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Modeling the impact of 13RS-HB358: HPV vaccination for school entry in a high-prevalence state

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ABSTRACT

Prophylactic cancer vaccination presents novel opportunities to improve the health and well-being of populations. Since the approval of a cervical cancer vaccine against human papillomavirus (HPV) in 2006, only three states have passed legislation adding it to their school-entry schedules of required vaccinations. Despite ample evidence of its safety and efficacy, the vaccine remains controversial, and national vaccination rates among both girls and boys remain low. Risk for HPV-related cancers varies by population, and Appalachian Kentucky has among the highest HPV-related morbidity and mortality in the nation. Annual attempts to pass HPV vaccine legislation in Kentucky have so far failed in the absence of directly targeted quantitative data on the risks and rewards of action vs. inaction. We herein present the first known impact assessment of an HPV vaccine school entry requirement for the state of Kentucky, using a transmission-dynamic model to simulate vaccine scenarios in the context of Kentucky's high HPV disease burden and unique population characteristics. Our findings suggest that over the lifetime of those first vaccinated after passage, such a policy could prevent approximately 18 thousand cancers and 3 thousand deaths; preserve 18 thousand life-years and more than 34 thousand quality-adjusted life years; and save as much as 1.3 billion USD in the state of Kentucky.

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ACRONYMS AND ABBREVIATIONS

13RS-HB358 – 2013 Regular Session, House Bill 358
4vHPV – Quadrivalent HPV
9vHPV – Nonavalent HPV
AAFP – American Academy of Family Physicians
AAP – American Academy of Pediatrics
ACIP – Advisory Committee on Immunization Practices
ACOG – American College of Obstetricians and Gynecologists
ACP – American College of Physicians
ASTHO – Association of State and Territorial Health Officials
CAST – Centre for Applied Health Services Research and Technology
CDC – Centers for Disease Control and Prevention
CPSTF – Community Preventive Services Task Force
DCC – Distant Metastatic Cervical Cancer
FDA – Food and Drug Administration
HHS – Department of Health and Human Services
HPV – Human Papillomavirus
HPV-MOK – Human Papillomavirus Model of Kentucky
ICER – Incremental Cost-Effectiveness Ratio
JORRP – Juvenile Onset Recurrent Respiratory Papillomatosis
LCC – Locally Invasive Cervical Cancer
NGO – Non-governmental Organization
OECD – Organization for Economic Co-operation and Development
Pap – Papanicolaou
PCE – Personal Consumption Expenditure
PV – Present Value
QALY – Quality Adjusted Life Year
RCC – Regionally Invasive Cervical Cancer
SIS – Susceptible-Infectious-Susceptible
TDAP – Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
USA – United States of America
USD – United States Dollar
WHO – World Health Organization

INTRODUCTION

The possibility of cancer prevention by vaccination has tantalized physicians, scientists, and the public health community for over a century, at least since Coley's attempts to use bacterial immunotherapy for cancer treatment laid the foundation for the use of Bacillus Calmette-Guérin to prevent the recurrence of superficial bladder cancer.[1] Later, vaccination against Hepatitis B to prevent hepatocellular carcinoma was based on Blumberg's Nobel Prize-winning work demonstrating the causal link between hepatitis B and HCC during the 1960s and '70s.[1]

But these developments were only harbingers of the idea's potential, recurrent bladder and hepatitis B-related liver cancers being relatively rare. The biggest breakthrough in cancer vaccination to date emerged during the early 1990s from clinical trials testing the safety and efficacy of vaccines against two human papillomavirus (HPV) types implicated in cervical cancer[1] - the second most common cancer among women in highly developed countries, and a leading female malignancy and cause of death among middle-aged women in 'developing' nations.[2] The Food and Drug Administration (FDA) subsequently approved a quadrivalent HPV (4vHPV) vaccine (Gardasil™, Merck & Co., Inc.)[3] covering types 6, 11, 16, and 18 for the prevention of genital warts and cervical cancers in 2006,[1] making it the first licensed vaccine against a common sexually transmitted infection.[4] Together, these four HPV types etiologically account for approximately 68% of squamous cell cervical cancers, 83% of adenocarcinomas of the cervix, 90% of anogenital condylomas,[5] and a large fraction of all other anogenital and oropharyngeal dysplasias and malignancies in both males and females.[5,6] A nonavalent (9vHPV) vaccine was approved by the FDA in 2015, which adds the high-risk types 31, 33, 45, 52, and 58, and has the potential to prevent the large majority of all health-relevant HPV infections.[7]

Though the vast majority of countries set vaccine policy at the national level, the United States (USA) does not. Instead, each state, district, or territory retains authority to set public health policy, including vaccine policy. Nevertheless, the USA has a long history of mandatory vaccination, with conditions for school entry dating back to the early 1800s.[8] Today, all 50 of her states have school-entry vaccine laws, but only three states or districts – Washington, D.C., Virginia, and Rhode Island – have so far added the HPV vaccine to their respective school entry schedules, despite strong endorsement of school entry policies to increase vaccine schedule adherence from the Community Preventive Services Task Force (CPSTF),[9] the Association of State and Territorial Health Officials (ASTHO),[10] and public health agencies throughout the USA. The Centers for Disease Control and Prevention (CDC) HPV vaccine recommendations are for both females and males, but so far only Rhode Island's legislation has included males in its mandate.[11]

The reasons for failure of state lawmakers to move HPV vaccine legislation forward are complex. Here, it is sufficient to note that this failure is not due to a lack of evidence for, or informed support of, the effectiveness of school entry requirements to increase vaccine uptake, population coverage, and disease reduction. According to the CPSTF's systematic review of seventeen scientific studies examining the effectiveness of state or local vaccination requirements on changes in vaccination rates, the median change was an increase of 18%.[12] Other studies reviewed in their report found significant reductions in vaccine-preventable disease rates in states with school entry laws requiring that vaccine.[9,12]

Kentucky was among the first states to propose HPV vaccine legislation immediately following the FDA's approval and the CDC's recommendation release in 2006. But here, as elsewhere in the country, the legislation faced a large pushback that continues today. Kentucky-

specific quantitative data is one critical factor missing from the HPV vaccine policy discussion in Kentucky's capital, Frankfort. Until recently, the epidemiology of HPV in Kentucky was presumed to match that estimated for the USA's general population. But data published in 2017 identified prevalence rates in Appalachian Kentucky 2-5 times higher than national age-matched averages,[13] consistent with the high incidence of HPV-related cancers at-large in Kentucky, and the even higher rates observed in the Appalachian region of the state.

New information creates new possibilities. New targeted prevalence data can now be used to inform population-specific modeling of the potential impact of legislation adding the HPV vaccine to the school entry schedule in Kentucky. This paper presents one such quantitative estimate of impact, and thus fills a critical gap necessary for rational, evidence-based health policy discussion in the Commonwealth.

BACKGROUND

Papillomaviruses are a ubiquitous family of non-enveloped DNA viruses infecting virtually all amniotes, including humans.[14] More than 150 human papillomavirus (HPV) types have been sequenced and are divided into five evolutionary groups[15] found to infect epithelial mucosa, cutaneous membranes, or both. Clinically relevant HPV types are categorized by their known associations with human cancers, as either high-risk or low-risk serotypes.

HPV is the most common sexually transmitted infection in the world, with an estimated 6 million or more new infections annually in the United States alone.[8] We now know that HPV is the necessary cause of cervical[16] and other cancers,[17] being found in 99.7% of all cervical cancer tissue specimens, low- and high-grade squamous intraepithelial lesions, and abnormal Papanicolaou (Pap) test results.[18] Yet, as recently as 1970, the HPV virus was assumed to be a monotypic, medically irrelevant, spontaneously cleared nuisance.[19] Only during the decades following the advent and development of recombinant DNA technology[20] did a fuller picture emerge of the diversity of its biology and disease-causing capacity.[4,21]

HPV exposure most commonly, but not necessarily, results from sexual contact. Though most infections resolve over time, persistent infections with oncogenic types have been shown to cause cervical cancer[17] – the second most common cancer among women worldwide – and plays a central role in subsets of several other invasive cancers, including those of the vagina, vulva,[22] penis,[23] anus,[24] oral cavity and pharynx.[25] Other diseases associated with HPV types include precancerous lesions of the cervix (cervical intraepithelial neoplasias),[26] oral papillomas, genital warts, respiratory papillomatosis, and in rare cases, epidermodysplasia verruciformis among the immunocompromised.[27]

Estimates of global deaths attributable to cervical cancer alone[28] approximate estimates of global all-cause maternal mortality[29] – the subject of far more international attention than the former. As much as 88% of these deaths occur in low-income countries.[28] Projection of cervical cancer mortality through 2030 is bleaker, with half a million annual deaths expected. Furthermore, rates in sub-Saharan Africa are expected to double,[30] even though the vast majority could be prevented by existing vaccine technology. Overall, the direct annual medical costs attributable to HPV in the USA during the period of 2004-07 was estimated to have been between 4 and 14 billion USD.[31]

HPV Vaccine Policy

During the first decade of the HPV vaccine era, national programs have been successfully implemented, either preemptive or subsequent to WHO recommendations, in countries such as Australia,[32] Belgium,[33] Canada,[34] Denmark,[35,36] France,[37] Greece,[38] Iceland,[39] Israel,[40] Italy,[41] Japan,[42] New Zealand,[43] Norway,[44] Portugal,[45] Singapore,[46] Spain,[47] Sweden,[48] and the United Kingdom of Great Britain and Northern Ireland.[49] Further, many middle- and low-income, recently developed or developing countries such as Argentina,[50] Brazil,[51–53] Brunei,[54] Mexico,[55] Slovenia and Macedonia,[56] and Uganda[57], among others, have begun national vaccination campaigns. As of 2016, a total of 86 countries had added the HPV vaccine to their national vaccination schedules.[58] However, international vaccine pricing practices favor high-income countries, for whom the sum health and economic benefits from the vaccine are greatest,[59] which furthers the irony of low policy and programmatic adoption in the USA.

There is no national vaccination program in the USA. The federal government is highly limited in its role within vaccine policy and delivery to one of setting agendas, guidelines, and recommendations. Instead, each state regulates vaccination within its borders largely through

laws that require students to prove adherence to a medically-informed, but politically-derived, vaccination schedule before allowed entry to schools, and in some cases, daycares and colleges.

The Advisory Committee on Immunization Practices (ACIP),[60] which informs the official policies of both the CDC and the Department of Health and Human Services (HHS), recommends both males and females ages 11 or 12 receive the HPV vaccine. It further recommends that unvaccinated females between 13-26 and males 13-21 years of age also receive the full series.[61] Many other federal and state health or disease agencies have added HPV vaccination for both girls and boys before sexual debut to their priority agendas, including the President's Cancer Panel,[62] the National Foundation for Infectious Diseases,[63] and the National Cancer Institute.[64] National medical non-governmental organizations (NGOs) and advocacy groups, too, have published supportive positions on universal HPV vaccination, including the American College of Obstetricians and Gynecologists (ACOG),[65] the American Academy of Family Physicians (AAFP),[66] the American Academy of Pediatrics (AAP),[67] and the American College of Physicians (ACP).[68]

For years, HPV vaccine uptake in the USA had remained one of the lowest among the Organization for Economic Co-operation and Development (OECD) nations, due, in part, to the fractured and inconsistent nature of healthcare policy and delivery in the US system. But recently, the USA has made progress in relation to its peers: In 2015, 52.2% (+/- 1.8) of girls and 39% (+/- 1.7) of boys between ages 13-17 had received at least 2 HPV vaccine doses, though rates varied significantly by region, and state,[69] placing the USA more squarely near the mean for high-income countries (48.5% [CI: 38.6 - 59.3]).[70]

HPV in Kentucky

In arguing for a transformative framework for global health justice, and in reference to impoverished and developing nations, Gostin argued that health inequalities represent an enduring and consequential global health challenge.[71] Yet one need not travel beyond US borders to identify dramatic examples of "the inequitable distribution of disease and early death".[71]

The Appalachian cultural region, which includes parts of 13 eastern USA states and approximately 25 million people, is characterized by poor socioeconomic, health, and environmental indicators,[72] especially in the central Appalachian states of West Virginia, Ohio, and Kentucky.[73] Appalachian Kentucky, in a state recognized for its high HPV-related cancer burden[74] and low HPV vaccination rates,[75] has among the highest HPV-related cancer death rates – for both males and females – in the United States.[76] In addition to the social determinants that shape health status in Appalachian Kentucky, specific risk factors for the development of HPV-related cancers are common is this population. High smoking rates, risky sexual behavior,[77] lower screening and vaccination rates, high comorbidities,[78] and even fatalistic beliefs[79] may all be contributing factors.

The HPV-related cancer incidence rate in non-Appalachian Kentucky has been assessed at 22.0 and 21.3 per hundred thousand for females and males, respectively. The rate for Appalachian Kentucky is even higher, at 24.6 and 21.9, female and male.[76] Another study calculated the relative risk of Appalachian Kentuckians for cervical cancer as 1.23 that of non-Appalachian Kentuckians.[80] For some counties of Appalachia, like Harlan County, KY, the rate is nearly three times (21.1) the national rate per hundred thousand (8.1; all values age-adjusted to the 2000 US Standard Million Population).[76] Mortality rates from HPV-related cancers in

Kentucky are similarly high: 3.2 for cervical cancer (but 4.8 for African American Kentuckians), 0.8 for vaginal and vulvar cancers, and 3.0 for oral and pharyngeal cancers (per hundred thousand; age-adjusted).[81] Therefore, any study of Kentucky health policy must consider the disparate distribution of disease burden within the state, and therefore the inevitably disparate distribution of health policy effects.

Until now, Kentucky-specific HPV infection prevalence data has not been available. However, data collected between 2013 and 2014 by Crosby and Vanderpool, et al.[82] has recently been analyzed for type-specific prevalence and risk factors among a co-screening aged cohort of 398 women in Appalachian Kentucky.[13] Any-type HPV prevalence was found to be 55.6%; 33.3% for high-risk, and 45.5% for low-risk types. Fifty percent of those infected were infected with at least one nonavalent (9vHPV; Gardasil 9™) vaccine type, and 70.5% of infected women had multiple simultaneous infections. For women in the youngest age group in the study, aged 30-34, the any-type prevalence was 58.3%. This is an important point, because in most studies of HPV epidemiology to date, the highest prevalence rates have been found among women under 30 years of age, and usually under 25. If similar ratios hold in Kentucky, then the risk pool into which young Appalachian Kentuckians are sexually debuting may carry a significantly higher viral load than reflected by these already high prevalence rates, and much higher than the age-matched national averages.

HPV Vaccination in Kentucky

Nationally, approximately 40% of girls aged 13-17 had received the (then) full 3-dose HPV vaccine series in 2014.[83] The rate among boys was much lower – nearly half, at 21.6% - but still an increase of more than 8% over the previous year.[83,84] Though the burden of HPV

infection and disease is higher in Kentucky than in most of the US, HPV vaccine uptake has lagged, especially among males. According to 2014 data collected and published by the CDC, the adolescent HPV vaccine completion rate in Kentucky was 37.5 and 13.3% for females and males, respectively.[83] Promisingly, since 2016, CDC guidelines now recommend a 2-dose schedule for girls and boys under 14 years of age, which is likely to improve compliance rates going forward, though the degree of its effect is not yet known.[85]

HPV Vaccine Policy in Kentucky

HPV vaccine legislation has been debated in Kentucky since the 2006 legislative session, when bills 143, 345, and 327 were introduced in the House. Since then, at least six other bills have been proposed. During the 2013 regular session, house bill 358 (13RS-HB358), which proposed to amend KRS 214.034 to require the HPV vaccine for females (ages 9-16) and males (ages 10-16) entering 6th grade, and to require parental withholding of consent be kept on file by schools, died in the Kentucky Senate following house passage, 54-40.[86] 13RS-HB358 is the closest to evidence-based HPV legislation Kentucky has come, and has therefore been used to define this study's simulation parameters for HPV legislation in Kentucky.

The questions addressed by this study, of whether and to what degree Kentucky's current vaccination rates may contribute to a herd immunity; or may reduce the overall prevalence of HPV infection in the Commonwealth; or may impact the health outcomes of current cohorts compared to those preceding and unvaccinated; or may compare to future cohorts with even greater vaccine coverage – should legislation like 13RS-HB358, which proposed to add the HPV vaccine to the state's school entry schedule of required vaccines, pass in Kentucky – are both timely and consequential.

METHODS

Study Goal, Objectives, Aims

Our goal was to generate novel, population-specific quantitative data and to analyze its practical implications for vaccine policy in the Commonwealth of Kentucky, USA.

The main objectives of this study were twofold. First, to broadly assess the HPV vaccine landscape, an overview of the virus' biology, pathology, and epidemiology has been included, as well as a brief account of the efforts so far put forth to develop, test, distribute, and legislate the HPV vaccine (see Background section, above).

Second, to address the central question of the impact of HPV vaccine legislation (such as 13RS-HB358) in Kentucky, we have developed a quantitative computer model of HPV infection, transmission, clearance, and sequelae capable of simulating multiple vaccine policy scenarios. To facilitate evidence-based health policy decision-making relating to the HPV vaccine, we focused on the outcomes of three relevant scenarios:

1. No vaccination: a vaccination rate of zero was used as a control for comparison of scenarios 2 and 3 to a pre-vaccine baseline. In this way, both the progress so far, as well as the health and economic impacts of vaccine legislation, could be estimated.
2. Current vaccination: the current HPV vaccination rates[83] were used to simulate Kentucky's current trajectory and expected benefits should rates remain at current levels.
3. Required vaccination: the HPV vaccination rate was matched to the average compliance rates for Kentucky's currently scheduled 6th-grade entry vaccines (the TDAP booster and the meningococcal vaccine; 2014-16) to simulate passage of legislation similar to 13RS-HB358.

The simulation model herein described was adapted from a previously developed and published model[87] originally tailored to Danish[36] and Irish populations.[88] Parameters of the model

were calibrated to reflect Kentucky's unique incidence, prevalence, risk factors, and population characteristics. Using an agent-based transmission approach, the model simulates infection and disease dynamics over time. At simulation endpoint, model agent states were interpreted as population outcomes, translated to measures of health impact, or extrapolated to address questions of economic impact.

Using this policy impact model for 13RS-HB358, several specific aims were addressed. The primary aim was to determine and compare the epidemiological patterns of infection (in terms of type-specific prevalences) and health outcomes (in terms of cancers prevented and lives saved, measured from baseline) of scenarios 2 and 3.

Next, we calculated the health impact of 13RS-HB358 in terms of the differences in life years and quality-adjusted life years (QALYs) gained over baseline between the two vaccine scenarios.

Finally, to assess the long-term direct economic impact of 13RS-HB358, we calculated the society-payer perspective costs associated with vaccination against future healthcare expenditures averted as an incremental cost-effectiveness ratio (ICER), or cost per QALY, using the oft-cited benchmark of 50,000 USD as the comparative measure of utility.

The Model: Policy Simulations

With the recent arrival of cervical cancer vaccines, modeling studies have become increasingly common and complex, with researchers and agencies alike eager to inform historic policy developments in countries all over the world. The models used vary in step with the complexity of the variables involved, creating a large number of distinguishing characteristics and a variety of model strengths to consider.

To determine which model type would be best suited to this study's goals and objectives, many different characteristics were evaluated: time horizons and discounting; comprehensiveness of included diseases and their natural histories; effectiveness and duration of vaccine-induced protections; herd and cross immunities (i.e., protections to those not directly vaccinated, and protections to HPV types not specifically included in the vaccine, respectively); quality of life; costs and payer perspectives; uncertainty;[89] and the flexibility to accommodate the sex behaviors, age distribution, relevant risk factors, type-specific prevalences, and disease progression rates unique to the population of interest.[90]

Model Type and Targets

In the end, a stochastic, susceptible-infectious-susceptible (SIS), agent-based dynamic model, originally developed by Jens Olsen with the Centre for Applied Health Services Research and Technology Assessment (CAST), University of Southern Denmark, was selected. Commissioned by the Danish government to inform its national HPV vaccine policy, the model simulated the transmission biology of HPV types 6, 11, 16, and 18 under the condition of several assumptions, including 100% vaccine effectiveness and lifetime duration of immunity. Herd immunity is accounted for by the dynamic modelling environment, but it does not recognize cross-immunity to other HPV types. The stochastic agent-based model allows for fine calibration of the sex behaviors, age-specific prevalences, and disease progression rates to the study population. The model uses the NETLOGO multi-agent modeling environment (version 5.3.1; http://ccl.northwestern.edu/netlogo/). For this study, the model was significantly expanded to include all viral types covered by the 9-valent HPV vaccine, and adapted to Kentucky's unique population to address the following scenarios (Table 1):

1. No Vaccination: the cumulative outcomes given no vaccination as a baseline measure against which to compare each of the experimental scenarios
2. Current Vaccination: the cumulative outcomes given 9vHPV vaccination rates of 37.5 and 13.3 percent among 11-year-old girls and boys, respectively
3. Required Vaccination: the cumulative outcomes given 9vHPV vaccination of 83.125 percent[91] of 11-year-old boys and girls

Table 1. Vaccination coverage of 11-year-olds for HPV-MOK simulation scenarios.

Scenario	Vaccination coverage, girls	Vaccination coverage, boys
1. No vaccination (pre-vaccine era)	0%	0%
2. Current vaccination (present day)[83]	37.5%	13.3%
3. Required vaccination (13RS-HB358)[91]	83.125%	83.125%

Disease Model Characteristics

The new model, forthwith referred to as the HPV Model of Kentucky (HPV-MOK), simulates the infection dynamics of the high-risk types 16, 18, 31, 33, 45, 52, and 58, as covered by the nonavalent (9vHPV) vaccine, Gardasil 9. These types have been shown to account for most cervical, vulvar and vaginal, anal, oropharyngeal, and penile precancers and cancers, including 90% of all cervical cancers.[61] In addition, the model simulates low-risk types 6 and 11, also covered by the 9vHPV vaccine, which are believed to cause at least 90% of all anogenital warts,[92] and at least 90% of juvenile onset recurrent respiratory papillomatosis (JORRP).[93] HPV-MOK was also programmed to simulate Kentucky's unique epidemiology of HPV-related cervical diseases (Table 2).

Table 2. HPV-MOK pre-simulation calibration parameters, targets, and values.

Parameter	**Prevalence Target***, %	**Value achieved**, %
HPV6	2.66	2.30
HPV11	0.16	1.12
HPV16	5.03	5.13
HPV18	1.87	2.08
HVP31	2.38	2.52
HPV33	1.13	1.55
HPV45	1.87	2.03
HPV52	3.33	3.27
HPV58	1.59	1.62
Parameter	**Incidence Target,** %	**Value achieved**, %
CIN1	0.29[94]	0.32
Cervical Cancer, incidence	0.015[81]	0.014
Parameter	**Value**	**Source**
Cervical cancer screening rate	81.3; Present KY screening rate	CDC BRFSS[95]
Age at death	76.26; Present KY life expectancy	US Census data
Initial age distribution	Present Kentucky age distribution	US Census data
Initial gender distribution	Present Kentucky gender distribution	US Census data

*Estimated KY prevalences from national (NHANES[96]) and regional (Appalachian Kentucky[13]) data, adjusted by geographic population distribution and age.

Model Assumptions and Variables

With any model, the advantages of simplifications are weighed against their effects on the validity and reliability of predictions. In this case, several simplifications of transmission and clearance dynamics were assumed:

- Heterosexual population
- HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 only
- Persistent HPV infections with an exponential distribution of duration
- No natural immunity
- No cross protection

- No vaccine failure and no waning efficacy
- No risk factors beyond sexual behavior

Because non-cervical HPV infection and disease course progression are poorly understood, it is difficult to realistically model the underlying biological processes of these conditions. To simplify the model while maintaining coherence with real-world measures, the incidences of HPV-related non-cervical disease were assumed to decrease proportionately with that of cervical cancer, which HPV-MOK models directly and in detail. Population variables include viral transmission and clearance dynamics, disease progression and regression probabilities, and similar universally-applicable probabilities. Other variables are agent-specific, distinguishing this class of dynamic modeling from static procedures (see Table 3 for a full list of simulation variables).

Table 3. HPV-MOK simulation variables.

Variable	Value	Source
HPV → CIN1	0.009; Probability per month	Elbasha et al.[97]
CIN1 → HPV/clear (regress)	0.329; Probability per year	
CIN1 → CIN2	0.136; Probability per year	Values determined from model calibration
CIN2 → CIN1 (regress)	0.133; Probability per year	
CIN2 → CIN3	0.10; Probability per year	
CIN3 → CIN2 (regress)	0.03; Probability per year	
CIN3 → LCC → RCC → DCC	0.10 per progression; Probability per year	
HPV 6/11 → genital warts	0.075; Probability per year	
Risk of HPV 6/11/16 infection	0.35; probability per intercourse	Elbasha et al.[97]
Risk of HPV 18, 31, 33, 45, 52, or 58 infection	Proportional to HPV 16 based on measured prevalence ratios	Modified compared to the HPV 16 risk to reflect their lower prevalences
Concurrent partners	0, 1, or 2, uniform/block distribution	Estimate
Duration of relationship (in months)	Dependent on age: the older, the longer duration (Y = abs random-normal (0.8·age – 12) (age/0.5)·12).	Estimate
Frequency of sexual intercourse	Random-gamma distribution with a mean of 9.48 per month; SD 9.95	Burchell et al.[98]
Vaccination status	0 or 1	
Duration of infections: HPV 6 HPV 11 HPV 16 HPV 18 HPV 31 HPV 33 HPV 45 HPV 52 HPV 58	Exponential distribution means: 11.32 9.50 14.6 11.26 11.518 11.3 11.51 12.40 11.14	Values independently defined during model calibration
Duration of genital warts	Random-gamma 6 1.5	

Following the "expert consensus" described by Ultsch et al. for dynamic model simulations,[89] the simulations were allowed to run until epidemiological equilibrium was achieved to assure that all positive and negative effects of the experimental variable (vaccination rate) would be captured across policy scenarios. The model was repeatedly run for 250 simulated

years, its output analyzed, and the type-specific durations of infection were calibrated until the model achieved a viral prevalence steady-state consistent with Kentucky's real-world rates (Table 2). Type-specific prevalences were calculated from both national and regional published epidemiological data. NHANES, a nationally representative health dataset with HPV prevalence measures from the pre-vaccine era was used as proxy for non-Appalachia Kentucky. Though limited, existing data from Appalachian Kentucky suggests regional HPV prevalences significantly higher than national averages, so proportionately weighted composite age-adjusted prevalences drawn from both sources were used to define the HPV-MOK seed population. A model limitation was identified during calibration involving the low prevalence target for HPV 11. The virus type could not be stabilized at such a low rate in the relatively small simulated populations. However, by adjusting the probability of condyloma formation, the condyloma prevalence rate target was still matched.

Next, the model was again repeatedly run for 250 years in order to calibrate the pathology progression and regression variables to reproduce known Kentucky cervical cancer incidence at steady-state rates (Table 3).

Model Outputs

Once calibrated, the scenarios were run in 4 replicates, each with an initial population of 25,000 nodes. A post-analysis time horizon of 66 years was adopted to accommodate the full lifespan of the first vaccinated cohorts. Model outputs for each scenario were collected, replicate data were combined, and all data were transformed and analyzed using Google Sheets (Google Inc, 2017, Mountain View, CA), a web-based spreadsheet software.

The 9vHPV type-specific prevalences were calculated and are reported as population proportions for each scenario. The HPV-related disease incidences and mortality rates across

scenarios were assessed, adjusted (Table 4), and are reported for scenarios 2 and 3 as cancers prevented and lives saved per hundred thousand persons without discounting.

Table 4. HPV-MOK post-simulation pathology parameter adjustment targets.

Pathology	9vHPV proportion	Incidence*,[81]	Mortality*,[81]	Mean age at diagnosis
Cervical Cancer	0.90[99]	16.7	3.2	49[100]
Vulvar Cancer	0.63[101]	10.1	0.6	68[102]
Vaginal Cancer	0.73[101]	1.9	0.3	60[103]
Anal Cancer	0.95[104]	2.4	0.2	61[105]
Oropharyngeal Cancers	0.66[101]	13.3	3.0	53[106]
Penile Cancer	0.57[101]	2.0	0.2	68[107]
Condyloma	1.0[108]	194.5[109]	N/A	
JORRP	1.0[110]	4.3[111] (per 100k <14yo)		

*Annual rate, per 100 thousand population

The QALYs gained in scenarios 2 and 3 were calculated by comparing the reduction in morbidity and mortality in each from those in the baseline control scenario (see Table 5 for QALY weights by age and disease burden). Life-years gained were determined from differences in the age distributions for cancer deaths versus the general population, multiplied by the annual HPV-related cancer mortality rates in each scenario. Future life-years and QALYs were discounted at the same rate as future monetary costs and savings.

Table 5. HPV-MOK life-year quality adjustments and unit costs per variable.

Variable	QALY Modifier[87,112]	Unit Cost*; PV, USD
Age Group		**N/A**
00-08	1.0	
09-14	1.0	
15-19	0.92880	
20-24	0.92880	
25-29	0.92880	
30-34	0.92365	
35-39	0.90475	
40-44	0.89405	
45-49	0.89005	
50-54	0.86560	
55-59	0.87060	
60-64	0.86495	
65-69	0.84495	
70-74	0.83785	
75-79	0.81330	
CIN1	0.91	2,412.84[113]
CIN2	0.87	6,215.17[114,115]
CIN3	0.87	7,056.49[114,115]
Locally invasive Cervical Cancer (LCC)	0.76	45,291.20[114,115]
Regionally invasive Cervical Cancer (RCC)	0.67	48,516.54[114,115]
Distant metastasis Cervical Cancer (DCC)	0.48	77,715.20[114,115]
Vulvar Cancer	0.68	30,802.80[116]
Vaginal Cancer	0.68	35,342.15[116]
Anal Cancer	0.68	53,414.27[116]
Oropharyngeal Cancers	0.68	77,769.26[106]
Penile Cancer	0.68	25,802.67[116]
Condyloma	0.91	991.84[116]
JORRP	0.69	143,411.45[116]
Vaccination		**476.74**
Vaccine (x2)		204.87[60]
Administration (x2)		33.00[119]
Mild reaction (probability: 0.00105)	0.001[117]	65.42[120,121]
Severe reaction (probability 0.00009)	0.076[118]	4,768.18[120,121]
Screening		**165.94**[122]
Office visit		30.96
Cytology		37.15
HPV DNA test		68.11
Patient time		29.72

*Medical costs of treatment, estimated cost of vaccination, or estimated cost of cervical cancer screening per incident.
PV: Present value. USD: United States dollars.

Following Gold et al.'s recommendations,[123] HPV-MOK uses a societal perspective that includes costs – vaccination costs, cancer screening costs, and future healthcare sector costs of treatment for HPV-associated diseases – and benefits, regardless of payer or beneficiary. The direct policy costs were limited to the financial cost of the 2 dose HPV vaccine series, set at 204.87 USD per dose per person,[124] plus 33.00 USD for each vaccine administration,[119] and any medical costs associated with rare vaccine reactions (Table 5).[120] These are reported in USD after adjustment for inflation and discounting.

The nature of prevention regularly puts the costs of intervention near the present, with subsequent benefits delayed into the far future. This distinctive characteristic of prevention renders decisions based on evaluations of relative value, whether by legislators considering policy or an individual considering personal choices, vulnerable to the irrational biases inherent to human psychology. The HPV-MOK uses a 3.0% discount rate for all future costs (whether incurred or averted) and benefits to account for the time value of money, but does not further discount for time preference.[125]

Future averted costs of treatments for genital warts, JORRP, CIN1-3 and atypia, cervical cancer, genital cancers, and head & neck cancers were estimated from the available literature to reflect present value (Table 5) and are described in USDs. Results from simulations were discounted and adjusted for inflation. Because the cost of healthcare is expected to continue to outpace the general economic inflation rate for the foreseeable future, both a healthcare inflation factor and a consumer price index inflation factor were incorporated in our estimates (Table 6). A broader projection of total economic costs relating to the modeled policy, including the opportunity, legislative, and implementation costs (recurrent and operational) was not included in this analysis.

Table 6. Economic and population terms.

Variable	Value, %	Reference
Personal Consumption Expenditure (PCE) price index average inflation (2006-15)	1.62	Bureau of Economic Analysis, US Department of Commerce National Accounts (NIPA) data archive[126]
CMS NHEA healthcare inflation rate, averaged projections (2017-26)	5.49	Centers for Medicare & Medicaid Services, Office of the Actuary National Health Expenditure Account[127]
Discount rate for both costs and effects	3.0	Second Panel on Cost-Effectiveness in Health and Medicine[128]
Annual population growth, Kentucky	0.42	Kentucky State Data Center Projections of Population and Households[129]

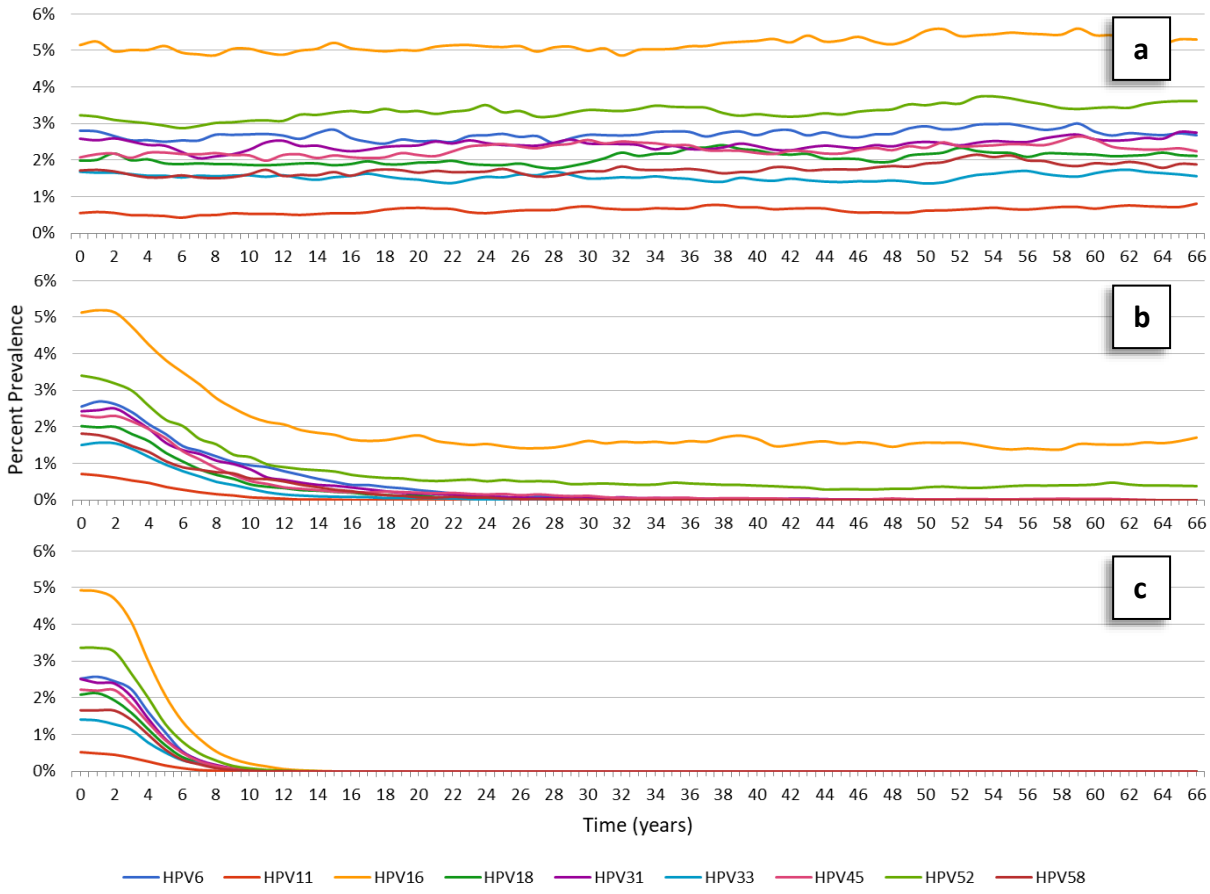
The World Health Organization (WHO) recommends that cost-effectiveness be considered in HPV vaccine policy decisions.[130] We therefore incorporated the adjusted monetary values for costs and benefits into calculations of incremental cost (defined as direct policy costs minus future costs averted, in USD) per QALY gained (without equity weightings)[131] to assess the potential cost-effectiveness of legislation similar to 13RS-HB358 in Kentucky.

RESULTS

Aim 1: Patterns of Infection and Health Outcomes

HPV type-specific prevalences varied across scenarios (Figure 1). While prevalences were fairly stable through time in Scenario 1 (steady-state), both vaccination scenarios resulted in a steep decline in all HPV types soon after vaccine introduction (at time point zero). In Scenario 2, several of the modelled types were eventually eliminated from the population despite relatively low vaccination coverage, suggesting a strong herd effect. Also in Scenario 2, types 16 and 52 achieved a new steady-state prevalence in the population approximately 25 years after vaccine introduction (Figure 1-b). In contrast, Scenario 3 saw all 9 types eliminated from the population within about 13 years of vaccine introduction (Figure 1-c).

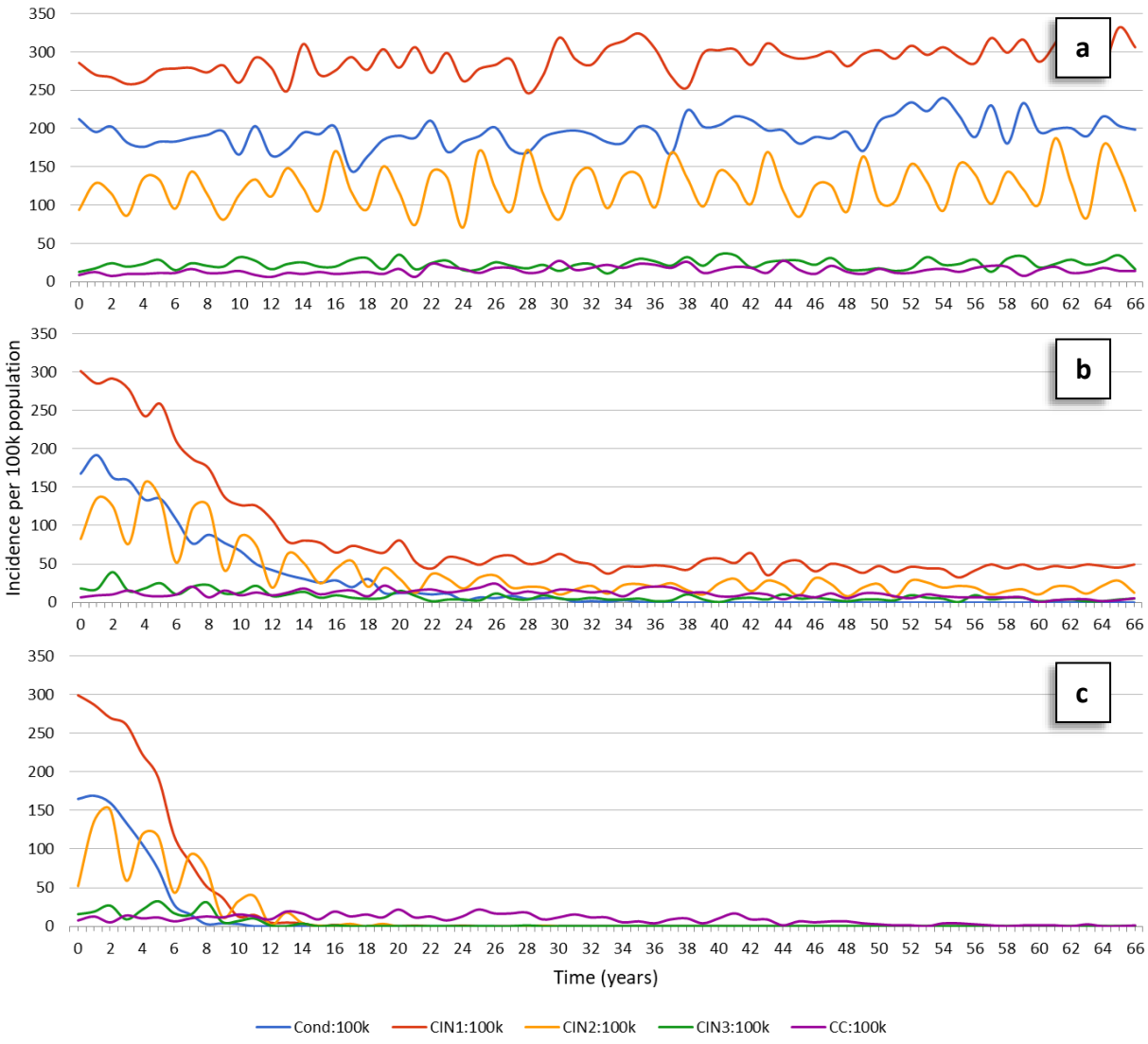
Figure 1. 9vHPV type-specific prevalences among scenarios 1 – no vaccination (a), 2 – current vaccination rates (b), and 3 – required vaccination under proposed policy (c).



The cervical disease burden associated with the 9 HPV types studied was, in the pre-vaccine world modelled by Scenario 1, stable and comparable to real-world historical incidence rates observed for Kentucky (Figure 2-a and Table 2). Upon vaccine introduction in both Scenarios 2 and 3, 9vHPV-related cervical disease incidences dropped precipitously, with condylomas eventually being eradicated from the simulated populations. Scenario 2 saw an average drop in CIN1 incidence by nearly three-quarters and achieved low steady-state rates of all cervical precancerous pathologies within 25 years (Figure 2-b). Meanwhile, new precancerous lesions were eliminated completely in Scenario 3 within just 15 years (Figure 2-c).

Cervical cancer, attributable to older uncleared infections, followed a slower decline in both scenarios, and was eventually eliminated from scenario 3 once the pre-vaccine era population had expired (the last cancer case occurred in year 64 after vaccine introduction; Figure 2-c).

Figure 2. 9vHPV-related cervical disease among scenarios 1 – no vaccination (**a**), 2 – current vaccination rates (**b**), and 3 – required vaccination under proposed policy (**c**).



Non-cervical cancers were not directly modelled but were assumed to track proportionally with cervical cancer. Additionally, incidences of JORRP were assumed to decline proportionally with the declining prevalences of HPV types 6 and 11 in the vaccination scenarios. Figure 3 shows the relative annual incidences of non-cervical 9vHPV-related cancers calculated from simulation outputs. In both vaccination scenarios, incidences of non-cervical cancers fell, and were virtually eliminated over the full time horizon of Scenario 3 (Figure 3-c).

Figure 3. 9vHPV-related non-cervical cancer incidence rates among scenarios 1 – no vaccination (**a**), 2 – current vaccination rates (**b**), and 3 – required vaccination under proposed policy (**c**).

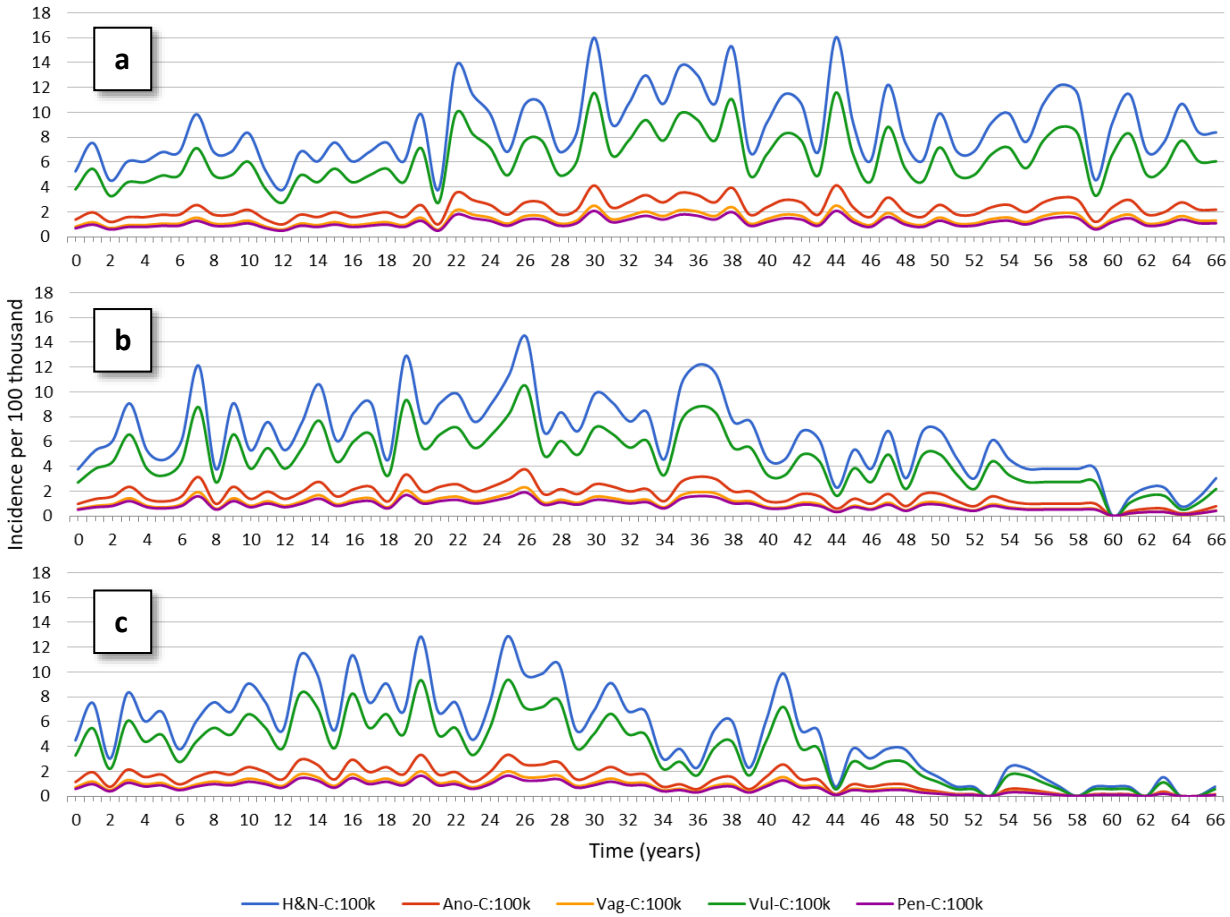


Table 7 shows the annual incidence averages of 9vHPV-related diseases per hundred thousand population. Again, only cervical diseases, including condylomas, were directly simulated by the HPV-MOK model; other pathologies were extrapolated proportionately from model outputs. Nevertheless, the results are consistent, showing a dose-effect decline in all 9vHPV-related pathologies with increasing vaccine coverage in the population.

Table 7. Average annual incidences per hundred thousand population for 9vHPV-related diseases across three HPV-MOK simulation scenarios of Kentucky's next 66 years.

Diseases	S1: incidence rates	S2: incidence rates	S3: incidence rates
Cervical Pre-cancers			
CIN1	290.00	82.82	27.86
CIN2	122.98	37.04	14.39
CIN3	23.55	7.45	3.22
Cancers			
Cervical	15.03	10.94	8.76
Oropharyngeal	8.78	6.39	5.12
Anogenital	2.28	1.66	1.33
Vaginal	1.39	1.01	0.81
Vulvar	6.36	4.63	3.71
Penile	1.14	0.83	0.66
Condylomas	194.50	25.93	12.83
JORRP	0.88	0.16	0.08

Deaths attributable to the 9vHPV types, which were calculated as a proportion of cervical cancer mortality rates, declined over time following introduction of the 9-valent vaccine in scenarios 2 and 3 (Figure 4 and Table 8). The required vaccination policy in Scenario 3 nearly eliminated 9vHPV-related deaths within the lifetime of the first policy cohort (Figure 4-c).

Figure 4. 9vHPV-related mortality among scenarios 1 – no vaccination (**a**), 2 – current vaccination rates (**b**), and 3 – required vaccination under proposed policy (**c**).

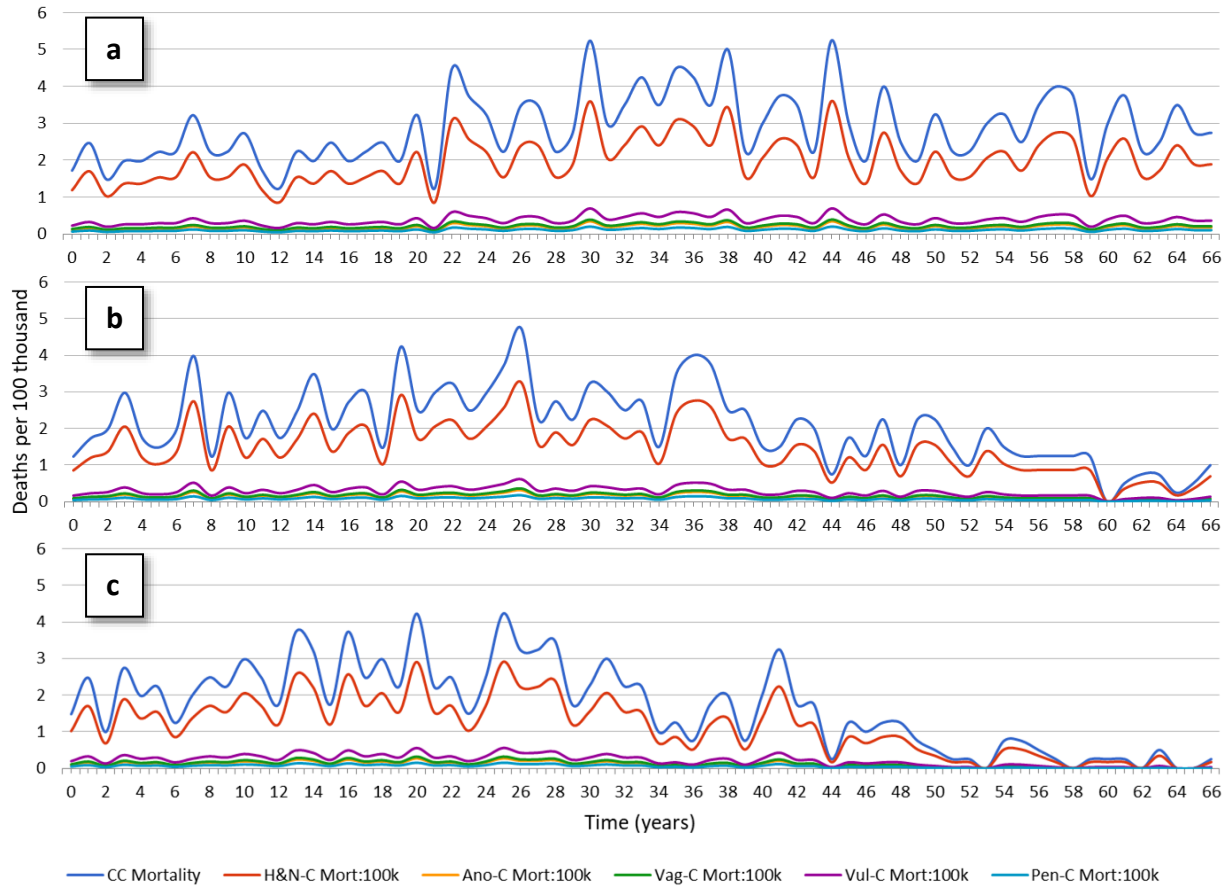


Table 8. Annual averages per hundred thousand population for 9vHPV-related mortality across three HPV-MOK simulation scenarios of Kentucky's next 66 years.

Diseases	S1: mortality rates	S2: mortality rates	S3: mortality rates
Cancers			
Cervical	2.88	2.10	1.68
Oropharyngeal	1.98	1.44	1.15
Anogenital	0.19	0.14	0.11
Vaginal	0.22	0.16	0.13
Vulvar	0.38	0.28	0.22
Penile	0.11	0.08	0.07

Aim 2: Health Impact

From disease-specific mortality rates, life-years and QALYs lost were calculated. When compared to the pre-vaccine conditions of Scenario 1, both vaccine scenarios showed an inverse linear relationship between vaccine coverage and cancer deaths (Figure 4), and a positive linear relationship of coverage with both life years (Figure 5) and QALYs gained (Figure 6). As expected, Scenario 3's higher vaccination rate produced the greater slope, though the model's dramatic herd effect reduced the proportional rate of return for vaccination overall. On average annually, Scenario 1 lost 55.4 life years per 100 thousand population to 9vHPV-related cancers; Scenario 2 lost 47.5, and Scenario 3 lost 42.4 life years per 100 thousand. A more dramatic ratio was observed for QALYs lost, with Scenario 1 losing an average of 87.4 QALYs per 100 thousand population to 9vHPV-related diseases annually, compared to 61.8 and 51.4 in Scenarios 2 and 3, respectively.

Figure 5. Annual life-years gained per 100k population over 66 years in two 9vHPV vaccination scenarios vs. no vaccination.

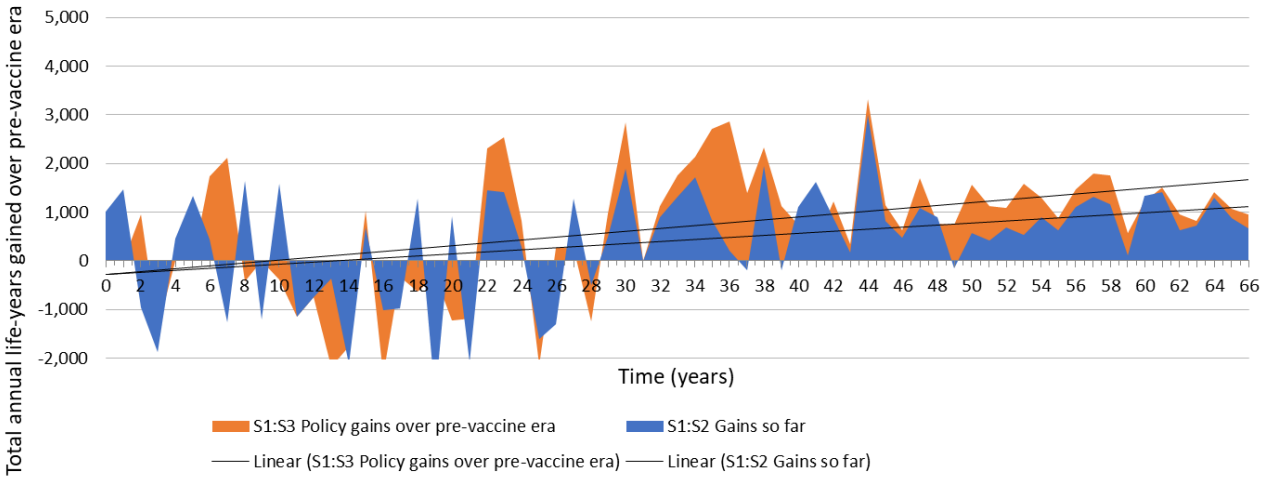
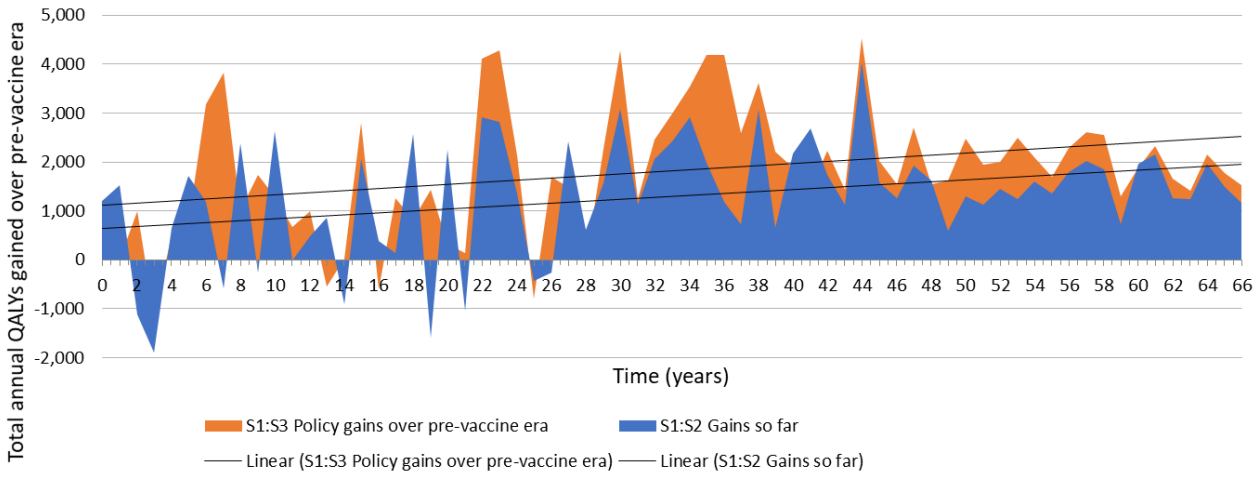


Figure 6. Annual QALYs gained per 100k population over 66 years in two 9vHPV vaccination scenarios vs. no vaccination.



Aim 3: Economic Impact

Figure 7 shows the total annual economic costs per hundred thousand population for prevention, screening, and treatment of diseases associated with 9 types of HPV, at current value after discounting and adjusting for general inflation. Scenario 1 predicted an annual screening and treatment cost range of 5.1m to 12.4m (8.4m average) USD per hundred thousand over the next 66 years, vs. the 4.5m to 7.5m (5.8m average) predicted by Scenario 2, and the 4.4m to 7.2m (5.4m average) predicted by Scenario 3 (Table 9), which both include the additional costs associated with the HPV vaccine. Total costs remained close during the first 20 years of simulations, with a dramatic annual savings attributable to vaccination emerging and growing after that.

Figure 7. Total discounted costs per 100k population for prevention, screening, and treatment of 9vHPV-related diseases over 66 years among scenarios 1 – no vaccination, 2 – current vaccination rates, and 3 – required vaccination under proposed policy.

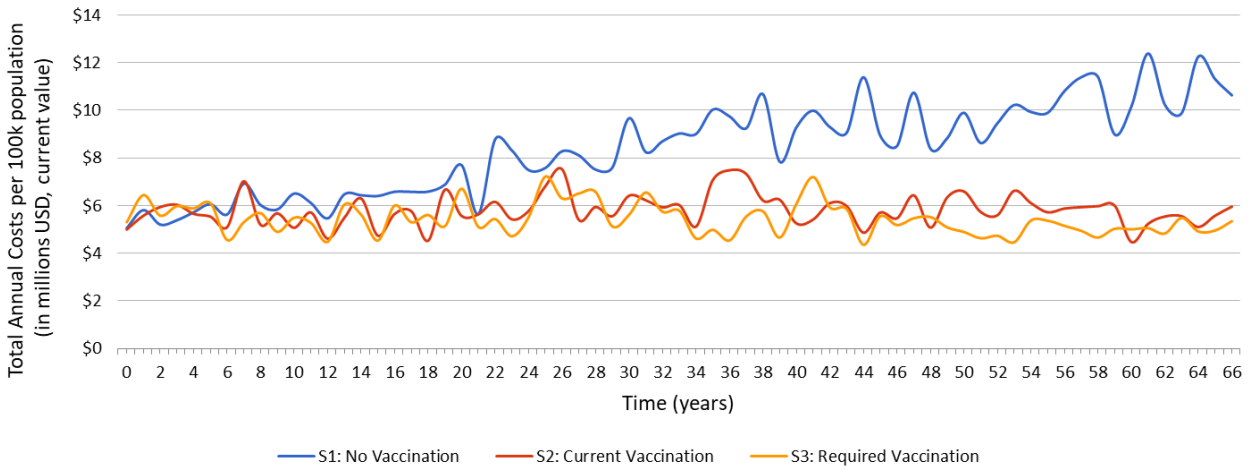


Table 9. HPV-MOK breakdown of annual averages per hundred thousand population for 9vHPV-related costs across three scenarios of Kentucky's next 66 years.

Expenditures	**S1: costs** (PV; USD)	**S2: costs** (PV; USD)	**S3: costs** (PV; USD)
Vaccination	N/A	212,892	696,718
Screening	3,123,826	3,123,826	3,123,826
Treatment	5,279,080	2,463,323	1,611,607
Totals:	8,402,906	5,800,041	5,432,151

PV: present value. USD: United States dollars.

DISCUSSION

Using a stochastic, susceptible-infectious-susceptible (SIS), agent-based dynamic model, the long-term health and economic impacts of legislation adding the 9vHPV vaccination to the 6th grade school entry schedule for both boys and girls in the state of Kentucky was estimated. The model simulated the transmission dynamics of 9 HPV types, and the pathological progression of related cervical disease. Model outputs were aggregated, extended to account for other HPV-related pathologies, and analyzed to determine such legislation's health effects and cost-effectiveness.

Major Findings

Given base assumptions of stable screening rates, stable healthcare and general economic inflation, stable population growth, exclusive use of the 9vHPV vaccine and stable vaccine costs, 100% vaccine efficacy, and a discount rate of 3.0% applied to economic and health impact measures, Scenario 1, which represented the state of Kentucky from the pre-vaccine era, predicted a total of approximately 118 thousand 9vHPV-related cancers and 19.5 thousand subsequent deaths, together costing 180 thousand life-years, 283 thousand quality-adjusted life-years, and 28.6 billion USD in direct healthcare utilization in the state of Kentucky over 66 years.

Scenario 2, based on current vaccination coverage in the state, predicted fewer total cancers (83.6 thousand), cancer deaths (13.8 thousand), life-years lost (151 thousand), QALYs lost (195 thousand), and reduced direct costs (19.4 billion USD) over the next 66 years, giving us a picture of what might be expected from the real-world status quo.

Scenario 3, representing Kentucky after passage of legislation similar to 13RS-HB358, and using an estimated vaccine uptake rate of 83.125%, predicted still fewer 9vHPV-related

cancers, deaths, life-years and QALYs lost, and lower direct costs than Scenarios 1 and 2 (Table 10).

Table 10. HPV-MOK cumulative HPV-related disease outcomes and costs across three vaccination scenarios of Kentucky's next 66 years under base assumptions.

	S1: No Vaccination	S2: Current Vaccination	S3: Required Vaccination
Cancers	118,104	83,560	65,607
Deaths	19,452	13,763	10,806
Life-years lost (PV)	179,699	151,251	133,299
QALYs lost (PV)	282,675	195,378	160,706
Costs (PV; USD)	28.615b	19.439b	18.144b

PV: present value. USD: United States dollars.

HPV-MOK predicted that uptake of the 9vHPV vaccine at current levels (as in Scenario 2) will, over 66 years, prevent 34.5 thousand cancers, save nearly 6 thousand lives, preserve 28 thousand life years and 87 thousand QALYs, and save 9.176 billion USD in healthcare expenditures that would have occurred in Kentucky over 66 years had the vaccine not been developed or adopted. This large effect is out of proportion to the scale of direct vaccine coverage in Scenario 2, indicating a large herd effect predicted by the model's transmission algorithms that may not reflect real-world dynamics and outcomes.

When simulating higher vaccination rates consistent with what could be expected from passage of legislation requiring the 9vHPV vaccine for school entry in Kentucky, HPV-MOK predicts the prevention of a total of 52.5 thousand cancers and nearly 9 thousand deaths, saving 46 thousand life-years, 122 thousand QALYs, and 10.470 billion USD that would have been lost

without the vaccine (Table 11). But neither of these comparisons tells us what effect a policy like 13RS-HB358 could have in the real post-vaccine world of Kentucky in 2018.

Looking forward over 66 years along 2 diverging paths, one representing policy inaction and stagnant vaccine uptake growth, the other legislative action adding the 9vHPV vaccine to the school entry schedule for all 6th graders in the state, the latter could see Kentucky prevent 18 thousand cancers and 3 thousand deaths, saving nearly 18 thousand life years, 35 thousand QALYs, and 1.294 billion USD, for an estimated ICER per QALY of negative 37 thousand USD over the former path of policy inaction (Table 11). From this, we conclude that a bill like 13RS-HB35 would not only be cost-effective in Kentucky, but could be cost-saving. This is likely attributable to 1) Kentucky's high HPV prevalence and high HPV-related disease burden, 2) the state's currently low rates of HPV vaccination, especially among boys, 3) this study's comprehensive inclusion of all direct 9vHPV-related costs and effects, and 4) the savings realized from fewer required vaccine doses (from 3 to 2 doses per most recent guidelines).

Table 11. Vaccine impact: vaccine era vs. pre-vaccine era under base assumptions.

	S1:S2 Current gains over pre-vaccine era	S1:S3 Potential policy gains over pre-vaccine era	S2:S3 Policy Impact over current vaccination rates
Cancers prevented	34,544	52,497	**17,953**
Lives saved	5,690	8,647	**2,957**
Life-years gained (PV)	28,449	46,400	**17,952**
QALYs gained (PV)	87,296	121,969	**34,672**
Savings (PV; USD)	9.176b	10.470b	**1.294b**
ICER (PV; USD)	-105,114	-85,845	**-37,330**

PV: present value. USD: United States dollars.

Sensitivity Analysis

The sensitivity of the model's predictions to discount rate and time horizon was explored, per expert consensus.[89] Table 12 shows that, even though outcome and impact benefits are heavily weighted to the far future, and even though Scenario 2 produced a much larger herd immunity effect than expected, which reduced the measured impact of Scenario 3 by comparison, ICERs per QALY in the policy scenario remained well below the 50,000 USD threshold for utility even with the most unfavorable tested values for vaccine cost, time horizon, and discount rate. Thus the conclusion of cost-effectiveness is robust despite the model's sensitivity to discounting, discount rate, vaccine pricing and dosing, and time horizon.

Table 12. HPV-MOK policy impact: sensitivity to discounting, discount rate, dosing, and time horizon, S2:S3.

Impact measures At time horizons; PV	**Discount Rates**				
	1.5%*	1.5%	3.0%	5.0%	10.0%
66-years					
QALYs gained	107,025	58,893	34,672†	19,035	6,763
Cost (USD)	-2.6b	-2.6b	-1.3b†	-0.5b	-65m
3-dose cost (USD)	-1.1b	-1.1b	-0.5b	-0.1b	67m
ICER (USD)	-24,155	-43,897	-37,330†	-28,003	-9,732
3-dose ICER (USD)	-10,254	-18,634	-13,667	-6,210	9,915
40-years					
QALYs gained	52,259	34,592	23,695	15,131	6,433
Cost (USD)	-0.9b	-0.9b	-0.6b	-0.3b	-52m
3-dose cost (USD)		-0.3b	-0.1b	-14m	71m
ICER (USD)	-17,411	-26,303	-23,579	-19,250	-8,126
3-dose ICER (USD)		-9,436	-5,991	-944	11,062
20-years					
QALYs gained	8,013	7,222	6,512	5,681	4,065
Cost (USD)	-24m	-24m	-20m	-15m	~500k
3-dose cost (USD)		0.2b	0.2b	0.1b	97m
ICER (USD)	-3,053	-3,388	-3,165	-2,585	119
3-dose ICER (USD)		26,811	25,414	24,176	23,802

PV: present value. USD: United States dollars.
*Discounting applied to monetary values only; Life-years and QALYs not discounted.
†Base case conditions.

Limitations

This study has a number of limitations common to complex simulations. First, none of the model's assumptions hold perfectly with reality. Screening rates, economic terms, natural immunity, vaccine efficacy and duration of immunity, and many others are simplifications that affect the model's fidelity in unmeasured ways. Second, because only heterosexual transmission was considered, the effects of transmission dynamics and elevated prevalence rates among homosexuals were left out of simulations. Third, the model assumes a closed society, though globalization and regional economics drive immigration and emigration patterns in Kentucky now and likely even more so in the future. Fourth, the model assumes cervical cancer screening practices will remain constant into the future, though this is unlikely given the effectiveness of the HPV vaccine, especially if there is widespread state-level legislative action in the near term. Whatever changes to screening practices may unfold in the future, they are unaccounted for here. Fifth, multiple sources originally documenting differing populations and dates were necessarily used to compile QALY weights, treatment cost estimations, disease incidences, and type-specific prevalences, which can lead to discrepancies and inaccuracies when combined, though all efforts were made to minimize such instances. Finally, natural variations in 9vHPV type prevalences and related disease incidences that might occur in the future were not considered by the HPV-MOK, which bounds our findings temporally to policy action in the near-term. Should a policy decision be significantly delayed, the accuracy of the current analysis may wane.

Conclusions

Based on the results of this study, Kentucky could prevent cancers, save lives, and save money by vaccinating as many 11-year-old boys and girls with the 9vHPV vaccine as possible. Given the slow pace of vaccine uptake in the state since 2006, the most effective path toward universal vaccination is likely through legislative action at the state level. Despite sensitivity to variable variances, the conclusion of cost-effectiveness is robust. Further, through much of the variance range, the model predicts overall cost savings from legislation passage. Most importantly, the model predicts that HPV vaccine legislation could save many lives and prevent a great deal of suffering for present and future generations in the Commonwealth.

REFERENCES

1. Lippman SM, Hawk ET. Cancer Prevention: From 1727 to Milestones of the Past 100 Years. Cancer Res 2009;69(13):5269–84.

2. Bosch FX, Sanjosé S de. Chapter 1: Human Papillomavirus and Cervical Cancer—Burden and Assessment of Causality. J Natl Cancer Inst Monogr 2003;2003(31):3–13.

3. Research C for BE and. Approved Products - Gardasil [Internet]. [cited 2016 Apr 24];Available from: http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm094042.htm

4. Lehtinen M, Paavonen J. Vaccination against human papillomaviruses shows great promise. The Lancet 2004;364(9447):1731–2.

5. Markowitz L, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent Human Papillomavirus Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP) [Internet]. CDC Morbidity and Mortality Weekly Report (MMWR). 2007 [cited 2016 Apr 24];Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5602a1.htm

6. Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer 2008;113(S10):3036–46.

7. Research C for BE and. Approved Products - Gardasil 9 [Internet]. [cited 2016 Apr 24];Available from: http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm426445.htm

8. Javitt G, Berkowitz D, Gostin LO. Assessing Mandatory HPV Vaccination: Who Should Call the Shots? The Journal of Law, Medicine & Ethics 2008;36(2):384–95.

9. Guide TC. The Community Guide - Summary(a) - Vaccination: Requirements for Child Care, School and College Attendance [Internet]. [cited 2016 Apr 24];Available from: http://www.thecommunityguide.org/vaccines/requirements_school.html

10. Policy Statement on Immunization | State Public Health | ASTHO [Internet]. [cited 2016 Apr 24];Available from: http://www.astho.org/Policy-and-Position-Statements/Immunization-Policy-Statement/

11. Immunization Information for Schools & Childcare Providers: Department of Health [Internet]. State of Rhode Island Department of Health. [cited 2016 Apr 25];Available from: http://www.health.ri.gov/immunization/for/schools/

12. Guide TC. The Community Guide - TFFRS - Vaccination: Requirements for Child Care, School and College Attendance [Internet]. [cited 2016 Apr 25];Available from: http://www.thecommunityguide.org/vaccines/RRrequirements_school.html

13. Ware SL, Crosby R, Fisher R, Hagensee ME. Human Papillomavirus Prevalence Is Associated With Socioeconomic Gradients Within a Medically Underserved Appalachian Region. Sex Transm Dis 2017;

14. Doorbar J, Quint W, Banks L, et al. The Biology and Life-Cycle of Human Papillomaviruses. Vaccine 2012;30, Supplement 5:F55–70.

15. Bernard H-U, Burk RD, Chen Z, van Doorslaer K, Hausen H zur, de Villiers E-M. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 2010;401(1):70–9.

16. Walboomers JMM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189(1):12–9.

17. Jemal A, Simard EP, Dorell C, et al. Annual Report to the Nation on the Status of Cancer, 1975–2009, Featuring the Burden and Trends in Human Papillomavirus (HPV)–Associated Cancers and HPV Vaccination Coverage Levels. JNCI J Natl Cancer Inst 2013;djs491.

18. Ault KA. Epidemiology and Natural History of Human Papillomavirus Infections in the Female Genital Tract. Infect Dis Obstet Gynecol [Internet] 2006 [cited 2016 Apr 24];2006. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1581465/

19. Stanley M. Immunobiology of HPV and HPV vaccines. Gynecologic Oncology 2008;109(2, Supplement):S15–21.

20. Lenzi RN, Altevogt BM, Gostin LO, Committee C on the IR and A of the A of the NRDA, Policy B on HS, Medicine I of. Historical and Policy Timelines for Recombinant DNA Technology. 2014 [cited 2016 Apr 23];Available from: http://www.ncbi.nlm.nih.gov/books/NBK195888/

21. zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer 2002;2(5):342–50.

22. Madeleine MM, Daling JR. Cancers of the Vulva and Vagina [Internet]. In: Schottenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. Oxford University Press; 2006 [cited 2016 Apr 23]. p. 1068–74.Available from: http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780195149616.001.0001/acprof-9780195149616-chapter-55

23. Bleeker MCG, Heideman D a. M, Snijders PJF, Horenblas S, Dillner J, Meijer CJLM. Penile cancer: epidemiology, pathogenesis and prevention. World J Urol 2008;27(2):141–50.

24. Frisch M, Glimelius B, van den Brule AJC, et al. Sexually Transmitted Infection as a Cause of Anal Cancer. New England Journal of Medicine 1997;337(19):1350–8.

25. Mayne ST, Morse DE, Winn DM. Cancers of the Oral Cavity and Pharynx [Internet]. In: Schottenfeld D, Fraumeni JF, editors. Cancer Epidemiology and Prevention. Oxford University Press; 2006 [cited 2016 Apr 23]. p. 674–96.Available from: http://www.oxfordscholarship.com/view/10.1093/acprof:oso/9780195149616.001.0001/acprof-9780195149616-chapter-35

26. Schiffman MH, Bauer HM, Hoover RN, et al. Epidemiologic Evidence Showing That Human Papillomavirus Infection Causes Most Cervical Intraepithelial Neoplasia. JNCI J Natl Cancer Inst 1993;85(12):958–64.

27. Cubie HA. Diseases associated with human papillomavirus infection. Virology 2013;445(1–2):21–34.

28. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010;127(12):2893–917.

29. WHO | Maternal mortality [Internet]. WHO. [cited 2016 Apr 25];Available from: http://www.who.int/mediacentre/factsheets/fs348/en/

30. Wittet S, Goltz S, Cody A. Progress in Cervical Cancer Prevention: The CCA Report Card 2015 [Internet]. Cervical Cancer Action Coalition; 2015 [cited 2016 Apr 25]. Available from: http://cervicalcanceraction.org/pubs/CCA_reportcard_low-res_2015.pdf

31. Chesson HW, Ekwueme DU, Saraiya M, Watson M, Lowy DR, Markowitz LE. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. Vaccine 2012;30(42):6016–9.

32. Health AGD of. Human Papillomavirus (HPV) [Internet]. [cited 2016 Apr 24];Available from: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv

33. team EC for DP and C (ECDC)-HCU-E editorial. Introduction of human papillomavirus (HPV) vaccination in Belgium, 2007-2008 [Internet]. 2009 [cited 2016 Apr 24];Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19407

34. Government of Canada PHA of C. Update On Human Papillomavirus (HPV) Vaccines - Canada Communicable Disease Report Monthly - Public Health Agency of Canada [Internet]. 2012 [cited 2016 Apr 24];Available from: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/12vol38/acs-dcc-1/index-eng.php

35. Krause TG, Jakobsen S, Haarh M, Molbak K. The Danish vaccination register [Internet]. Eurosurveillance, Volume 17 Issue 17. 2012 [cited 2016 Apr 24];Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20155

36. Olsen J, Jørgensen TR. Revisiting the cost-effectiveness of universal HPV-vaccination in Denmark accounting for all potentially vaccine preventable HPV-related diseases in males and females. Cost Effectiveness and Resource Allocation 2015;13:4.

37. Fagot J-P, Boutrelle A, Ricordeau P, Weill A, Allemand H. HPV vaccination in France: uptake, costs and issues for the National Health Insurance. Vaccine 2011;29(19):3610–6.

38. Donadiki EM, Jiménez-García R, Hernández-Barrera V, Carrasco-Garrido P, López de Andrés A, Velonakis EG. Human papillomavirus vaccination coverage among Greek higher education female students and predictors of vaccine uptake. Vaccine 2012;30(49):6967–70.

39. Haverkate M, D'Ancona F, Giambi C, et al. Mandatory and recommended vaccination in the EU, Iceland and Norway: results of the VENICE 2010 survey on the ways of implementing national vaccination programmes [Internet]. Eurosurveillance, Volume 17, Issue 22. 2012 [cited 2016 Apr 24];Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20183

40. Vaccine against Papilloma Virus - HPV, Ministry of Health [Internet]. [cited 2016 Apr 24];Available from: http://www.health.gov.il/English/Topics/Vaccination/HPV/Pages/default.aspx

41. Giambi C, Del Manso M, D'Ancona F, et al. Actions improving HPV vaccination uptake - Results from a national survey in Italy. Vaccine 2015;33(21):2425–31.

42. Gilmour S, Kanda M, Kusumi E, Tanimoto T, Kami M, Shibuya K. HPV vaccination programme in Japan. The Lancet 2013;382(9894):768.

43. HPV immunisation programme [Internet]. Ministry of Health NZ. [cited 2016 Apr 24];Available from: http://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/hpv-immunisation-programme

44. Childhood Immunisation Programme in Norway - FHI [Internet]. [cited 2016 Apr 24];Available from: http://www.fhi.no/eway/default.aspx?pid=240&trg=MainContent_6894&Main_6664=6894:0:25,7661:1:0:0:::0:0&MainContent_6894=6706:0:25,7663:1:0:0:::0:0

45. Pista A, de Oliveira CF, Cunha MJ, Paixao MT, Real O. Prevalence of Human Papillomavirus Infection in Women in Portugal: The CLEOPATRE Portugal Study. International Journal of Gynecological Cancer 2011;21(6):1150–8.

46. FAQs on HPV and HPV immunisation [Internet]. [cited 2016 Apr 24];Available from: http://www.hpb.gov.sg/HOPPortal/health-article/8768

47. Limia A, Pachon I. Coverage of human papillomavirus vaccination during the first year of its introduction in Spain [Internet]. Eurosurveillance, Volume 16, Issue 21. 2011 [cited 2016 Apr 24];Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19873

48. Tegnell A, Dillner J, Andrae B. Introduction of human papillomavirus (HPV) vaccination in Sweden [Internet]. Eurosurveillance, Volume 14, Issue 6. 2009 [cited 2016 Apr 24];Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19119

49. Choices NHS. Human papilloma virus (HPV) cervical cancer vaccine - NHS Choices [Internet]. 2015 [cited 2016 Apr 24];Available from: http://www.nhs.uk/conditions/vaccinations/pages/hpv-human-papillomavirus-vaccine.aspx

50. Patel H, Wilson E, Vizzotti C, Parston G, Prestt J, Darzi A. Argentina's Successful Implementation Of A National Human Papillomavirus Vaccination Program. Health Aff 2016;35(2):301–8.

51. Fregnani JHTG, Carvalho AL, Eluf-Neto J, et al. A School-Based Human Papillomavirus Vaccination Program in Barretos, Brazil: Final Results of a Demonstrative Study. PLoS ONE 2013;8(4):e62647.

52. Baker ML, Figueroa-Downing D, Chiang EDDO, et al. Paving pathways: Brazil's implementation of a national human papillomavirus immunization campaign. Revista Panamericana de Salud Pública 2015;38(2):163–6.

53. Novaes HMD, de Soárez PC, Silva GA, et al. Cost-effectiveness analysis of introducing universal human papillomavirus vaccination of girls aged 11 years into the National Immunization Program in Brazil. Vaccine 2015;33, Supplement 1:A135–42.

54. HABB R, Begawan AS. Free HPV vaccination [Internet]. The Brunei Times. [cited 2016 Apr 24];Available from: http://mail.bruneitimes.com.bn/news-national/2012/01/05/free-hpv-vaccination

55. Progress Toward Implementation of Human Papillomavirus Vaccination --- the Americas, 2006--2010 [Internet]. CDC Morbidity and Mortality Weekly Report (MMWR). 2011 [cited 2016 Apr 24];Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6040a2.htm

56. Seme K, Maver PJ, Korać T, et al. Current status of human papillomavirus vaccination implementation in central and eastern Europe. Acta Dermatovenerol Alp Pannonica Adriat 2013;22(1):21–5.

57. WHO | Reaching teenagers with three-times jab is a first for most countries [Internet]. WHO. [cited 2016 Apr 24];Available from: http://www.who.int/bulletin/volumes/90/12/12-021212/en/

58. Gallagher KE, LaMontagne DS, Watson-Jones D. Status of HPV vaccine introduction and barriers to country uptake. Vaccine 2018;36(32, Part A):4761–7.

59. Herlihy N, Hutubessy R, Jit M. Current Global Pricing For Human Papillomavirus Vaccines Brings The Greatest Economic Benefits To Rich Countries. Health Aff 2016;35(2):227–34.

60. Petrosky E, Bocchini J, Hariri S, et al. Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of the Advisory Committee on Immunization Practices. Morbidity and Mortality Weekly Report [Internet] [cited 2015 Sep 19];Available from: http://www.cdc.gov/mmWr/preview/mmwrhtml/mm6411a3.htm

61. Markowitz LE, Dunne EF, Saraiya M, et al. Human Papillomavirus Vaccination: Recommendations of the Advisory Committee on Immunization Practices (ACIP) [Internet]. CDC Morbidity and Mortality Weekly Report (MMWR). 2014 [cited 2016 Apr 24];Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6305a1.htm

62. Accelerating HPV Vaccine Uptake: Urgency for Action to Prevent Cancer: Preface [Internet]. [cited 2016 Apr 24];Available from: http://deainfo.nci.nih.gov/advisory/pcp/annualReports/HPV/Preface.htm#sthash.JhdoVDup.dpbs

63. HPV (Human papillomavirus) [Internet]. [cited 2016 Apr 24];Available from: http://www.adolescentvaccination.org/vpd/hpv

64. Human Papillomavirus (HPV) Vaccines [Internet]. National Cancer Institute. [cited 2016 Apr 24];Available from: http://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-vaccine-fact-sheet

65. Human Papillomavirus Vaccination - the American College of Obstetricians and Gynecologists committee on Adolescent Health Care Immunization Expert Work Group opinion on the human papillomavirus vaccination. [Internet]. Committe Opinion Number 641, September 2015. [cited 2016 Apr 24];Available from: http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Adolescent-Health-Care/Human-Papillomavirus-Vaccination

66. Human Papillomavirus Vaccine (HPV) [Internet]. American Academy of Family Physicians. [cited 2016 Apr 24];Available from: http://www.aafp.org/patient-care/immunizations/disease-population/hpv.html

67. AAP Recommends HPV Vaccines For Both Males and Females [Internet]. [cited 2016 Apr 24];Available from: https://www.aap.org/en-us/about-the-aap/aap-press-room/pages/AAP-Recommends-HPV-Vaccines-For-Both-Males-and-Females.aspx

68. Organizations Urge Physicians to Recommend Human Papillomavirus Vaccination [Internet]. 2014 [cited 2016 Apr 24];Available from: http://www.infectioncontroltoday.com/news/2014/02/organizations-urge-physicians-to-recommend-human-papillomavirus-vaccination.aspx

69. Reagan-Steiner S. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2015. MMWR Morb Mortal Wkly Rep [Internet] 2016 [cited 2018 Aug 6];65. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm6533a4.htm

70. Bruni L, Diaz M, Barrionuevo-Rosas L, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. The Lancet Global Health 2016;4(7):e453–63.

71. Gostin LO. A framework convention on global health: Health for all, justice for all. JAMA 2012;307(19):2087–92.

72. Morrone M, Kruse N, Chadwick A. Environmental and Health Disparities in Appalachian Ohio: Perceptions and Realities. Journal of Health Disparities Research and Practice [Internet] 2015;7(5). Available from: http://digitalscholarship.unlv.edu/jhdrp/vol7/iss5/5

73. Hopenhayn C, King JB, Christian A, Huang B, Christian WJ. Variability of cervical cancer rates across 5 Appalachian states, 1998–2003. Cancer 2008;113(S10):2974–80.

74. Wingo PA, Tucker TC, Jamison PM, et al. Cancer in Appalachia, 2001–2003. Cancer 2008;112(1):181–92.

75. CDC. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2013 [Internet]. CDC; 2014 [cited 2016 Apr 3]. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6329a4.htm

76. Reiter PL, Fisher JL, Hudson AG, Tucker TC, Plascak JJ, Paskett ED. Assessing the burden of HPV-related cancers in Appalachia. Hum Vaccin Immunother 2013;9(1):90–6.

77. Reiter PL, Katz ML, Ferketich AK, Iv MTR, Paskett ED. Measuring cervical cancer risk: development and validation of the CARE Risky Sexual Behavior Index. Cancer Causes Control 2009;20(10):1865–71.

78. Reiter PL, Katz ML, Ruffin MT, et al. HPV Prevalence among Women from Appalachia: Results from the CARE Project. PLoS ONE 2013;8(8):e74276.

79. Vanderpool RC, Dressler EVM, Stradtman LR, Crosby RA. Fatalistic Beliefs and Completion of the HPV Vaccination Series Among a Sample of Young Appalachian Kentucky Women. The Journal of Rural Health 2015;31(2):199–205.

80. Sr P, R H. Cost-benefit analysis on the HPV vaccine in Medicaid-enrolled females of the Appalachian region of Kentucky. J Ky Med Assoc 2008;106(6):271–6.

81. Cancer-Rates.info | Kentucky [Internet]. [cited 2016 Apr 28];Available from: http://cancer-rates.info/ky/index.php?datasource=mort

82. Crosby RA, Hagensee ME, Vanderpool R, et al. Community-Based Screening for Cervical Cancer: A Feasibility Study of Rural Appalachian Women. Sex Transm Dis 2015;42(11):607–11.

83. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2014 [Internet]. [cited 2016 Apr 27];Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6429a3.htm

84. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2013 [Internet]. [cited 2016 Apr 27];Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6329a4.htm

85. Meites E. Use of a 2-Dose Schedule for Human Papillomavirus Vaccination — Updated Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb

Mortal Wkly Rep [Internet] 2016 [cited 2018 Jun 1];65. Available from: https://www.cdc.gov/mmwr/volumes/65/wr/mm6549a5.htm

86. Watkins D, Burch T, Jenkins J, Marzian M. AN ACT relating to immunizations. [Internet]. [cited 2018 Apr 27]. Available from: http://www.lrc.ky.gov/record/13RS/HB358.htm

87. Olsen J, Jepsen MR. Human papillomavirus transmission and cost-effectiveness of introducing quadrivalent HPV vaccination in Denmark. International Journal of Technology Assessment in Health Care 2010;26(02):183–191.

88. Usher C, Tilson L, Olsen J, Jepsen M, Walsh C, Barry M. Cost-effectiveness of human papillomavirus vaccine in reducing the risk of cervical cancer in Ireland due to HPV types 16 and 18 using a transmission dynamic model. Vaccine 2008;26(44):5654–61.

89. Ultsch B, Damm O, Beutels P, et al. Methods for Health Economic Evaluation of Vaccines and Immunization Decision Frameworks: A Consensus Framework from a European Vaccine Economics Community. PharmacoEconomics 2015;1–18.

90. Van de Velde N, Brisson M, Boily M-C. Understanding differences in predictions of HPV vaccine effectiveness: A comparative model-based analysis. Vaccine 2010;28(33):5473–84.

91. Sands H, Brawley R. Kentucky Annual School Immunization Survey Report 2015-2016 [Internet]. Kentucky Immunization Program, Division of Epidemiology and Health Planning, Kentucky Department for Public Health, Cabinet for Health and Family Services; 2017 [cited 2018 Mar 29]. Available from: http://chfs.ky.gov/NR/rdonlyres/173AD772-8408-4DF4-A66B-DF7C2B6C9DB8/0/20152016SupplementalReportFINAL.pdf

92. Tay EH, Garland S, Tang G, et al. Clinical trial experience with prophylactic HPV 6/11/16/18 VLP vaccine in young women from the Asia-Pacific region. Int J Gynaecol Obstet 2008;102(3):275–83.

93. Recurrent Respiratory Papillomatosis: Background, Pathophysiology, Epidemiology. 2017 [cited 2018 Apr 27];Available from: https://emedicine.medscape.com/article/302648-overview#a4

94. CDC - Cancer - NBCCEDP Screening Program Summaries - Kentucky [Internet]. 2018 [cited 2018 May 18];Available from: https://www.cdc.gov/cancer/nbccedp/data/summaries/kentucky.htm

95. State Cancer Profiles > Screening and Risk Factors Table [Internet]. [cited 2018 Apr 27];Available from: https://statecancerprofiles.cancer.gov/risk/index.php?stateFIPS=00&topic=women&risk=v17&race=00&sex=2&type=risk&sortVariableName=name&sortOrder=asc#results

96. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of hpv infection among females in the united states. JAMA 2007;297(8):813–9.

97. Elbasha EH, Dasbach EJ, Insinga RP. Model for Assessing Human Papillomavirus Vaccination Strategies. Emerging Infectious Diseases 2007;13(1):28–41.

98. Burchell AN, Richardson H, Mahmud SM, et al. Modeling the Sexual Transmissibility of Human Papillomavirus Infection using Stochastic Computer Simulation and Empirical Data from a Cohort Study of Young Women in Montreal, Canada. Am J Epidemiol 2006;163(6):534–43.

99. Luckett R, Feldman S. Impact of 2-, 4- and 9-valent HPV vaccines on morbidity and mortality from cervical cancer. Hum Vaccin Immunother 2015;12(6):1332–42.

100. Cervical Cancer - Cancer Stat Facts [Internet]. [cited 2018 May 7];Available from: https://seer.cancer.gov/statfacts/html/cervix.html

101. Saraiya M, Unger ER, Thompson TD, et al. US Assessment of HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccines. J Natl Cancer Inst [Internet] 2015 [cited 2018 May 7];107(6). Available from: https://academic.oup.com/jnci/article/107/6/djv086/872092

102. Vulvar Cancer - Cancer Stat Facts [Internet]. [cited 2018 May 7];Available from: https://seer.cancer.gov/statfacts/html/vulva.html

103. All About Vaginal Cancer | OncoLink [Internet]. [cited 2018 May 7];Available from: https://www.oncolink.org/cancers/gynecologic/information-about-gynecologic-cancers/vaginal-cancer/all-about-vaginal-cancer

104. Stier EA, Chigurupati NL, Fung L. Prophylactic HPV vaccination and anal cancer. Hum Vaccin Immunother 2016;12(6):1348–51.

105. Anal Cancer - Cancer Stat Facts [Internet]. [cited 2018 May 7];Available from: https://seer.cancer.gov/statfacts/html/anus.html

106. Ward G, Mehta V, Moore M. Morbidity, mortality and cost from HPV-related oropharyngeal cancer: Impact of 2-, 4- and 9-valent vaccines. Human Vaccines & Immunotherapeutics 2016;12(6):1343–7.

107. What Are the Risk Factors for Penile Cancer? [Internet]. [cited 2018 May 7];Available from: https://www.cancer.org/cancer/penile-cancer/causes-risks-prevention/risk-factors.html

108. Wangu Z, Hsu KK. Impact of HPV vaccination on anogenital warts and respiratory papillomatosis. Hum Vaccin Immunother 2016;12(6):1357–62.

109. Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. BMC Infectious Diseases 2013;13:39.

110. Carifi M, Napolitano D, Morandi M, Dall'Olio D. Recurrent respiratory papillomatosis: current and future perspectives. Ther Clin Risk Manag 2015;11:731–8.

111. Derkay CS. Task force on recurrent respiratory papillomas. A preliminary report. Arch Otolaryngol Head Neck Surg 1995;121(12):1386–91.

112. Boiron L, Joura E, Largeron N, Prager B, Uhart M. Estimating the cost-effectiveness profile of a universal vaccination programme with a nine-valent HPV vaccine in Austria. BMC Infectious Diseases 2016;16:153.

113. Insinga RP, Glass AG, Rush BB. The health care costs of cervical human papillomavirus–related disease. American Journal of Obstetrics and Gynecology 2004;191(1):114–20.

114. Chesson HW, Ekwueme DU, Saraiya M, Markowitz LE. Cost-effectiveness of Human Papillomavirus Vaccination in the United States. Emerging Infectious Diseases [Internet] 2008 [cited 2018 May 7];14(2). Available from: https://wwwnc.cdc.gov/eid/article/14/2/07-0499_article

115. Kim JJ, Goldie SJ. Health and Economic Implications of HPV Vaccination in the United States. New England Journal of Medicine 2008;359(8):821–32.

116. Hu D, Goldie SJ. THE ECONOMIC BURDEN OF NONCERVICAL HUMAN PAPILLOMAVIRUS DISEASE IN THE UNITED STATES. Am J Obstet Gynecol 2008;198(5):500.e1-500.e7.

117. Lee GM, Riffelmann M, Wirsing von Konig CH. Cost-effectiveness of adult pertussis vaccination in Germany. Vaccine 2008;26(29–30):3673–9.

118. Prosser LA, Meltzer MI, Fiore A, et al. Effects of Adverse Events on the Projected Population Benefits and Cost-effectiveness of Using Live Attenuated Influenza Vaccine in Children Aged 6 Months to 4 Years. Arch Pediatr Adolesc Med 2011;165(2):112–8.

119. Centers for Medicare & Medicaid Services (CMS), HHS. Medicaid program; payments for services furnished by certain primary care physicians and charges for vaccine administration under the Vaccines for Children program. Final rule. Fed Regist 2012;77(215):66669–701.

120. Fisman DN, Chan CH, Lowcock E, Naus M, Lee V. Effectiveness and cost-effectiveness of pediatric rotavirus vaccination in British Columbia: A model-based evaluation. Vaccine 2012;30(52):7601–7.

121. Vichnin M, Bonanni P, Klein NP, et al. An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015. Pediatr Infect Dis J 2015;34(9):983–91.

122. Goldhaber-Fiebert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-Effectiveness of Cervical Cancer Screening With Human Papillomavirus DNA Testing and HPV-16,18 Vaccination. J Natl Cancer Inst 2008;100(5):308–20.

123. Gold M, Siegel J, Weinstein M, Russel L. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.

124. VFC | Current CDC Vaccine Price List | CDC [Internet]. 2018 [cited 2018 May 7];Available from: https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html

125. Attema AE, Brouwer WBF, Claxton K. Discounting in Economic Evaluations. Pharmacoeconomics 2018;36(7):745–58.

126. US Department of Commerce BEA. Bureau of Economic Analysis [Internet]. [cited 2018 May 8];Available from: https://www.bea.gov/histdata/fileStructDisplay.cfm?HMI=7&DY=2017&DQ=Q4&DV=Third&dNRD=March-29-2018

127. Medicare C for. CMS.gov Office of the Actuary National Health Expenditure Account projections, 2017-26 [Internet]. 2018 [cited 2018 May 8];Available from: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsProjected.html

128. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA 2016;316(10):1093–103.

129. Population projections | Kentucky State Data Center [Internet]. [cited 2018 Apr 15];Available from: http://www.ksdc.louisville.edu/data-downloads/projections/

130. Human papillomavirus vaccines. WHO position paper. Wkly Epidemiol Rec 2009;84(15):118–31.

131. Methods for the development of NICE public health guidance (third edition) | 6-incorporating-health-economics | Guidance and guidelines | NICE [Internet]. [cited 2016 Apr 27];Available from: https://www.nice.org.uk/article/pmg4/chapter/6-Incorporating-health-economics