaccines can reduce missed opportunities and lead to higher coverage rates for all adolescent vaccines (21).

In 2019, the ACIP updated their HPV catch-up vaccine recommendations to include all persons through age 26, independent of sex. They also state that the HPV vaccine "may be given" through age 45 with shared clinical decision making. Although HPV infection is often acquired in adolescence within the first year or two of sexual debut (35), a significant proportion of adult females may still be at risk of acquiring new oncogenic HPV infections (23). Therefore, HPV vaccination in adulthood has the potential to further decrease the burden of disease in the population. There have been fewer studies which examine HPV vaccination outside of the commonly studied teen years, but coverage estimates range anywhere from 29-48% in young adults (18-29 years) to under 10% in mid-adults (30-45 years) (22–24). According to Kasting et al (2020), it is unclear if adults who report having received at least one dose of the HPV vaccine received it during adolescence or during adulthood (23). Thus, it is vital that further research highlight temporal patterns in HPV vaccine initiation and uptake to identify opportunities for enhanced vaccine communication and catch-up programs.

Attitudes around HPV vaccines

Although the HPV vaccine has been recommended for routine use in adolescents for over 10 years, HPV vaccine uptake consistently lags behind that of other common vaccines. As previously stated, in 2020 90.1% of adolescents aged 13-17 reported receipt of at least one dose of Tdap and 89.3% reported receipt of at least one dose of MenACWY. The high coverage

estimates of Tdap and MenACWY directly juxtapose coverage estimates of HPV in the same age group. In the same year, only 75.1% of adolescents reported receiving at least one dose of the HPV vaccine, with only 58.6% being fully up-to-date (3).

Myriad research studies have investigated why HPV vaccine uptake is consistently lower than that of other routine adolescent vaccines. Misconceptions about the risk of HPV infection and safety of the vaccine-- coupled with stigmas surrounding sexual promiscuity-- have been shown to negatively impact HPV vaccine uptake in adolescents around the country (21). Szilagyi et al (2020) identified patterns in HPV vaccine hesitancy across the United States and found that 23% of US parents of adolescents are hesitant about the vaccine. Many parents in this study did not believe the vaccine was beneficial (22%) or that it protects against HPV-related cancers (21%) (36). Contrary to hesitancy among adolescent populations, safety and sexuality concerns are not always to main reasons for vaccine hesitancy in vaccine-eligible adults. In one study by Domgue et al (2020), many adults in Texas did not know about the vaccine (18.5%) and others said their provider did not recommend it to them (14.5%) (37). Further research is needed to document and understand the discrepancies in HPV vaccine uptake and catch-up vaccinations within different age groups and populations to better design HPV-related messaging and immunization campaigns.

Trends in HPV Vaccine Coverage

The United States failed to meet the Healthy People 2020 target and achieve 80% HPV vaccination coverage of adolescents aged 13-15 by 2020 (38). This failure can be attributed to

significantly low vaccine uptake rates among adolescents across the country. In recent years, HPV vaccine coverage rates have increased moderately, but they still lag far behind other routine adolescent vaccines, as indicated in the summary figure below (39).

United States Adolescents Ages 13-17 Up-To-Date with Routine Adolescent Vaccines, NIS-Teen

Year	HPV up-to-date	Tdap ≥ 1 dose	MenACWY ≥ 1 dose
2016	43.4%	88.0%	82.2%
2017	48.6%	88.7%	85.1%
2018	51.1%	88.9%	86.6%
2019	54.2%	90.2%	88.9%
2020	58.6%	90.1%	89.3%

In the period from 2011-2018, HPV up-to-date (UTD) rates rose by 31.9% among boys but only by 6.6% among girls (10). Although HPV coverage has improved since its original licensure, recent increases were modest compared with previous years, and most increases were primarily observed among males (11). In comparison to other high-income countries with HPV vaccines integrated into the national immunization program, the US continues to exhibit much lower levels of coverage (40). For instance, in 2017, Australia reported UTD coverage estimates exceeding 75% in girls and 69% in boys age 13-17 (41). The United States needs to increase HPV vaccine coverage rates in their adolescent population to minimize the resulting health and economic burden of HPV infection and related cancers.

HPV vaccine coverage rates among adults in the US are lower than that of adolescents. Patterns and trends in HPV vaccine coverage in the young adult and adult populations are less commonly

studied than that of the 13-17 year old adolescent population. However, some national databases collect information on the proportion of adults who have received at least one dose of the HPV vaccine. Lu et al (2021) states that in 2018, among 19-26 year old young adults, 52.8% of females and 26.3% of males self-report having received at least one dose of the HPV vaccine (42). In the same year, among 13-17 year old adolescents, 69.9% of females and 66.3% of males report having received at least one dose (39). It is important to note that these estimates do not directly compare changes in vaccine coverage among members of the same birth cohort. Further research is needed to understand how HPV vaccine coverage evolves *within the same birth cohort* as adolescents emerge into young adulthood.

Current Demographic Trends in HPV Vaccine Coverage

HPV vaccine coverage is not homogenous across demographic groups or geographic regions in the United States. One study found that caretakers in the rural South attributed their low vaccination rates to a lack of information about the HPV vaccine or its purpose (43). Walker et al (2019) reports, "coverage with ³ 1 dose of HPV vaccine was higher among adolescents whose parents reported receiving a provider recommendation." The prevalence of provider recommendations varies by state and metropolitan area, which therefore influences the likelihood that adolescents in certain regions are encouraged by their provider to receive an HPV vaccine. To this effect, in 2018 HPV vaccination coverage in 13-17 year olds was lower in rural areas than in urban areas. Similarly, adolescents with Medicaid had higher HPV vaccination coverage than those with private health insurance (11). One study explained that even with the Vaccines for Children (VFC) program providing uninsured children with access to the HPV vaccine, lack of parental awareness and misconceptions about the program may serve as barriers to its

utilization (33). Geographic location and health insurance status both play a role in understanding patterns and trends in HPV vaccination coverage in the United States.

HPV vaccination uptake differs by demographic characteristics as well. Chido-Amajuoyi et al (2021) reports from 2011-2018, "non-Hispanic Black and Hispanic individuals had higher rates of initiation and HPV-UTD than non-Hispanic white individuals," (10). In 2018, non-Hispanic white adults were more likely than Hispanic adults to have ever received at least one dose of HPV vaccine (44). However, unlike trends seen among adults, HPV vaccine series initiation in adolescents exhibits atypical demographic patterns. Series initiation is higher among Hispanic and black teens compared to white teens. Additionally, boys and girls below the federal poverty line exhibited higher rates of vaccine initiation than did those at or above the poverty line (45). The discrepancy between adult and adolescent demographic patters in HPV vaccine coverage highlights the need to further evaluate coverage patterns by birth cohort as adolescents continue into young adulthood and beyond.

Current Understanding of HPV Vaccine Coverage Trends among Birth Cohorts

Many studies that aim to estimate HPV vaccination coverage utilize data from the National Immunization Survey-Teen (NIS-Teen) or the National Health Immunization Survey (NHIS) datasets. NIS-Teen collects a wide-range of information about immunization history of adolescents aged 13-17. HPV-related vaccination data from NIS-Teen can be self-reported or provider verified, depending on if the respondent gives consent for medical records to be accessed. The official HPV vaccination coverage estimates from NIS-Teen which are published

in CDC's Morbidity and Mortality Weekly Reports (MMWR), exclusively utilize provider-verified data (3). On the other hand, NHIS collects self-reported health data for civilians of any age in the United States, not limiting its respondents to those that are 13-17 years old. NHIS only contains self-reported data on HPV vaccination.

One recent study by Chido et al (2021) utilized NIS-Teen data to examine changes to HPV vaccine coverage estimates among adolescents using specific birth cohorts over time. This study analyzed trends in HPV vaccination initiation and completion between 2008 and 2018. To achieve this aim, they restricted their study to solely focus on the HPV vaccination status of 13-year-old cohorts for each year since the national HPV vaccination program began. Analyzing immunization data specific to 13-year old cohorts allowed them to track how HPV vaccination initiation and UTD rates in 9-12 year olds have changed in recent years. Findings from their study suggest that vaccine initiation rates in 9-12 year olds rose from 17.3% in 2008 to 62.8% in 2018. Additionally, only 13.5% of the study population was up-to-date (UTD) with their HPV vaccination series in 2011, whereas 32.8% of the population was UTD in 2018. Similar to the findings from Bednarczyk et al (2014), they found that Hispanic adolescents had higher HPV uptake rates than non-Hispanic black or non-Hispanic white populations (10,45).

Although the analysis by Chido et al (2021) analyzed temporal trends in HPV vaccination coverage using a birth cohort approach, they did not extend their analysis to include coverage trends as cohorts span into young adulthood and beyond (7). Broad assessments of vaccination coverage at 13 years old misses key cohort effects in young adulthood that are vital to understand

the evolving landscape of HPV vaccinations. Studies which restrict their analyses to the 13-17 year old population may miss documenting key birth cohort effects in vaccination coverage after individuals enter into young adulthood. Further research is needed to understand catch-up vaccination among birth cohorts after they are outside of the commonly studied teenage years. We must analyze how race, socioeconomic status, geography, or health insurance status influence patterns in adolescent HPV vaccine uptake and if these patterns are maintained in adulthood.

There is a need to model and understand the discrepancy between projected HPV vaccination coverage from adolescent vaccine assessments and actual HPV vaccination coverage from adult vaccine assessments among birth cohorts. We need to understand how patterns in vaccine coverage may be expanding beyond the commonly studied teenage years. Overall, in order to assess statistical vaccine coverage measurements and catch-up vaccination programs, it is important to investigate how HPV vaccine coverage by birth cohort spans into young adulthood.

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Chapter 3: Manuscript

Contribution of Student: Beginning in Summer 2021, I worked closely with Dr. Bednarczyk to develop a conceptual framework and approach to analysis. I significantly contributed to the data cleaning, data analysis, writing of the manuscript, and tables and figures generation.

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Abstract

To our knowledge, this is the first analysis which utilizes a birth cohort approach to directly compare projections of HPV vaccination coverage from adolescent vaccination assessments to actual coverage estimates from adult vaccination assessments. Our analysis identifies discrepancies between adolescent and adult HPV vaccination estimates using two national immunization surveillance systems, NIS-Teen and NHIS. To achieve our research aims, we constructed each birth cohort using data from the NHIS (2013-2018) and the NIS-Teen (2008-2017) datasets. Coverage projections were generated using a survey-weighted Poisson regression analysis of adolescent data from NIS-Teen. Survey-weighted point estimates of adult vaccination coverage were calculated from NHIS data. Birth cohorts were selected if they had HPV vaccination data for all adolescent years (13-17) and at least one year of adult data (19+). HPV vaccination coverage was measured through either parental-report or self-report of having received at least one dose of the HPV vaccine.

Our analysis found that the projected HPV vaccination coverage estimates for young adults are higher than the actual coverage estimates, thereby indicating a plateau in the rate of vaccine uptake after mid-adolescence (13-17 years). Our findings also draw attention to potential reporting issues between NIS-Teen and NHIS, as the estimated vaccination coverage in young adults is lower than the estimated coverage of the same birth cohort in adolescence. Our project highlights the need for further investigation into the impact of the HPV vaccine uptake plateau seen in young adult populations in the United States.

Introduction

Human Papilloma Virus (HPV) infects millions of people in the United States each year. Although there is a safe and effective vaccine to prevent against infection with HPV, coverage still consistently lags behind that of other routine adolescent vaccines (3). There is a need to document and understand how patterns in HPV vaccine coverage within specific birth cohorts span into young adulthood to assess vaccine coverage measurements and understand the landscape of HPV catch-up vaccinations.

In 2006, the United States Food and Drug Administration (FDA) approved the first HPV vaccine, HPV4, for use in females ages 9-26 (4). In 2011, the HPV4 routine recommendation was subsequently expanded to include males ages 9-21 and men who have sex with men (MSM) up to age 26 (5). In 2014, the US FDA updated their recommendation to include HPV9 for routine use in males and females aged 9-26 (6). It is ideal for the HPV vaccination series to be initiated in early adolescence. Although vaccination coverage increased drastically following the original FDA approvals, in the period from 2011-2018, HPV up-to-date (UTD) rates only rose by 6.6% among girls ages 9-12 (10). Recent coverage increases were modest compared with previous years, and most were primarily observed in boys (11). If HPV vaccination coverage in the United States continues to trend towards an eventual plateau, the burden of HPV infection will continue increasing in the population.

To date, there has not been a comprehensive study to evaluate trends in HPV vaccine coverage as adolescent birth cohorts span into young adulthood. There are no studies which compare the statistical measurements of these birth cohorts between the National Immunization Survey- Teen

(NIS-Teen) and National Health Interview Survey (NHIS) datasets and identify the differences between them. If national databases, such as NIS-Teen and NHIS, provide drastically different estimates of HPV vaccination coverage among identical birth cohorts, our understanding of HPV vaccination coverage in the population will vary widely. Appropriate, timely, and effective public health interventions require guidance from robust and evidence-based recommendations

Our analysis will answer the following questions. 1) Do projections in HPV vaccination coverage among birth cohorts from NIS-Teen match actual adult HPV vaccination coverage estimates from NHIS? 2) How do trends in HPV vaccination coverage within birth cohorts differ between the NIS-Teen and NHIS national databases?

The results of our analysis allow us to identify the discrepancies in HPV vaccination coverage estimates between the NIS-Teen and NHIS national databases. Our analysis also enables us to identify possible biases which contribute to coverage discrepancies between the databases. There is a need to ascertain how vaccine coverage may be expanding beyond the routinely studied 13-17 adolescent years to better understand the landscape of HPV catch-up vaccination. Highlighting missed opportunities in vaccine initiation and catch-up vaccination will better inform our understanding of HPV vaccination in the United States.

Methods

We compared coverage projections from the National Immunization Survey-Teen to actual coverage estimates from the National Health Immunization Survey. We analyzed this comparison among specific birth cohorts and investigated temporal trends as HPV vaccination

coverage changed each year. To achieve our research aims, we performed a quantitative analysis of HPV vaccination data from the aforementioned datasets. Utilizing a survey-weighted Poisson regression analysis, we estimated average annual percent change, by birth cohort, and used these values to generate predicted coverage estimates into adulthood, comparing these estimates to the actual coverage estimates reported in NHIS.

Data Sources

The HPV vaccination coverage projections in this project were conducted using the National Immunization Survey -Teen (NIS-Teen) database, available through the US Centers for Disease Control and Prevention. The NIS-Teen is a nationally representative telephone survey that monitors vaccination coverage among teens ages 13-17 years. NIS-teen provides population based, state and local area estimates of vaccination coverage among teens. The surveys collect data by interviewing parents or guardians in all 50 states, the District of Columbia, and some U.S. territories. The telephone survey asks parents about the HPV immunization history of their child and verifies their responses with healthcare providers.

Actual HPV vaccination coverage estimates for young adults were calculated using data from the National Health Interview Survey (NHIS). This survey collects health-related information through personal household interviews. All data is available through the US Centers for Disease Control and Prevention. All participants in the survey are within the civilian noninstitutionalized population of the United States. This analysis only utilized NHIS data for participants ages 19-24 to maintain consistency with other reports of HPV vaccination coverage derived from NHIS data. (1)

Self-reported HPV vaccination status from NIS-Teen was used in this analysis to maintain consistency with self-reported HPV vaccination data from NHIS. (2) NIS-Teen collects two types of HPV-related data: self-report and provider-verified. In this analysis, vaccination coverage projections from NIS-Teen are based off adolescents' parents who self-report their child having received at least one dose of the HPV vaccine, regardless of if they are up-to-date on their vaccination series. NHIS does not contain a sufficient counterpart to the provider verified data from NIS-Teen, as it only collects self-reported data on HPV vaccination status. To account for differences in data collection between the two databases, we decided to exclude provider-verified NIS-Teen data from our analysis. However, to document potential biases with this approach, we conducted a sensitivity analysis using the provider-verified weight variable and compared the resulting differences in coverage estimates.

Procedure

We utilized a birth cohort approach to examine and compare HPV vaccination projections and coverage estimates. Beginning with the NIS-Teen (2008-2019) datasets, we grouped adolescents ages 13-17 by their birth year to assign them to a respective birth cohort. We used SAS to create a new variable named "cohort," assigning all adolescents born in 1996 to the "1996" cohort, those born in 1995 to the "1995" cohort, and so on. We restricted our analysis to only include cohorts with complete data for all five years of adolescent vaccine evaluation by NIS-Teen (ages 13-17) to ensure that all generated estimates were as rigorous as possible.

Adolescents in the final analytic cohorts were born in 1995-2002 for females and in 1997- 2002 for males. If a cohort did not have data on each year of adolescence (13-17), the resulting HPV vaccination coverage projection would have been generated from fewer data points. Ensuring

that each cohort had five years of consecutive data helped maintain consistency in the regression analysis.

After classifying respondents by birth cohorts, we stratified each cohort by sex. Historically, until 2011, ACIP recommendations for HPV vaccination differed by sex, with HPV vaccination in males being recommended three years after it was recommended in females (3,4). Therefore, rates of HPV vaccine uptake and coverage have evolved separately among males and females. While current adolescent HPV vaccine uptake estimates are presented for all adolescents, we stratified each cohort by sex to account for these differences given the historical nature of this analysis.

Poisson Regression Analysis for NIS-Teen

After categorizing NIS-Teen participants into birth cohorts and stratifying by sex, we conducted a survey weighted Poisson regression analysis to calculate the average annual percent change in HPV vaccination coverage among each birth cohort during adolescence. We utilized the results of the regression analysis to generate projections of HPV vaccination coverage as the cohorts enter young adulthood. After conducting the initial survey weighted Poisson regression analysis, we identified missing stratum variables in male and female cohorts from 1997-1998 and 1995-1998, respectively. A simple analysis identified the small proportion of missing stratum variables in the cohorts all collected during 2011 (N=589). We excluded these individuals from the analysis to enable the regression analysis to proceed.

To calculate average annual percent change of HPV vaccination coverage in each birth cohort, we generated risk ratios using survey-weighted Poisson regression. We calculated the average annual percent change by subtracting 1, the null value, from the relevant risk ratio. The resulting

value represented how vaccination coverage changed over the five years of adolescence (13-17 years).

The average annual percent change generated from the Poisson regression analysis enabled us to predict HPV vaccination coverage in young adulthood, where coverage was assessed by NHIS. To generate these projections, we began by using point estimates to determine the starting coverage values at age 13. Mirroring the formula of compound interest in economics (5), we multiplied the average annual percent change with the starting coverage value of HPV vaccination to estimate the coverage value at age 14. We subsequently multiplied the average annual percent change by this predicted coverage value at 14 to calculate the estimation for age 15, and so on until age 17.

Comparison of modeled NIS-Teen estimates to actual NHIS vaccine coverage

We categorized NHIS participants into birth cohorts by subtracting the participant's age from the year of data collection, thereby computing their estimated birth year. We used PROC SURVEYMEANS to generate point estimates of HPV vaccination coverage for each year of data collection and each birth cohort. HPV vaccination status was analyzed dichotomously; those that reported "having received at least one dose of vaccine," were included in vaccination coverage estimates, whereas all other responses (e.g. "Refused," "Not ascertained," "Don't know," etc.) were not included. An overview of birth cohorts, age, and year of data collection is presented in Figure 1.

Overall, within each birth cohort, we compared the estimates of adult vaccination coverage generated from NHIS data to the projected adolescent coverage estimates generated from NIS-Teen data.

Variable Construction

When using SAS for survey-weighted regression analyses, we followed the instructions regarding the cluster, stratum, and weight variables outlined in the NIS-Teen and NHIS data user guides (1,6).

Sensitivity Analysis

To support the exclusion of provider verified data from NIS-Teen, we conducted a sensitivity analysis using provider-verified weight variables in the survey weighted Poisson regression model. We based this sensitivity analysis on the assumption that coverage estimates from self-report data would be higher than that from provider-verified data, as recall bias likely plays a role in reporting immunization histories.

Analytic Approach

Analyses were performed using SAS Studio 3.81 (SAS Institute, Inc., Cary, North Carolina) using PROC GENMOD with Poisson regression and appropriate sample weighting as provided in the NIS-Teen data documentation. We utilized the NIS-Teen stratum and weight variables in the regression analysis to account for the complex survey design and generate valid coverage estimates for the broader US population. We included the unique participant ID as the repeated subject variable to treat each participant as a cluster in the regression analysis. Analysis to determine the actual HPV vaccination coverage estimates was performed using PROC SURVEYMEANS and appropriate sample weighting as provided in the NHIS data documentation. All vaccination coverage projections and estimates were based on self-report data.

Ethical Considerations

This analysis was determined to be IRB-exempt because it is a secondary analysis of previously collected, publicly available, deidentified data. It is not research with “human subjects” nor is it a "clinical investigation" as defined in the federal regulations.

Results

Birth Cohort Regression Analysis

Using the average annual percent change and starting coverage estimates from the survey-weighted Poisson regression analysis, we found that among all cohorts, the projected HPV vaccination coverage surpasses 99.99% by age 23 (*Table 1, 2, 4-11)*. Coverage projections exceeded 100% by age 21 in four of the six cohorts that collected data on 21 year olds (*Table 2, 4-7, 9*). Beginning in the 1997 male and female cohorts and continuing onwards, the projected vaccination coverage exceeds 100% for ages 20 and older (*Table 2, 5-11*). Given the high starting coverage and average annual percent change for 1997 females, the estimated coverage values for ages 19 and older all exceed 100% (*Table 5*).

In every cohort, the HPV vaccination coverage projections from NIS-Teen at age 19 are higher than the actual coverage estimates from NHIS at age 19. Additionally, in all ten cohorts the NHIS HPV vaccination coverage estimates at age 19 are consistently below the actual adolescent coverage values from NIS-Teen. When confidence intervals included in the analysis, nine out of ten cohorts still display this discrepancy between actual adolescent and young adult coverage estimates (*Table 1,2,4-11*).

Within each birth cohort, the point estimates of adult vaccination coverage from NHIS do not exhibit a homogenous increase in vaccination coverage over time (*Tables 1,2,4-11*). Given that we categorized the data into birth cohorts and further stratified by sex, the resulting 95% confidence intervals for the point estimates are wide and overlap with one another. Therefore, vaccination coverage among young adults in each birth cohort may exhibit a homogenous positive trend given the width of the confidence intervals.

On average, male cohorts exhibited a higher average annual percent change and lower starting coverage value at age 13 than did their female counterparts. The younger male birth cohorts exhibited lower average annual percent changes and higher values for the starting coverage at age 13 than the older male birth cohorts. On the other hand, when compared to the older female birth cohorts, younger female birth cohorts had higher starting coverage values at age 13. There was no discernable pattern between birth cohort age and average annual percent change among the female birth cohorts.

Sensitivity Analysis

The NIS-Teen sensitivity analysis was conducted for all cohorts included in the analysis. Results are displayed in Table 3. The range of deviation between HPV vaccine series initiation using self-report and provider-verified data is 0.01% to 6.62%. While there is some deviation, the results are nearly consistent as almost all provider verified data is higher. In the instances where the provider verified estimates are lower, the differences only range from 0.01%-1.71%. Therefore, given these findings, there is a slight bias towards under estimating vaccine coverage using self-reported data. However, the consistency in this minimal level of bias indicates that while point estimates may be biased, the results are qualitatively similar to that of the self-reported data.

Discussion

To our knowledge, this is this first analysis which directly compares HPV vaccination coverage estimates among adolescents from the National Immunization Survey-Teen with adult coverage estimates from the National Health Immunization Survey using consistent birth cohorts for long-term evaluation. Our analysis found that the projected coverage estimates for young adults, extrapolated from adolescent vaccine coverage, are higher than the actual coverage estimates, thereby indicating a plateau in the rate of vaccine uptake after mid-adolescence (13-17 years). These findings highlight the need to address the HPV vaccine uptake lag seen in young adult populations in the United States to reduce the overall burden of HPV-related disease.

The current HPV vaccination schedule in the United States recommends the first dose of the HPV vaccine to be given to males and females between ages 11 and 12, although it can be administered as early as age 9 (7). Current research indicates that only 58.6% of adolescents ages 13-17 are up-to-date on their HPV vaccination, with young adult populations exhibiting lower coverage estimates around 30%-50% (8–11). Although our analysis examined the proportion of US adolescents and young adults who had received *at least one dose* of the HPV vaccine (and therefore may not be fully up to date with their vaccine series), our results still indicate there is a discrepancy between adolescent and young adult HPV vaccination coverage across distinct birth cohorts. Irrespective of sex, vaccination coverage projections from adolescent data consistently overestimated the vaccination coverage of young adults within each birth cohort. The rate of vaccine uptake seen among adolescents is not maintained in young adulthood, which may be attributed to a variety of factors. Self-reported HPV vaccination status in young adults may underestimate true vaccination coverage, especially if the participant received their HPV vaccines at ages 11-12. Young adults who received their HPV vaccine in early adolescence may

not remember or be aware of their immunization history if given that administration occurred 7+ years prior.

Consistent with current research, Gerend et al (2015) discusses the importance of provider recommendations in the determination to receive the HPV vaccination. Their findings indicated that patients ages 18-21 years were more likely to report having received a provider recommendation than patients ages 22-26 years (12). Similarly, Vadaparampil et al (2011) also found that young adults ages 18-26 were less likely to receive a provider recommendation than adolescents ages 13-17 (13). Therefore, the results of our analysis are supported given the positive correlation between provider recommendation and HPV vaccine receipt, coupled with the decreased likelihood of receiving a provider recommendation in young adulthood. The interaction between provider recommendation and patient age likely contributes to our findings that the rate of vaccine uptake in adolescents was not maintained in young adulthood.

On a more granular level, we utilized the average annual percent change from adolescent vaccine assessments to generate projections of vaccine coverage in young adulthood. Although vaccination coverage estimates which surpass 100% are not feasible, these projections are useful to display the stark contrast between expected and observed realities of HPV vaccination coverage in the United States. Prior research supports the steady increase in HPV vaccination coverage throughout commonly studied teen years (14), while citing that recent increases were primarily observed among males and were modest compared with previous years (15). Our findings support the diminishing rate of vaccine uptake in older adolescents and young adults, as exemplified by the discrepancy between observed and projected vaccination coverage among each birth cohort.

The male cohorts in our analysis exhibited a greater average annual percent change than their female counterparts. This result is likely correlated to the delayed licensure and recommendation of the HPV vaccination for males, as well as the higher rates of vaccine initiation among male adolescents in recent years (15,16). Given that the HPV vaccine had been administered in females for three years before it was recommended in males, vaccine acceptance and demand among males was higher in the immediate period following vaccine licensure. Therefore, the average annual percent change in the older male cohorts reflect the increased demand and display drastic increases in vaccine uptake in adolescents. It is important to note that even among the male cohorts with a more moderate average annual percent change, the actual coverage estimates in young adults were still lower than the projected estimates. The results seen among the male cohorts support the overall conclusions that vaccine uptake declines in young adulthood regardless of the birth cohort, starting coverage at age 13, or average annual percent change in adolescence. Our findings are supported by data in CDCs TeenVaxView, as the trajectory of initial HPV vaccination uptake among males is far greater than that of females, though increases have been more moderate in recent years (17).

In addition to identifying a vaccine uptake plateau occurring after adolescence, the findings of our analysis also draw attention to potential reporting issues between NIS-Teen and NHIS. We identified a discrepancy between 17 year old coverage estimates from NIS-Teen and 18 year old coverage estimates from NHIS. In all cohorts, the coverage estimates for 18 year olds are lower than the estimates for 17 year olds in the same cohort. Considering that HPV vaccination is a permanent and lifelong status, it is not feasible for true vaccination coverage to decline between ages 17 and 18. This discrepancy in our analysis may be attributed to a variety of factors. There may be a difference in data reliability between parental-report for 17 year olds and self-report for

18 year olds. A parent may be better suited to correctly recall their 17 year old child's vaccination history, whereas an 18 year old young adult may not remember if they received their HPV vaccination up to 9 years prior. As postulated by Zell et al (2000), population-wide vaccine coverage estimates which rely on parental report or vaccination verification may incorrectly estimate vaccination coverage (18). Our sensitivity analysis on the parental-report data for NIS-Teen indicated minimal qualitative differences between parental-report and provider verified adolescent data, however the lack of provider verified data in NHIS prevented us from conducting a direct comparison of provider-verified data. While provider reports are generally more accurate and complete than self-reports of immunization history (19), they may still underestimate true vaccination coverage levels (18). Therefore, potential reporting issues from NIS-Teen and NHIS may contribute to error in our assessment of HPV vaccination coverage in the United States.

This project highlighted the limitations of of monitoring vaccine uptake and coverage using a national level registry. Although each state maintains their own Immunization Information System (IIS), the United States does not have a national vaccine verification system (20). This patchwork of state-level IIS data yields the potential for an incomplete data sharing pipeline between states and may impede the true estimation of national level vaccine coverage estimates. Other countries have tried to circumvent this limitation by utilizing the International Certificate of Vaccination or Prophylaxis (ICVP) or "Yellow Card" to authenticate an individual's vaccination history. Created by the World Health Organization, this document is internationally recognized and is interoperable between international surveillance systems (21). Some countries, such as Nigeria, are developing digital ICVP certificates with QR codes to electronically verify the vaccination history of each individual (22). Although digitized ICVP cards are still subject to

imperfections, in some settings they have the ability to reduce the impact of recall bias and reporting issues on resulting immunization coverage estimates. Given the complex nature of immunization reporting and monitoring among the US population, however, employing this approach in the US may not be beneficial for all routine childhood, adolescent, and adult vaccines.

The suboptimal levels of HPV vaccination coverage in adolescents and young adults exposes the need for continued support of HPV vaccination surveillance, education, and outreach. Our analysis further supports the need to improve HPV vaccination uptake programs in adolescents ages 13-17, as well as address the vaccine uptake plateau observed in young adulthood. In addition to educating healthcare providers on the importance of HPV vaccine recommendations in adolescent and young adult populations (23), further resources are needed to bolster catch-up vaccination programs amongst young adult populations. Immunization programs, such as the *HPV VAX NOW* campaign which targets 18-26 year olds in the southern United States, should increase awareness of HPV-related disease and encourage young adults to complete their HPV vaccine series (24). Aligning HPV vaccination initiatives with the "Catch-up to Get Ahead" campaign from the Department of Health and Human Services will further support HPV vaccine initiation in young adult populations (25).

The strengths of this study include its use of a nationally representative sample from NIS-Teen and NHIS datasets. Our project also addresses a gap in knowledge regarding the landscape and evolution of HPV vaccination among birth cohorts in the United States. Additionally, the HPV vaccination coverage estimates generated in our analysis are consistent with current published estimates using NIS-Teen and NHIS data sources (8,26,27).

This study is subject to several limitations. As previously discussed, our estimations of HPV vaccination coverage are based on receipt of one or more doses of the HPV vaccine. Depending on the age of series initiation, HPV vaccination is a two or three dose series. Therefore, our results are not indicative of the proportion of the population that are up-to-date with the HPV vaccine (28). Although completing this analysis with an up-to-date vaccination metric would provide valuable insight into the landscape of HPV vaccination in the United States, NHIS does not collect data on the up-to-date status of its participants. Therefore, to maintain consistency in analysis across the NIS-Teen and NHIS datasets, we chose to analyze receipt of at least one dose of HPV vaccine. Second, our reliance on parental-report data from NIS-Teen and self-report data from NHIS yields the opportunity for recall bias to influence the estimates we generated (18). To investigate the influence of this potential bias, we conducted a sensitivity analysis with NIS-Teen provider-verified data and found qualitatively similar results between the two data types. Third, creating birth cohorts based on the survey year and age of participant may have introduced misclassification bias into our analysis. If this bias occurred, it would likely have been non-differential misclassification bias and would not have significantly influenced our results. Lastly, due to the different sampling methodology between NIS-Teen and NHIS, the same group of individuals were not sampled for each component of the analysis. However, given the incorporation of survey weights into the analysis, results from NIS-Teen and NHIS are both generalizable to the greater population of the United States and provide a sense of broad patterns in vaccination coverage over time.

The delimitations of our study include the restriction of only using birth cohorts with five consecutive years of HPV vaccination data from NIS-Teen and at least one year of HPV vaccination data from NHIS. All years of NHIS data collected after 2018 were excluded for

either insufficient data on individual-level HPV vaccination coverage (2019) or exclusion of HPV-related questions from the survey design (2020-2021). Additionally, data 18 year old respondents from NHIS was excluded to maintain consistency with other published estimates that use NHIS data.

The results from our analysis support the hypothesis that HPV vaccination uptake declines in young adulthood and does not uphold the rate of change seen in the commonly studied teen years (ages 13-17.) Harmonizing methods in monitoring immunization surveillance across the nation to provide accurate and reliable data for resulting programmatic and policy decisions could assist in a better understanding of vaccine uptake across time and age groups. Our project highlights the discrepancy between adolescent and young adult HPV vaccine uptake while encouraging further inquiry into the mechanisms behind the vaccine uptake plateau in young adult populations in the United States. Furthermore, our project provides support to encourage policymakers and public health officials to address missed opportunities for HPV catch-up vaccinations in young adulthood. In conjunction with the ACIP recommendation to initiate HPV vaccination between ages 9-12, the American Academy of Pediatrics and American Cancer Society also recommend routine immunization to begin between ages 9-12 (29–31). Effectively communicating that these respected organizations recommend HPV vaccine initiation in pre-adolescent years may increase overall coverage and reduce the burden of vaccination from catch-up programs and campaigns. In summary, future interventions should minimize the discrepancy between the HPV vaccination landscape in adolescence and young adulthood to improve vaccination coverage and reduce the burden of HPV-related disease in the United States.

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Tables and Figures

Table 1. A Comparison of HPV Vaccination Coverage Estimates in the 1995 Female Birth Cohort National Immunization Survey-Teen and National Health Immunization Survey

Cohort	**Average Annual Percent Change**		**Starting Coverage at 13**	
1995 Females	16.73		26.21	
Age	Estimated Coverage (%)	Actual Coverage (%)	Actual Coverage 95% CI	
14	30.59	32.66	30.04	35.28
15	35.71	34.93	31.93	37.92
16	41.69	45.90	42.92	48.88
17	48.66	48.17	44.68	51.67
18	56.80	34.94	28.23	41.64
19	66.31	44.95	32.18	57.73
20	77.40	40.34	33.11	47.57
21	90.35	41.91	33.03	50.79
22	>99.99 *	51.39	42.36	60.43
23	>99.99 *	44.48	34.71	54.24
24	>99.99 *	47.28	38.28	56.29

* These estimated coverages are modeled based on the average annual percent change and thirteen-year-old starting coverage value. With continued application of the average annual percent change, eventually coverage estimates will exceed 100%. At that point, we indicated > 99.99% coverage for that age and subsequent ages.

Table 2. A Comparison of HPV Vaccination Coverage Estimates in the 1997 Male Birth Cohort National Immunization Survey-Teen and National Health Immunization Survey

Cohort	**Average Annual Percent Change**		**Starting Coverage at 13**	
1997 Males	72.10		1.97	
Age	Estimated Coverage (%)	Actual Coverage (%)	Actual Coverage 95% CI	
14	3.39	7.98	6.26	9.71
15	5.83	22.10	19.28	24.92
16	10.04	28.14	25.29	31.00
17	17.28	40.29	37.34	43.24
18	29.74	21.59	15.65	27.53
19	51.19	21.88	14.54	29.21
20	88.09	30.82	20.40	40.81
21	> 99.99 *	24.49	14.39	34.59
22	> 99.99 *	33.80	25.39	42.21

* These estimated coverages are modeled based on the average annual percent change and thirteen-year-old starting coverage value. With continued application of the average annual percent change, eventually coverage estimates will exceed 100%. At that point, we indicated > 99.99% coverage for that age and subsequent ages.

Table 3. Sensitivity Analysis of National Immunization Survey-Teen (NIS-Teen) HPV Vaccination Coverage Estimates, 1995-2000 Birth Cohorts

Cohort	Metric	Parent-Reported	Provider-Verified
1995 Females	AAPC	16.73	18.31
	Starting Coverage	26.21	28.72
1996 Females	AAPC	15.57	13.86
	Starting Coverage	25.73	32.35
1997 Females	AAPC	22.32	21.60
	Starting Coverage	29.86	29.85
1998 Females	AAPC	20.92	20.25
	Starting Coverage	30.09	33.15
1999 Females	AAPC	16.36	17.70
	Starting Coverage	35.11	37.58
2000 Females	AAPC	13.12	11.60
	Starting Coverage	38.61	43.07
1997 Males	AAPC	72.10	75.73
	Starting Coverage	1.97	1.85
1998 Males	AAPC	46.63	47.38
	Starting Coverage	6.28	6.14
1999 Males	AAPC	26.24	26.68
	Starting Coverage	18.88	19.60
2000 Males	AAPC	17.77	18.37
	Starting Coverage	25.42	27.57

Sensitivity analysis of National Immunization Survey-Teen HPV vaccination data comparing parent-reported and provider-verified data. Average Annual Percent Change (APPC) and Starting Coverage at Age 13 metrics estimated using 2014-2018 National Immunization Survey-Teen data.

Figure 1. Birth Cohort Matrix for NIS-Teen and NHIS Participants.

	Year of Data Collection												
Birth Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
1995	10	11	12	13	14	15	16	17	18	19	20	21	22
1996	9	10	11	12	13	14	15	16	17	18	19	20	21
1997	8	9	10	11	12	13	14	15	16	17	18	19	20
1998	7	8	9	10	11	12	13	14	15	16	17	18	19
1999	6	7	8	9	10	11	12	13	14	15	16	17	18
2000	5	6	7	8	9	10	11	12	13	14	15	16	17

Figure 1. Values in the cells above denote the age of cohort members. Cohorts with five consecutive years of NIS-Teen HPV-related data are highlighted in yellow. Birth cohorts are identified by their birth year as shown on the leftmost column.

Chapter 4: Public Health Implications

It is our understanding that this is the first analysis which uses consistent birth cohorts to directly compare HPV vaccination coverage estimates among adolescents from the NIS-Teen with adult coverage estimates from the NHIS. We found that the projected coverage estimates for young adults (19-24) are higher than the actual coverage estimates, thereby indicating a plateau in the rate of vaccine uptake after mid-adolescence (13-17 years). Our findings encourage further inquiry into two main topics related to HPV vaccination in the US. First, it is vital that rates of vaccine uptake increase in pre-adolescence (9-12) and continue to increase in adolescence (13-17) to improve coverage with HPV vaccine across the population. Second, catch-up vaccination programs must aim to sustain the rate of vaccine uptake seen among adolescents as birth cohorts become young adults. Preventing a vaccine-uptake plateau from occurring early in young adulthood will limit the amount of missed opportunities for HPV vaccination initiation in this population.

Additionally, our analysis shed light on potential reporting issues in vaccination coverage between NIS-Teen and NHIS. It is vital that the national immunization surveillance systems which guide our recommendations yield dependable and comparable estimates of vaccination coverage in the population. Additional research should further investigate the discrepancies between NIS-Teen and NHIS to homogenize immunization monitoring in the United States.

In summary, this analysis quantifies temporal trends in HPV vaccination coverage as seen among specific birth cohorts. We identified discrepancies in HPV vaccination coverage projections and estimates between the NIS-Teen and NHIS national databases. We aim for this analysis to

encourage further research into potential missed opportunities for HPV vaccination and ultimately reduce the burden of HPV-related disease in the United States.

Appendix

Table 4. A Comparison of HPV Vaccination Coverage Estimates in the 1996 Female Birth Cohort National Immunization Survey-Teen and National Health Immunization Survey

Cohort	**Average Annual Percent Change**		**Starting Coverage at 13**	
1996 Females	15.57		25.73	
Age	Estimated Coverage (%)	Actual Coverage (%)	Actual Coverage 95% CI	
14	29.74	35.42	27.08	32.65
15	34.37	41.55	38.59	44.50
16	39.72	49.66	46.39	52.93
17	45.90	52.56	49.11	56.01
18	53.05	39.37	24.95	53.80
19	61.31	38.89	29.95	47.83
20	70.85	49.86	40.65	59.08
21	81.88	49.07	39.13	59.01
22	94.63	54.28	43.62	64.94
23	>99.99 *	51.78	43.17	60.40

* These estimated coverages are modeled based on the average annual percent change and thirteen-year-old starting coverage value. With continued application of the average annual percent change, eventually coverage estimates will exceed 100%. At that point, we indicated > 99.99% coverage for that age and subsequent ages.

Table 5. A Comparison of HPV Vaccination Coverage Estimates in the 1997 Female Birth Cohort National Immunization Survey-Teen and National Health Immunization Survey

Cohort	**Average Annual Percent Change**		**Starting Coverage at 13**	
1997 Females	22.32		29.86	
Age	Estimated Coverage (%)	Actual Coverage (%)	Actual Coverage 95% CI	
14	36.52	36.98	34.20	39.77
15	44.68	43.79	40.57	47.02
16	54.65	52.51	49.12	55.89
17	66.85	61.52	58.40	64.65
18	81.77	50.65	43.19	58.11
19	>99.99 *	49.90	41.49	58.31
20	>99.99 *	38.66	29.01	48.32
21	>99.99 *	44.78	34.67	54.89
22	>99.99 *	59.23	50.92	67.53

* These estimated coverages are modeled based on the average annual percent change and thirteen-year-old starting coverage value. With continued application of the average annual percent change, eventually coverage estimates will exceed 100%. At that point, we indicated > 99.99% coverage for that age and subsequent ages.

Table 6. A Comparison of HPV Vaccination Coverage Estimates in the 1998 Female Birth Cohort National Immunization Survey-Teen and National Health Immunization Survey

Cohort	**Average Annual Percent Change**		**Starting Coverage at 13**	
1998 Females	20.92		30.09	
Age	Estimated Coverage (%)	Actual Coverage (%)	Actual Coverage 95% CI	
14	36.38	39.28	35.98	42.58
15	44.00	47.3	43.97	50.64
16	53.20	59.88	56.90	62.68
17	64.33	64.64	61.98	67.30
18	77.79	44.99	35.41	54.57
19	94.06	51.93	42.08	61.78
20	> 99.99 *	44.23	33.20	55.27
21	> 99.99 *	50.4	40.28	60.51

* These estimated coverages are modeled based on the average annual percent change and thirteen-year-old starting coverage value. With continued application of the average annual percent change, eventually coverage estimates will exceed 100%. At that point, we indicated > 99.99% coverage for that age and subsequent ages.

Table 7. A Comparison of HPV Vaccination Coverage Estimates in the 1999 Female Birth Cohort National Immunization Survey-Teen and National Health Immunization Survey

Cohort	**Average Annual Percent Change**		**Starting Coverage at 13**	
1999 Females	16.36		35.11	
Age	Estimated Coverage (%)	Actual Coverage (%)	Actual Coverage 95% CI	
14	40.85	44.28	41.01	47.56
15	47.54	55.26	51.92	58.59
16	55.31	61.64	58.92	64.37
17	64.36	65.72	63.06	68.38
18	74.89	59.11	48.91	69.31
19	87.15	50.95	38.44	63.46
20	> 99.99 *	53.41	44.35	62.47

* These estimated coverages are modeled based on the average annual percent change and thirteen-year-old starting coverage value. With continued application of the average annual percent change, eventually coverage estimates will exceed 100%. At that point, we indicated > 99.99% coverage for that age and subsequent ages.

Table 8. A Comparison of HPV Vaccination Coverage Estimates in the 2000 Female Birth Cohort National Immunization Survey-Teen and National Health Immunization Survey

Cohort	**Average Annual Percent Change**		**Starting Coverage at 13**	
2000 Females	13.12		38.61	
Age	Estimated Coverage (%)	Actual Coverage (%)	Actual Coverage 95% CI	
14	43.68	52.93	49.95	55.91
15	49.41	58.45	55.60	61.30
16	55.89	61.83	59.25	64.41
17	63.22	68.6	66.17	71.02
18	71.51	53.12	41.83	64.38
19	80.90	51.6	41.48	61.73

Table 9. A Comparison of HPV Vaccination Coverage Estimates in the 1998 Male Birth Cohort National Immunization Survey-Teen and National Health Immunization Survey

Cohort	**Average Annual Percent Change**		**Starting Coverage at 13**	
1998 Males	46.63		6.28	
Age	Estimated Coverage (%)	Actual Coverage (%)	Actual Coverage 95% CI	
14	9.21	18.91	16.27	21.54
15	13.50	27.61	24.78	30.44
16	19.80	40.12	36.96	43.28
17	29.03	45.26	42.44	48.07
18	42.57	29.80	20.43	39.17
19	62.42	26.38	16.89	35.87
20	91.52	29.08	19.86	38.30
21	>99.99 *	39.23	29.36	49.12

* These estimated coverages are modeled based on the average annual percent change and thirteen-year-old starting coverage value. With continued application of the average annual percent change, eventually coverage estimates will exceed 100%. At that point, we indicated > 99.99% coverage for that age and subsequent ages.

Table 10. A Comparison of HPV Vaccination Coverage Estimates in the 1999 Male Birth Cohort National Immunization Survey-Teen and National Health Immunization Survey

Cohort	**Average Annual Percent Change**		**Starting Coverage at 13**	
1999 Males	26.24		18.88	
Age	Estimated Coverage (%)	Actual Coverage (%)	Actual Coverage 95% CI	
14	23.83	25.59	22.76	28.41
15	30.09	42.18	39.11	45.24
16	37.98	45.07	42.14	48.00
17	47.95	50.75	47.97	53.53
18	60.53	31.97	21.92	42.02
19	76.42	38.97	28.12	49.83
20	96.47	40.16	29.65	50.68

Table 11. A Comparison of HPV Vaccination Coverage Estimates in the 2000 Male Birth Cohort National Immunization Survey-Teen and National Health Immunization Survey

Cohort	**Average Annual Percent Change**		**Starting Coverage at 13**	
2000 Males	17.77		25.42	
Age	Estimated Coverage (%)	Actual Coverage (%)	Actual Coverage 95% CI	
14	29.94	37.69	34.76	40.62
15	35.26	44.06	41.23	46.90
16	41.52	47.67	44.98	50.35
17	48.90	54.33	51.61	57.05
18	57.59	30.54	20.02	41.05
19	67.82	41.17	28.93	53.40