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Hpv Vaccine Effectiveness In New Haven County, Connecticut Women Age 18-39, 2008-2012

Jennifer Lynn Berry
Yale University, jennifer.berry@gmail.com

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Jennifer L. Berry

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Yale School of Public Health

First Reader: Linda Niccolai, PhD

Second Reader: Daniel Weinberger, PhD

Abstract

Background: HPV vaccines have demonstrated high efficacy in clinical trials against cervical lesions and infections by HPV vaccine types 16 and 18. Together these two types are responsible for approximately 70% of cervical cancer. Data on HPV vaccine effectiveness in general populations is limited.

Methods: Surveillance data monitoring high-grade cervical lesions in Connecticut was used. Medical records were reviewed and patients were interviewed to ascertain HPV vaccine history. Patients' biopsy specimens were typed to determine the presence of vaccine or non-vaccine type HPV. Odds ratios were determined using logistic regression, adjusting for age at diagnosis, grade of cervical lesion, race/ethnicity, and insurance type.

Results: From 2008-2012, 788 women with known vaccine status and typed biopsy specimens were analyzed. 8.9% of women received at least one vaccine dose. Adjusted vaccine effectiveness for at least one dose was estimated to be 53%. Vaccine type HPV was strongly associated with higher grade cervical lesions, but other statistically significant associations were not found.

Conclusions: The data suggests that HPV vaccination provides protection against vaccine type high-grade cervical lesions in women. Although these results are promising, more long term data and greater sample sizes are required to better estimate vaccine effectiveness.

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Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States [1]. The overall prevalence for genital HPV infection is 26.8% for American women between 14 and 59 years old, with the highest prevalence in women 20-24 years old (44.8%) [2]. There are over 100 human papillomavirus types that infect humans [3]. Of these, more than 40 types of HPV that infect the anogenital tract have been identified [4]. Most HPV infections are cleared without treatment in about 12 months, nononcogenic strains clearing faster than oncogenic strains [5]. Persistent infections that do not clear can progress to precancerous cervical lesions and cervical cancer. HPV is detected in over 99% of cervical carcinomas and is a necessary cause of cervical cancer [6]. HPV is also associated with a high number of vaginal, anal, vulvar, and penile cancers, as well as various head and neck cancers and genital warts [7].

HPV types can be categorized as high risk, probable high risk, and low risk [4]. Low risk types are generally associated with genital warts and high risk with cervical lesions and cancer. Worldwide, approximately 70% of invasive cervical cancer is caused by HPV types 16 and 18 [8]. Gardasil, a quadrivalent vaccine that protects against high risk types 16 and 18 and low risk types 6 and 11 was approved by the Food and Drug Administration (FDA) for use in females age 9-26 in 2006 [9]. In 2009, a bivalent vaccine that protects against types 16 and 18, Cervarix, was approved for females age 10-25 [10]. The current Advisory Committee for Immunization Practices (ACIP) recommendations are routine vaccination for females age 11-12 with either the quadrivalent or bivalent vaccine and for males age 11-12 with the quadrivalent vaccine

only [9, 11, 12]. Permissive or catch-up vaccination is recommended up to age 26. Both the quadrivalent and bivalent vaccines have shown over 95% efficacy in clinical trials for prevention of cervical infections in HPV-naïve women [13-16]. The bivalent vaccine has also shown cross-protective efficacy against four oncogenic non-vaccine types and three low risk types [17, 18].

In 2012, 34.5% of women age 19-26 in the United States were estimated to have received at least one dose of HPV vaccine [19]. This was a slight increase from 29.5% coverage in 2011 and 20.7% coverage in 2010 [20, 21]. Among girls age 13-17, the estimated coverage for one dose or more has increased from 25.1% in 2007 to 53.8% in 2012 [22]. The 2012 coverage for the state of Connecticut of 57.6% was slightly higher than the national average, however there was no increase from 60.5% estimated coverage in 2011 [23, 24].

Cervical intraepithelial neoplasia (CIN) and adenocarcinoma in situ (AIS) are precancerous cervical lesions caused by HPV. These lesions do not necessarily progress into cancer and some may regress [25, 26]. The high risk strains are usually associated with these lesions, but low risk strains can also cause CIN 1 and CIN 2 [27]. CIN is 1 referred to as a low-grade lesion, while CIN 2, CIN 3, and AIS are considered high-grade. CIN 2 is the current recommended treatment threshold, but observation is the preferred course of action for younger women who are more likely to have natural regression [28]. In 2010, screening guidelines changed to no longer screen women under the age of 21 because of the rarity of cervical cancer in women that age and high probability of regression [29]. Cervical cancer incidence and mortality has overall declined greatly in developed nations since the 1960s and 1970s due to screening

programs and improved treatment. However, there are recent increases in young women in some countries, which may be a result of generational differences in sex habits [30].

Evidence of overall vaccine impact can currently be best detected through prevalence of vaccine type HPV and diagnoses of genital warts, while vaccine impact on high-grade cervical lesions and cancer will take longer to fully demonstrate because these conditions take years to decades to develop [31]. Reports of reduced prevalence of vaccine type HPV and genital warts in the United States and other countries provides early evidence of vaccine impact [32]. Previous HPV-IMPACT results also suggest vaccine impact; a significantly lower proportion of CIN2+ caused by vaccine type HPV was found in women who were vaccinated greater than 24 months before their trigger Pap [33].

In Australia, an extensive vaccination program began in 2007 for in school routine vaccination for girls 12-13 and catch-up vaccination for girls 13-17, along with community catch-up vaccination for women 18-26. The incidence of high-grade cervical lesions in females under age 18 was found to be significantly reduced after induction of this program; however, incidence for females in other age groups did not change significantly [34]. Evidence for quadrivalent vaccine effectiveness against cervical abnormalities has begun to emerge from this program in Australia as well. A case-control study using anonymous, linked registry data for vaccination status and development of cervical abnormalities detected upon first Pap screening found statistically significant protection against these abnormalities in young women [35].

The Connecticut HPV-IMPACT group has already reported significantly declining rates of high-grade cervical lesions in the state for women ages 21-24 years [36]. The same analysis also found significant declines in census tracts with lower proportions of the population black, Hispanic, or living below the federal poverty level and in nonurban areas. Another study by the group found black race, Hispanic ethnicity, and higher area-based poverty to be associated with lower likelihood of vaccine-type HPV [37]. This suggests that the vaccine may have lower impact among these women. The group has published other findings on racial/ethnic and economic disparities in HPV vaccination and high-grade cervical lesion diagnoses [38-40].

Pooled analysis of quadrivalent vaccine efficacy from three clinical trials demonstrates over 95% efficacy against high-grade cervical lesions for per-protocol treatment [13]. However in these trials participants were excluded if they had prior abnormal Pap results, over four lifetime sex partners, or prior confirmed HPV disease. This does not accurately represent actual populations of women at risk for high-grade cervical lesions. Similarly high efficacy was found for the bivalent vaccine in clinical trials, and in addition women were included irrespective of their HPV status and cytology, but were excluded if they had more than six lifetime sex partners or previous colposcopy [14]. This is more inclusive, but still not fully representative and may not be as applicable, as almost all HPV vaccines administered in the United States from 2006-2010 were the quadrivalent vaccine [41].

In 2010, over 11,800 women were diagnosed with cervical cancer in the United States and over 3,900 women died from the disease [42]. Over one million women are diagnosed with low-grade cervical lesions each year and approximately 500,000 are

diagnosed with high-grade lesions [28, 43]. The cost for one instance of these diagnoses can range from approximately $1,000 for CIN1 to over $3,000 for CIN3, and overall cost of management of precancerous cervical lesions was approximately 17% of total cervical HPV related costs for one health plan [44]. The estimated annual baseline cost per case for cervical cancer was $38,800 in 2010 US dollars [45]. Diagnoses with these conditions can also have negative psychological impact such as fear of cancer, infertility, or loss of sexual function; depression; sleep disturbance; anxiety; and embarrassment [46, 47].

Given the physical, financial, and psychological burden of HPV related cervical lesions, there is a definite need for preventative action. HPV vaccines have shown very high efficacy in clinical trials, but at this time there is limited data on the effectiveness of these vaccines at preventing vaccine type lesions in real world populations. This analysis attempts to estimate vaccine effectiveness in the entire population of young women in New Haven County, Connecticut using surveillance data. This study aims to fill the knowledge gap on HPV vaccine effectiveness against high-grade cervical lesions using individual vaccination status and typed HPV specimens.

Methods

Surveillance System

In 2008, the Centers for Disease Control and Prevention (CDC) began monitoring HPV vaccine impact through the Emerging Infections Program (EIP) network using population-based surveillance of high-grade cervical lesions [48]. On January 1st, 2008, the Connecticut Department of Public Health designated CIN 2 and higher and AIS as

mandatory reportable diseases in the state [49]. All pathology labs in the state are required to report these diagnoses. The reports contain the diagnostic information and patient demographics. Reports were reviewed by EIP staff for eligibility and accuracy and then entered into a database.

Medical Record Review and Patient Interviews

Enhanced surveillance was conducted for New Haven County residents between 18 and 39 years old at the time of diagnosis. EIP staff reviewed available medical records of these patients from the provider who performed the biopsy that produced the diagnosis. Medical records were reviewed for HPV vaccination status, cervical cancer screening history (including the date and results of the abnormal "trigger" Pap that lead to the biopsy and diagnosis), as well as demographic and contact information that may have been missing from the initial report. EIP staff then conducted telephone interviews with these patients which touched on similar information to the medical record review. Patients were asked if they received the vaccine. Patients who reported receiving the vaccine were then asked if it was the quadrivalent or bivalent vaccine and when and from which provider they received each dose. All patients were then asked demographic questions concerning race, ethnicity, and type of insurance at the time of diagnosis.

Vaccination history was verified with providers for patients who reported being vaccinated. The Connecticut HPV-IMPACT group has previously analyzed the concordance of vaccination history from patient interviews and medical records [50]. Concordance of vaccination history was found to be relatively high at 83%, with 96%

sensitivity (percentage of women who had a history of vaccination from medical record and reported vaccination from patient interview) and 97% specificity (percentage of women who had did not have a history of vaccination from medical record and reported not being vaccinated during patient interview). Although concordance was good, there was a high frequency of missing data. Vaccination history was missing from 34% of medical records and 43% of patients could not be reached for interview.

HPV Typing

Biopsy specimens from New Haven County women age 18-39 were requested from pathology laboratories. For patients with more than one available tissue block, the block representative of the highest grade lesion was selected by a pathologist. Available samples were shipped to the CDC for DNA extraction and HPV typing. HPV typing was performed using polymerase chain reaction (PCR); more detailed methods have been described elsewhere [33, 51].

Covariates

For this analysis, age at diagnosis was collapsed into five categories, 18-20, 21-24, 25-29, 30-34, and 35-39. These categories were chosen to remain consistent with other HPV-IMPACT analyses [51]. Race categories for patient interviews were white, African American, Asian, American Indian/Alaskan American, other, unknown, and multi-race. Ethnicity was recorded as Hispanic, not Hispanic, or unknown. Race and ethnicity were combined for this analysis as Hispanic, White (not Hispanic), African American (not Hispanic), other (not Hispanic), and unknown. Asian, American

Indian/Alaskan American, other, and multi-race were combined into the other category because of low frequency. Insurance was categorized as private, public (Medicaid, state assistance, or Medicare), uninsured (no coverage or self-pay), other, and unknown. Diagnosis was categorized as CIN 2, CIN 2/3, CIN 3, and AIS (AIS alone or in conjunction with CIN 2, CIN 2/3, or CIN 3).

Case Definition and Vaccination Status

HPV type was categorized as 16/18 (vaccine type), other high risk types, possible high risk types, and low risk types. Risk categories were chosen to be consistent with previous HPV-IMPACT analyses and current HPV epidemiologic classification [4, 51]. Patients who tested positive for two or more different HPV types were categorized using a hierarchy ranked in the order of 16/18, other high risk, possible high risk, and low risk. Samples were categorized into the highest hierarchical group. This was further collapsed into vaccine type (16/18) and non-vaccine type (other high risk, possible high risk, and low risk) for analysis.

Vaccine status was defined as having at least one dose of either HPV vaccine. Vaccine status was categorized using time from the date of the first dose of the vaccine to the date of the trigger Pap that lead to the high-grade cervical lesion diagnosis. Vaccination status was classified as not vaccinated, vaccinated at or after trigger Pap, vaccinated within one year before trigger Pap, vaccinated within two years before trigger Pap, vaccinated within three years before trigger Pap and vaccinated three or more years before trigger Pap. Patients with verified vaccination status and unknown trigger Pap dates were classified as vaccinated at or after trigger Pap. Vaccine status

was further collapsed for the analysis so that only patients vaccinated two years or more before trigger Pap were considered vaccinated. Patients vaccinated less than two years before trigger Pap were considered unvaccinated. The time frame of two years or more was chosen based on previous HPV-IMPACT results showing significantly lower proportion of vaccine type HPV in women vaccinated at this time and no significant effect on women vaccinated less than 24 months before trigger Pap [33].

Statistical Analysis

Analysis was restricted to women with known vaccine status and known HPV type. If a patient had more than one high-grade cervical lesion event reported, only the first event was used. Chi-square tests were used to assess associations between HPV type and covariates, using $P<0.05$ level of significance. Unadjusted and adjusted odds ratios and 95% confidence intervals were estimated using logistic regression. The model was reduced to adjust for covariates using backwards elimination. Vaccine effectiveness was estimated using the formula (1 – adjusted odds ratio) x 100%. All analyses were done using SAS statistical software (version 9.3, SAS Institute, Cary, NC). Flowchart was constructed using Lucidchart (https://www.lucidchart.com/).

Results

In total, 4,327 individual women were diagnosed with high-grade cervical lesions in New Haven County from 2008-2014 (from the inception of surveillance to the beginning of data analysis). Of these women, 2,129 had known vaccine status (1,890 not vaccinated, 239 vaccinated) and 2,198 had unknown vaccine status. The total

number of typed specimens was 1,308 (740 non-vaccine type, 568 vaccine type) for all women. HPV type was not available for the remaining 3,019 women for various reasons, including pending specimen requests from pathology labs, samples that were insufficient for typing, or specimens that tested negative for all HPV types; this has been discussed in a previous HPV-IMPACT study [37]. Overall 520 typed specimens were excluded because of missing vaccine history and 169 vaccine status known women were excluded because of unknown HPV type. See figure 1 for further detail on inclusion and exclusion frequency.

When unknown strata were excluded, the included and excluded groups had similar distribution by percentage for HPV type, vaccination status, and age at first vaccine dose. Age at diagnosis distribution was skewed slightly towards older age groups in the excluded women, with mean and median age for the included women (27.4±5.25, 26.6) slightly lower than the excluded women (28.3±5.16, 27.8). There was a small difference between the two groups for diagnosis distribution, with higher grade outcomes in the excluded group. For known race/ethnicity in the two groups, the percentage black and other were similar, but the included groups had a higher percentage white (63.38% to 50.35%) and lower percentage Hispanic (20.07% to 33.82%). There were also differences between the two groups for insurance type. The included women had a higher percentage private insurance (73.10% to 56.95% and lower percentage public insurance (24.80% to 38.04%).

A total of 788 women with known vaccine status and HPV type were used in the final analysis. Typed specimens were only available for 2008-2012. Tables 1 and 2 present the basic demographics for the sample analyzed. There were no statistically

significant differences between the vaccine type and non-vaccine type groups for vaccine history, age at vaccination, age at diagnosis, race/ethnicity, type of insurance, and year of diagnosis. There was a significant difference between the two groups for cervical lesion diagnosis. The vaccine type group had more higher grade outcomes than the non-vaccine type group.

Odds ratios are presented in table 3. Odds ratios for AIS were not calculated due to small sample size. Differences in odds ratios between the unadjusted, full, and reduced models were small. The most statistically significant covariate was cervical lesion grade in all models. Although race/ethnicity and insurance were not found to be statistically significant in any model, they were kept in the final model because they have been found to be significantly associated with vaccine type HPV in previous HPV-IMPACT studies [37]. The final adjusted odds ratio for vaccinated status compared to unvaccinated was 0.47 (95% confidence interval 0.27-0.82) for vaccine type HPV. This equates to a vaccine effectiveness of 53%.

Figure 2 displays vaccine type trends through total typed cases per year, regardless of vaccination history of patients, to demonstrate crude potential vaccine impact on type distribution over time. Non-vaccine and vaccine types were charted as a percentage of total specimens with known type per year, with frequencies for each year tabled under the figure. There was a large difference in number of cases for both types between the different years, but this is attributable to more complete data from earlier years, with more pending data on HPV type for later years.

Discussion

A significant association was found between vaccine status and HPV type. Estimated vaccine effectiveness of 53% is consistent with other HPV vaccine effectiveness analyses, although an analysis using outcome measures of high-grade cervical lesion diagnoses and HPV type is not currently available to the best of our knowledge. The 2013 analysis by Markowitz et al using nationally representative US data from the National Health and Nutrition Examination Surveys (NHANES) reported 82% effectiveness for at least one dose of the quadrivalent vaccine against types 6, 11, 16, and 18 infection in females 14-19 years old [41]. This study also found no difference in pre and post vaccine period HPV prevalence in other age groups. The 2014 study by Crowe et al reported 46% effectiveness against high-grade lesions and 34% effectiveness against other abnormalities for the complete three dose series of the quadrivalent vaccine in females 11-27 years old in Queensland, Australia [35]. This study used cervical abnormalities caused by any HPV type as an outcome measure and specimens were not typed.

Of women who were ever vaccinated, 38% received the first dose at or after the date of their trigger Pap. This is consistent with previous analysis of this study population. It was suggested that abnormal cytology prompted vaccination and racial disparities in vaccination before and after this time were noted [38]. Significant differences in age, race, and insurance status have also been reported for patients with vaccine initiation at or after trigger pap [33].

Our study has several strengths, the first being use of individual HPV type, high-grade cervical lesion diagnosis, and vaccination history together in one analysis. Second, vaccination history was verified and not based solely on self-report. Third, medical records were reviewed for almost every case (approximately 1% of medical records are unavailable for review) [50]. Fourth, because high-grade cervical lesions are a mandatory reportable condition in the state of Connecticut, our raw data represents outcomes in our entire population at risk. In addition, these conditions are reported using a common grading system, helping to ensure accurate disease classification.

There are some limitations to our study. First, we had a large amount of missing data. HPV type was not available for 70% of patients and vaccine status was unknown for 51% of women. Race and ethnicity data was also not available for 28% of women analyzed. Missing data resulted in a smaller sample size and more limited time frame for analysis. This also limited ability to analyze trends in HPV type over time to monitor vaccine impact. Second, there is a possibility of selection bias in patient interviews with respect to women who were able to be contacted and agreed to the interview and those who were not interviewed. Third, sample size for vaccinated women was very small compared to unvaccinated women; however, this may be accurately representative of the population and not due to selection bias.

Lastly, cervical cancer screening guidelines changed in 2010 to discontinue screening women under the age of 21 [29]. Data from before and after the change in recommendations might no longer be as comparable, as fewer cases may be captured now. However, it is unknown at this time how many providers are following these new

guidelines and what the magnitude of difference in screening for women age 18-20 is before and after the change in guidelines. In addition, new 2012 guidelines for screening once every three years for women age 21-29, and once every five years for women 30 and over may have similar effects [52]. This likely had little impact on the current study, but will be something to consider in the future. It is possible that high grade cervical lesion rates will decline in our population in the upcoming years, but whether the declines are the result of vaccine impact or changes in screening guidelines will need to be examined more closely.

Our analysis adds to the limited evidence for HPV vaccine effectiveness against vaccine type high-grade cervical lesions. Over time, larger sample size and increased vaccine impact should strengthen data for this project. Vaccine effectiveness estimates should become clearer as more vaccinated women reach an age of greater risk for these high-grade lesions. These preliminary results on vaccine effectiveness in our population are encouraging and provide support to current recommendations of routine HPV vaccination for girls.

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Table 1. Sample description for women with known vaccination status and typed specimens, 2008-2012

	Frequency	Percent
HPV type		
16/18 Vaccine Type	340	43.15
Other High Risk	392	49.75
Possible High Risk	44	5.58
Low Risk	12	1.52
Vaccination status		
Not vaccinated	541	68.65
At or after trigger Pap	99	12.56
1 year or less before trigger Pap	28	3.55
1-2 years before trigger Pap	50	6.35
2-3 years before trigger Pap	35	4.44
3+ years before trigger Pap	35	4.44
Age at first vaccine dose		
Not Vaccinated	541	68.65
15-16	5	0.63
17-18	20	2.54
19-20	48	6.09
21-22	75	9.52
23-24	60	7.61
25-26	34	4.31
27 or older	5	0.63
Age at diagnosis		
18-20	58	7.36
21-24	247	31.35
25-29	253	32.11
30-34	144	18.27
35-39	86	10.91
Diagnosis		
CIN2	523	66.37
CIN2/3	94	11.93
CIN3	167	21.19
AIS/AIS+CIN	4	0.51
Race and ethnicity		
Hispanic	114	14.47
White, not Hispanic	360	45.69
Black, not Hispanic	74	9.39
Other, not Hispanic	20	2.54
Race and ethnicity NA	220	27.92

Table 1. Continued

	Frequency	Percent
Insurance		
Private	557	70.69
Public	189	23.98
Uninsured	14	1.78
Other Insurance	2	0.25
Insurance NA	26	3.3
Year of diagnosis		
2008	295	37.44
2009	187	23.73
2010	171	21.7
2011	122	15.48
2012	13	1.65

Column percentages
NA = not available

Table 2. Sample description for women with known vaccine status stratified by HPV type

	Non-vaccine Type n (%)	Vaccine Type n (%)	Total	X^2 probability
Vaccine status				0.0200
Not vaccinated	399 (89.06)	319 (93.82)	718	
Vaccinated	49 (10.94)	21 (6.18)	70	
Total	448	340	788	
Age at vaccination				0.0855
Not Vaccinated	294 (65.63)	247 (72.65)	541	
15-20	48 (10.71)	25 (7.35)	73	
21+	106 (23.66)	68 (20.00)	174	
Diagnosis				<.0001
CIN2	336 (75.00)	187 (55.00)	523	
CIN2/3	43 (9.60)	51 (15.00)	94	
CIN3	69 (15.40)	98 (28.82)	167	
AIS/AIS+CIN	0 (0)	4 (1.18)	4	
Age at diagnosis				
18-20	34 (7.59)	24 (7.06)	58	0.0919
21-24	144 (32.14)	103 (30.29)	247	
25-29	127 (28.35)	126 (37.06)	253	
30-34	87 (19.42)	57 (16.76)	144	
35-39	56 (12.50)	30 (8.82)	86	
Race and ethnicity				
Hispanic	66 (14.73)	48 (14.12)	114	0.0812
White, not Hispanic	186 (41.52)	174 (51.18)	360	
Black, not Hispanic	48 (10.71)	26 (7.65)	74	
Other, not Hispanic	13 (2.90)	7 (2.06)	20	
Race and ethnicity NA	135 (30.13)	85 (25.00)	220	
Insurance type				
Private	309 (68.97)	248 (72.94)	557	0.5537
Public	113 (25.22)	76 (22.35)	189	
Uninsured	7 (1.56)	7 (2.06)	14	
Other Insurance	1 (0.22)	1 (0.29)	2	
Insurance NA	18 (4.02)	8 (2.35)	26	
Year of diagnosis				
2008	167 (37.28)	128 (37.65)	295	0.3880
2009	115 (25.67)	72 (21.18)	187	
2010	89 (19.87)	82 (24.12)	171	
2011	68 (15.18)	54 (15.88)	122	
2012	9 (2.01)	4 (1.18)	13	

Column percentages

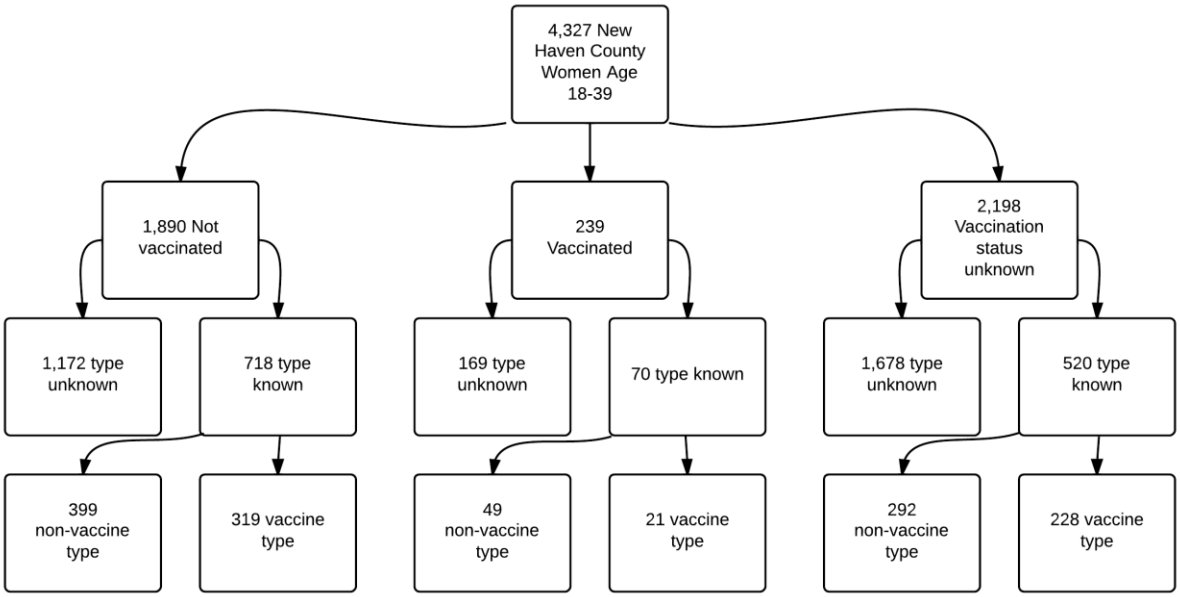
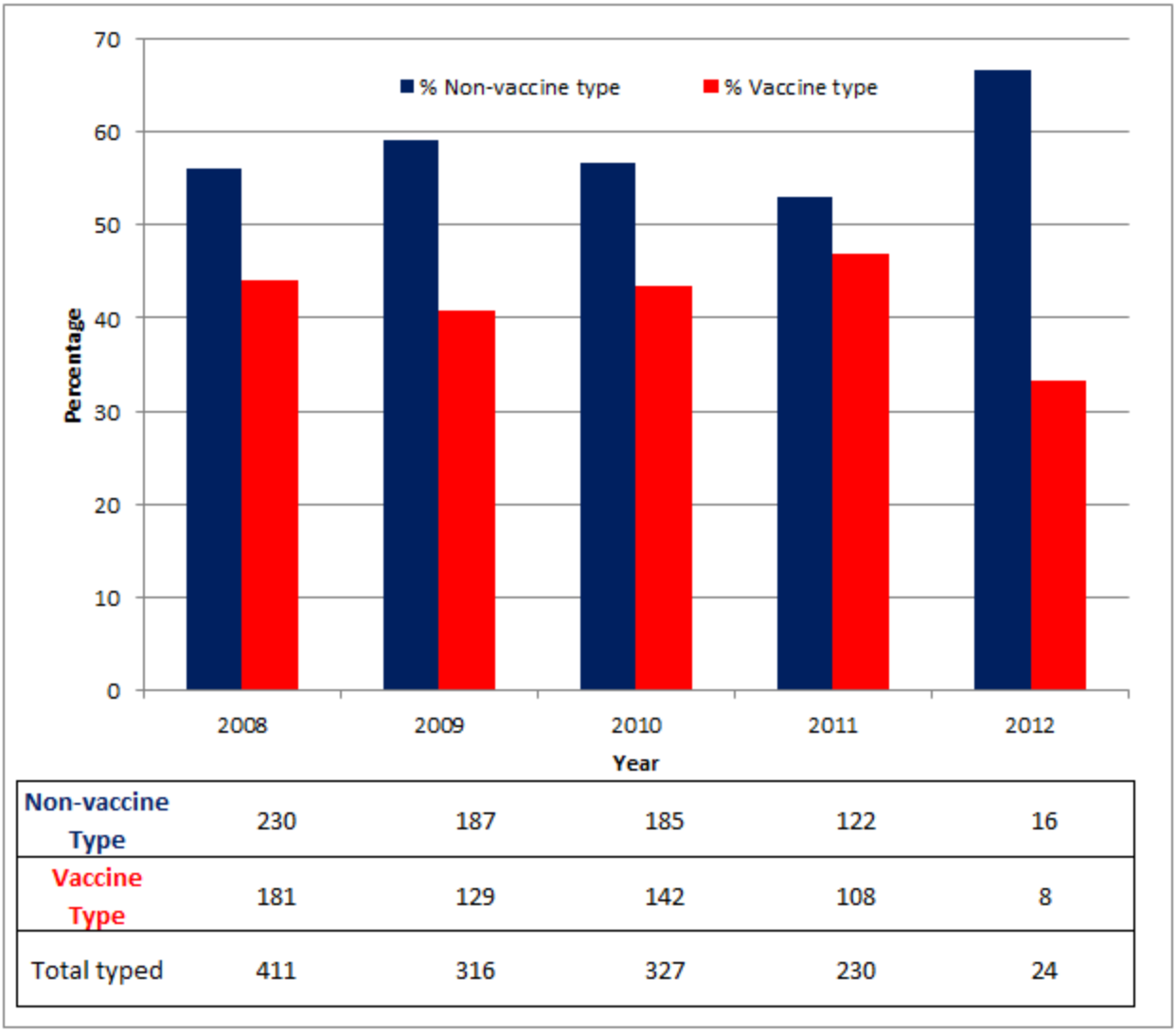


Figure 1. Flow chart of New Haven County women diagnosed with CIN2+, 2008-2014



Non-vaccine Type	230	187	185	122	16
Vaccine Type	181	129	142	108	8
Total typed	411	316	327	230	24

Figure 2. Bar graph of changes in non-vaccine type and vaccine type distribution over time as a percentage of total specimens, with table of all typed specimens per year below

Table 3. Unadjusted and adjusted odds ratios for vaccine type

	Unadjusted OR (95% CI)	Full model OR (95% CI)	Reduced model OR (95% CI)
Vaccination status			
Not Vaccinated	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Vaccinated	0.54 (0.32-0.91)**	0.57 (0.30-1.08)*	0.47 (0.27-0.82)***
Age at first vaccine dose			
Not Vaccinated	1.00 (Reference)	1.00 (Reference)	
15-20	0.62 (0.37-1.04)*	0.74 (0.37-1.49)	
21+	0.76 (0.54-1.08)	0.74 (0.48-1.12)	
Age at diagnosis			
18-20	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
21-24	1.01 (0.57-1.81)	0.97 (0.50-1.87)	0.99 (0.54-1.80)
25-29	1.41 (0.79-2.51)	1.11 (0.55-2.23)	1.23 (0.68-2.24)
30-34	0.93 (0.50-1.73)	0.68 (0.32-1.42)	0.80 (0.42-1.52)
35-39	0.76 (0.38-1.51)	0.48 (0.21-1.07)*	0.56 (0.27-1.16)
Diagnosis			
CIN 2	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
CIN 2/3	2.13 (1.37-3.32)***	2.13 (1.35-3.35)***	2.14 (1.36-3.37)***
CIN 3	2.55 (1.79-3.64)***	2.61 (1.81-3.77)***	2.65 (1.83-3.82)***
AIS	Sample size too small		
Race/ethnicity			
White, not Hispanic	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Hispanic	0.90 (0.60-1.35)	0.91 (0.59-1.40)	0.93 (0.60-1.43)
Black, not Hispanic	0.67 (0.41-1.11)	0.74 (0.43-1.25)	0.76 (0.45-1.29)
Other	0.67 (0.26-1.70)	0.68 (0.26-1.80)	0.69 (0.26-1.83)
Insurance type			
Private	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Public	0.86 (0.62-1.20)	0.78 (0.54-1.12)	0.78 (0.55-1.13)
Uninsured	1.28 (0.44-3.69)	0.95 (0.32-2.86)	1.00 (0.33-2.97)
Other	1.28 (0.08-20.52)	1.41 (0.08-23.62)	1.41 (0.08-23.68)

OR= odds ratio; CI = confidence interval
*P<0.10; **P<0.05; ***P<0.01