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The effect of co-vaccination on HPV vaccine outcomes:
Analysis of the National Immunization Survey Teen, 2014

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The effect of co-vaccination on HPV vaccine outcomes: Analysis of the National Immunization Survey Teen, 2014

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An abstract of a thesis submitted to the Faculty of the
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Abstract

The effect of co-vaccination on HPV vaccine outcomes:
Analysis of the National Immunization Survey Teen, 2014

By Anyie Li

Background: HPV vaccine initiation and completion still lags far behind that of other adolescent vaccines. We evaluated patterns in human papillomavirus (HPV) vaccine initiation.
Methods: This study conducted analysis of the 2014 National Immunization Survey Teen publicly available dataset from the US Centers for Disease Control and Prevention (CDC). The main exposure of interest was co-vaccination status with other adolescent vaccines. We were interested in HPV vaccine outcomes including completion of the second and third dose, the dosing intervals between doses, and the age at first receipt. Vaccine recommendations were based on recommendations from the CDC Epidemiology and Prevention of Vaccine-Preventable Diseases (Pink Book) and Advisory Committee on Immunization Practices (ACIP).
Results: Among adolescents that received at least one dose of HPV vaccine, 26% received all three adolescent vaccines concurrently, 55% received two adolescent vaccines concurrently, and 19% received none of the adolescent vaccines concurrently. Males that received tetanus, diphtheria, and pertussis *(*Tdap) and meningococcal conjugate (MenACWY) together had higher odds of completion of both the second (odds ratio [OR] 1.5 (95% confidence interval [CI] 1.1, 2.1)) and third (OR 1.5 (95% CI 1.1, 1.9)) dose of HPV vaccine, compared to those that received none of the vaccines concomitantly. Among females, the odds of completion of the series were higher among those that received Tdap and HPV concomitantly (OR 1.8 (95% CI 1.2, 2.9)), compared to those that received none of the vaccines concomitantly. Receiving concomitant vaccination with HPV vaccine at an age greater than 12 years was statistically significant in second and third dose completion of HPV vaccine models for both sexes. Those that initiated older than 12 years old had lower odds of completing the second and third doses.
Conclusions: Appropriate receipt of Tdap vaccine is influential for HPV vaccine outcomes. There needs to be increased efforts in recommending all three adolescent vaccines concurrently, without differentiation, to improve completion and compliance with HPV vaccine recommendations.

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Literature Review

Introduction

There are currently three vaccines recommended for routine administration to adolescents in the US: tetanus, diphtheria, and pertussis (Tdap), quadrivalent meningococcal conjugate (MenACWY), and human papillomavirus (HPV). In the US, all three vaccines are recommended at age 11 or 12 for both males and females.[1] HPV vaccine is the only vaccine that requires more than one dose for the initial series, and rates of HPV initiation and completion lag behind that of Tdap and MenACWY. In 2014, Tdap vaccination coverage in the US was 88%, MenACWY was 79%, and HPV initiation was 60% for females and 42% for males.[2] HPV completion among those that initiated was 69% for females and 58% for males.[2] Although coverage has increased yearly, HPV vaccination still lags far behind the other adolescent vaccines.[2]

Background on Adolescent Vaccines

Tetanus, Diphtheria, and Pertussis

Tdap vaccines were first recommended for use in the US in 2005.[3,4] Tdap vaccines protect against tetanus, diphtheria, and pertussis.[5] Diphtheria and pertussis are transmitted person to person while tetanus is introduced through wounds and lacerations.[5,6] Tetanus causes muscle tightening throughout the body and tightening of muscles in the head and neck can lead to difficulty swallowing and breathing.[5] Diphtheria can cause a mucous lining in the upper respiratory tract, which can lead to respiratory issues and heart failure.[6,7] Pertussis, commonly known as whooping cough, is a bacterial infection of the respiratory tract that can cause violent coughing spells, complications with breathing, and vomiting.[5,6]

Currently, there are two adolescent Tdap vaccines available in the US: Boostrix and Adacel.[3,4] Boostrix is available for those ten years or older and contains three pertussis components, while Adacel is appropriate for those 10 to 64 years and contains five pertussis antigens.[3] The Advisory Committee on Immunization Practices (ACIP) recommends one dose of Tdap vaccine for adolescents ages 11 or 12, and up to age 18, who have completed the recommended childhood diphtheria and tetanus toxoids and pertussis and diphtheria and tetanus toxoids and pertussis vaccines (DTP/DTaP).[3,4,8] Coverage of Tdap vaccine is the highest among the three adolescent vaccines and there are varying explanations for why Tdap has the highest coverage. Tdap has been required since 2005. It is also included in the childhood vaccination schedule (DTaP), likely improving awareness of the need for boosters.[3,9] Additionally, 46 states, and Washington, DC, require Tdap for middle school entry.[9] *Healthy People 2020* aimed to increase Tdap vaccination coverage among adolescents aged 13 to 15 to 80%, which was surpassed in 2011.[10] Coverage among adolescents aged 13 to 17 years old increased to 88% in 2014.[2]

Meningococcal Conjugate

The meningococcal conjugate vaccines (MenACWY) protect against meningococcal disease, caused by the bacterium *Neisseria meningitidis*.[11] The most common presentation of meningococcal disease is meningitis, which is characterized by a sudden onset of fever, headache, and stiff neck.[11] Other illnesses include meningococcal sepsis, which occurs in 5 to 20% of meningococcal infections, and pneumonia, arthritis, otitis media, and epiglottitis.[11] Incidence of meningococcal disease in the US is roughly 0.3 cases per 100,000 people, with a persistent peak among adolescents and adults ages 16 to 21 years old.[11] In the US,

meningococcal outbreaks are also rare with less than 2% of reported cases resulting in outbreaks.[11] There are currently three licensed meningococcal vaccines in use.[11] Menactra (MenACWY-D) and Menveo (MenACWY-CRM) are single component vaccines while MenHibrix (Hib-MenCY-TT) is a combination vaccine that also includes *Haemophilus influenzae* serogroup B.[11] ACIP recommends one dose of MenACWY at age 11 or 12, with an additional booster dose at age 16.[11] Coverage of MenACWY has increased yearly in a similar trend to Tdap, though coverage is still below that of Tdap. Although they were both introduced in 2005, some of the differences in coverage can be attributed to the fact that MenACWY is only mandated for school attendance in 21 states and Washington, DC, as opposed to the 46 states for Tdap.[9] MenACWY vaccination coverage increased to 79% by 2014 and is close to achieving the *Healthy People 2020* goal of 80% coverage among adolescents.[2,12]

Human Papillomavirus

Human Papillomavirus (HPV) is a sexually transmitted infection that is spread through anal, oral, or vaginal sex or skin to skin contact with an infected person.[13,14] HPV can cause cancers of the cervix, vagina, and vulva in women, cancer of the penis in men, and can cause cancers of the anus, mouth, and oropharynx in both sexes.[15] Currently, there are 79 million people infected with HPV in the US and 14 million become newly infected each year, with around half of those newly infected between the ages of 15 to 24.[13] There are over 150 strains of HPV.[16] HPV type 16 is associated with about 50% of cervical cancers and types 16 and 18 combined are associated with 70% of cervical cancer cases.[13] HPV is also thought to be the cause of 90% of anal cancers, 71% of vulvar, vaginal, or penile cancers, and 72% of oropharyngeal cancers in the US.[13] Without vaccination, most sexually-active men and women

will become infected in their lifetime.[14] Vaccination coverage of at least one dose of HPV vaccine increased to 60% among females and 42% among males by 2014.[2] The target *Healthy People 2020* goal for HPV vaccination is a coverage of 80% for both males and females ages 13 to 15 years old receiving at least three doses.[17,18]

Currently there are three HPV vaccines available: HPV2 (Cervarix), HPV4 (Gardasil), and Gardasil-9.[13,16,19] HPV2 is specific to females ages 9 to 25, while the two formulations of Gardasil can be given to both males and females ages 9 to 26.[13] HPV2 protects against strains 16 and 18.[13,16] Strains 16 and 18 are responsible for most cervical cancer cases in the world, while HPV4 additionally protects against strains 6 and 11, which can cause cervical cell abnormalities, genital warts, and laryngeal papillomas.[13,16] The 9-valent vaccine was introduced in 2015, to additionally protect against strains 31, 33, 45, 52, and 58.[19,20] Because Gardasil-9 was only released in 2015, its use is not included in the data used for this study and will not be discussed in this paper.

Both vaccines had a high seroconversion rate among both sexes in efficacy trials.[16,21,22] Efficacy of the HPV2 vaccine was evaluated in one phase II and one phase III trial among females.[23,24] End of trial efficacy against strains 16 and 18 was 95% (98% and 87%, respectively) for the phase III trial.[25] There were three randomized trials (one phase II and two phase III) among females and one phase III trial among males evaluating the efficacy of HPV4 vaccines.[26-29] The overall efficacy among females in the three trials against all four strains of HPV covered in the vaccine was 98%, while efficacy against strains 6 and 11 was 99% in the phase III trials.[16,22,26,27,29,30] Among males, the efficacy was 89% for all four strains.[28] There is evidence to show that the protection offered by the vaccines is long lasting; however, additional longitudinal studies are currently underway to determine the exact duration of protection.[16,31,32]

Currently, the longest study of 9.4 years showed no diminished effects of the vaccine over that time-period.[31] Additionally, concomitant vaccination with the other vaccines does not reduce efficacy.[16]

HPV Dosing Recommendations

The HPV2 and HPV4 vaccines are given in a three-dose series. The US Centers for Disease Control and Prevention (CDC) recommends the first dose be given at age 11 or 12, but can be given as early as age 9.[13] HPV vaccine is most effective when given before possible exposure to HPV.[16]

According to the CDC Epidemiology and Prevention of Vaccine-Preventable Diseases (Pink Book), the second dose of HPV vaccine should follow the first dose by 1 to 2 months and the third dose should come 6 months after the first dose.[13] It also recommends that the third dose come 24 weeks after the first dose.[13] The third dose does not need to be repeated as long as there is a minimum interval of 16 weeks between the first and third dose, and 12 weeks between the second and third dose.[13]

In contrast, the ACIP, a group that develops vaccine recommendations for the US, provides dosing recommendations in weeks. The minimum interval between the first and second dose is 4 weeks, between the second and third dose, 12 weeks, and between the first and third dose, 24 weeks.[16] See *Figure 1* for possible vaccination schedules within these recommendations.

There is a small discrepancy when considering the dosing recommendations in months as opposed to weeks, when converted to days. Using the recommendations in months, 1 to 2 months would translate into 28 to 62 days, given the smallest and largest number of days in a month.[33] However, using 4 to 8 weeks as the recommendation would translate to 28 to 56 days, using

seven-day weeks. Clear recommendations are necessary to ensure maximum efficacy as physicians are more likely to recommend the vaccine when dosing recommendations are clear.[34] Dosing intervals used in this study are presented in the *Methods* section.

When looking specifically at the time to completion between the second and third doses of HPV vaccine, there were significant differences among socio-demographic factors, with minority adolescents and those below the poverty line taking significantly longer to receive the second dose.[35] The median time between the first and second dose was 2.6 months among all groups.[35] This is longer than the recommended interval of 1 to 2 months, keeping with findings that actual intervals between doses are typically longer than recommended.[16,35,36] Additionally, one study showed that of those that completed all three doses of HPV vaccine, only 51% received all three doses on time, based on ACIP guidelines.[37] However, even this is an overestimate of actual time to completion, as that study expanded their interval between doses beyond the ACIP recommendations and provided an additional buffer of one month between the first and second dose and two months between the second and third dose.[37] Anther study found that knowledge of HPV plays a crucial role in completion, with higher knowledge associated with a shorter interval in time to completion of the three doses.[38] Insufficient dosing and dosing intervals may require re-administration of the vaccine to maximize efficacy.[16]

There is ongoing research on the dosing schedule and debate about reducing the number of doses. Initial trials show that the estimates of efficacy of receiving two doses were non-inferior to receiving three doses.[16,39-45] The Strategic Advisory Group of Experts (SAGE), the advisory group for the World Health Organization (WHO), currently recommend a two-dose schedule, with a minimum of six months between doses for adolescent girls under 15 years old.[46,47] The SAGE recommendation for adolescent girls over 15 years old follows that of the

US.[46,47] Currently, there is no SAGE recommendation for boys.[46,47] If the US were to adopt the SAGE and WHO recommendations, HPV complete coverage would increase nearly four percentage points to 29%.[35] This is based on an analysis of those that met the ACIP HPV guidelines (25% based on 2013 National Immunization Survey (NIS) Teen data) and adding those that completed the series according to SAGE guidelines.[35] Additionally, Blacks and Hispanics would see the greatest increases in coverage (6.3 and 6.2 percentage points, respectively).[35] Other considerations also include that a two-dose schedule may increase acceptability of the vaccine and would help to reduce logistical and financial concerns of HPV vaccine.[21]

HPV Vaccine Coverage in the US

According to 2014 NIS Teen estimates, HPV initiation and completion trails that of Tdap and MenACWY.[2] Initiation is 60% among females and 42% among males.[2] Completion among those that received at least one dose of HPV vaccine is 69% for females and 58% for males.[2] Overall, the proportion of adolescents completing HPV vaccine series is 40% for females and 22% for males.[2] Furthermore, current receipt at the recommended age range of 11 or 12 is low, with only 56% of girls initiating the vaccine before age 13 in 2014.[48] However, this has increased substantially since 2008 when only 14% of girls initiated HPV vaccine series before age 13.[48]

Multiple studies have examined patterns in coverage, as well as barriers and missed opportunities, in attempts to provide targeted intervention recommendations and increase coverage.[2,34,49-76]

There are known patterns of the socio-demographic factors that influence HPV vaccine initiation. Females are more likely to both initiate and complete the series than males.[2,77] There

are varying reasons for this difference including that the first HPV vaccines were not licensed for males until 2009.[78] In terms of race and ethnicity, minority adolescents are more likely to initiate than Whites.[49,66,72,79] One study found that both Blacks and Hispanics have significantly higher odds of initiation than White patients for both boys and girls.[49,68,80] Similar trends have been found between low-income adolescents and those with public insurance, as compared to middle or high income adolescents and those with private insurance.[49,66,68,72,80] Mothers with a high school education or higher are associated with lower vaccination initiation as compared to those with lower education levels.[63,68,81,82] Geographically, adolescents living in the Southern part of the US have lower initiation than those living in the Northeast and Western parts of the US.[63,68,81,82] Those living in metropolitan areas are also more likely to initiate than those in non-metropolitan areas, but there are no differences between metropolitan areas in the US.[81] Additionally, community composition plays a role. Initiation among Hispanics living in predominantly Hispanic or mixed race communities is higher than among Hispanic girls living in non-Hispanic White or Black communities.[80]

However, looking at completion provides another picture. Whites, as compared to Blacks, and those on private insurance, as compared to those on public insurance, are more likely to complete the series.[36] Those that initiate the series earlier, at ages 9 or 10, may have higher rates of overall timely completion.[83] Increased interaction with the medical system is associated with both higher levels of initiation and completion, although there are no differences between the various types of medical institutions.[36,70] Those living in the Northeast and those that received a provider-verified influenza vaccine are also more likely to complete the series.[82] Patterns across socio-demographic factors for both initiation and completion give insight into groups that need additional targeting and interventions.

More recently, studies have explored differences between adolescents looking beyond traditional socio-demographic factors. Among those that are older than the recommended HPV initiation age, lesbians are less likely to initiate the vaccine as compared to heterosexuals, although knowledge of the vaccine is comparable across groups.[50] Additionally, both males and females that have an older sister who received at least one dose of HPV vaccine had higher rates of receiving at least one dose as well.[56] One study also found seasonal variation with HPV vaccination rates at their highest in June, July, and August.[69] These peaks can be attributed to vaccination requirements for Tdap and MenACWY for school entry and the carry-over effects to HPV vaccine.[69]

Whereas looking at various socio-demographic factors lend themselves to more pointed targeting for interventions, there are also other articles that point to more population-based strategies as effective for increasing coverage such as school-based programs and healthcare practice-based strategies.[52,65,84] Despite the intervention strategy, exploration of socio-demographic factors allows for a deeper understanding of the patterns of HPV coverage among multiple groups in the US.

Barriers and Missed Opportunities

Several articles identify missed opportunities for HPV vaccine given that it is meant to be recommended along with Tdap and MenACWY vaccines, both of which have high coverage.[2,55,67,76,85] A missed opportunity is a point of contact with the medical system where another vaccine is given, but HPV vaccine is not.[67] Barriers to HPV vaccination that contribute to missed opportunities and low coverage include a lack of knowledge and information among adolescents, parents, and providers, concerns about the effect on sexual behavior, side-effects

and efficacy, perceived risk, cost and access, the three-dose requirement, and lack of a school-entry vaccination requirement.[51,53,62,64,73,86,87]

A provider recommendation is known to be one of the most influential factors in uptake of HPV vaccine and parents often seek straightforward recommendations from providers.[34,51,52,57,58,60,64,66,71,82,88-92] This is not only limited to HPV vaccine. A provider recommendation is statistically significantly associated with receipt of each of the two other adolescent vaccines.[60] However, the rates of recommendation for Tdap (95%) and MenACWY (87%) are higher than HPV vaccine (73%).[92]

In studies examining provider beliefs and actions surrounding recommendation of HPV vaccine, there were strong differences in provider knowledge and recommendations. Studies conducted from 2006-2015 found that providers more often recommend HPV vaccine to those older than the recommended 11 to 12 years.[54,77,89,92] Only 29% of parents of an adolescent female reported receiving a provider recommendation to initiate at the recommended age.[77] There are differences in provider recommendation based on sex. Parents of adolescent females more frequently reported a provider recommendation than parents of adolescent males.[77] One study of providers found that some providers did not even know the benefit of vaccination for males.[93] Providers are also more likely to recommend the vaccine to White as opposed to Black or Hispanic adolescent females and to females than males.[61,71,74,89,93] Another study found that 67% of primary care physicians were only *likely* to recommend HPV vaccine to 11 or 12 year olds, and only 75% acknowledged that a recommendation at this age was important.[34,92] Only 13% of physicians felt that there was parental support for HPV vaccine.[92] There were also significant differences in knowledge of HPV among providers with some presenting HPV vaccine as

optional.[54,89,90] Another study of providers found that even despite ACIP recommendations, some providers' earlier opinions surrounding HPV vaccine may not change.[51]

In addition to differences in populations and knowledge about HPV vaccination, there were also differences in the strength and quality of recommendations. In one study, only 36% of the study population received high quality recommendations.[91] Quality was assessed on various indicators including strength of the endorsement, the prevention message, and urgency.[91] 16% received a low-quality recommendation and almost half received no recommendation at all.[91] This is even relatively high compared to another study where only 20% of providers recommended the vaccine to females ages 11 to 26 years old.[54] The odds of vaccine initiation among those who received a high quality recommendation were nine times that of those that received no recommendation at all.[91]

Provider knowledge and a provider recommendation are also crucial in preventing missed opportunities. Among girls not vaccinated before age 13, 80% had at least one missed opportunity for the first dose of HPV vaccine.[67] Had these girls been captured during these missed opportunities, the difference between actual and potential HPV vaccination initiation coverage was 46 percentage points.[67]

Several studies provide compelling evidence as to the role and the magnitude of the role of providers in mitigating some of the key barriers to HPV initiation and completion and avoiding potential missed opportunities.[34,58,64,66,67,71] This illustrates the importance of not only targeting adolescents and parents but also providers with interventions.

As an extension of providers presenting a barrier, other missed opportunities are a result of health service delivery of the provider's clinic or hospital. Those seen in hospitals and private facilities have higher odds of completion among females than those seen in public facilities.[94]

The ability of clinics to track, monitor, and follow-up with patients for their second or third doses also influences completion of HPV vaccine.[75] One study found that the majority of parents whose adolescent had initiated the vaccine, intended to complete the series, but were not reminded by the health facility or had other logistical barriers.[95]

These barriers and missed opportunities, specifically in relation to healthcare providers and the healthcare system, have been studied extensively. Targeting and mediating these issues are crucial to overcoming obstacles in regards to HPV vaccination coverage.

Co-Vaccination of Adolescent Vaccines

There are few studies that specifically consider the effect of co-vaccination on HPV vaccination rates.[67,69,94,96,97] One study compares HPV vaccine completion for those ages 9 to18 and 19 to 25 using the University of Virginia's Clinical Repository Data, based on co-vaccination with at least one other vaccine.[96] However, the study does not identify the vaccine of co-vaccination or receipt within recommendation guidelines.[96]

Another study examines co-vaccination of adolescent vaccines in New York following the New York State requirement that all students 11 years or older entering sixth grade receive one dose of Tdap vaccine.[97] However, this study does not specifically look at differences in HPV vaccine completion, but trends over time of all three adolescent vaccines following this policy shift to illustrate the effectiveness of school entry requirements.[97]

A third study recommends the co-vaccination of all three adolescent vaccines in one visit in relation to a high percentage of adolescents with missed opportunities for HPV vaccination, but does not analyze the specific effect of co-vaccination.[67] Another study shows that the odds of completing HPV vaccine are higher among those that have also received the influenza, Tdap, or

MenACWY vaccine, but not necessarily concomitantly.[94] Finally, another study showed peaks of co-vaccination with HPV vaccine during the summer months of June, July, and August.[69]

Although Tdap, MenACWY, and HPV vaccines should be recommended at the same time, and the ACIP states that receiving all three vaccines at the same time increases the likelihood of receiving them on time, there are only a few studies that examine the effect of concomitant vaccination.[16,67,69,94,96,97] Additionally, these studies do not address many issues including differences in co-vaccination of specific vaccines and whether these vaccines are received following general recommendations. This study fills the gap in the literature by examining those issues. This study illustrates the effect of co-vaccination on HPV vaccine outcomes including receipt of dosages, completion, and recommendation compliance, looking at the specific concomitant adolescent vaccines.

Conclusion

In the US, there are three recommended adolescent vaccines: Tdap, MenACWY, and HPV.[1] HPV vaccine is the only vaccine that requires three doses, and both initiation and completion rates of HPV vaccine lag far behind that of Tdap and MenACWY for both sexes.[2,16] The difference can be attributed to various factors including lack of knowledge of the vaccine and HPV, concerns regarding the implications on sexual behavior, perceived lack of risk or necessity, and provider hesitancy.[64] Within HPV vaccination rates, there are variations in coverage by socio-demographic factors. Overall, girls are more likely to initiate and complete the series than boys.[2] Minorities are more likely to initiate, but less likely to complete the series.[36,49,66,72] Furthermore, the majority of all adolescents are not receiving the vaccine at the recommended time.[35,48] The current body of knowledge has provided crucial information on

patterns of HPV vaccine coverage in order to develop targeted interventions; however, there is limited research on the effect of co-vaccination of adolescent vaccines.[67,69,94,96,97] Therefore, there still remains a need for additional knowledge to increase HPV vaccination coverage to levels comparable to the other adolescent vaccines.

Figures

Figure 1. Sample Vaccination Schedule based on Advisory Committee on Immunization Practices (ACIP) Recommendations[16]

Week	Adolescent 1	Adolescent 2	Adolescent 3
First Dose	X	X	X
1			
2			
3			
4			
5	X		
6			
7			X
8		X	
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27	X		
28			
29			
30			
31			
32		X	
33			
34			
35			X

Three possible vaccinations schedules are shown, all of which meet the ACIP recommendations. X indicates receipt of either the first, second, or third dose of HPV vaccine. Light shading indicates the number of weeks between receipt of the first and second dose, while darker shading indicates the number of weeks between receipt of the second and third doses of HPV vaccine.

Disclaimer

All analyses, interpretations, and conclusions reached are attributed to the author and not to the National Center for Health Statistics (NCHS), which is responsible only for the initial data.

Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the US.[16] HPV vaccine is one of three adolescent vaccines recommended in the US at ages 11 or 12.[1] The other adolescent vaccines: tetanus, diphtheria, and pertussis (Tdap) and meningococcal conjugate (MenACWY) have much higher coverage in the US (88% and 79%, respectively) than HPV vaccine (51% for initiation and 64% for completion among initiators).[2] Not only do HPV initiation and completion rates lag far behind that of Tdap and MenACWY, but there is also little compliance with stated age recommendations for HPV vaccine. While guidelines recommend the vaccine at age 11 or 12, in 2014, only 56% of adolescent girls initiated the vaccine before age 13.[48]

The Advisory Committee on Immunization Practices (ACIP) states that receiving all three vaccines together increases the likelihood of receiving all three vaccines on time.[16] There are few studies that consider the effect of co-vaccination of another vaccine with HPV vaccination.[16,51,67,69,94,96,97] However, these studies do not address which vaccines were given concurrently and how this concomitant vaccination may be related to compliance with dose-specific timing recommendations.

The purpose of this study is two-fold: to identify patterns in HPV vaccine initiation and completion, and compliance with dosing recommendations in terms of co-vaccination with Tdap and MenACWY adolescent vaccines. This is crucial in understanding how to increase adolescent vaccine coverage within the US.

Methods

This study used provider-verified data from the publicly available Centers for Disease Control and Prevention (CDC) 2014 National Immunization Survey (NIS) Teen.[98] The NIS is implemented by the National Center for Immunization and Respiratory Diseases (NCIRD) and the National Center for Health Statistics (NCHS) of the CDC. Established in 1992 to improve vaccine coverage monitoring, NIS annually gathers data on immunization coverage in the US among children and teens using random-digit dialing of land and cellphone lines.[99] NIS Teen data was first collected in 2006.[99]

Survey Instrument

The survey instrument consisted of six main sections: screener, available shot records, no shot records, demographics, provider questions, and a health insurance module.[100] The same survey instrument was used in all areas.

Study Population

The 2014 NIS Teen captured adolescents in the US ages 13 to 17. Sampling weights were adjusted to account for non-response, multiple adolescents in a household, and other factors, to ensure that the sample was representative of the target population.[99]

Variables

We retrieved data directly from the CDC website in SAS 9.4 (The SAS Institute, Cary, North Carolina) format for analysis. We cleaned the data to isolate variables of interest and eliminate implausible values. We then conducted exploratory analysis to glean relevant descriptive statistics.

The outcome variables of interest were provider-verified completion of each HPV vaccine dose, time (in days) between completion of the first and second, second and third, and

first and third HPV vaccine doses, and age at first HPV vaccination receipt. Cervarix and Gardasil were the only HPV vaccines included in this study. Gardasil-9 was released in 2015 and its use was not included in this study. We calculated time between doses based on the age at completion of exactly one, exactly two, or three or more doses of HPV vaccine. We converted age, in weeks, at time of completion of exactly 2 doses of HPV vaccine to days and collapsed it into four categories: less than 28 days older, 28 to 64 days older, greater than 64 to 124 days older, and greater than 124 days older than at receipt of the first dose HPV vaccine. We eliminated receiving the second vaccine dose at less than 28 days after initiation due to the small percentage of individuals falling within this category (0.1%).

The ACIP and CDC Epidemiology and Prevention of Vaccine-Preventable Diseases (Pink Book) guidelines state that the second dose should be administered one to two months after the first dose and the ACIP specifically states a minimum interval of four weeks.[13,16] We created the categories based on these recommendations. The shortest interval following the recommendation is 28 days and the longest interval between two months is 62 days.[33] This accounts for the largest interval possible when following a recommendation using either months or weeks.

We applied the same method to create variables for time between the second and third dose and the first and third dose, based on recommendations from the ACIP and Pink Book, using seven-day weeks.[13,16] We calculated the interval between the second and third dose of HPV vaccine and created intervals of less than 84 days and greater than or equal to 84 days. Similarly, we created intervals of less than 168 days and greater than or equal to 168 days for the interval between the first and third dose of HPV vaccine.

We created the outcome variable age at first HPV vaccine receipt based on the age, in days, at the time of first dose receipt. This was provided by the publicly available NIS Teen dataset. We created the age categories based on 365-day years.

The exposure variable of interest was adolescent co-vaccination status. We created five categories of exposure: receiving all three adolescent vaccines (Tdap, MenACWY, HPV) on the same day, two of the vaccines on the same day (Tdap and MenACWY or Tdap and HPV or MenACWY and HPV), or none of the vaccines on the same day. We created these categories based on exact matches of age, in days, of vaccine receipt of each of the adolescent vaccinations.

We were also interested in demographic variables including sex, age at receipt of first adolescent vaccine, educational level of mother, poverty status, region of residence, and type of health insurance. These variables were included in the publicly available NIS Teen dataset, with the exception of age at first adolescent vaccination. We determined this based on the age at receipt of each vaccination, which was provided by the dataset.

Statistical analysis

We applied sampling weights to all analysis in accordance with the NIS data users guide.[99] This study used the sampling weights for adolescents with adequate provider-verified data, excluding Puerto Rico.

We restricted bivariate analysis, using procedures for analysis of complex survey designs, to adolescents who had received at least one dose of HPV vaccine and stratified by sex. We conducted chi-square testing on demographic variables to ascertain differences between co-vaccination of the adolescent vaccines. We obtained odds ratios for the relationships between co-vaccination status and HPV vaccination outcome variables. Receiving none of the three adolescent vaccines concomitantly served as the reference group for all analysis.

Finally, we built descriptive models to assess the relationship between completion of the second and third dose of HPV vaccine and co-vaccination, adjusting for other variables, for males and females separately. We included all demographic variables and the concomitant receipt of adolescent vaccines variable in the full model. We further collapsed some variables for model building including the variable for concomitant vaccination. This was collapsed to receiving two, three, or no vaccines on the same day, regardless of the type of vaccine. We recoded other demographic variables to reduced multi-level variables except for mother's education, which was left as collected by the NIS Teen, and geographic variables, for which we created dummy variables. In model building, we removed covariates based on least significant p-value (α=0.05). Then, we assessed the odds ratios of each of the covariates for confounding based on a 10% change in odds ratio from the previous model. If the change was greater than 10%, we determined that there was confounding and retained the covariate in the model and proceeded to remove the next least significant variable based on p-value. We forced the variable for adolescent concomitant vaccination into each model because this was the primary exposure of interest. Final models include both statistically significant covariates and confounders.

Ethical approval

This was a secondary analysis of publicly available data. Emory University Institutional Review Board found this study to not meet the definition of research with "human subjects" or a "clinical investigation."

Results

Overall, 81% of adolescents that received one dose of HPV vaccine received a second dose, and 61% completed the series (data not shown in tables). Of those that received at least one dose of HPV vaccine, over half were female (57%) (Table 1). About one-third (31%) of all

adolescents received the second dose within the recommended time interval and 97% received the third dose in accordance with the recommended dosing interval between the second and third dose (data not known in tables). 46% of all adolescents received the first dose of HPV vaccine at the recommended age of 11 or 12 (data not shown in tables).

Co-vaccination status

Table 1 shows demographics of the sample by co-vaccination status of the three adolescent vaccines stratified by sex and Table 2 shows demographics by co-vaccination status overall. Among adolescents who received at least one dose of HPV vaccine (52% of the weighted total sample with adequate provider data), 26% received all three vaccines on the same day and 19% received none of the adolescent vaccines concurrently. Half (50%) of females received the first dose of HPV vaccine in conjunction with at least one other vaccine, compared to only approximately a third of males (32%). However, almost half of males received only Tdap and MenACWY concomitantly (46%), compared to approximately a third of females (32%). Approximately half (49%) of all adolescents received the first dose of HPV vaccine at an age older than 12 (data not shown in tables).

Overall, those who received all three vaccines on the same day, or received Tdap and MenACWY on the same day, had the largest groups receiving their first adolescent vaccine at the recommended age of 11 or 12 (84% for Tdap, MenACWY, and HPV and 82% for Tdap and MenACWY for both sexes; data not shown in tables). Among females living above the poverty line with an income >$75,000, 38% received Tdap and MenACWY together for their first adolescent vaccines while over half of males (52%) received the same combination. Within the same income bracket, 23% of females received all three adolescent vaccines concomitantly, compared to only 12% of males. Among those living below the poverty line, 31% of all

adolescents received all three vaccines concomitantly and 33% received only Tdap and MenACWY concomitantly. Across demographics, these comparisons were statistically significant for both sexes independently, except when considering race and ethnicity among males.

HPV Vaccine Dose Completion

Of those that received one dose of HPV vaccine, 84% of females completed the second dose and 67% completed the series (Table 3). Comparatively, 77% of males received a second dose and 53% received a third dose of HPV vaccine. Males that received Tdap and MenACWY together had higher odds of completion of both the second (odds ratio [OR] 1.5 (95% confidence interval [CI] 1.1, 2.1)) and third (OR 1.5 (95% CI 1.1, 1.9)) HPV vaccine dose, compared to those that received none of the vaccines on the same day. Among females, there were no statistically significant relationships for completion of the second dose of HPV vaccine. Considering completion of the third dose, the odds of completion were higher among females that received Tdap and HPV vaccine concomitantly (OR 1.8 (95% CI 1.2, 2.9)). There were also statistically significant differences in completion of the third dose among females across all co-vaccination groups ($p<0.01$) (data not shown in tables).

HPV Vaccine Compliance with Recommendations

In terms of receiving HPV vaccine within recommendations, there were no statistically significant differences among vaccination pairings in compliance with dosing intervals between the first and second, second and third, and first and third dose of the vaccine, except for two vaccination pairings among males (Table 3). Among adolescent males, the odds of having the recommended interval between the first and second dose was lower if the adolescent received

Tdap and MenACWY concomitantly (OR 0.66 (95% CI 0.5, 0.9)) and the odds of having the recommended minimum interval between the second and third dose was lower if the adolescent received the MenACWY and HPV vaccine concomitantly (OR 0.1 (95% CI <0.1, 0.6)), as compared to receiving none of the adolescent vaccines on the same day. There were differences in the age at first HPV vaccination. The odds of receiving the first HPV vaccine dose at age 11 or 12 was higher for all adolescents who received any combination of vaccines that included HPV vaccine, compared to not receiving any of the vaccines on the same day (data not shown in tables). This was also true when stratified by sex, except for adolescent males receiving Tdap and HPV vaccine concurrently at an age less than 11 years.

Descriptive models for HPV vaccine series completion

We forced the variable representing the adolescent co-vaccination pairing into all models and the covariate was not statistically significant in any of the models (Table 4). We retained age at first adolescent vaccine receipt for all models based on statistical significance. Receipt at an age greater than 12 was statistically significant for all models. Health insurance was also significant for completion of both the second and third dose of HPV vaccine for females ($p=0.03$ and $p<0.01$, respectively). We retained geographic variables for completion of the third dose of HPV vaccine for males. Living in the southern US was statistically significant in the model ($p<0.01$).

Discussion

The purpose of this study was to identify patterns in completion and compliance with HPV vaccine recommendations based on concomitant vaccination with Tdap and MenACWY. Because the purpose of this study was to examine the effect of pairings of adolescent vaccines,

we retained concomitant vaccination status in each model. However, this variable was not statistically significant in any of the models, after adjusting for other covariates. The relationship between adolescent vaccination pairings and completion of the second and third dose of HPV vaccine was likely confounded by other demographic variables. Looking only at the relationship between completion of the third dose and the co-vaccination pairings among females, there were statistically significant differences across the groups ($p<0.01$). However, although the variable was not statistically significant within the model, the implications of the importance of recommending and receiving adolescent vaccines concomitantly should not be disregarded due to the significance of Tdap vaccine in several of the HPV vaccine outcomes.

These results illustrate the importance of concomitant Tdap vaccine receipt in HPV vaccine dosage completion. Receiving Tdap concomitantly with the first HPV vaccine dose was associated with higher odds of completion of the second and third dose. Three doses are needed to complete the series and insufficient dosing may require re-administration of the vaccine to maximize efficacy.[16] Additionally, concurrent adolescent vaccination can have an impact on overall cost and efficiency of healthcare by reducing the need for vaccination-specific visits.

In addition to receiving the additional doses of HPV vaccine, these results illustrate the importance of Tdap in receiving the vaccine at the recommended age. Adolescents who received all three adolescent vaccines or Tdap and MenACWY on the same day had the highest percentages of adolescents receiving HPV vaccine at age 11 or 12. Receiving the vaccine at the recommended age is important in preventing HPV-related illnesses. HPV vaccine is most effective when given before sexual debut and vaccinating at earlier ages is associated with a stronger immune response to the vaccination.[16,22,25,94,101,102] Additionally, the age at initiation effects the completion of the vaccine series. Those initiating at an age greater than 12 years had

lower odds of completing the additional doses. Appropriate Tdap vaccination appears to play a crucial role in three major HPV vaccine outcomes that are still lacking: completion of the second dose, completion of the third dose, and receipt at the recommended age.

There were few differences between co-vaccination parings in compliance with dosing intervals. In terms of the interval between the second and third dose and the first and the third dose of HPV vaccine, while there are recommended minimum intervals, there are no recommended maximum intervals.[16] Adolescents often take longer between doses and the lack of minimum interval recommendations between these dosages likely aids adolescents' compliance with recommendations.[35,36] A study analyzing 2013 NIS Teen data found that overall, the majority of adolescents were receiving vaccination dosages in compliance with recommendations.[35] There were likely not many differences between co-vaccination pairings because compliance is already high within the recommendations. However, although adolescents are generally receiving the dosages within the recommended intervals, this only accounts for those that received either the second or third dose of HPV vaccine. Therefore, there still needs to be better efforts to increase second and third dose HPV vaccine receipt, including better integration of reminder and recall systems and utilization of state and local immunization information systems.

There are limitations to this study. Because this study is based on NIS Teen data, it is subject to limitations of the survey including low response rates from landlines and cellular phones, and exclusion of households without a phone.[99] Additionally, the present study only uses those records with adequate provider-verified data. This subset population may have characteristics substantially different from the rest of the population. Although weighting of the data aimed to address these issues, there may still be some lingering bias. However, this dataset

is the only publicly available, nationally representative immunization dataset for adolescents, which allows for generalizability of the results to the entire US. Additionally, those who had shorter than recommended dosing intervals between the first and second dose of HPV vaccine were dropped from analysis as the relatively small proportion (0.1%) precluded meaningful analysis. Similarly, this population may have differed markedly from the rest of the population.

Only two outcomes were included for model-building: completion of the second and third dose of HPV vaccine. There may be other findings relevant to other HPV vaccine outcomes in terms of age at initiation and compliance with dosing recommendations that could be considered in future modeling. Additionally, this study only measured the impact of co-vaccination with other adolescent vaccines but there may be associations of HPV outcomes with co-vaccination of other regularly received vaccines such as influenza vaccine. Because we were only interested in concomitant vaccination, we did not consider vaccination order for instances when all three adolescent vaccines were not received on the same day. Finally, we retained geographic variables such as living in the Midwest, South, and West part of the US in the model for completion of the third dose of the vaccine for males. While there are known differences in HPV vaccination status by geography, this warrants further exploration on the specific effect on males, a population with lower vaccination coverage.[68] These additional factors were all outside the scope of this study.

Conclusion

While there were differences in various HPV outcomes among the adolescent pairings, the most influential factor was the inclusion or exclusion of Tdap vaccine. Receiving HPV vaccine along with Tdap vaccine was associated with higher completion of the second and third HPV vaccine doses and receipt at the recommended age. This study adds to the body of

knowledge on patterns of HPV vaccine coverage and provides new data to support recommendations to providers to strongly advocate for all three adolescent vaccines at the same time and to include HPV vaccine when they recommend Tdap and MenACWY. Increased efforts to educate providers on strategies for the language to use during recommendations and the importance of not differentiating between the three vaccines are needed. Additionally, analysis of the 2014 NIS Teen data shows that completion of the second and third dose are still low. In addition to strong guidelines for initiation recommendations, adequate follow-up mechanisms are needed to ensure that the series is completed.

Public Health Implications

HPV vaccine is one of three adolescent vaccines recommended for routine administration in the US. Tdap, MenACWY, and HPV vaccines are recommended at ages 11 and 12 for both males and females, and HPV vaccine is the newest of the three adolescent vaccines.[1] However, HPV vaccine is the only vaccine that requires more than one dose and both initiation (60% for females and 42% for males) and completion (69% for females and 58% for males) of the vaccine among those that initiated lag behind coverage of Tdap (88%) and MenACWY (79%) vaccines.[2]

Currently, there are 79 million people infected with HPV in the US and 14 million become newly infected each year, with around half of those newly infected between the ages of 15 to 24.[13] HPV can cause cancers of the cervix, vagina, and vulva in women and cancer of the penis in men.[15] There are over 150 strains of HPV.[16] HPV type 16 is associated with about 50% of cervical cancers and 16 and 18 combined are associated with 70% of cervical cancer cases.[13] HPV is also thought to be the cause of 90% of anal cancers, 71% of vulvar, vaginal, or penile cancers, and 72% of oropharyngeal cancers in the US.[13] Without vaccination, most sexually-active men and women will become infected in their lifetime.[14]

HPV vaccine is the most cost-effective way to decrease the burden of HPV and HPV-related diseases.[16,103] Prior to the introduction of the vaccine, the US spent nearly $8 billion dollars in health costs on the treatment and prevention of HPV-related diseases.[16,104] Studies have shown a decrease in both HPV vaccine-type prevalence and genital warts within years of introducing HPV vaccine in the US.[16,105-107] Other countries have also shown similar patterns in a decrease in disease burden.[16,107,108] There are known health and economic burdens of HPV and HPV-related diseases. HPV vaccine provides an opportunity to mitigate these disease burdens through increasing coverage of the vaccine.

There are various reasons for the differences in vaccination rates of HPV versus the two other adolescent vaccines including a lack of information, stigma surrounding the vaccine due to sexuality, the three-dose requirement, perceived risk, and financial constraints and access.[51,53,62,64,73] There have been numerous studies to find patterns in coverage as well as to understand these various barriers in efforts to develop interventions aimed at increasing coverage among low-vaccinated populations. A provider recommendation is known to be one of the most influential factors in uptake of HPV vaccine and rates of provider recommendation are higher for Tdap (95%) and MenACWY (87%) than HPV vaccine (73%).[34,51,57,58,60,64,66,71,82,84,86,88-90,92]

This study fills an important gap in knowledge of ways to increase HPV vaccine uptake to a level comparable to other adolescent vaccines. By examining the effect of co-vaccination on HPV vaccine outcomes including HPV compliance with recommendations and completion, this study identified important patterns in co-vaccination with the other adolescent vaccines. The results provide strong evidence of the importance of appropriate Tdap vaccination in terms of both completing HPV vaccine series and receiving the vaccine at the recommended age of 11 or 12 years old. Receiving improper or incomplete dosages may require re-administration and the three-dose series is necessary to maximize vaccine efficacy.[16] Additionally, it is critical to receive HPV vaccine at the recommended ages of 11 or 12 as adolescents have the most optimal immune response to the vaccination at this age and it is found to be most effective when given before the adolescent's sexual debut.[16,22,25,94,101,102]

From these results, distinct recommendations can be made to increase HPV vaccine completion and compliance. Because a provider recommendation is known to be largely influential on HPV vaccine uptake, increased efforts should be placed on educating providers on the importance of recommending all three vaccines at the same time and not differentiating

between vaccinations.[34,51,57,58,60,64,66,71,82,84,86,88-90,92] It is important that adolescents that are recommended and receive Tdap vaccine, are also given the necessary information on HPV vaccine.

HPV causes a significant disease burden in the US and its potential health effects can cause serious and long-lasting disease.[13] Increasing HPV vaccine coverage in the US continues to be an evolving process with continuing studies on identifying patterns in HPV vaccine outcomes. This study provides evidence that encouraging HPV vaccine receipt concurrently with other adolescent vaccines, particularly Tdap vaccine, is a promising strategy to increase HPV vaccine three-dose completion and compliance with receipt at recommended ages.

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Tables and Figures

Table 1A - Demographic characteristics of the weighted sample stratified by co-vaccination status and sex (female)	**Total sample^** (weighted %)	**Co-Vaccinations*~**					**p-value**
		T & M & H %	**T & M** %	**T & H** %	**M & H** %	**T / M / H** %	
Total		25.6	38.1	5.1	11.9	19.4	
Females	57.4	30.4	32.0	6.9	13.1	17.6	<0.001
Age at first adolescent vaccine							
<11	24.4	1.9	24.9	11.4	16.7	45.2	<0.001
11	51.3	36.1	37.9	5.2	11.4	9.4	
12	16.7	47.1	28.2	5.0	13.4	6.3	
13-14	6.4	45.1	21.7	10.0	14.8	8.4	
≥15	1.2	51.6	33.2	1.6	5.4	8.3	
Poverty Status							<0.001
Above Poverty >$75,000	35.4	23.2	38.4	5.6	12.6	20.2	
Above Poverty ≤$75,000	32.5	35.4	29.3	7.3	13.0	15.0	
Below Poverty	26.8	33.9	28.2	8.5	14.0	15.4	
Unknown	5.3	29.2	25.6	5.6	13.3	26.3	
Region of Residence							<0.001
Northeast	17.0	18.0	41.4	4.5	10.9	25.2	
Midwest	21.6	29.2	29.2	9.3	12.9	19.5	
South	35.6	32.9	34.0	6.4	11.1	15.6	
West	25.7	36.0	25.4	7.2	17.7	13.6	
Race/Ethnicity							0.038
White	49.6	25.9	34.1	6.6	14.0	19.3	
Black	16.4	32.3	32.4	8.0	11.6	15.7	
Hispanic	25.1	36.8	29.2	7.6	12.5	14.0	
Other	8.9	33.3	27.5	4.6	13.3	21.3	
Health Insurance							0.047
Employer-Based Insurance	54.7	24.6	36.0	6.6	12.8	20.0	
Medicaid	15.7	37.8	25.5	6.7	13.5	16.5	
S-CHIP	12.7	35.4	25.8	7.7	16.1	15.0	
Indian Health Service, etc.`	6.1	37.2	33.0	5.5	7.6	16.6	
Other	10.9	28.8	32.1	6.4	17.4	15.3	
Educational Level of Mother							<0.001
Less than 12 years	15.8	32.0	25.3	5.8	19.7	17.2	
12 years	23.6	35.6	27.6	8.9	12.1	15.9	
More than 12 years, non-college grad	25.4	32.6	33.3	7.6	10.9	15.6	
College grad	35.3	24.5	37.1	5.6	12.5	20.2	

* Co-vaccination pairings are based on the three adolescent vaccines: Tdap (T), MenACWY (M), and HPV (H). Co-vaccination pairings include receiving all three adolescent vaccines on the same day (T & M & H), receiving two vaccines on the same day (T & M, T & H, M & H), or receiving none of the three adolescent vaccines on the same day (T/M/H)

~ Rows for each demographic level stratified by co-vaccination status equals 100%

` Includes Indian Health Service, Military Health Care, Tricare, Champus, or Champ-VA

^ Total sample column percentages equal 100% for each demographic level

Source: CDC, NCRID and NCHS (2015), 2014 National Immunization Survey – Teen.[98]

Table 1B - Demographic characteristics of the weighted sample stratified by co-vaccination status and sex (male)	**Total sample^** (weighted %)	**Co-Vaccinations*~**					**p-value**
		T & M & H %	**T & M** %	**T & H** %	**M & H** %	**T / M / H** %	
Total		25.6	38.1	5.1	11.9	19.4	
Males	42.6	19.3	46.2	2.5	10.1	21.8	<0.001
Age at first adolescent vaccine							
<11	18.1	<0.1	13.1	7.5	18.7	60.7	<0.001
11	54.6	17.6	58.2	1.3	7.8	15.2	
12	18.6	30.3	48.5	1.4	9.6	10.3	
13-14	7.4	46.2	36.1	3.0	6.8	7.7	
≥15	1.3	50.0	30.3	1.4	15.7	2.6	
Poverty Status							<0.001
Above Poverty >$75,000	34.3	12.4	52.5	2.0	7.2	26.0	
Above Poverty ≤$75,000	33.6	20.7	46.3	2.9	9.6	20.5	
Below Poverty	27.7	26.0	38.7	3.2	13.5	18.6	
Unknown	4.4	20.6	44.1	0.3	15.2	19.9	
Region of Residence							<0.001
Northeast	19.2	10.4	49.9	1.7	7.6	30.5	
Midwest	19.7	17.0	48.5	3.1	9.3	22.2	
South	33.9	19.5	47.5	2.8	10.4	19.8	
West	27.2	27.1	40.4	2.4	12.2	18.0	
Race/Ethnicity							0.062
White	48.4	17.1	47.9	2.2	8.4	24.4	
Black	13.4	19.1	44.7	4.4	11.1	20.8	
Hispanic	28.9	23.9	45.1	2.6	11.9	16.5	
Other	9.3	17.1	42.8	1.2	12.2	26.7	
Health Insurance							<0.001
Employer-Based Insurance	55.3	16.4	49.8	1.6	7.4	24.9	
Medicaid	13.6	30.8	38.4	6.2	9.9	14.7	
S-CHIP	14.0	18.2	47.1	1.8	17.0	15.9	
Indian Health Service, etc.`	6.0	26.2	42.4	1.4	11.9	18.0	
Other	11.0	11.3	52.9	4.5	7.9	23.3	
Educational Level of Mother							<0.001
Less than 12 years	18.4	24.4	40.5	1.5	16.1	17.5	
12 years	23.9	23.2	46.5	4.0	6.9	19.4	
More than 12 years, non-college grad	22.2	23.7	42.0	2.7	12.0	19.6	
College grad	35.4	11.2	51.6	2.0	8.0	27.2	

* Co-vaccination pairings are based on the three adolescent vaccines: Tdap (T), MenACWY (M), and HPV (H). Co-vaccination pairings include receiving all three adolescent vaccines on the same day (T & M & H), receiving two vaccines on the same day (T & M, T & H, M & H), or receiving none of the three adolescent vaccines on the same day (T/M/H)
~ Rows for each demographic level stratified by co-vaccination status equals 100%
` Includes Indian Health Service, Military Health Care, Tricare, Champus, or Champ-VA
^ Total sample column percentages equal 100% for each demographic level
Source: CDC, NCRID and NCHS (2015), 2014 National Immunization Survey – Teen.[98]

Table 2 - Demographic characteristics of the weighted sample stratified by co-vaccination status	**Total sample^** (weighted %)	**Co-Vaccinations*~**					**p-value**
		T & M & H %	**T & M** %	**T & H** %	**M & H** %	**T / M / H** %	
Total		25.6	38.1	5.1	11.9	19.4	
Sex							<0.001
Male	42.6	19.3	46.2	2.5	10.1	21.8	
Female	57.4	30.4	32.0	6.9	13.1	17.6	
Age at first adolescent vaccine							<0.001
<11	21.8	1.2	20.7	10.0	17.4	50.7	
11	52.7	28.0	46.9	3.4	9.8	12.0	
12	17.5	39.5	37.4	3.4	11.7	8.1	
13-14	6.8	45.6	28.4	6.8	11.1	8.1	
≥15	1.2	50.9	32.0	1.5	9.9	5.8	
Poverty Status							<0.001
Above Poverty >$75,000	35.0	18.6	44.3	4.1	10.4	22.6	
Above Poverty ≤$75,000	33.0	29.0	36.7	5.4	11.5	17.4	
Below Poverty	27.2	30.5	32.8	6.2	13.8	16.8	
Unknown	4.9	25.9	32.7	3.5	14.0	23.8	
Region of Residence							<0.001
Northeast	17.9	14.5	45.3	3.2	9.4	27.6	
Midwest	20.8	24.3	37.0	6.8	11.4	20.6	
South	34.9	27.3	39.6	4.9	10.8	17.3	
West	26.4	32.1	32.0	5.1	15.3	15.6	
Race/Ethnicity							0.001
White	49.1	22.2	40.0	4.8	11.6	21.4	
Black	15.1	27.3	37.0	6.6	11.4	17.6	
Hispanic	26.7	30.8	36.6	5.3	12.2	15.1	
Other	9.1	26.2	34.2	3.1	12.8	23.7	
Health Insurance							<0.001
Employer-Based Insurance	54.9	21.1	41.9	4.5	10.5	22.1	
Medicaid	14.8	35.1	30.6	6.5	12.1	15.8	
S-CHIP	13.2	27.7	35.4	5.0	16.5	15.4	
Indian Health Service, etc.`	6.1	32.6	37.0	3.8	9.4	17.2	
Other	10.9	21.3	41.0	5.6	13.3	18.7	
Educational Level of Mother							<0.001
Less than 12 years	16.9	28.5	32.4	3.8	18.0	17.4	
12 years	23.7	30.3	35.7	6.8	9.9	17.4	
More than 12 years, non-college grad	24.0	29.1	36.7	5.7	11.3	17.2	
College grad	35.3	18.8	43.3	4.1	10.6	23.2	

* Co-vaccination pairings are based on the three adolescent vaccines: Tdap (T), MenACWY (M), and HPV (H). Co-vaccination pairings include receiving all three adolescent vaccines on the same day (T & M & H), receiving two vaccines on the same day (T & M, T & H, M & H), or receiving none of the three adolescent vaccines on the same day (T/M/H)

~ Rows for each demographic level stratified by co-vaccination status equals 100%

^ Total sample column percentages equal 100% for each demographic level

`Includes Indian Health Service, Military Health Care, Tricare, Champus, or Champ-VA

Source: CDC, NCRID and NCHS (2015), 2014 National Immunization Survey – Teen.[98]

Table 3 - HPV vaccination outcomes stratified by co-vaccination status and sex

	Co-Vaccinations*^											
Females	**Overall**	**T & M & H**		**T & M**		**T & H**		**M & H**		**T / M / H**	
	%	**%**	OR (95% CI)	**%**	OR (95% CI)	**%**	OR (95% CI)	**%**	OR (95% CI)	**%**	
HPV Completion - 2nd Dose											
Yes~	84.0	86.0	1.18 (0.79, 1.77)	84.1	1.02 (0.68, 1.52)	87.6	1.36 (0.78, 2.36)	77.8	0.68 (0.40, 1.15)	83.8	Ref
No	16.0	14.0		15.9		12.4		22.2		16.2	
HPV Completion - 3rd Dose											
Yes~	67.3	71.4	1.39 (1.02, 1.90)	66.2	1.09 (0.80, 1.48)	76.7	1.83 (1.16, 2.90)	59.2	0.81 (0.54, 1.22)	64.3	Ref
No	32.7	28.6		33.8		23.3		40.8		35.7	
HPV 1st and 2nd dose Interval											
28-64 days~	33.4	32.2	1.08 (0.78, 1.51)	35.5	1.25 (0.92, 1.71)	36.5	1.31 (0.74, 2.31)	33.3	1.14 (0.73, 1.79)	30.5	Ref
>64	66.6	67.8		64.5		63.5		66.7		69.5	
HPV 2nd and 3rd dose Interval											
<84 days	2.1	1.8		2.8		2.6		1.0		1.8	
≥84 days~	97.9	98.2	1.02 (0.31, 3.39)	97.2	0.66 (0.24, 1.83)	97.4	0.69 (0.16, 2.97)	99.0	1.76 (0.43, 7.20)	98.2	Ref
HPV 1st and 3rd dose Interval											
<168 days	1.2	1.0		1.8		0.4		0.5		1.3	
≥168 days~	98.8	99.0	1.38 (0.41, 4.67)	98.2	0.75 (0.22, 2.54)	99.6	3.76 (0.89, 15.81)	99.5	2.56 (0.31, 21.02)	98.7	Ref
Age at first HPV dose											
11 or 12~	54.6	87.0		31.7		70.2		58.7		31.1	Ref
<11	8.2	1.5	26.95 (13.49, 53.84)	13.2	1.14 (0.71, 1.83)	11.9	2.81 (1.44, 5.49)	0.7	41.90 (16.05, 109.42)	14.8	
>12	37.2	11.5	13.14 (8.88, 19.45)	55.1	1.00 (0.74, 1.36)	17.9	6.84 (3.65, 12.83)	40.6	2.51 (1.67, 3.79)	54.1	
Males	**Overall**	**T & M & H**		**T & M**		**T & H**		**M & H**		**T / M / H**	
	%	**%**	OR (95% CI)	**%**	OR (95% CI)	**%**	OR (95% CI)	**%**	OR (95% CI)	**%**	
HPV Completion - 2nd Dose											
Yes~	76.6	74.4	1.11 (0.73, 1.70)	80.1	1.54 (1.12, 2.12)	82.2	1.76 (0.82, 3.79)	72.8	1.02 (0.62, 1.70)	72.3	Ref
No	23.4	25.6		19.9		17.8		27.2		27.7	
HPV Completion - 3rd Dose											
Yes~	52.9	53.6	1.29 (0.90, 1.86)	56.4	1.45 (1.09, 1.92)	39.2	0.72 (0.37, 1.42)	51.0	1.16 (0.75, 1.79)	47.2	Ref
No	47.1	46.4		43.6		60.8		49.0		52.8	
HPV 1st and 2nd dose Interval											
28-64 days~	27.4	25.2	0.67 (0.44, 1.01)	25.0	0.66 (0.47, 0.92)	27.2	0.74 (0.25, 2.16)	30.6	0.87 (0.51, 1.49)	33.6	Ref
>64	72.6	74.8		75.0		72.8		69.4		66.4	
HPV 2nd and 3rd dose Interval											
<84 days	3.1	4.0		1.8		6.9		11.0		1.3	
≥84 days~	96.9	96.0	0.32 (0.04, 2.4)	98.2	0.73 (0.15, 3.42)	93.1	0.18 (0.03, 1.11)	89.0	0.11 (0.02, 0.60)	98.7	Ref
HPV 1st and 3rd dose Interval											
<168 days	1.3	0.8		1.0		1.9		4.3		1.2	
≥168 days~	98.7	99.2	1.48 (0.37, 5.89)	99.0	1.11 (0.31, 4.05)	98.1	0.60 (0.07, 4.93)	95.7	0.26 (0.05, 1.36)	98.8	Ref
Age at first HPV dose											
11 or 12~	33.7	78.5		20.0		51.2		42.3		16.7	Ref
<11	1.6	<0.1	184.03 (25.59, 999.99)	2.4	0.52 (0.16, 1.68)	10.9	0.30 (0.07, 1.21)	0.1	18.12 (2.07, 158.72)	1.0	
>12	64.7	21.0	18.54 (11.73, 29.31)	77.6	1.27 (0.86, 1.87)	37.9	6.67 (2.91, 15.25)	57.5	3.63 (2.24, 5.90)	82.3	

* Co-vaccination pairings are based on the three adolescent vaccines: Tdap (T), MenACWY (M), and HPV (H). Co-vaccination pairings include receiving all three adolescent vaccines on the same day (T & M & H), receiving two vaccines on the same day (T & M, T & H, M & H), or receiving none of the three adolescent vaccines on the same day (T/M/H)

~ CDC Recommendation

^ Total sample column percentages equal 100% for each HPV vaccination outcome level

Source: CDC, NCRID and NCHS (2015), 2014 National Immunization Survey – Teen.[98]

Table 4 – Descriptive modeling

Logistic Regression, Completion of the second dose of HPV vaccine							
Females				**Males**			
Variable	**OR**	**95% CI**	**p-value**	**Variable**	**OR**	**95% CI**	**p-value**
Adolescent co-vaccination (ref: T/M/H)*				Adolescent co-vaccination (ref: T/M/H)*			
3 vaccines	0.71	0.42, 1.18	0.18	3 vaccines	0.78	0.47, 1.31	0.35
2 vaccines	0.88	0.58, 1.32	0.53	2 vaccines	1.37	1.00, 1.88	0.05
Age at first HPV vaccination (ref: 11 or 12)				Age at first HPV vaccination (ref: 11 or 12)			
<11	2.03	0.93, 4.44	0.08	<11	0.86	0.28, 2.63	0.79
>12	0.28	0.20, 0.39	<0.01	>12	0.57	0.38, 0.83	<0.01
Health Insurance	0.74	0.55, 0.98	0.03				
Logistic Regression, Completion of the third dose of HPV vaccine							
Females				**Males**			
Variable	**OR**	**95% CI**	**p-value**	**Variable**	**OR**	**95% CI**	**p-value**
Adolescent co-vaccination (ref: T/M/H)*				Adolescent co-vaccination (ref: T/M/H)*			
3 vaccines	0.92	0.63, 1.34	0.67	3 vaccines	0.96	0.64, 1.44	0.83
2 vaccines	1.02	0.74, 1.40	0.90	2 vaccines	1.31	0.99, 1.74	0.06
Age at first HPV vaccination (ref: 11 or 12)				Age at first HPV vaccination (ref: 11 or 12)			
<11	1.86	1.03, 3.34	0.04	<11	2.21	0.81, 6.04	0.12
>12	0.31	0.23, 0.40	<0.01	>12	0.56	0.42, 0.74	<0.01
Health Insurance	0.68	0.54, 0.85	<0.01	Poverty	0.99	0.76, 1.30	0.95
				Midwest	0.83	0.62, 1.10	0.19
				South	0.63	0.48, 0.84	<0.01
				West	0.77	0.53, 1.12	0.17

* Co-vaccination pairings are based on the three adolescent vaccines: Tdap (T), MenACWY (M), and HPV (H). Co-vaccination pairings include receiving all three adolescent vaccines on the same day (T & M & H), receiving two vaccines on the same day (T & M, T & H, M & H), or receiving none of the three adolescent vaccines on the same day (T/M/H)

Source: CDC, NCRID and NCHS (2015), 2014 National Immunization Survey – Teen.[98]