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A decade of data: Adolescent vaccination in the vaccine safety datalink, 2007 through 2016



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ARTICLE INFO

Article history:

Received 19 August 2021

Received in revised form 21 January 2022

Accepted 24 January 2022

Available online 4 February 2022

Keywords:

Human papillomavirus vaccine
Meningococcal conjugate vaccine
Tetanus, diphtheria, and acellular pertussis vaccine
Adolescent vaccination
Vaccine coverage
Vaccine administration
Vaccine Safety Datalink

ABSTRACT

Background: Between May 2005 and March 2007, three vaccines were recommended by the Advisory Committee on Immunization Practices for routine use in adolescents in the United States: quadrivalent meningococcal conjugate vaccine (MenACWY), tetanus, diphtheria and acellular pertussis vaccine (Tdap), and human papillomavirus vaccine (HPV). Understanding historical adolescent vaccination patterns may inform future vaccination coverage efforts for these and emerging adolescent vaccines, including COVID-19 vaccines.

Methods: This was a descriptive, retrospective cohort study. All vaccines administered to adolescents aged 11 through 18 years in the Vaccine Safety Datalink population between January 1, 2007 and December 31, 2016 were examined. Vaccination coverage was assessed by study year for ≥ 1 dose Tdap or Td, ≥ 1 dose Tdap, ≥ 1 dose MenACWY, ≥ 1 dose HPV, and ≥ 3 dose HPV. The proportion of vaccine visits with concurrent vaccination (≥ 2 vaccines administered at the same visit) was calculated by sex and study year. The most common vaccine combinations administered in the study population were described by sex for two time periods: 2007–2010 and 2011–2016.

Results: The number of 11–18-year-olds in the study population averaged 522,565 males and 503,112 females per study year. Between January 2007 and December 2016 there were 4,884,553 vaccine visits in this population (45% among males). The overall proportion of concurrent vaccine visits among males was 43% (33–61% by study year). Among females, 39% of all vaccine visits included concurrent vaccination (32–48% by study year). Vaccine coverage for Tdap, MenACWY, and 1- and 3-dose HPV increased across the study period. A wide variety of vaccine combinations were administered among both sexes and in both time periods.

Conclusions: The high vaccine uptake and multitude of vaccine combinations administered concurrently in the adolescent population of the Vaccine Safety Datalink provide historical patterns with which to compare future adolescent vaccination campaigns.

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Abbreviations: 2vHPV, bivalent human papillomavirus vaccine; 4vHPV, quadrivalent human papillomavirus vaccine; 9vHPV, nine valent human papillomavirus vaccine; ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; EUA, Emergency Use Authorization; MenACWY, quadrivalent meningococcal conjugate vaccine; NIS, National Immunization Survey; Tdap, tetanus, diphtheria and acellular pertussis vaccine; Td, tetanus and diphtheria vaccine; VSD, Vaccine Safety Datalink.

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<https://doi.org/10.1016/j.vaccine.2022.01.051>

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1. Introduction

Between May 2005 and March 2007, three new vaccines were recommended by the Advisory Committee on Immunization Practices (ACIP) for routine use in adolescents and/or young adults in the United States: quadrivalent meningococcal conjugate vaccine (MenACWY), tetanus, diphtheria and acellular pertussis vaccine (Tdap), and quadrivalent human papillomavirus vaccine (4vHPV) [1–3]. Bivalent (2vHPV) and nine valent (9vHPV) human

papillomavirus vaccines were subsequently recommended by the ACIP in 2010 and 2015, respectively [4,5]. The ACIP recommendation for routine vaccination for all three vaccines is administration at age 11–12 years; prior to these recommendations, only the tetanus and diphtheria (Td) booster was routinely recommended for that age group [6].

Concurrent (simultaneous) administration of more than one indicated vaccine during the same visit is specifically approved or recommended in the ACIP recommendations for each of these vaccines [1,3]. Benefits of concurrent administration for vaccine recipients include earlier protection from vaccine-preventable disease and a decrease in total office visits [7]. The ACIP specifically urges that MenACWY and Tdap be given at the same visit, if both are indicated, and recommends that all vaccines due be administered at that visit [2]. The ACIP also states that HPV vaccines can be administered at the same visit as other vaccines given to adolescents without impacting the immunogenicity of the vaccines [8,9]. Few studies have evaluated the frequency or patterns of concurrent administration of these adolescent vaccines [10,11].

In 2006, the Centers for Disease Control and Prevention (CDC) incorporated adolescent vaccination coverage, including uptake of Tdap and MenACWY, into the National Immunization Survey (NIS-Teen); 4vHPV vaccine uptake was added in the 2007 survey [12,13]. NIS-Teen reports vaccine coverage but does not examine patterns of co-administration. Moss and colleagues, however, did use provider data from the 2008–2012 NIS-Teen surveys to evaluate concurrent vaccination in that population, finding an increase in concurrent vaccination over the study period [14].

As of 2021, COVID-19 vaccination is recommended for individuals aged 5 years and older in the United States [15–17]. Current ACIP recommendations state that the COVID-19 vaccine can be given alone or concurrently with other vaccines [18]. Understanding historical patterns of individual and concurrent administration of adolescent vaccines can provide a baseline understanding of vaccine patterns to serve as a comparison for future assessments of uptake as more vaccines are added to the adolescent vaccine schedule. Specifically, this baseline data may allow for an examination of how the addition of COVID-19 vaccine leads to changes in patterns of uptake, as compared to this historical assessment.

The objectives of the current study are to (1) describe individual and concurrent administration of all vaccines among a large adolescent population over a ten-year period, (2) examine the change in coverage of adolescent vaccines over the period 2007–2016, and within that time period (3) identify the most common vaccine combinations administered in this population and the frequency of their use. Results from these analyses will inform adolescent care providers and vaccine policy makers about adherence to adolescent vaccination recommendations. Findings may be used to design studies of the safety of concurrent vaccine administration in adolescents, including concurrent administration of COVID-19 vaccines, as concurrent vaccine administration is not examined in pre-licensure clinical trials for individual vaccines.

2. Materials and methods

2.1. Study design

This was a descriptive, retrospective cohort study; adolescent cohorts aged 11 through 17 were defined for each calendar year, 2007 through 2016. All vaccines administered in the study population between January 1, 2007, and December 31, 2016, were examined.

2.2. Study population

The Vaccine Safety Datalink (VSD) is a collaboration between the Centers for Disease Control and Prevention (CDC) and nine

integrated health care delivery systems (sites) [19–21]. The collaboration was created to monitor vaccine safety and address possible vaccine safety-related research gaps. The VSD utilizes standardized electronic health record (EHR)-derived data on insurance enrollment, demographic characteristics, medical encounters from all settings, vaccination, and prescribed medications. Each VSD member has a unique, randomized VSD identification number used to link data on demographics, enrollment, and medical services.

The data for these analyses derived from six VSD sites: Kaiser Permanente Colorado (Denver, CO), Kaiser Permanente Northern California (Oakland, CA), Kaiser Permanente Northwest (Portland, OR), Kaiser Permanente Southern California (Pasadena, CA), Kaiser Permanente Washington (Seattle, WA), and the Marshfield Clinic Research Institute (Marshfield, WI). The Institutional Review Boards of all participating sites and CDC approved the study protocol and procedures.

All adolescents aged 11 through 18 years with ≥ 6 months of continuous enrollment at a VSD site during the study period were included in the cohort. Inclusion began January 1, 2007, for those in the age range or at the 11th birthday, and ended at the end of the study period or the 18th birthday, whichever occurred first. Adolescents needed a minimum of 30 days enrollment in a calendar year to be included in analyses for that year. All vaccines administered within the study population at a medical encounter during the study period (2007 through 2016) were included in analyses.

2.3. Case definitions

Administration of each vaccine was defined as either *concurrent* or *individual*. Vaccination was considered concurrent if at least two vaccines were administered to one person on the same date, in separate syringes. While the Tdap vaccine contains multiple antigens, it was considered a single vaccine in this analysis. Because there are no other recommended combination vaccines (e.g., vaccines containing multiple antigens in one syringe) in this population, we assumed that if two or more vaccines were given on one date, administration was concurrent. If only one vaccine was administered on a given day, the vaccination was considered to have been administered individually.

All vaccines administered in the study population were examined. *Adolescent vaccines* were defined as any dose of MenACWY, Tdap, or any HPV vaccine (2vHPV, 4vHPV, 9vHPV). A *non-adolescent vaccine* was defined as any vaccine administered within the study population that was not MenACWY, Tdap, or HPV. Because influenza vaccine was not recommended for all children in this age group during the entire study period, it was considered a non-adolescent vaccine [22].

2.4. Data analysis

2.4.1. Vaccine administration

Uptake of all vaccines in the study population was captured by vaccine and by sex for each year of the study. Total number of vaccine doses was assessed in addition to the number of vaccine visits. A vaccine visit was defined as any outpatient or emergency encounter at which ≥ 1 vaccine was administered; two or more vaccines administered on the same day were assumed to be given at the same visit. The proportion of vaccine visits with concurrent vaccination was calculated by study year. Due to the differences in HPV recommendations by sex during the study period [3,23,24], the proportion of vaccine visits with concurrent vaccination are described by sex.

2.4.2. Vaccine coverage

Vaccination coverage was assessed by study year for ≥ 1 Tdap or Td, ≥ 1 dose Tdap, ≥ 1 dose MenACWY, ≥ 1 dose HPV, and ≥ 3 doses

HPV. The ‘Tdap or Td’ group was included due to the 2006 ACIP recommendation that adolescents previously vaccinated with Td wait 5 years before receipt of Tdap [2]. Coverage for HPV vaccine was assessed separately for males and females, with coverage analyses for males beginning in 2011 [23]. Vaccine coverage was calculated as the proportion of adolescents who had received each vaccine as of the date of their 13th (on time coverage) or 18th (catch up coverage) birthday among all adolescents in the study population who turned 13 or 18 in the respective study year. Eligibility for each vaccination was assessed according to ACIP recommendations.

2.4.3. Vaccine combinations

Vaccine combinations administered in the study population were identified and the most common combinations were described. As the HPV vaccine was not recommended for males until 2011, the combinations are described by sex for two time periods: 2007–2010 and 2011–2016. Frequency of administration of specific vaccine combinations was assessed in addition to the proportion of total vaccine visits attributable to that combination (i.e., proportion of all vaccine visits for that sex in each time period, including visits with individual vaccination).

2.4.4. Data quality and cleaning

Duplicate vaccination records were defined as two records with the same vaccine type that occurred within 14 days of each other; only the initial vaccine administration was retained in the analysis file.

3. Results

3.1. Vaccine administration

The number of 11–18-year-olds in the study population averaged 522,565 males and 503,112 females per study year. Between January 2007 and December 2016 there were 4,884,553 vaccine visits in this population (45% among males). At these visits, 10,788,934 total vaccine doses were administered, including 6,492,980 (60%) adolescent vaccines (HPV [any type, any dose], MenACWY [any dose], or Tdap). The most frequent non-adolescent vaccines administered in this population were influenza, varicella, and hepatitis A, in that order (Table 1). The overall proportion of concurrent vaccine visits among males was 43% (33–61% by study year). Among females, 39% of all vaccine visits included concurrent vaccination (32–48% by study year). The proportion of visits with concurrent vaccine administration decreased over the study period among both males and females (Fig. 1).

Table 1

Total vaccine doses administered to adolescents aged 11 through 18 years, by sex and vaccine type – 2007–2016.

	Males		Females	
	Vaccine Doses	% Total Doses*	Vaccine Doses	% Total Doses*
MenACWY	1,039,725	21%	1,040,358	18%
Tdap	755,307	15%	747,653	13%
HPV-1	473,036	9%	719,334	12%
HPV-2	354,586	7%	615,348	11%
HPV-3	252,916	5%	494,717	9%
Influenza	1,368,050	27%	1,410,067	24%
Varicella	299,237	6%	292,456	5%
Hepatitis A	278,958	6%	285,484	5%
Td	10,004	0%	7800	0%
All Others	167,985	3%	175,913	3%
Total Doses	4,999,804	100%	5,789,130	100%

Notes: HPV-1, first dose HPV vaccine (any product type); HPV-2, second dose HPV vaccine (any product type); HPV-3, third dose HPV vaccine (any product type). A total of 2,909,937 HPV vaccine doses (any dose number, any vaccine type) were administered over the study period – 1,080,538 (37%) to males and 1,829,399 (63%) to females. There were a total of 5,225,647 males and 5,031,119 females in the study population.

* Sex-specific percentages (e.g., 1,039,725 male MenACWY doses made up 21% of total male vaccine doses).

3.2. Vaccine coverage

Vaccine coverage increased for Tdap, MenACWY, and 1- and 3-dose HPV across the study period. Among 13-year-olds, at the conclusion of the study period on time vaccination coverage was highest for ≥1 dose MenACWY, at 85%, followed by ≥1 dose Tdap at 82%. In the same time period, on time vaccination coverage with ≥1 dose HPV vaccine was 65% and 66% among 13-year-old males and females, respectively (Fig. 2). Among 18-year-olds, at the conclusion of the study period catch up vaccination coverage was highest for ≥1 dose MenACWY, at 84%, followed by ≥1 dose Tdap at 80%. In the same time period, catch up vaccination coverage with ≥1 dose HPV vaccine was 69% and 76% among 18-year-old males and females, respectively (Fig. 3).

3.3. Vaccine combinations

A wide variety of vaccine combinations were administered among both sexes and in both the 2007–2010 and 2011–2016 periods; no one combination predominated. The five most common vaccine combinations are shown by sex for each time period in Table 2. The most common vaccine combination administered to males in both time periods was Tdap + MenACWY, which accounted for 17% and 11% of all vaccination among males in 2007–2010 and 2011–2016, respectively. The most common vaccine combination administered to females in both time periods was Tdap + MenACWY + HPV, which accounted for 6% and 8% of all vaccination among females in those time periods, respectively. In the 2011–2016 period, HPV was included in two of the top five vaccine combinations for males; the vaccine was included in four of the top five vaccine combinations for females in both time periods (Table 2).

4. Discussion

More than 10.7 million vaccine doses were administered to adolescents within this integrated health care population over the 2007–2016 study period, allowing for in-depth examination of vaccine administration. Less than half of all vaccines in this population were administered concurrently. Despite ACIP recommendations for concurrent administration [1], between 2007 and 2016, 19% of all Tdap doses were administered individually. Concurrent administration of vaccines decreased with improved uptake of the multi-dose HPV vaccine among females and following the ACIP recommendation for use of multi-dose HPV vaccine in males. While concurrent vaccination occurred at 43% and 39% of all male

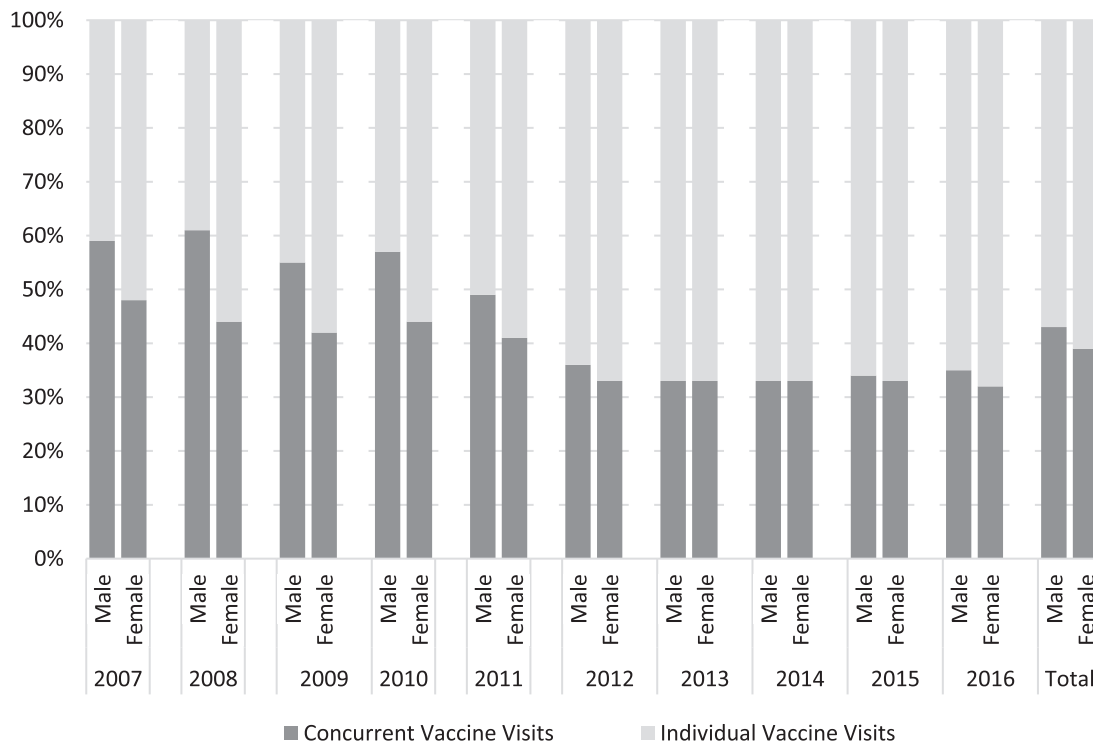


Fig. 1. Proportions of individual and concurrent vaccine visits among adolescents aged 11 through 18 years, by sex – 2007–2016 and overall. Note: There were a total of 4,884,553 total vaccine visits across the 2007–2016 study period. This included 2,215,593 visits among males and 2,668,960 among females where any vaccine was administered.

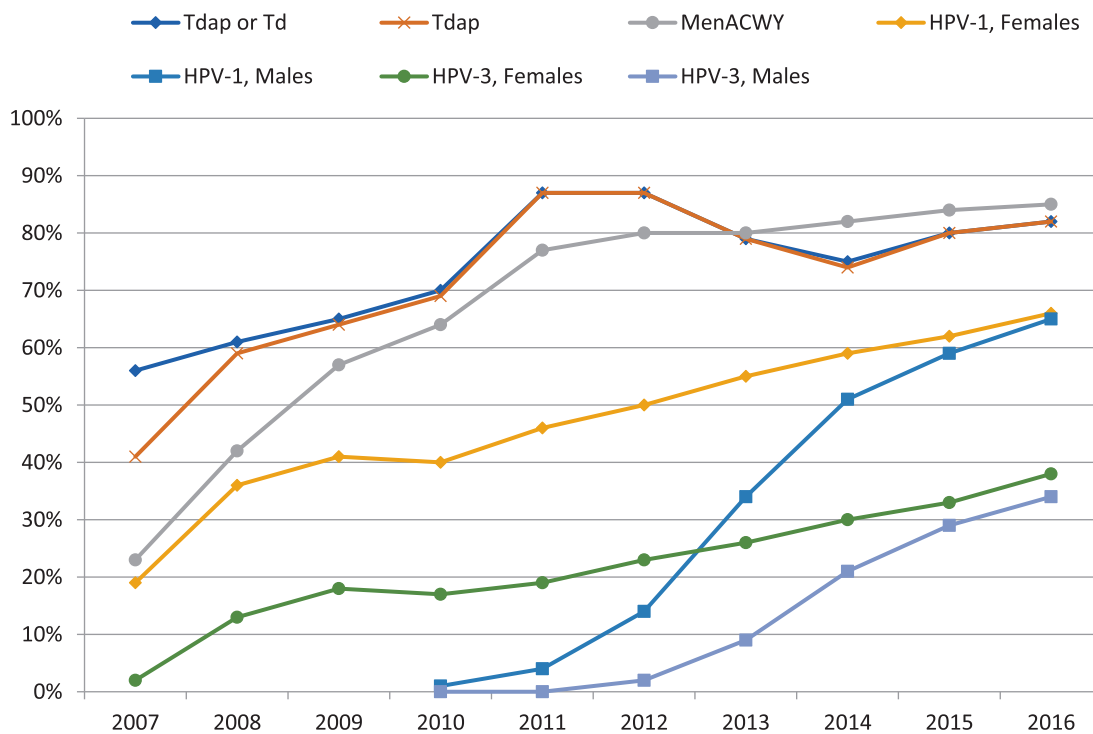


Fig. 2. Vaccine coverage as of adolescents' 13th birthday – 2007–2016. Notes: HPV-1 indicates at least one dose of HPV vaccine (any product type); HPV-3 indicates at least three doses of HPV vaccine (any product type). The HPV-1 and HPV-3 groups are not mutually exclusive, as the HPV-3 group is a subset of the HPV-1 group (by sex). Coverage among all members of the study population who turned 13 in the respective study year, as of the date of their 13th birthday.

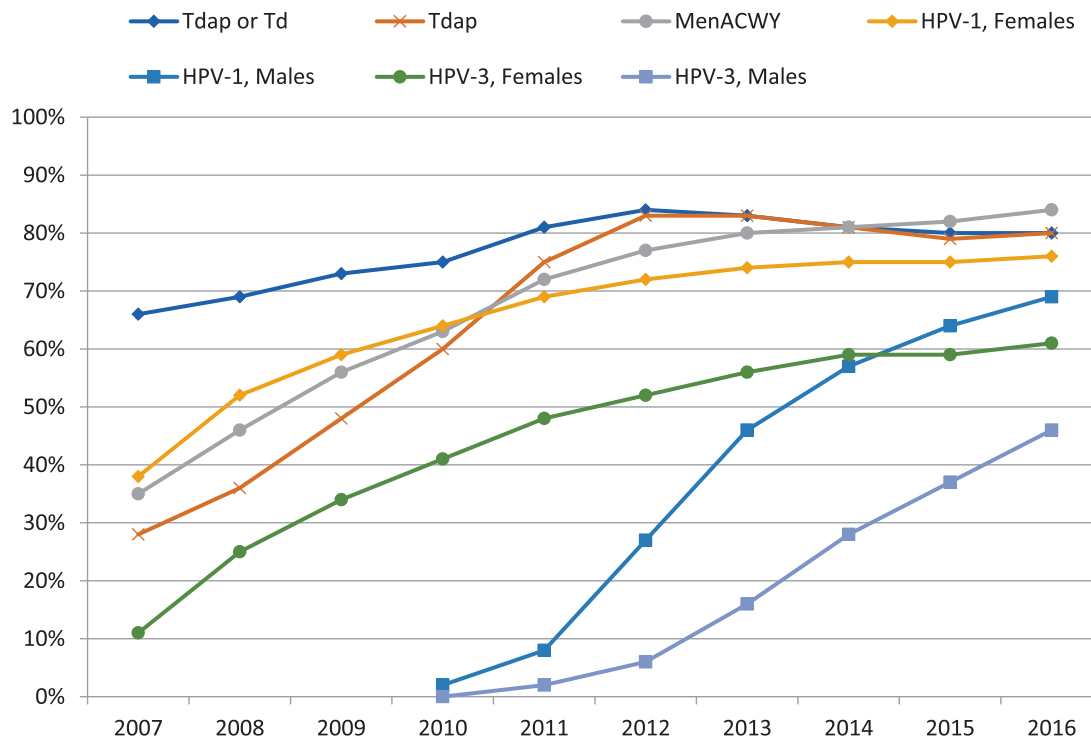


Fig. 3. Vaccine coverage as of adolescents' 18th birthday – 2007–2016. Notes: HPV-1 indicates at least one dose of HPV vaccine (any product type); HPV-3 indicates at least three doses of HPV vaccine (any product type). The HPV-1 and HPV-3 groups are not mutually exclusive, as the HPV-3 group is a subset of the HPV-1 group (by sex). Coverage among all members of the study population who turned 18 in the respective study year, as of the date of their 18th birthday.

Table 2
Most common vaccine combinations administered to adolescents aged 11 through 18, by sex – 2007–2010 and 2011–2016.

	Males	Freq. (%)*	Females	Freq. (%)*
2007–2010				
1	Tdap + MenACWY	106,262 (17.0)	Tdap + MenACWY + HPV	64,730 (5.8)
2	Tdap + MenACWY + Var	60,791 (9.7)	MenACWY + HPV	55,063 (4.9)
3	Tdap + MenACWY + Hep A	29,337 (4.7)	Tdap + MenACWY	43,545 (3.9)
4	Tdap + MenACWY + Var + Hep A	27,910 (4.5)	Tdap + MenACWY + HPV + Var	32,495 (2.9)
5	MenACWY + Var	24,781 (4.0)	HPV + Hep A	31,342 (2.8)
2011–2016				
1	Tdap + MenACWY	83,397 (11.1)	Tdap + MenACWY + HPV	64,787 (8.2)
2	MenACWY + HPV	63,793 (8.5)	MenACWY + HPV	51,563 (6.5)
3	Tdap + MenACWY + HPV	36,118 (4.8)	Tdap + MenACWY	48,954 (6.2)
4	Tdap + MenACWY + Var	19,055 (2.5)	HPV + Hep A	13,837 (1.8)
5	Tdap + MenACWY + Var + Hep A	8622 (1.1)	Tdap + MenACWY + HPV + Var	10,878 (1.4)

Notes: HPV includes any dose of the HPV vaccine (any product type).

* Frequency of vaccine visits in which the specific vaccine combination was administered. Percent of total vaccine visits for that sex for that time period, including visits with individual vaccination.

and female vaccine visits in the study population, respectively, no one vaccine combination predominated over the study period. The variety of commonly administered vaccine combinations identified in this population helps with the design of future vaccine safety studies focusing on concurrent vaccination in the adolescent population. As the uptake of COVID-19 vaccines in medical offices expands among adolescents and as concurrent administration of COVID-19 vaccines increases, there will be heightened demand to monitor and evaluate the uptake and safety of adolescent vaccine patterns.

The adolescent vaccine coverage estimates noted in this study are comparable to United States estimates reported elsewhere for this time period, with the exception of higher HPV vaccine coverage identified within this population [25,26]. The 2016 NIS-Teen survey reported ≥ 1 dose HPV coverage of 52.4% and 54.7% among

13-year-old males and females, respectively [25]. The difference in the ≥ 1 dose HPV coverage estimates among 13-year-olds reported here (66% and 65%, respectively) may be due to differences in the VSD and NIS-Teen populations, notably differences in race, income, and Medicaid status [21]. The 2016 NIS-Teen estimates for ≥ 1 dose MenACWY and Tdap coverage are more similar to our 2016 findings, comparing the 13-year-old and the NIS-Teen 17-year-old age groups to those reported here. While the NIS-Teen provides coverage estimates for a broader geographic region than the VSD, the random-digit-dial design, low response rate, and limited access to adequate provider data contrast with the robust population studied here. To our knowledge, this is the most robust examination of patterns of concurrent administration of the HPV, MenACWY and Tdap vaccines among adolescents, in terms of both duration and size. Moss, et al. examined provider records from

70,000 adolescents over five years of NIS-Teen [14], and Vielot, et al. used claims databases to examine patterns of administration over a six-year period [10]. A smaller, single-state study looked at concurrent adolescent vaccination over three years [11]. The ten-year post-licensure study period and 11 million adolescent population presented here provide a rich data source on the historical patterns of adolescent vaccination, and the novel data on frequencies of specific vaccine combinations may be used to inform future studies of adolescent vaccination.

Our study does have several limitations. Because vaccinations were only used in the analyses if the individual had a medical encounter (e.g., an in-person nurse or physician visit) on the same day as the vaccination, it is possible that we missed a small proportion of vaccinations; in the integrated care setting this is less common and typically limited to influenza vaccination. Possible reasons for lack of an encounter on the date of vaccination include administrative errors during data entry and the back-loading of previous immunization history into VSD data source files. Because our study period ended in 2016, we were unable to examine the impact of the 2-dose HPV recommendation for adolescents who initiate the series before age 15, which was released by ACIP in December 2016 [27]. We also did not specifically examine 2-dose MenACWY coverage following the 2010 ACIP recommendation for a booster dose at age 16 [28]. Finally, these analyses examine the ten years following licensure of the MenACWY, Tdap, and 2v/4v/9vHPV vaccines; data from 2017 to 2021 were not included in this analysis. While we feel the current analysis provides useful insight into the study period, patterns of administration will continue to evolve over time.

In conclusion, within the Vaccine Safety Datalink adolescent population uptake of adolescent vaccines is high and increased over the study period. This finding, coupled with the immense number of vaccine combinations administered concurrently in this population, provides further evidence that the VSD is an important data source for future vaccine safety studies in the adolescent population, including the safety of routine adolescent vaccines administered concurrently with COVID-19 vaccines. Ongoing work within the VSD will further examine the impact of the COVID-19 pandemic on adolescent vaccination coverage and explore concurrent administration of COVID-19 vaccines within the VSD's adolescent population.

Funding

Funding for this study was provided by the Centers for Disease Control and Prevention, Contract 200–2012–53584. Findings and conclusions of this study are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ms. Irving, Ms. Groom, Ms. Dandamudi, Drs. Daley, Myers, Stokley and Ms. Gee have no conflicts to report. Dr. Donahue reports receiving grants from Janssen Vaccines & Prevention outside the submitted work. Dr. Hechter reports grants from Gilead Science Inc and Novartis for research studies outside the submitted work. Dr. Jackson reports an organization research contract with Pfizer, outside the submitted work. Dr. Klein reports grants from Pfizer, Merck, GlaxoSmithKline, Sanofi Pasteur, and Protein Sciences (now Sanofi Pasteur), outside the submitted work. Dr. Liles reports research funding from Merck, Pfizer, Epigenomics, and Medical Solutions, outside the submitted work.

Acknowledgements

The authors wish to thank the following individuals with their assistance: Allison Naleway (Kaiser Permanente Northwest, protocol development and manuscript review) and Erica Scotty (Marshfield Clinic Research Institute, data collection). We also thank the VSD project managers for their contributions.

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