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Fangming Qian Date

Model-based impact of HPV vaccination on HPV type 16/18 infection prevalence in the US

By

Fangming Qian

Master of Public Health

Epidemiology

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Robert A. Bednarczyk, PhD

Committee Chair

Model-based impact of HPV vaccination on HPV type 16/18 infection prevalence in the US

By

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Bachelor of Medicine, Jilin University, 2015

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An abstract of

A thesis submitted to the Faculty of the

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Abstract

Model-based impact of HPV vaccination on HPV type 16/18 infection prevalence in the US

By Fangming Qian

Background: Persistent human papillomavirus (HPV) infection can result in cervical cancer, a leading cause of cancer mortality among females. HPV vaccines provide protection against certain types of human papillomavirus that cause most cervical cancer cases. HPV vaccination was first recommended for female adolescents by the Advisory Committee on Immunization Practices (ACIP) in 2006, but coverage has remained suboptimal.

Methods: We modeled the prevalence of HPV type 16/18 was analyzed for females aged 14 to 34 from 2007 to 2012 using existing data on age-specific vaccine uptake, vaccine efficacy, and baseline infection rates. We computed models for baseline, best and worst scenario sensitivity models based on confidence intervals, and an ideal condition assuming meeting Healthy People 2020 vaccination goals.

Results: Between 2007 and 2012, HPV vaccination at currently levels reduced the prevalence of HPV type 16/18 infection by 39% among 14-19 year-olds (5.8% to 3.6%), 24.8 % for 20-24 year-olds (13.7% to 10.3%), 9.5% reduction for females aged 25 to 29 (7.4% to 6.7%), while infections increased by 2.7% among female who are aged 30 to 34, who had the lowest opportunity for vaccination. Accounting for the uncertainty in the estimates used for our data inputs, these estimates can range from decreases of 36.5% to 40.0% for 14-19 year-olds, 22.3% to 27.2% for those who are 20-24 years old, and 8.0% to 11.1% for females aged 25-29. While vaccination reduced infection prevalence to 3.6% for 14-19 year-old females, if Healthy People 2020 goals were reached, infection prevalence in this age group could have been reduced to 1.7%. While this corresponds to a decrease of over 446,000 infections in this age group compared to the pre-vaccine era, there are still over 242,000 infections occurring that could have been prevented by reaching HP2020 goals.

Conclusion: Although improvements have been made in preventing high-risk HPV infections by vaccination, there is room for improvement since we do not reach optimal vaccination levels every year. This finding indicates we need apply multi-focal interventions to improve HPV vaccination coverage among adolescents and young adults.

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Introduction

Cervical cancer has been a leading cause of cancer mortality among women around the world, responsible for 12,820 cases per year, an estimated of 4210 deaths occurred in 2016. Cervical cancer is the result of persistent infection with Human papillomavirus(HPV). [1] In addition to cervical cancer, persistent HPV infection is associated with cervical, anal, penile, vaginal, and vulvar cancers. In a meta-analysis by De Vuyst et al., it was estimated that 40.4% of vulvar carcinomas, 69.9% of vaginal carcinomas and 84.3% of anal carcinomas are caused by HPV. [2] Among all subtypes of HPV, high risk types 16 and18 contribute to an estimated 70% of cervical cancers and precancerous cervical lesion. [3]

Human papilloma virus (HPV) vaccines are vaccines that provide protection against certain types of human papillomavirus. [4] It is estimated that HPV vaccine may prevent 70% of cervical cancer, 80% of anal cancer, 60% of vaginal cancer, 40% of vulvar cancer. [5-7] The Advisory Committee on Immunization Practices (ACIP) has recommended routine HPV vaccination since mid-2006 for females aged 11 to 12 years, with catch-up vaccination for females aged 13 to 26. It is shown that HPV vaccines have high efficacy for preventing HPV-type infection, [8-10] HPV infection prevalence among females can be substantially reduced by vaccination programs. [11] As Markowitz et al.'s research reported, HPV prevalence has been declined compared to pre-vaccine era, especially for females aged 14 to 24. For females who have not been infected with any of the HPV vaccine type, full benefit would be received from HPV vaccination; even for those who have been infected with some of HPV vaccine types, protection from vaccination would be expected though the effect would be less. [12]

While rates of HPV vaccination have been increasing in the past years, widespread coverage has not been obtained. It is found that 57% of female adolescents had received at least one dose and only 38% had received three doses, [13] reflecting the challenges of increasing rate of vaccine uptake and promoting complete vaccine series. With more than a decade of suboptimal vaccination since HPV vaccine was recommended, many women who could have been protected from cervical cancer remain unprotected. However, we are not aware of any estimates of the number of HPV infections that could have been prevented, with greater vaccine coverage, that were not prevented. We have estimated the cumulative total of preventable HPV infections that have occurred due to low vaccine coverage in the US by a mathematical model considering current age-specific infection rates, vaccine coverage and vaccine efficacy.

Method

Model structure

A model-based approach was used to synthesize the available evidence to estimate HPV type 16 and 18 cases averted through vaccination as well as the potential cases that could have been prevented but were not, due to suboptimal vaccination. Excel-based models were developed to synthesize estimates of infection prevalence at the population level. [14] Models were generated using ranges of infection prevalence, coverage and vaccine efficacy assumptions. Models were constructed as a static cohort, simulating multiple birth cohorts of girls for their lifetimes, comparing health outcomes without HPV vaccination programs, one dose and three doses HPV vaccination programs. Given current vaccination strategy, the annual proportional reduction in infection incidence for

females aged from 14 to 34 were derived within Microsoft Excel 2003, to compare with the baseline and ideal scenario.

Input data

The model uses the best available population-based demographic data, such as age structure and target vaccine coverage, and epidemiologic data including age-specific prevalence of type 16 and 18 HPV infections with assumed dose-specific vaccine efficacy and coverage to estimate reduction in type 16 and 18 HPV infections at different age.

Details of the model parameterization process, can be found in previously published findings. [15-18] Vaccine efficacy against type 16 and 18 HPV infections were derived from previous publication for those receiving one dose and those have taken full dose vaccination (three doses). [19-20] Age specific population and type 16/18 HPV infection prevalence are described in Table 1. [21-22] Epidemiological data used to establish calibration targets, coverage and vaccine efficacy for 1 dose and 3 doses including their 95% confidence intervals are provided in the Appendix I-IV. [23-24]

Model development

For each model, we considered age-specific coverage with 1 and 3 doses of HPV vaccine, accounting for published efficacy against infection for both 1 and 3 dose vaccination, to compute the fraction of the population considered unprotected (either unvaccinated, or vaccinated but not fully protected) and protected from HPV infection. These proportions

protected by HPV vaccination were applied to baseline age-specific HPV infection rates to compute estimates of infection post-vaccination implementation. These estimates were compared across models (see Sensitivity analysis, below).

Sensitivity analysis

The initial model was created using point estimates from published data. Additionally, we modeled a best case scenario – utilizing the higher bound of the confidence interval for vaccine coverage and lower bound of the confidence interval for infection prevalence, and a worst case scenario – utilizing the lower bound of the confidence interval for vaccine coverage and higher bound of the confidence interval for infection prevalence. We also estimated an ideal condition, assuming 80% uptake of the three dose HPV vaccine series, in accordance with Healthy People 2020 goals. [25]

Result

We estimate that between 2007 and 2012, HPV vaccination at currently documented levels reduced the prevalence of HPV infection by 39% among 14-19 year-olds (5.8% to 3.6%), 24.8 % reduction in the prevalence among 20-24 year-olds (13.7% to 10.3%), and 9.5% for females aged 25 to 29 (7.4% to 6.7%). With little vaccination among older age groups, we observed a small increase in infection prevalence of 2.7% among females aged 30 to 34. (Figure 1. A)

Accounting for the uncertainty in the estimates used for our data inputs through modeling best and worst case confidence interval combinations, these estimates can range from 36.5% to 40.0% for 14-19 year-olds, 22.3% to 27.2% for those who are 20-24 years old,

8.0% to 11.1% for females aged 25-29 and an increased prevalence up to 2.7% for females who are 30 to 34 years old. (Figure 1. B-C) A summarization of infection cases that have already been protected and could have been averted for each age group were shown in appendix V-VI)

Figure 2. A-C documents the gap of potentially prevented HPV infections that are not prevented due to suboptimal HPV vaccine coverage, compared to Healthy People 2020 goals. For example, we estimate that by 2012, the HPV infection prevalence among 14-19 year-olds is 3.6%, whereas with 80% HPV vaccine coverage, this could be reduced to 1.7%. While this corresponds to a decrease of over 446,000 infections in this age group compared to the pre-vaccine era, there are still over 242,000 infections occurring that could have been prevented by reaching HP2020 goals. A summary of these prevented, and potentially prevented, infections is shown in table 2.

Discussion

Our model estimates that between 2007 and 2012, HPV vaccination has prevented 1,131,327 HPV type 16/18 infections in females aged 14 to 34. While this is a positive step in reducing the burden of HPV-related cancers, continued suboptimal HPV vaccine uptake, particularly relative to the Healthy People 2020 goals, there have been 1,929,613 infections estimated to occur that could have been prevented with HPV vaccine uptake meeting the Healthy People 2020 goals.

Compared to prior estimates of HPV infection in the pre- and post-vaccine era, [21] our estimates of infections in the post-vaccine era are higher for females aged 14-19 and 30-34, but lower for 25-29 years-old. This may be due to possible effects of herd immunity which were not modeled in this assessment. [14] Additionally, the use of multiple different data sources with different sampling and assessment methods may have contributed to differences in estimates.

To our knowledge, this is the first effort to quantify the number of HPV infections that could have been averted with optimal utilization of HPV vaccine in the US setting, compared to the current vaccine uptake levels. HPV infection is extremely common. As Bui, T etc.' study report, the prevalence of HPV infection is estimated to be 48.6%, [26] it is claimed by Tom, A. etc. that an estimated 80% of individuals infected by HPV at some point during their lifetime. [27] Therefore, while there have been substantial decreases in the number of HPV infections in the US, even with suboptimal vaccine uptake, it is important to know how many HPV infections can be could be protected by a more complete vaccination strategy.

One of our strengths of this study is to evaluate infection prevalence over time. Analyzing HPV type 16/18 infection rates over time from 2007 to 2012 enables us to evaluate the magnitude of these changes with increasing HPV vaccine coverage. [13] [28-39] . An additional strength of this study is using data obtained from multiple large studies in recent years as inputs for our model. This provided us with the opportunity to assess not just point estimates, but best and worst case scenarios assuming higher coverage and

lower infection prevalence, and lower coverage and higher infection prevalence, respectively, based on published confidence intervals.

However, there are some limitations of this study. In this study, we intended to estimate the potential infection that could have been avoided by type 16/18 HPV vaccination for females aged 14 to 34 in the US. A simple Excel-based static model was developed to assess the avertable burden by calculating infection cases. Without constructing a micro-simulation model, [40-42] a detailed natural disease history cannot be reflected, in addition, uncertainties regarding natural history of disease were not able to be considered. For example, the effect of herd immunity is difficult to be estimated, which may overestimate the performance of vaccination; additionally, effectiveness of type 16/18 HPV vaccination can be underestimated because of the potential for cross-protection between non-vaccine HPV types. [14] Moreover, our target population only include females instead of both genders, thus we were not able to account for infection related to transmission between males and females. Future studies, as adequate data are collected for male vaccine coverage, should be conducted for both genders. Additionally, we considered only infection prevalence; other measures, such as lifetime risk of cancer, DALYs and incremental cost-effectiveness ratios can be further explored using similar comparison methodologies in future analysis.

While using multiple large data sources was a strength to our study, it was also a limitation. For some age groups where complete 3-dose vaccine coverage was not available, we extrapolated coverage levels from the most recent age/period cohorts (e.g.

3-dose coverage for 18-year-olds, when not directly available, was assumed to be the same as 3-dose coverage for 17-year-olds during the previous year). As the result of extrapolation, some infection prevalence values were not able to be adequately computed due to extrapolated 3-dose vaccine coverage being higher than documented 1-dose vaccine coverage. In these cases, we set these values to 0 infections, to obtain a more conservative estimate of the infection prevalence.

In conclusion, large gains have been made in prevention of high-risk HPV infections due to vaccination, but we are still falling short of documented vaccination goals. Every year that we do not reach optimal vaccination levels, potentially preventable HPV infections will continue to occur. This highlights the need for multi-focal interventions to improve HPV vaccination coverage among adolescents and young adults.

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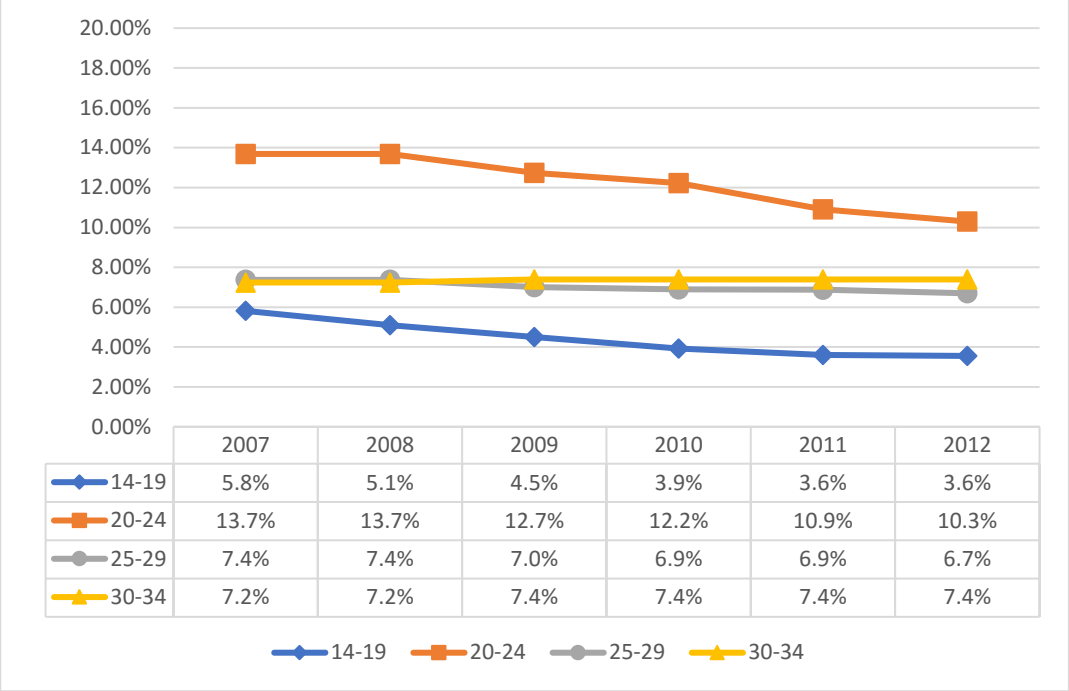
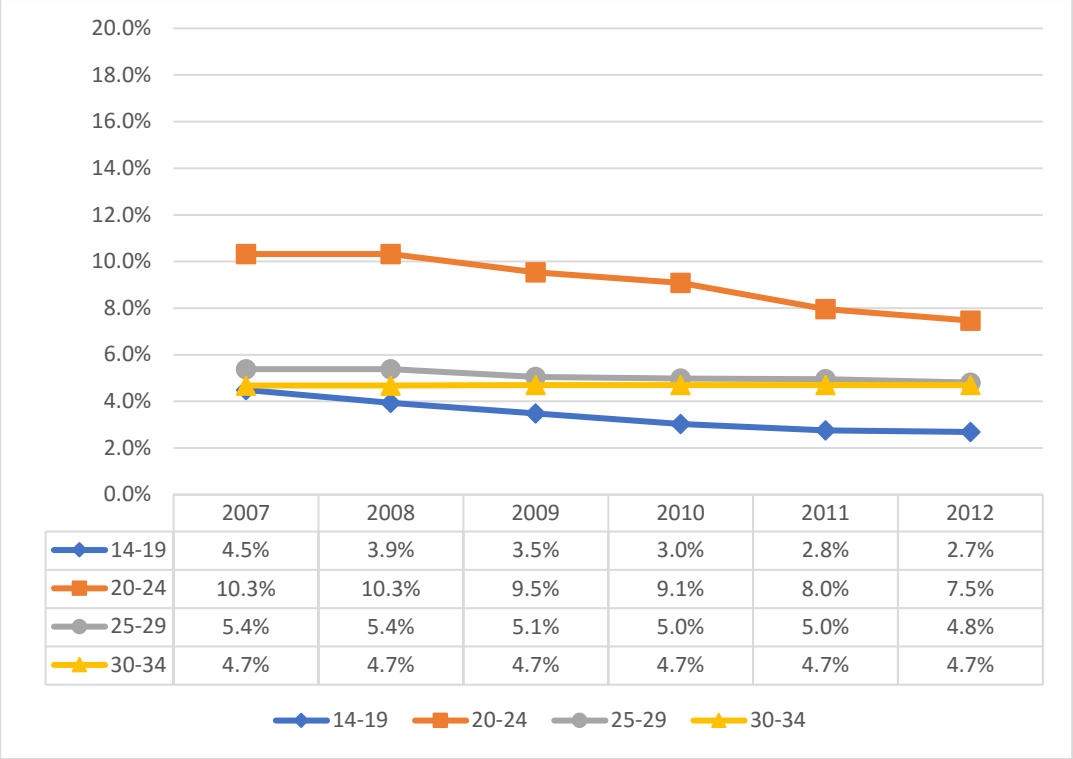
Figures and Tables



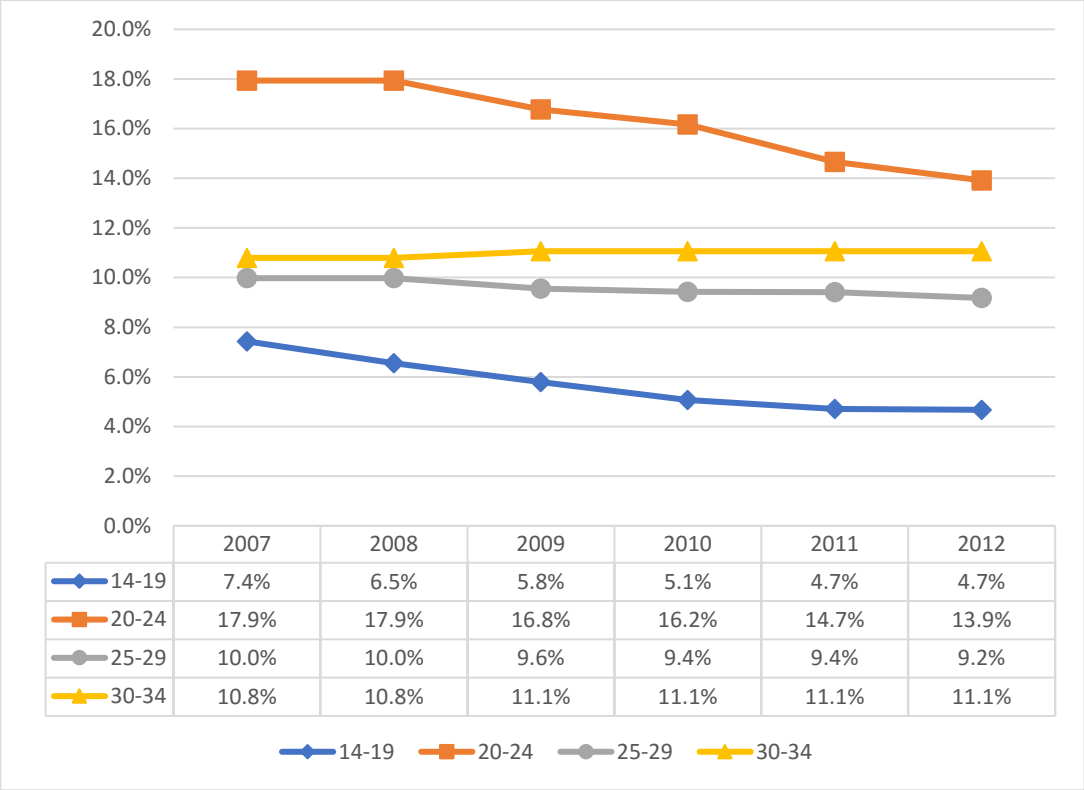
	2007	2008	2009	2010	2011	2012
14-19	5.8%	5.1%	4.5%	3.9%	3.6%	3.6%
20-24	13.7%	13.7%	12.7%	12.2%	10.9%	10.3%
25-29	7.4%	7.4%	7.0%	6.9%	6.9%	6.7%
30-34	7.2%	7.2%	7.4%	7.4%	7.4%	7.4%

Figure1. A Trend of infection prevalence of HPV type 16/18 at current HPV vaccine coverage levels from 2007 to 2012, United States.



	2007	2008	2009	2010	2011	2012
14-19	4.5%	3.9%	3.5%	3.0%	2.8%	2.7%
20-24	10.3%	10.3%	9.5%	9.1%	8.0%	7.5%
25-29	5.4%	5.4%	5.1%	5.0%	5.0%	4.8%
30-34	4.7%	4.7%	4.7%	4.7%	4.7%	4.7%

Figure 1. B Trend of infection prevalence of HPV type 16/18 in a best case scenario based on estimate bounds for vaccine coverage and infection prevalence, from 2007 to 2012, United States.



	2007	2008	2009	2010	2011	2012
14-19	7.4%	6.5%	5.8%	5.1%	4.7%	4.7%
20-24	17.9%	17.9%	16.8%	16.2%	14.7%	13.9%
25-29	10.0%	10.0%	9.6%	9.4%	9.4%	9.2%
30-34	10.8%	10.8%	11.1%	11.1%	11.1%	11.1%

Figure 1. C Trend of infection prevalence of HPV type 16/18 in a worst case scenario, based on estimate bounds for vaccine coverage and infection prevalence, from 2007 to 2012, United States.

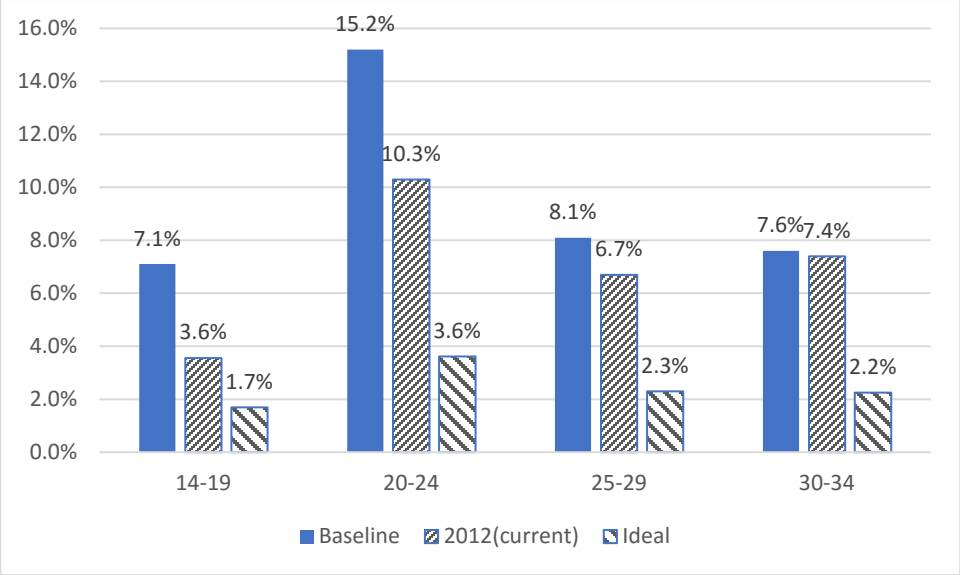


Figure 2. A Cumulative infection prevalence of HPV type 16/18 at current vaccine coverage level for each age group, 2007-2012, United States.

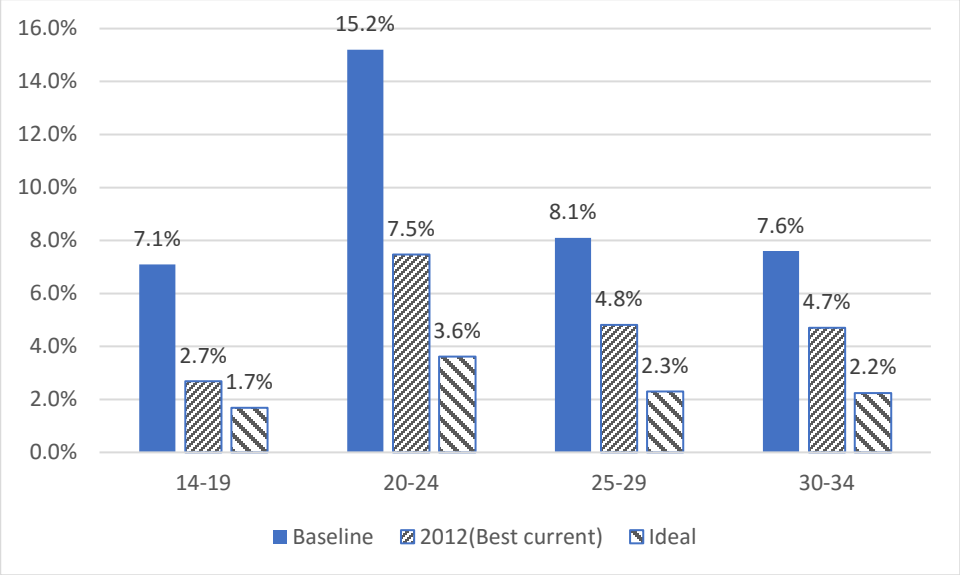


Figure 2. B Cumulative infection prevalence of HPV type 16/18 in a best case scenario, based on estimate bounds for vaccine coverage and infection prevalence, for each age group, 2007-2012, United States.

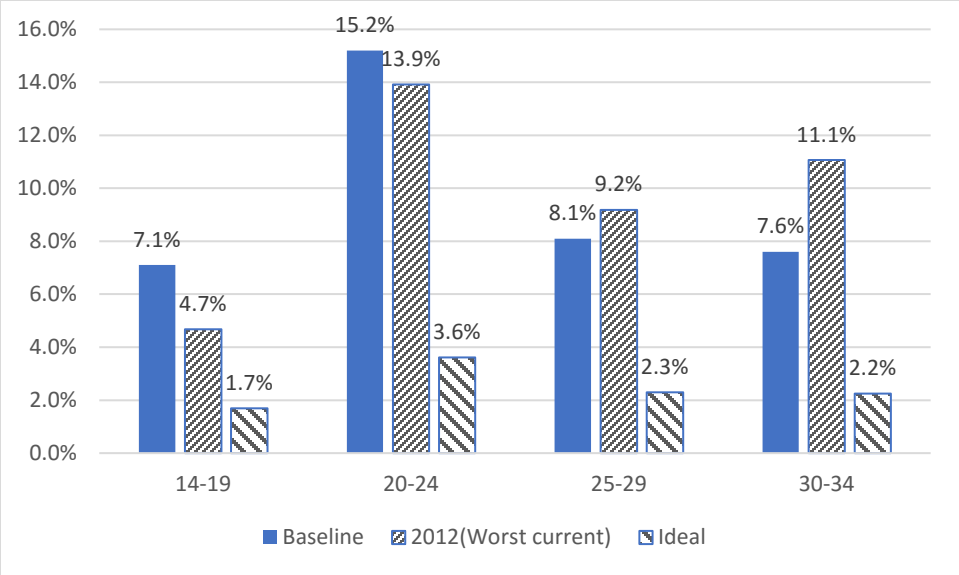


Figure 2. C Cumulative infection prevalence of HPV type 16/18 in a worst case scenario, based on estimate bounds for vaccine coverage and infection prevalence, for each age group, 2007-2012, United States.

Table 1. Parameters used in models

Item	Source	Value (95% CI)
Age-specific population	American factfinder[22]	Age 13-2,013,099 Age 14-2,030,439 Age 15-2,065,798 Age 16- 2,100,105 Age 17- 2,132,142 Age 18- 2,195,382 Age 19- 2,243,250 Age 20- 2,210,810 Age 21- 2,131,096 Age 22- 2,086,845 Age 23- 2,057,772 Age 24- 2,085,300 Age 25- 2,101,042 Age 26- 2,055,217 Age 27- 2,108,218 Age 28- 2,096,644 Age 29- 2,105,137 Age 30- 2,124,866 Age 31- 1,982,063 Age 32- 1,992,371 Age 33- 1,943,287 Age 34- 1,923,012
Age-specific Infection prevalence (%)	Markowitz, L., Liu, G., Hariri, S., Steinau, M., Dunne, E., & Unger, E. (2016). Prevalence of HPV After Introduction of the Vaccination Program in the United States. *PEDIATRICS*, *137*(3), e20151968-e20151968. [21]	Age 14-19 7.1 (5.8-8.7) Age 20-24 15.2 (11.7-19.5) Age 25-29 8.1 (6.1-10.7) Age 30-34 7.6 (5.0-11.2)
1 dose coverage	1). The National Immunization Survey-Teen 2008-2012[23][48-57] 2). The National Health Interview Survey (NHIS)[24-57]	Appendix I
3 dose coverage	1). The National Immunization Survey-Teen 2008-2012 [23][48-57] 2). The National Health Interview Survey (NHIS) [24-57]	Appendix II
Ideal coverage	Healthy people 2020[25]	80%

Item	Source	Value (95% CI)
1 dose VE	Bellew, S. & Del Rosso, J. (2010). Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Yearbook Of Dermatology And Dermatologic Surgery*, *2010*, 189-190. http://dx.doi.org/10.1016/s0093-3619(10)79624-6[19] Schiller, J., Castellsagué, X., & Garland, S. (2012). A Review of Clinical Trials of Human Papillomavirus Prophylactic Vaccines. *Vaccine*, *30*, F123-F138. http://dx.doi.org/10.1016/j.vaccine.2012.04.108[43]	Appendix III
3 dose VE	Khardori, N. (2009). Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24–45 years: a randomised, double-blind trial. *Yearbook Of Medicine*, *2009*, 147-148. http://dx.doi.org/10.1016/s0084-3873(09)79608-7[20] X Castellsague´*,1, N Mun˜oz2, P Pitisuttithum3, D Ferris4, J Monsonego5, K Ault6, J Luna2, E Myers7, S Mallary8, X Castellsague´*,1, N Mun˜oz2, P Pitisuttithum3, D Ferris4, J Mo (May 2011) "End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24–45 years of age ". British Journal of Cancer (2011) 105: 28-37[44]	Appendix IV

Table 2. Cumulative reduction of HPV Type 16/18 infection prevalence by 2012 for each age group, United States.

	Number of reduced cases (n)	Additional number of cases that could have been averted compared to ideal level(n)
14-19	446,849	242,575
20-24	518,019	708,312
25-29	146,528	460,515
30-34	19,931	518,211

Appendix I- Coverage with at least 1 dose of HPV vaccine, as estimated by national surveys [23-24][48-57]

Age/Year	2007	2008	2009	2010	2011	2012
14	0.228	0.338	0.406	0.455	0.455	0.494
15	0.274	0.422	0.46	0.564	0.564	0.539
16	0.244	0.357	0.499	0.592	0.592	0.558
17	0.25	0.385	0.471	0.628	0.628	0.642
18	0.105	0.251	0.372	0.443	0.487	0.53
19	0.105	0.105	0.171	0.207	0.431	0.443
20	0.105	0.105	0.171	0.207	0.431	0.443
21	0.105	0.105	0.171	0.207	0.431	0.443
22	0.105	0.105	0.171	0.207	0.215	0.282
23	0.105	0.105	0.171	0.207	0.215	0.282
24	0.105	0.105	0.171	0.207	0.215	0.282
25	0.105	0.105	0.171	0.207	0.215	0.282
26	0.105	0.105	0.171	0.207	0.215	0.282
27	0.103	0.103	0.147	0.147	0.147	0.147
28	0.103	0.103	0.147	0.147	0.147	0.147
29	0.103	0.103	0.147	0.147	0.147	0.147
30	0.057	0.057	0.033	0.033	0.033	0.033
31	0.057	0.057	0.033	0.033	0.033	0.033
32	0.057	0.057	0.033	0.033	0.033	0.033
33	0.057	0.057	0.033	0.033	0.033	0.033
34	0.057	0.057	0.033	0.033	0.033	0.033

Appendix II- Coverage with 3 dose coverage of HPV vaccine, as estimated by national surveys [23-24][48-57]

Age/Year	2007	2008	2009	2010	2011	2012
14	0.059	0.166	0.232	0.292	0.292	0.287
15	0.059	0.185	0.257	0.378	0.378	0.353
16	0.059	0.188	0.332	0.4	0.4	0.391
17	0.059	0.209	0.267	0.445	0.445	0.445
18	0.213125	0.059	0.179	0.267	0.319	0.348
19	0.213125	0.213125	0.346	0.346	0.346	0.346
20	0.095408	0.095408	0.181	0.181	0.181	0.181
21	0.095408	0.095408	0.181	0.181	0.181	0.181
22	0.095408	0.095408	0.181	0.181	0.181	0.181
23	0.095408	0.095408	0.181	0.181	0.181	0.181
24	0.095408	0.095408	0.181	0.181	0.181	0.181
25	0.054035088	0.054035088	0.088	0.088	0.088	0.088
26	0.054035088	0.054035088	0.088	0.088	0.088	0.088
27	0.061659864	0.061659864	0.088	0.088	0.088	0.088
28	0.061659864	0.061659864	0.088	0.088	0.088	0.088
29	0.061659864	0.061659864	0.088	0.088	0.088	0.088
30	0.020727273	0.020727273	0.012	0.012	0.012	0.012
31	0.020727273	0.020727273	0.012	0.012	0.012	0.012
32	0.020727273	0.020727273	0.012	0.012	0.012	0.012
33	0.020727273	0.020727273	0.012	0.012	0.012	0.012
34	0.020727273	0.020727273	0.012	0.012	0.012	0.012

Appendix III- Vaccine efficacy with at least 1 dose of HPV vaccine [19][43]

Age/Year	2007	2008	2009	2010	2011	2012
14	0.899	0.899	0.899	0.899	0.899	0.899
15	0.899	0.899	0.899	0.899	0.899	0.899
16	0.899	0.899	0.899	0.899	0.899	0.899
17	0.899	0.899	0.899	0.899	0.899	0.899
18	0.899	0.899	0.899	0.899	0.899	0.899
19	0.899	0.899	0.899	0.899	0.899	0.899
20	0.899	0.899	0.899	0.899	0.899	0.899
21	0.899	0.899	0.899	0.899	0.899	0.899
22	0.899	0.899	0.899	0.899	0.899	0.899
23	0.899	0.899	0.899	0.899	0.899	0.899
24	0.899	0.899	0.899	0.899	0.899	0.899
25	0.899	0.899	0.899	0.899	0.899	0.899
26	0.809	0.809	0.809	0.809	0.809	0.809
27	0.809	0.809	0.809	0.809	0.809	0.809
28	0.809	0.809	0.809	0.809	0.809	0.809
29	0.809	0.809	0.809	0.809	0.809	0.809
30	0.809	0.809	0.809	0.809	0.809	0.809
31	0.809	0.809	0.809	0.809	0.809	0.809
32	0.809	0.809	0.809	0.809	0.809	0.809
33	0.809	0.809	0.809	0.809	0.809	0.809
34	0.809	0.809	0.809	0.809	0.809	0.809

Appendix IV- Vaccine efficacy with 3 dose of HPV vaccines[20][44]

	2007	2008	2009	2010	2011	2012
14	0.953	0.953	0.953	0.953	0.953	0.953
15	0.953	0.953	0.953	0.953	0.953	0.953
16	0.953	0.953	0.953	0.953	0.953	0.953
17	0.953	0.953	0.953	0.953	0.953	0.953
18	0.953	0.953	0.953	0.953	0.953	0.953
19	0.953	0.953	0.953	0.953	0.953	0.953
20	0.953	0.953	0.953	0.953	0.953	0.953
21	0.953	0.953	0.953	0.953	0.953	0.953
22	0.953	0.953	0.953	0.953	0.953	0.953
23	0.953	0.953	0.953	0.953	0.953	0.953
24	0.953	0.953	0.953	0.953	0.953	0.953
25	0.953	0.953	0.953	0.953	0.953	0.953
26	0.881	0.881	0.881	0.881	0.881	0.881
27	0.881	0.881	0.881	0.881	0.881	0.881
28	0.881	0.881	0.881	0.881	0.881	0.881
29	0.881	0.881	0.881	0.881	0.881	0.881
30	0.881	0.881	0.881	0.881	0.881	0.881
31	0.881	0.881	0.881	0.881	0.881	0.881
32	0.881	0.881	0.881	0.881	0.881	0.881
33	0.881	0.881	0.881	0.881	0.881	0.881
34	0.881	0.881	0.881	0.881	0.881	0.881

Appendix V - Reduction of HPV Type 16/18 infection cases by 2012 (best scenario) for each age group

	Number of reduced cases (n)	Additional number of cases that could have been averted compared to ideal level(n)
14-19	561,753	127,671
20-24	814,030	412,301
25-29	345,387	261,656
30-34	289,002	249,140

Appendix VI - Reduction of HPV type 16/18 infection cases by 2012 (worst scenario) for each age group

	Number of reduced cases (n)	Additional number of cases that could have been averted compared to ideal level (n)
14-19	306,411	383,013
20-24	137,434	1,088,898
25-29	-115,129	722,172
30-34	348,796	886,938