CALIFORNIA
HEALTH BENEFITS REVIEW PROGRAM

Analysis of Assembly Bill 1429: Human Papillomavirus Vaccination

A Report to the 2007-2008 California Legislature
April 17, 2007

CHBRP 07-02

The California Health Benefits Review Program (CHBRP) responds to requests from the State Legislature to provide independent analyses of the medical, financial, and public health impacts of proposed health insurance benefit mandates and proposed repeals of health insurance benefit mandates. CHBRP was established in 2002 to implement the provisions of Assembly Bill 1996 (*California Health and Safety Code*, Section 127660, *et seq*.), and was reauthorized by Senate Bill 1704 in 2006 (Chapter 684, Statutes of 2006). The statute defines a health insurance benefit mandate as a requirement that a health insurer or managed care health plan (1) permit covered individuals to obtain health care treatment or services from a particular type of health care provider; (2) offer or provide coverage for the screening, diagnosis, or treatment of a particular disease or condition; or (3) offer or provide coverage of a particular type of health care treatment or service, or of medical equipment, medical supplies, or drugs used in connection with a health care treatment or service.

A small analytic staff in the University of California's Office of the President supports a task force of faculty from several campuses of the University of California, as well as Loma Linda University, the University of Southern California, and Stanford University, to complete each analysis within a 60-day period, usually before the Legislature begins formal consideration of a mandate bill. A certified, independent actuary helps estimate the financial impacts, and a strict conflict-of-interest policy ensures that the analyses are undertaken without financial or other interests that could bias the results. A National Advisory Council, drawn from experts from outside the state of California and designed to provide balanced representation among groups with an interest in health insurance benefit mandates, reviews draft studies to ensure their quality before they are transmitted to the Legislature. Each report summarizes scientific evidence relevant to the proposed mandate, or proposed mandate repeal, but does not make recommendations, deferring policy decision making to the Legislature. The State funds this work through a small annual assessment of health plans and insurers in California. All CHBRP reports and information about current requests from the California Legislature are available at the CHBRP Web site, www.chbrp.org.

A Report to the 2007-2008 California State Legislature

Analysis of Assembly Bill 1429: Human Papillomavirus Vaccination

April 17, 2007

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PREFACE

This report provides an analysis of the medical, financial, and public health impacts of Assembly Bill 1429, a bill to mandate coverage of the human papillomavirus vaccination. In response to a request from the California Assembly Committee on Health on February 27, 2007, the California Health Benefits Review Program (CHBRP) undertook this analysis pursuant to the provisions of Senate Bill 1704 (Chapter 684, Statutes of 2006) as chaptered in Section 127600, et seq., of the California Health and Safety Code.

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CHBRP gratefully acknowledges all of these contributions but assumes full responsibility for all of the report and its contents. Please direct any questions concerning this report to:

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California Health Benefits Review Program Analysis of Assembly Bill 1429: Human Papillomavirus Vaccination

The California Legislature has asked the California Health Benefits Review Program (CHBRP) to conduct an evidence-based assessment of the medical, financial, and public health impacts of Senate Bill 1429. In response to a request from the California Assembly Committee on Health on February 27, 2007, CHBRP undertook this analysis pursuant to the provisions of Senate Bill 1704 (Statutes of 2006, Chapter 684) as chaptered in Section 127600, et seq., of the California Health and Safety Code.

AB 1429 would amend Section 1367.66 of the Health and Safety Code and Section 10123.18 of the Insurance Code. These sections of the Health and Safety Code and Insurance Code currently mandate coverage for cervical cancer screening tests. AB 1429 would amend current law to require health plans and insurance policies that include coverage for treatment or surgery of cervical cancer to provide coverage for a human papillomavirus (HPV) vaccination. AB 1429 is intended to prevent cervical cancer and other conditions caused by HPV by requiring health insurance carriers to provide coverage for HPV vaccine preparations approved by the U.S. Food and Drug Administration (FDA).

HPV is the most common form of sexually transmitted infection, affecting approximately 27% of females aged 14 to 59 years in the United States. HPV infection has been identified as a necessary condition for cervical cancer. This means that only in rare cases is cervical cancer diagnosed in women not infected with HPV. Cervical cancer is a relatively rare cancer, making up approximately 1% of all new cancers cases each year.

There is currently one quadrivalent vaccine—meaning that it is designed to protect against four strains of HPV—approved by the FDA. The vaccine, Gardasil by Merck, protects girls and young women from the four HPV strains that cause 70% of cervical cancers and 90% of genital warts. Another HPV vaccine, Cervarix by GlaxoSmithKline, may be submitted to the FDA for approval as early as spring 2007. This bivalent vaccine is designed to protect against the two HPV strains that cause 70% of cervical cancers.

Medical Effectiveness

- The *Medical Effectiveness* section summarizes the published literature on the quadrivalent HPV vaccine (Gardasil) that has been approved by the FDA and the bivalent vaccine (Cervarix) that is in clinical trials.

- While the quadrivalent HPV vaccine is recommended for females aged 11 to 26 years, the available studies reported on clinical trials that limited enrollment to females aged 16 to 26 years. The vaccine provides a high level of protection (95% or more) against HPV 6, 11, 16, and 18 infection to females aged 16 to 26 years who:

    - have not had prior infection with HPV 6, 11, 16, and 18 viral types, and

- were compliant with the three-injection vaccination regimen

Protection extends to HPV infection, anogenital warts, and precancerous cervical lesions related to the four HPV types (6, 11, 16, and 18) contained in the vaccine.

- One clinical trial for the approved quadrivalent vaccine has been published to date. Due to its controlled environment, the actual effectiveness of the vaccine may be less than reported in the scientific literature. When used in the general population, vaccine performance in protecting against HPV-caused conditions may be reduced for the following reasons:
  - HPV infection acquired prior to vaccination
  - Imperfect compliance with the vaccination regimen
  - Disease caused by HPV types not included in the vaccine formulation
- The approved quadrivalent vaccine appears safe at 5 years post-vaccination with minimal side effects such as transient injection-site discomfort common to many vaccines.
- Duration of protection is unknown beyond five years. Continuing Phase III trials (which are expanded trials after preliminary evidence demonstrating the effectiveness of the vaccine) are monitoring durability to assess the need for a future booster vaccination.
- As a result of these factors, the CDC expects a 22% to 60% reduction in cervical cancer attributable to this vaccine in the general population. Effectiveness should be highest for groups less likely to have been exposed to HPV, such as preadolescent girls and females without a history of sexual activity. Reduction in cervical cancer risk will only become apparent several decades after vaccination due to the long latency for HPV-related cancer.
- In view of the imperfect performance of the vaccine, Pap tests remain recommended.

Utilization, Cost, and Coverage Impacts

- Coverage
  - About 3,382,600 females aged 11 to 26 years are currently covered by health plans that would would be subject to AB 1429.
  - Privately insured females aged 11 to 26 years account for 67%, or 2,281,600 of enrollees in plans subject to AB 1429.
  - Based on its survey of major California health plans, CHBRP estimates that approximately 27,400 privately insured females aged 11 to 26 years do not have coverage for the HPV vaccine and will gain this coverage after the passage of AB 1429. These individuals account for less than 1% of the females aged 11 to 26 years enrolled in plans subject to AB 1429.

- Utilization
    - Utilization rates for a new technology like the HPV vaccine are dynamic during the first few years it becomes available. Thus, the utilization estimates presented in this analysis could be lower if there is a substantial increase in HPV vaccination during 2007 due to its recent availability. If more females aged 11 to 26 years receive the vaccine during 2007—the year prior to the implementation of the mandate—there will be fewer who need the vaccine in 2008 when the mandate goes into effect.
    - In a given year, the annual vaccination rate for females aged 11 to 18 years with coverage for the HPV vaccine is estimated to be approximately 64.0%. This estimate is based on the annual rates of preventive services visits among this population. Approximately 80% of females aged 11 to 18 years would have a preventive service visit and 80% of those would be vaccinated (80% x 80% = 64%).
    - In a given year, the annual vaccination rate of females aged 19 to 26 years with coverage for the HPV vaccine is estimated to be approximately 52.7%. This is based on the the annual rates of the preventive services among this population. Approximately 68% of females aged 19 to 26 years would have a Pap test and 80% of those would be vaccinated. About 3% of females aged 19 to 26 years would be pregnant and not eligible for vaccination. Thus the vaccination rate for this population is calculated to be 52.7% (68% x 80% x 97% = 52.7%).
    - In the absence of coverage, the annual vaccination rate of females is estimated to be 45% of the rate for females with coverage.
    - The weighted average of annual vaccination rate for females aged 11 to 26 years is estimated at 59% for those with coverage and 27% for those without coverage.
    - The vaccination rate in the mandate effective year, 2008, is lower than the annual vaccination rate because a small proportion of the population eligible for vaccination and without coverage will be vaccinated prior to the mandate effective date. The 2008 vaccination rate for females aged 11 to 26 years is estimated to be approximately 43.3% for those newly covered for the vaccine.
    - Approximately 23.7%, or 6,500 of the 27,400 females aged 11 to 26 years currently without coverage for HPV vaccination are estimated to receive HPV vaccination in the first year following passage of AB 1429.
- Costs
    - The expenditures presented in this section are projected for the year following the implementation of the mandate and are likely to significantly diminish over time as the the population becomes vaccinated. Over time (assuming that CDC recommendations remain the same) only girls aged 11 to 12 years would obtain the vaccine on an ongoing basis.
    - The unit cost of vaccination using Gardasil, the only HPV vaccine currently available, is estimated at $451 for those covered by private insurance, including the cost of the three-dose vaccine and the cost of administration of the vaccine. The unit cost of the vaccination for those covered by state-funded public programs is estimated to be lower,

because administration fees are set at a lower level by the state, and because the vaccine is provided by the federal government at no cost to the state for children up to age 18. On average, the unit cost for the entire state—both public and private programs—is estimated to be approximately $355.

- The overall increase in expenditures due to AB 1429 is estimated at $4,562,000, an increase of 0.006% in total California health care expenditures in the year following the mandate, assuming some prior vaccinations in this population before the passage of the mandate. This increase is relatively small because most health plans and insurers already cover HPV vaccination.
- The increase in expenditures is limited to health policies regulated by the California Department of Insurance (CDI) in the individual and the group (large and small) market segments. This is because these are the market segments that currently have gaps in coverage for female enrollees aged 11 to 26 years. CHBRP estimates that about $2,407,000 in out-of-pocket expenditures that would have been incurred without coverage would be shifted to the entire population of females aged 11 to 26 years insured by CDI policies in the form of premiums and member copayments.
- The increase in premium expenditures is largest in the indiviudal market ($3,714,000 or 0.067%).
- Employee share of premiums is expected to increase by $352,000 (or 0.003%) and out-of-pocket costs in the form of copayments and deductibles are expected to increase by $1,328,000 (0.026%).
- Because Department of Managed Health Care (DMHC) regulated plans, CalPERS, and other public managed care programs currently have coverage for the vaccine, no cost increases are expected for these plans due to AB 1429.
- Cost-effectiveness studies have examined both the long-term costs of vaccination as well as the long-term savings associated with reductions in adverse health events resulting from HPV infections. These studies found that the lifetime costs and benefits of HPV vaccination for a hypothetical cohort of girls aged 12 years, where the vaccine is most effective, produces incremental cost-effectiveness ratios (ICERs) of $22,755 and $20,600 per quality-adjusted life-year (QALY) saved based on two separate estimates. These estimates mean that the net cost, after accounting for all savings associated with the reductions in adverse health events, ranges from about $20,600 to $22,755 per additional QALY saved. Although there is no consensus about the most appropriate threshold, policymakers have routinely accepted technologies with estimated ICERs much higher than these.

Table 1. Summary of Coverage, Utilization, and Cost Impacts of AB 1429

	Before Mandate	After Mandate	Increase/ Decrease	% Change After Mandate
Coverage				
Number of individuals subject to the mandate	3,382,600	3,382,600	0	0.000%
Percentage of individuals with coverage for HPV vaccine	99%	100%	1%	0.817%
Number of individuals with coverage for HPV vaccine	3,355,200	3,382,600	27,400	0.817%
Utilization and Per-Unit Cost				
Total number of individuals receiving vaccine	802,600	809,100	6,500	0.810%
Average per vaccination cost - Private sector (All Ages)	$451.25	$451.25	0	0.000%
Average per vaccination cost - Public sector (Ages 11-18) (Administration only, drug cost covered by federal VFC program)	$27.00	$27.00	0	0.000%
Average per vaccination cost - Public sector (Ages 19-26)	$317.25	$317.25	0	0.000%
Expenditures				
Premium expenditures by private employers for group insurance	$43,944,936,000	$43,946,511,000	$1,575,000	0.004%
Premium expenditures for individually purchased insurance	$5,515,939,000	$5,519,653,000	$3,714,000	0.067%
CalPERS employer expenditures	$2,631,085,000	$2,631,085,000	$0	0.000%
Medi-Cal state expenditures	$4,015,964,000	$4,015,964,000	$0	0.000%
Healthy Families state expenditures	$627,766,000	$627,766,000	$0	0.000%
Premium expenditures by employees with group insurance or CalPERS, and by individuals with Healthy Families	$11,515,939,000	$11,516,291,000	$352,000	0.003%
Member copayments	$5,153,127,000	$5,154,455,000	$1,328,000	0.026%
Expenditures for noncovered services	$2,407,000	$0	–$2,407,000	–100.000%
Total annual expenditures	$73,407,163,000	$73,411,725,000	$4,562,000	0.006%

Source: California Health Benefits Review Program, 2007.
Notes: The population includes individuals and dependents covered by employer-sponsored insurance (including CalPERS), individually purchased insurance, or public health insurance provided by a health plan subject to the requirements of the Knox-Keene Health Care Service Plan Act of 1975. All population figures include enrollees aged 0 to 64 years and enrollees 65 years or older covered by employment sponsored insurance. Member contributions to premiums include employee contributions to employer sponsored health insurance and member contributions to public health insurance. Expenditures for adults insured through the Managed Risk Medical Insurance Board are included in Medi-Cal premiums. Medi-Cal state expenditures for members under 65 include expenditures for MRMIP and AIM programs.
Key: CalPERS = California Public Employees' Retirement System. VFC= Vaccine for Children

Public Health Impacts

- HPV is the most common sexually transmitted infection in the United States—with over 80% of females infected at some point in their lifetime. It is estimated that among females aged 14 to 59 years, 27% are currently infected with HPV and 3.4% are currently infected with HPV strains 6, 11, 16, or 18.

- Models predict that, assuming current screening practices, vaccinating at age 20 would result in a reduction in HPV infection, cervical intraepithelial neoplasia (CIN) 1, CIN 2, CIN 3, and cervical cancer by 18%, 18%, 34%, and 56% respectively. Thus, assuming 6,500 additional women get vaccinated in the first year after passage of the mandate, over 1,000 cases of HPV could be averted over the lifetimes of these women, thereby preventing almost 30 cases of cervical cancer and 10 cervical cancer-related deaths.

- Although no models have been developed to quantify the impact, it is likely that a reduction in cases of anal, vulvar, vaginal, penile, or oral cavity and pharynx cancer due to vaccination with an HPV vaccine would occur as a result of this mandate as well.

- Blacks and Hispanics have higher mortality rates from cervical cancer compared to other racial/ethnic groups. Providing coverage for vaccination may be one way to reduce these racial and ethnic disparities in terms of the prevalence of HPV, the prevalence of cervical cancer, and cervical cancer mortality. It is unknown, however, the extent to which this mandate will reduce these disparities.

- Modeling predicts that vaccination could decrease lifetime mortality from cervical cancer in a cohort of women vaccinated at age 20 by 56%. Thus, this mandate has the potential to prevent 10 deaths related to cervical cancer in the group of women vaccinated in the first year postmandate as well as other deaths from other cancers caused by HPV.

- CHBRP estimates that as a result of this mandate, roughly 10 deaths could be prevented over the lifetime of women vaccinated in the first year, yielding a total savings of nearly 300 person-years, valued at approximately $3.5 million in productivity.

INTRODUCTION

Cervical cancer was once the number one cause of cancer deaths among women in the United States. However, the use of the Pap test to routinely screen for cervical cancer has reduced cervical cancer to the 13th cause of cancer-related deaths in women in the United States (Saslow et al., 2002). Because cervical cancer is strongly linked to the presence of cancer-causing strains of the human papillomavirus (HPV) and because HPV is the most common form of sexually transmitted infection—affecting approximately 27% of females aged 14 to 59 years in the United States (Dunne et al., 2007)—there has been significant interest to developing a vaccine that would protect against those HPV strains that lead to the development of cervical cancer.

On June 8, 2006, the U.S. Food and Drug Administration (FDA) approved the first vaccine that would protect girls and young women from certain HPV strains. Gardasil, developed by Merck, is a three-dose quadrivalent vaccine—meaning that it protects against four strains of HPV. Gardasil protects girls and young women from the four HPV strains that cause 70% of cervical cancers and 90% of genital warts. According to existing federal guidelines, which will be discussed in further detail in the *Medical Effectiveness* section, the HPV vaccine is recommended for females aged 11 to 26 years but can be administered to girls as young as 9 years of age. Another HPV vaccine, Cervarix by GlaxoSmithKline, may be submitted to the FDA for approval as early as spring 2007. This bivalent vaccine protects against the two HPV strains that cause 70% of cervical cancers.

Under current law, health plans and insurers are required to (1) cover comprehensive preventive care for children aged 16 years and younger for group policies, and (2) offer coverage to groups for comprehensive preventive care for children aged 17 and 18 years. "Comprehensive preventive care" includes immunizations per the current version of the federal Recommended Childhood Immunization Schedule (CDC, 2007).[1] Current California law also requires that health plans, regulated under the Health and Safety Code by the Department of Managed Health Care (DMHC) cover "preventive health services," which would include childhood and adult immunizations.[2] Health insurers regulated under the Insurance Code by the California Department of Insurance (CDI) are not required to cover or offer coverage for adult immunizations.

California law requires that health plans and insurers provide coverage for cervical cancer screenings such as the Pap and HPV test. AB 1429 would amend this section of current law to require health plans and insurance policies that include coverage for treatment or surgery of cervical cancer, to provide coverage for an HPV vaccination.[3] AB 1429 is intended to prevent cervical cancer and other conditions caused by HPV by requiring health insurance carriers to provide coverage for HPV vaccine preparations approved by the FDA.

[1] Health and Safety Code Sections 1367.3 and 1367.35. Insurance Code Sections 10123.55 and 10123.5.
[2] Health and Safety Code Section 1345(b).
[3] AB 1429 would amend section 1367.66 to the Health and Safety Code and Section 10123.18 of the Insurance Code.

The HPV vaccine has been the focus of much debate at the state level as policymakers and advocates seek to mandate that girls aged 11 to 12 years be administered the vaccine before they enter the sixth or seventh grade. Debate has centered on the issues of vaccine safety and cost, parental choice, and the morality of requiring administration of a vaccine against a virus that is sexually transmitted. Twenty-five states, including California, and the District of Columbia have introduced the school-entry mandate legislation. Texas, through a gubernatorial executive order, made the vaccine mandatory for school-aged girls with some exceptions; however, the Legislature is currently seeking to overturn the executive order.

Fourteen states introduced legislation mandating health insurance coverage for the vaccine—Arizona, California, Colorado, Florida, Hawaii, Iowa, Mississippi, Pennsylvania, Nevada, New Jersey, New Mexico, New York, Oregon, and Rhode Island. None have been enacted as of March 2007.

In California, females aged 18 years and younger have access to the vaccine through one of the following mechanisms:

- Private insurance: As will be discussed in further detail in the *Utilization, Cost, and Coverage* section of this report, health plans and insurance policies tend to cover the vaccine for children per guidelines set by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (ACIP).
- Medi-Cal and the Vaccine for Children program (VFC): The VFC program pays for the vaccine for children 18 years or younger who are eligible for Medicaid, uninsured, or American Indian. Children who have insurance but whose coverage does not include vaccinations may also qualify. For children who are eligible for Medi-Cal, the VFC program pays for the HPV vaccine while the administration fees associated with the medical office visit are paid by the Medi-Cal program.
- California's State Children's Health Insurance Program (SCHIP)—Healthy Families: Coverage of ACIP-recommended vaccines is required for children 18 years and younger who are enrolled in these programs. These children would not qualify for the VFC program since they are in households with incomes that exceed Medi-Cal eligibility requirements.[4]

[4] Other California public programs include Access to Infants and Mothers (AIM), Family PACT, and the Cervical Cancer Screening program. AIM is a program designed for low- to middle-income pregnant women who do not have insurance coverage. AIM tends to cover the same level of benefits as Knox-Keene licensed DMHC-regulated plans. However there will likely be virtually no utilization for AIM enrollees since the HPV vaccine is not recommended during pregnancy. Family PACT is designed to provide comprehensive family planning services to clients at risk of pregnancy or causing pregnancy, who do not have Medi-Cal, access to health insurance and meet income eligibility requirements. Family PACT does not currently cover the HPV vaccine for adults. California's Cervical Cancer Screening program provides free access to Pap tests and pelvic exams for qualifying adults but it is unclear whether they provide the HPV vaccine free of charge.

Adult females aged 19 to 26 years may have coverage through their private insurance. However, as will be discussed in further detail in *Utilization, Cost and Coverage* section, there are some gaps in coverage for this population. Currently, there are no public programs for adults in California to pay for vaccines. Merck states that their Patient Assistance Program provides the vaccine free of charge for uninsured adults who qualify for financial assistance.

MEDICAL EFFECTIVENESS

HPV is the most prevalent sexually transmitted infection in the United States. It is estimated that among females aged 14 to 59 years, 27% are currently infected with HPV and 3.4% are currently infected with HPV strains 6, 11, 16, or 18 (Dunne, 2007). Most HPV infections are asymptomatic and transient. However, some infections may persist and lead to conditions ranging from anogenital warts to various malignancies, depending on the viral type. Among these, cervical cancer has drawn the most attention and is responsible for approximately 1,600 new cases and 400 deaths annually in California (California Cancer Registry, 2007).

HPV and Its Disease Burden

There are at least 40 HPV types affecting the genital epithelium, and these differ in their disease-causing behavior (Table 2). HPV types 6 and 11 cause 90% of anogenital warts, whereas types 16 and 18 are among the high-risk HPV types associated with high-grade abnormal Pap tests and cervical cancer. HPV is a necessary factor in the development of cervical cancer, and types 16 and 18 are responsible for approximately 70% of such cancers in the United States (National Network for Immunization Information, 2006).

Table 2. HPV-Related Diseases

HPV types	Condition	Percentage of Cases Due to Associated Types[b]	Health Burden
Types 6 and 11	Anogenital warts	90%	Approximately 10% lifetime risk[c]
Types 6 and 11	Juvenile laryngeal papillomas	100%	Very rare[d]
Types 16 and 18 Types 6 and 11	CIN[a]	25% 5%	Common
Types 16 and 18	CIN[a] 2 and 3	50% to 60%	Annual incidence 1.5%[e]
Types 16 and 18	Cervical cancer	70%	1,600 new cases and 400 deaths in CA annually[f]
Types 16 and 18	Anal cancer	80% to 90%	4,000 new cases and 620 deaths in U.S. annually[d]
Multiple types	Vulvar cancer	40%	3,870 new cases and 870 deaths in U.S. annually[d]
Multiple types	Penile, vaginal, urethral, vulvar, head, and neck cancers	Varying percentage	Various[c]

Source: California Health Benefits Review Program, 2007.

a) CIN (cervical intraepithelial neoplasia) describes the extent of cellular abnormality seen on cervical biopsy. CIN Grade 1 is common and benign and typically resolves spontaneously. CIN Grades 2 and 3 are progressively more worrisome, as they are considered pre-cancerous.

b) ACS, 2006

c) Munk et al., 1997; CDC, MMWR, 2007

d) ACS, 2006

e) This incidence rate was determined through study of the Kaiser Permanente Northwest population (Portland, OR) only (Insinga et al., 2004).

f) California Cancer Registry

Natural Course of HPV Infection

Exposure to HPV usually results from sexual activity with an infected partner who is shedding the virus. The virus infects cervical and other cells, inciting an immune response. In the majority of cases, the immune response leads to resolution of infection and clearing the virus. In some cases, however, the virus may persist in cells and shed periodically or continually. During viral shedding the individual may infect others, typically through sexual contact.

Persistence of the virus may lead to several health outcomes. The most benign of these are anogenital warts. However, cells infected with specific high-risk HPV types may undergo progressive change toward abnormality over years and eventually become cancerous. The cervix is the most common cancer site, although other sites are also affected, as shown in Table 2. Whereas infection with HPV is a necessary step in the causation of cervical cancer, most such infections do not eventuate in malignancy.

Cervical cells can be examined from samples taken during the Papanicolaou test (Pap smear). Abnormalities of cervical cells may indicate the presence of cervical intraepithelial neoplasia (CIN), which is confirmed with a cervical biopsy and graded 1, 2, or 3, indicating progressive severity of the abnormalities. CIN 1 is common and relatively benign, often resolving spontaneously. CIN 2 and CIN 3 represent increasing levels of abnormality and may ultimately lead to cervical cancer. Not all CIN 2 and CIN 3 lesions progress to cancer. Where such progression occurs, the sequence from initial infection to cancer takes approximately two decades on average (ACS, 2006).

Because CIN 2 and, especially, CIN 3 are considered precancerous lesions occurring early in the course of infection, they are useful markers of the level of protection afforded by the HPV vaccine. Documenting prevention of CIN 2 and CIN 3 is strong evidence of protection against later cervical cancer, because it represents an interruption of the path of development toward cancer. Reduction of cervical cancer in vaccinated individuals is the ultimate health outcome; however, proof of such a reduction due to the vaccine will not be available for several decades in view of the time required for such cancer to develop, especially in well-screened populations.

Mechanism of Action for the HPV Vaccine

The HPV vaccine works by exposing the immune system to nonliving virus-like particles so that antibodies against these are formed. Appearance of antibody following vaccine administration is evidence for successful vaccination. These antibodies are specific for the virus types used in the vaccine. When the individual is later exposed to the real virus of the same type, the antibodies attack the virus and prevent infection. The currently approved HPV vaccine (Gardasil) is quadrivalent, i.e., targeted against four HPV types: 6, 11, 16, and 18. A bivalent vaccine (Cervarix) targeted against HPV types 16 and 18 is currently under study. The targeted types were chosen because of their importance in causing human disease, as illustrated in Table 2.

Outcomes Associated with HPV Vaccination

Epidemiologic studies reviewed in this report address vaccine-related prevention of short-term outcomes such as antibody development following vaccination, prevention of persistent HPV

infections, reductions of HPV type 16- and 18-related CIN 2 and CIN 3 lesions (representing an interruption of the pathway toward cervical cancer), and reduction of anogenital warts.

Current Vaccination Recommendations

Following FDA approval of the quadrivalent HPV vaccine, several professional and governmental organizations issued immunization guidelines on its use. Three of these organizations—American Academy of Pediatrics (AAP), American Academy of Family Practice (AAFP), and the Advisory Committee on Immunization Practices (ACIP)—adopted substantially the same recommendations (Table 3). All of these organizations recommend vaccination for females aged 11 to 12 years, with catch-up vaccination for aged 13 to 26 years, and vaccination in some situations as young as age 9. The U.S. Preventive Services Task Force refers to ACIP for vaccine-related guidelines. The ACS only recommends vaccination through age 18, citing insufficient evidence of benefit for women aged 19 to 26 years. Vaccination is not recommended for pregnant women, persons with moderate or severe acute illnesses, or with sensitivity to vaccine components (MMWR, 2007).

All organizations recommend that women and their health care providers continue to follow current cervical cancer screening guidelines, including the Pap test, as the quadrivalent vaccine does not protect against the remaining 30% of cervical cancers caused by other types. Furthermore, women exposed to HPV types 16 or 18 prior to vaccination may be susceptible to cancer as well.

HPV vaccination is currently only recommended for girls and young women, as they will experience the most significant outcome of high-risk HPV infection: cervical cancer. No clinical trials in boys and men have been completed, although some are underway.

Table 3. Summary of HPV Vaccine Guidelines

Organization	Year Issued	Patient Age	Recommended Schedule	Comment
American Academy of Pediatrics (AAP)	2007	Females aged 11 to 12	Three doses at 0, 2, and 6 months	Minimum age: 9 years Catch-up Immunization Schedule: Administer vaccine series to females aged 13 to 18 years if not previously vaccinated.
American Academy of Family Physicians (AAFP)	2007	Females aged 11 to 12	Three doses at 0, 2, and 6 months	Minimum age: 9 years Catch-up Immunization Schedule: Administer vaccine series to females aged 13 to 26 years if not previously vaccinated.
American College of Obstetricians and Gynecologists (ACOG)	2007	Females aged 11 to 26	Three doses at 0, 2, and 6 months	Recommend discussing HPV and benefits of the vaccine and offering vaccination to adolescents and young women who have not received it.
American Cancer Society (ACS)	2007	Females aged 11 to 12	Three doses at 0, 2, and 6 months	Minimum age: 9 years Catch-up Immunization Schedule: administer vaccine series to females aged 13 to 18 years if not previously vaccinated. Currently there is insufficient data to recommend for or against universal vaccination of women aged 19 to 26 years. The decision should be made between the patient and her health care provider based on risk of previous exposure to HPV.
Centers for Disease Control and Prevention – Advisory Committee on Immunization Practices (ACIP)	2007	Females aged 11 to 12	Three doses at 0, 2, and 6 months	Minimum age: 9 years Catch-up Immunization Schedule: Administer vaccine series to females aged 13 to 26 years if not previously vaccinated.
Society for Adolescent Medicine (SAM)	2007	The SAM fully endorses the ACIP recommendations for the three-dose HPV vaccine.		
U.S. Preventive Services Task Force	Defers to the ACIP for vaccine-related recommendations.			

Source: California Health Benefits Review Program, 2007.

Evidence-Based Review Results

Published, Peer-Reviewed Literature

FDA-approved vaccine

There is a single randomized controlled trial for the approved quadrivalent (types 6/11/16/18) HPV vaccine (Gardasil) published in the peer-reviewed literature (Villa et al., 2006). The trial represents a Phase II efficacy trial, i.e., it involves a relatively small group of selected patients to evaluate the performance of the vaccine under ideal conditions (Table 4-a). The investigators randomly assigned 552 females aged 16 to 23 years from Brazil, Scandinavia, and the United States to receive the quadrivalent vaccine or a placebo with up to five years of follow-up. HPV DNA tests, anti-HPV serum tests, and Pap tests ("gold standard" techniques) were used at multiple monthly intervals to detect infection from HPV types 6, 11, 16, or 18. Subjects receiving the vaccine showed an antibody response to all four HPV types in magnitudes at or above those seen among persons naturally infected. The subset of 468 persons who had no evidence of prior infection and complied fully with the protocol experienced 95.6% efficacy (95% CI, 83.3% to 99.5%) against persistent infection from HPV 6, 11, 16, and 18. The authors report a 100% efficacy for prevention of CIN 1, 2, and 3 due to HPV 6, 11, 16, and 18; because only three women (all in the placebo group) had a CIN outcome, a test of statistical significance was not performed. Also, all CIN cases are lumped together, yet only CIN 2 and CIN 3 are considered precancerous. Thus, it is not possible to characterize vaccine performance more precisely against the precancerous CIN 2 and CIN 3 lesions. The authors also observed 100% efficacy for genital warts; statistical testing was not conducted because of a small number of cases.

When a modified intention-to-treat analysis was conducted for 510 of the subjects, observed efficacy against persistent infection decreased to 93.5% (95% CI, 82.5%-98.3%). The lower efficacy reflects the fact that this analysis included subjects who were not fully compliant with the protocol, more closely representing the situation that would pertain to the general population.[5]

Unapproved vaccine

CHBRP chose to present published literature on an unapproved bivalent vaccine currently undergoing clinical trials. It is anticipated that clinical data will be submitted to the FDA for vaccine approval in the foreseeable future. Should the FDA grant approval, a choice of vaccines will be available to consumers and their physicians. Therefore, these clinical data are included for consideration.

A single randomized controlled Phase II trial for the currently unapproved bivalent (types 16 and 18) HPV vaccine (Cervarix) has been reported in the peer-reviewed medical literature (Harper, 2004; Table 4-b). The study subjects were 1,113 females aged 15 to 25 years from Canada, Brazil, and the United States. In the initial publication, Harper and co-workers (2004) showed a

[5]A pure intention-to-treat analysis includes all patients assigned to a given treatment, regardless of whether they actually received any part of it. The modified intention-to-treat analysis described here included all persons assigned to treatment with the exclusion of those who did not receive at least one vaccination in the three-injection series.

100% reduction (95% CI, 76.8%-100%) for persistent HPV 16 and 18 infection (based on combined cervical and cervicovaginal samples) in the subset of 721 persons who had no evidence of prior infection with HPV 16 and 18 and were compliant with the protocol. When the analysis was conducted according to intention to treat, which included persons who had not been fully compliant with the protocol (total 1,113 subjects), the efficacy was less: there was an 87.5% (95% CI, 64.6%-95.6%) reduction of persistent infection with HPV 16 and 18 (based on combined cervical and cervicovaginal samples).

The second peer-reviewed publication from the same study represented a follow-up at 4.5 years post-vaccination (Harper, 2006). The study showed antibody levels following vaccination 14- to 17-fold above those seen with natural infection. There was a 96.0% efficacy (95% CI, 75.2%-99.9%) for persistent HPV 16/18 infections in the 799 persons compliant with the protocol. Slightly lower efficacy was seen in the 951 subjects included in the intention-to-treat analysis: there was a 94.4% reduction (95%CI, 78.2%-99.4%) of persistent infections from HPV 16 and 18. The intention-to-treat analysis showed 100% protection against CIN 2 and 3 lesions due to HPV 16/18 (95% CI, –7.7%-100%). The wide confidence interval here reflects the fact that there were few occurrences of CIN 2 and 3 (n=5) (Table 4-b).

Non-Peer–Reviewed Literature

FDA-Approved Vaccine

Phase III trials designed to evaluate quadrivalent vaccine performance in large groups of patients from the general population are currently underway. These have not yet been published in the peer-reviewed literature, but interim results are available from the FDA website (FDA, 2007), the vaccine package insert, a recent review by Saslow and colleagues (2006), and the ACIP recommendations published in the CDC's Morbidity and Mortality Weekly Report (MMWR, 2007). The trials comprise over 15,000 females aged 16 to 26 years at enrollment who are assigned to either a vaccine or placebo group. Combined analyses limited to patients with no prior history of infection and compliant with the study protocol showed high levels of efficacy. For example, the combined studies showed 93.7% efficacy (95% CI, 87.7%-97.2%) for preventing CIN 1, 2, and 3 or adenocarcinoma *in situ* (AIS) due to HPV 6, 11, 16, and 18 (Gardasil package insert, Table 2). When persons with prior evidence of infection and/or were not fully compliant with the vaccination regimen were included, the efficacy dropped to 46.4% (95% CI, 35.2%-55.7%). A similar picture was seen for genital warts related to HPV 6/11: patients with no evidence of prior infection experienced a 93.4% efficacy (95% CI, 87.0%-97.0%), whereas analysis including subjects with evidence of prior infection and/or who were not fully compliant with the vaccination regimen experienced a 68.5% efficacy (95% CI, 57.5%-77.0%). Of note, an interim analysis showed no significant differences in overall CIN 2/3 or AIS between vaccinated and unvaccinated women when including previous infections and all types of HVP, including those not covered by the vaccine (efficacy 12.2% [95% CI, –3.2%-25.3%]) (Gardasil package insert).

Side Effects and Safety

Undesirable side effects included local site reactions and fever, headache, and nausea. These occurred in similar frequency in the treatment and placebo groups (ACS, 2006). At five years

post-vaccination, no adverse health events were attributable to the vaccine. Five women who became pregnant within 30 days of Gardasil vaccination delivered children with congenital abnormalities vs. 2.4 cases that would be expected based on the frequency of congenital anomalies in the general population. The anomalies were of several types, and expert review judged these cases to not be related to the vaccine. The quadrivalent vaccine is classified as Category B on the basis of animal studies in rats showing no evidence of impaired fertility or harm to the fetus (MMWR, 2007); it is not recommend for use in pregnancy

Conclusion

Extant literature provides a consistent picture of the vaccine's ability, when given to previously uninfected females under ideal conditions, to yield antibody production and provide 90% to 100% protection against anogenital warts and CIN 1, 2, and 3 due to HPV 6, 11, 16, and 18 for up to five years following vaccination. Because infection with HPV is a necessary step in the path to cancer (although most HPV infections do not proceed to cancer), it is assumed that prevention of HPV infection will reduce cancers from HPV types covered by the vaccine. However, this reduction will not be evident for several decades because of the long latency between infection and cancer.

CHBRP cautions that these findings of near-perfect vaccine performance represent a select group of patients who had no prior evidence of infection and were compliant with the vaccination regimen. Furthermore, the small number of cases means that the true level of protection may be lower or higher than the value observed, as indicated by the wide confidence intervals. Also, effectiveness in patients from the general population is likely to be significantly lower than the idealized situation. In particular, the general population will include persons who have had prior infection with HPV and who are not fully compliant with the vaccination regimen. The net effect is reduced effectiveness in the real-world setting compared to clinical trials. In addition, high-risk HPV types not included in the vaccine will continue to cause CIN 2 and 3 and cervical cancer, although the current proportion of cases attributed to these types is less than that attributed to HPV 16 and 18.

The duration of immunity beyond five years and whether a booster vaccine will be required is still unknown. Villa and colleagues (2006) report that vaccine-induced antibody titers are at or above those occurring from naturally acquired infection at five years post-immunization. Continual monitoring of vaccine recipients in Phase III and Phase IV post-licensure studies will be critical to detecting a possible reduction in immunity.

Nevertheless, vaccine performance in younger, pre-adolescent groups may approach the idealized figures because this population is less likely to have been exposed to HPV. The FDA has approved use of the vaccine in girls as young as 9 years. The data for females younger than 16 are limited to safety and immunogenicity; the efficacy studies did not include females younger than 16. Post-pubertal girls and women who have not been exposed may also experience effectiveness mirroring those achieved in clinical trials. Effectiveness will be maximized by carefully observing the vaccination schedule.

Table 4-a. Summary of Published Studies on Effectiveness of Approved HPV Vaccine (Gardasil)

Citation	Outcome	Research Design[(1)]	Statistical Significance	Direction of Effect	Size of Effect	Generalizability	Conclusion
Villa et al., 2006	Genital warts, persistent infections, and cervical intraepithelial neoplasia (CIN, including grades 2 and 3, which are precursor lesions for cervical cancer) related to infection from HPV types 6, 11, 16, and 18 included in the quadrivalent vaccine (1 study)	• Level I: 1 study	• Statistically significant: 1 of 1 study • Not statistically significant: 0 studies • Not reported: 0 studies	• Protection for females receiving quadrivalent vaccine • No effect: 0 studies • Worse: 0 studies	At 5 years post-enrollment, for persons with no evidence of prior infection and compliant with the protocol, the vaccine: • prevented 96% (95% CI, 83-100) of persistent infection in HPV types 6, 11, 16, and 18 • 100% efficacious for genital warts at 5 years • 100% efficacy for HPV 16- and 18-related CIN 1, 2, and 3 at 5 years	• Somewhat generalizable in that the primary study analyses focused on persons with no prior HPV infection and who were compliant with the three-shot regimen	• Preponderance of evidence suggests HPV vaccination will prevent genital warts, persistent cervical HPV infection, and precursor lesions for cervical cancer related to HPV types included in the vaccine. Performance will be best in persons and groups without prior infections and compliant with the three-shot regimen.

Source: California Health Benefits Review Program, 2007.
Note: The FUTURE Study, Phase III of Merck's Gardasil vaccine, is ongoing and described in the *Medical Effectiveness* section.
(1) Level I = Well-implemented randomized controlled trials (RCTs) and cluster RCTs, Level II = RCTs and cluster RCTs with major weaknesses, Level III = Nonrandomized studies that include an intervention group and one or more comparison groups and time series analyses, Level IV = Case series and case reports, Level V = Clinical/practice guidelines based on consensus or opinion.

Table 4-b. Summary of Published Study on Effectiveness of Unapproved HPV Vaccine (Cervarix)

Citation	Outcome	Research Design[(1)]	Statistical Significance	Direction of Effect	Size of Effect	Generalizability	Conclusion
Harper et al., 2004, 2006	Persistent HPV infections and cervical intraepithelial neoplasia (CIN) grades 2 and 3, which are precursor lesions for cervical cancer, related to infection from HPV 16 and 18 included in the bivalent vaccine (2 studies)	• Level I: 2 studies (initial study and a follow-up study at 4.5 years)	• Statistically significant: 2 of 2 studies • Not statistically significant: 0 studies • Not reported: 0 studies	• Protection for females receiving bivalent vaccine • No effect: 0 studies • Worse: 0 studies	At 4.5 years post-enrollment, the vaccine yielded: • Immune response 14- to 17-fold higher than from natural infections, in the according-to-protocol population • 96.0% (95% CI, 75.2%-99.9%) efficacy in preventing persistent HPV 16- and 18-related infection, in the according-to-protocol population • 100% (95% CI, –7.7%-100%) efficacious in preventing HPV 16/18-related CIN 2/3 lesions, in the intention-to-treat population	• Somewhat generalizable in that the primary study analyses focused on persons with no prior HPV infection and who were compliant with the three-shot regimen	• Preponderance of evidence suggests that the HPV 16 and 18 vaccine is highly efficacious in establishing an immune response and in preventing persistent HPV 16- and 18-related infection. Performance will be best in persons and groups without prior infections and compliant with the three-shot regimen

Source: California Health Benefits Review Program, 2007.

(1) Level I = Well-implemented randomized controlled trials (RCTs) and cluster RCTs, Level II = RCTs and cluster RCTs with major weaknesses, Level III = Nonrandomized studies that include an intervention group and one or more comparison groups and time series analyses, Level IV = Case series and case reports, Level V = Clinical/practice guidelines based on consensus or opinion.

UTILIZATION, COST, AND COVERAGE IMPACTS

AB 1429 would apply to health care service plans licensed by the DMHC, and regulated under the California Health and Safety Code. AB 1429 would also apply to health insurance policies regulated by the CDI, subject to the California Insurance Code. AB 1429 would require these plans to cover HPV vaccination for their enrollees. The current Centers for Disease Control and Prevention (CDC) guidelines recommend the vaccine for females aged 11 to 26 years who are not pregnant.

AB 1429 would require:

- All Knox-Keene[6] licensed plans regulated by the DMHC to provide coverage for HPV vaccination, including enrollees in group (large and small) and individual markets.
- All policies regulated by the CDI, including enrollees in group (large and small) and individual markets.
- All Knox-Keene licensed plans regulated by the DMHC to provide coverage for HPV vaccination, under public programs including Medi-Cal and Healthy Families.

This section will present first the current, or baseline, costs and coverage related to HPV vaccination, and then the estimated utilization, cost, and coverage impacts of AB 1429. For further details on the underlying data sources and methods, please see Appendix C.

Present Baseline Cost and Coverage

Current Coverage of the Mandated Benefit

Coverage of the commercially insured population subject to the mandate

Approximately 20,694,000 individuals in California are enrolled in health plans or policies that would be affected by this legislation. Within this group, an estimated 3,382,600 are females aged 11 to 26 years and specifically impacted by AB 1429.

A survey of the seven largest health plans and insurers in California was conducted by CHBRP to examine current coverage levels for HPV vaccination for the population of females aged 11 to 26 years. All seven health plans and insurers responded to the survey representing 85% of the privately insured enrollees in the CDI-regulated market and 82% in the DMHC-regulated market.

DMHC-regulated plans represent about 91% of the privately insured market in California, while CDI-regulated plans represent 9%. The results of CHBRP's coverage survey of health plans indicate that all enrollees in DMHC-regulated plans have coverage for the HPV vaccine. Among CDI-regulated insurers, 93.6% of the large group, 92.7% of the small group, and 84.5% of the enrollees have coverage for this vaccine. These coverage gaps are restricted to those female

[6] Health maintenance organizations in California are licensed under the Knox-Keene Health Care Services Plan Act, which is part of the California Health and Safety Code.

enrollees aged 11 to 26 years in CDI-regulated policies that do not include preventive services. The total number of females aged 11 to 26 years without this benefit is approximately 27,400.

The HPV vaccine coverage, per mandate specification, is conditional upon referral of the patient's health care provider, including physician, surgeon, nurse practitioner, or a certified nurse midwife. Plans who report coverage of HPV vaccination stated that they cover this benefit following the existing ACIP guidelines, or per internally developed guidelines that are consistent with ACIP, which recommended the coverage of the HPV vaccine for all females aged 11 to 26 years.

Coverage of the publicly insured population subject to the mandate

All CalPERS and publicly insured individuals in California, including Medi-Cal Managed Care, Healthy Families, and MRMIP enrollees have coverage for HPV vaccination.

Current Utilization Levels and Costs of the Mandated Benefit

Current utilization levels

The HPV vaccine, Gardasil, was approved by the FDA for public use in June 2006. Unlike other CHBRP analyses of existing health benefits, the HPV vaccination rate is dynamic, most likely rapidly increasing, and has not reached equilibrium. Consequently, the current level of HPV vaccination would differ with the vaccination rate after AB 1429 would go into effect in 2008. Furthermore, utilization data on current HPV vaccination rates are not yet available.

In the absence of utilization data, and the dynamic nature of the utilization rate, CHBRP has assumed that individuals are most likely to receive the vaccine during routine visits or visits including a Pap test. For females aged 11 to 18 years, 80% had a preventive visit in the past year based on data from the 2001 California Health Interview Survey (CHIS). For females aged 19 to 26 years, 68% had a preventive visit in the past year that included a Pap test.

Data on acceptability—or willingness of the public to adapt to regular use of this vaccine—is limited. A recent representative survey of Californian parents revealed that 75% of parents of a daughter reported that they would be likely to vaccinate their daughters before age 13, while another 6% reported they would vaccinate between ages of 13 and 16, and another 18% would not vaccinate before age 16 (Constantine and Jerman, 2007). The authors did not examine the potential impact of insurance coverage on vaccination, but cited concerns over the impact of vaccination on sexual behavior, moral considerations, and safety of the vaccine as reasons for unacceptability of the vaccine at various ages. CHBRP assumes the rate of use of the HPV vaccine to be 80%, accounting for discrepancies between reported acceptability and actual compliance.

The vaccination rate is further discounted for the approximately 3% of the eligible population aged 19 to 26 years who is pregnant, based on 2005 CHIS data, and thus ineligible for the vaccine. Using these assumptions, the vaccination rate is estimated as 64% for females aged 11 to 18 years (80% use rate by 80% who have an annual routine visit) and 52.7% for those aged 19 to 26 years (80% use rate by 68% who have an annual Pap test, multiplied by 97% to account for

those who are pregnant) at the time of the implementation of the mandate. The weighted average of the above annual vaccination rates for those aged 11 to 26 is 59%.

Intensive advertising campaigns are already underway to promote this vaccine. Because of these campaigns, approximately 7,300 females aged 11 to 26 are expected to be vaccinated prior to, and independent of, AB 1429. In the years following 2008, or the year the mandate first goes into effect, the proportions of the insured females aged 11 to 26 years actually receiving this vaccination would drop exponentially and rapidly, because significant proportions would have already been vaccinated. So by 2012, for example, the great majority (over 95%) of females aged 11 to 26 years are estimated to be vaccinated for HPV. After that time period, vaccination rates would reflect primarily females who have just turned age 11 (the youngest age for which the CDC recommends vaccination). If the current analyses were conducted in four or more years from now, the one-year cost projection by CHBRP would have reflected those stable vaccination rates. This mandate is unique because it would become effective shortly after the mandated service is first available. Thus, the premium and cost impact estimates in this report reflect expected short-term utilization and costs, and as a result, overstate expected annual costs in the future.

The vaccination rates are assumed to be similar among the group (large and small) and individual market segments. The vaccination rates for CalPERS, Healthy Families, and Major Risk Medical Insurance Program (MRMIP) populations are assumed to be similar to that of privately insured. Approximately 17% of the Medi-Cal female population aged 19 to 26 years in California is estimated to be pregnant and will not receive the vaccine at that time, leading to a vaccination rate of 45.3% for this population based on 2005 CHIS data. For a detailed examination of the methods refer to Appendix C.

Unit price

The only FDA-approved HPV vaccine available on the market at the time of this report is Gardasil by Merck. This vaccine is effective against four HPV types and is currently priced at $119.75 per dose, for a cost of $359.25 for the full three-dose series. An additional cost of $92 for administration of the vaccine in the commercial insurance market is estimated and includes a cost of at least one routine office visit, leading to a full unit cost of $451.25 for HPV vaccination.

The unit price of the vaccine in the public sector is estimated to be the amount of the administration fee only for females aged 11 to 18 years of age and the administration fee plus three doses of vaccine for females aged 19 to 26 years. Currently, the CDC HPV vaccine price list indicates a public sector cost of $290.25 for the full three doses with an additional $27 for the cost of administration of the vaccine, amounting to an estimated unit cost of $317.25.[7] The actual unit cost of the vaccine in the public sector may be lower.

The unit price of the vaccine does not include cost estimates for booster shots. This is because current trials do not go beyond 5 years and the durability of the vaccine beyond that time period is unknown (please see the *Medical Effectiveness* section for more detail). If booster shots should become necessary, the unit price of the vaccine may increase by $150.35 ($119.75 for a single dose and $30.60 for the administration fee). However, these costs will not be reflected in

[7] See price list at: http://www.cdc.gov/nip/vfc/cdc_vac_price_list.htm

premiums until at least 5 years after the first wave of the vaccine (mid-2011) should the need for a booster shot become apparent after the first 5 years.

The baseline cost associated with the mandate given current utilization and unit price of the vaccine are presented in Table 5.

Table 5. Baseline (Premandate) Per Member Per Month Premium and Expenditures by Insurance Plan Type, California, 2007

	Large Group		Small Group		Individual		Cal-PERS	Medi-Cal Managed Care	Medi-Cal Managed Care	Healthy Families Managed Care	Total Annual
	DMHC Regulated	CDI Regulated	DMHC Regulated	CDI Regulated	DMHC Regulated	CDI Regulated	HMO	65 and Over	Under 65		
Population Subject to the Mandate	10,354,000	363,000	3,086,000	679,000	1,268,000	794,000	791,000	165,000	2,513,000	681,000	20,694,000
Average Portion of Premium Paid by Employer	$249.51	$323.69	$249.52	$281.52	$0.00	$0.00	$277.19	$181.00	$120.43	$76.82	$51,194,004,000
Average Portion of Premium Paid by Employee	$53.66	$74.60	$94.73	$61.82	$269.42	$148.66	$48.92	$0.00	$0.85	$5.78	$17,057,625,000
Total Premium	$303.17	$398.28	$344.26	$343.34	$269.42	$148.66	$326.11	$181.00	$121.29	$82.60	$68,251,629,000
Member expenses for covered benefits (Deductibles, copays, etc)	$16.35	$46.30	$25.58	$90.75	$45.45	$36.35	$16.82	$0.00	$0.56	$2.25	$5,153,127,000
Member expenses for benefits not covered	$0.00	$0.06	$0.00	$0.07	$0.00	$0.16	$0.00	$0.00	$0.00	$0.00	$2,407,000
Total Expenditures	$319.52	$444.65	$369.84	$434.16	$314.86	$185.18	$342.92	$181.00	$121.85	$84.85	$73,407,163,000

Source: California Health Benefits Review Program, 2007.

Note: The population includes individuals and dependents in California who have private insurance (group and individual) or public insurance (e.g., CalPERS, Medi-Cal, Healthy Families, AIM, MRMIP) under health plans or policies regulated by DMHC or CDI. All population figures include enrollees aged 0 to 64 years and enrollees 65 years or older covered by employment-based coverage. *Key:* CalPERS = California Public Employees' Retirement System; HMO = health maintenance organization and point of service plans; PPO = preferred provider organization and fee-for-service plans.

The extent to which costs resulting from lack of coverage are shifted to other payers, including both public and private entities

Currently, 27,400 females aged 11 to 26 years in CDI-regulated plans are without coverage for the HPV vaccine. Assuming those without coverage pay full out-of-pocket costs for preventive services, HPV vaccination rates would be expected to be 45% of the level of those with full coverage at best (Newhouse, 1993). For females without coverage, this translates to a vaccination rate of 20.5% for those aged 11 to 18 years and 18.4% for those aged 19 to 26 years, (assuming that some individuals without coverage had received the vaccine before AB 1429 goes into effect). The weighted average vaccination rate for those aged 11 to 26 years is estimated at 19.5%. The related costs of these vaccinations are estimated at $2,407,000 in 2008 and are expected to be borne by the individual (out-of-pocket costs) and not shifted to other entities with the following exceptions.

As discussed in the *Introduction* section, children without coverage for this vaccine and who meet financial eligibility requirements may be able to receive the vaccine through the VFC program. Adults without coverage for this benefit do not have access to the vaccine through publicly funded programs. Merck, through its Patient Assistance Program, may provide the vaccine at no charge for adults who do not have insurance or who do not have coverage for the vaccine if they meet certain financial eligibility requirements. Analyses of the 2005 CHIS reveals that of the population of females aged 11 to 26 years insured by CDI-regulated plans who are not pregnant, 50% live in families earning 300% of the federal poverty level (FPL) or above and are most likely to afford the costs of HPV vaccination.

While Medi-Cal does not currently cover the HPV vaccine for adults, Knox-Keene licensed Medi-Cal Managed Care plans are required to cover the vaccine per existing Knox-Keene requirements. The Healthy Families program is also required to cover all ACIP-recommended vaccinations. CHBRP queried four large Knox-Keene licensed Medi-Cal Managed Care plans and they indicated that females aged 11 to 18 years have coverage for the cost of the vaccine through the federal VFC program for their Medi-Cal eligible enrollees. They incorporate the cost of administering the vaccine in the capitation rates negotiated with the Department of Health Services (DHS) for Medi-Cal. However, the costs of the vaccine and its administration for females aged 19 to 26 years are currently covered by health plans with no additional adjustment to the capitation rates for the Medi-Cal population. If DHS changes its Medi-Cal Managed Care capitation rates to reflect the costs of the HPV vaccine and its administration to females aged 19 to 26 years, the total Medi-Cal expenditures to DHS will increase accordingly. Currently, the CDC HPV vaccine price list indicates a public sector cost of $290.25 for the full three doses with an additional $27 for the cost of administration of the vaccine, amounting to a potential unit cost of $317.25.[8] Actual Medi-Cal unit cost may vary and it is unknown if the Medi-Cal per member per month (PMPM) amounts will change to further compensate health plans for this vaccine. Therefore, future PMPM Medi-Cal expenditures are not estimated in this report.

Healthy Families Managed Care plans currently cover the vaccine and the administration cost per existing requirements. Those plans may also seek to negotiate with Major Risk Medical

[8] See price list at: http://www.cdc.gov/nip/vfc/cdc_vac_price_list.htm

Insurance Board (MRMIB) revised capitation rates to reflect the vaccine cost for the future years thus transferring some cost from the health plan to MRMIB.

Public Demand for Coverage

There has been a significant amount of public interest and advocacy surrounding the HPV vaccine. Given that it is a new vaccine that just became available only after approval in late-2006, consumer demand for the vaccine is likely to be high. CHBRP reports on the extent to which collective bargaining entities negotiate for, and the extent to which self-insured plans currently have coverage for, the benefits specified under the proposed mandate, following the criteria for analysis specified under SB 1704 (2006). Currently, the largest public self-insured plan—CalPERS preferred provider organization (PPO)—includes coverage for vaccinations according the ACIP recommendations. Based on conversations with the largest collective bargaining agents in California, no evidence exists that unions currently include such detailed provisions (specific to individual vaccinations) during the negotiations of their health insurance policies. In general, unions tend to negotiate for broader contract provisions such as coverage for dependents, premiums, deductibles, and coinsurance levels. In order to determine whether any local unions engage in negotiations at such detail, they would need to be surveyed individually.[9]

Impacts of Mandated Coverage

Impact on Per-Unit Cost

AB 1429 is not expected to impact the per-unit cost of the HPV vaccine since other market forces will be stronger drivers of the price of the vaccine. For example, the cost of Gardasil may decrease once another vaccine is introduced in the market and the supply increases. There may be inflationary pressure on the price if there is increased demand resulting from (1) mandatory vaccination requirements for entry into school; (2) advertising campaigns by the manufacturer; (3) public health and awareness campaigns; and/or (4) guidelines and recommendations by federal and professional organizations.

Postmandate coverage

AB 1429 has a minimal impact on coverage for the HPV vaccine because 99% of the insured females aged 11 to 26 years are covered for this benefit under their existing health plans or policies. Thus, the mandate is estimated to provide additional coverage to 1% of the insured population—all concentrated in the CDI-regulated market for 27,400 females aged 11 to 26 years.

Changes in coverage as a result of premium increases

Due to the relatively small size of the increase in premiums due to AB 1429, CHBRP does not anticipate loss of insurance coverage, changes in availability of the benefit beyond those subject to the mandate, changes in offer rates of insurance, changes in employer contribution rates, changes in take-up of insurance by employees, or purchase of individual policies.

[9] Personal communication with the California Labor Federation and member organizations on January 29, 2007.

The largest increase in premiums is estimated to occur in the individual CDI-regulated market, where CHBRP estimates premiums would increase by 0.262%. Thus, the premium increases associated with AB 1429 would be less than 1% and have no measurable impact on number of individuals who are uninsured.

How Will Utilization Change As a Result of the Mandate?

CHBRP considers the following potential sources of change in vaccination rates: changes in rates as a result of changes in coverage or lowered prices paid by enrollees; changes in rates as a result of enrollees demand and awareness; and changes in rates as a result of changes in physicians' practice patterns.

Changes in vaccination rates as a result of changes in coverage or lowered prices paid by enrollees

Calculation of postmandate utilization rates (or after AB 1429 goes into effect) are based on the annual vaccination rates of 64% and 52.7% previously discussed in the *Current Utilization* section, but also take into account vaccinations that have occurred *prior* to the mandate's effective date. Postmandate utilization rates also take into account the likely rate of acceptance of the vaccine during a preventive visit. These rates do not take into account individuals who may receive the vaccine during visits for acute problems or individuals who may receive the vaccine outside a conventional office visit, such as health fairs and other community outreach activities by community-based organizations. The rate of increase is assumed to be the same between the group (large and small) and individual market segments affected by the mandate.

CHBRP estimates an increase in the vaccination rate only for those females aged 11 to 26 years enrolled in CDI-regulated plans that are not currently covered for the HPV vaccine (27,400 females). CHBRP estimates a 45.6% utilization rate for those aged 11 to 18 years, and a 40.8% utilization for those aged 19 to 26 years in the year following the mandate, amounting to a weighted average rate of 43.3%. "In the absence of AB 1429 in 2008, CHBRP estimates the number of females vaccinated, among those not currently covered, to be approximately 12,600 (46% of 27,400) by the end of 2008. With the mandate, CHBRP estimates the number of females vaccinated, among those not currently covered, to be 19,100 (70% of 27,400) by the end of 2008." Thus, the total number of females aged 11 to 26 years vaccinated due to the mandate is estimated at 6,500.

Changes in vaccination rates as a result of enrollees demand and awareness

The only HPV vaccine currently on the market, Gardasil, is expected to be subject to an intensive marketing campaign to raise awareness of its availability and utility among females aged 11 to 26 years as well as among health care providers likely to administer the vaccine. Furthermore, increasing awareness campaigns of the vaccine are likely by organizations aiming to reduce HPV infections, including the CDC. However, these intense efforts are not due to the mandate and there is no indication that the population who is receiving coverage due to the mandate will have a differential rate of vaccination from other insured populations with this coverage. Therefore, no additional changes in vaccination rates for this mandate due to differential demand or awareness are expected.

Changes in vaccination rates as a result of changes in physicians' practice patterns

The predicted intense advertising and public health campaigns are expected to be targeted to physicians and are likely to lead to increased physician recommendations for HPV vaccinations. However, the physician recommendations are not expected to differ with respect to patients who will gain coverage due to this mandate compared with those who will receive this vaccination with existing coverage.

To What Extent Does the Mandate Affect Administrative and Other Expenses?

CHBRP assumes that if health care costs increase as a result of increased utilization or changes in unit costs, there is a corresponding proportional increase in administrative costs. CHBRP assumes that the administrative cost *proportion of premiums* is unchanged. All health care plans and insurers include a component for administration and profit in their premiums. CHBRP estimates that the increase in administrative costs of CDI-regulated plans will remain proportional to the increase in premiums.

CHBRP estimates that members currently without the HPV vaccine benefit subject to the mandate will collectively pay $2,407,000 in cost sharing above their share of premiums.

Impact of the Mandate on Total Health Care Costs

Changes in total expenditures

The overall increase in expenditures due to this mandate is limited to policies regulated by the CDI in the large and small group and the individual market segments. CHBRP estimates that total expenditures will increase by $4,562,000 or 0.006%, including $5,641000 in premiums and $1,328,000 in out-of-pocket expenditures. This increase translates to an estimated premium increase of 0.037% ($0.10 PMPM) in the large-group market, 0.046% ($0.13 PMPM) in the small-group market, and 0.262% ($0.32 PMPM) in the individual market.

Offsets

Clinical sequelae of HPV infection include anogenital warts, cervical cancer precursors (CIN 2 and 3), cervical cancer, other anogenital cancers and their precursor lesions, and recurrent respiratory papillomatosis. In the majority of cases, HPV infections will clear due to the immune response of the individual, resulting in no immediate medical expenditures. This includes 60% of CIN 1 and 30% to 40% of CIN 2 and 3 (MMWR, 2007). In such cases, vaccination does not offset any medical costs due to HPV infection if the infection is not discovered. Only 1% of CIN 1 cases lead to cervical cancer and more than 12% of CIN 2 and 3 lead to cervical cancer.

HPV testing, biopsies, and colposcopies are used to diagnose and type the HPV. Treatments for sequelae of HPV infections include various local approaches that remove the lesions, such as cryotherapy, electrocautery, laser therapy, and surgical excision. Genital warts also are treated with topical pharmacologic agents (MMWR, 2007). With an estimated effectiveness of near 95% in clinical trials, nearly all HPV infections with types 6, 11, 16, and 18 can be avoided as well as the subsequent use of services associated with these infections. However, the final offsets from HPV vaccinations are likely to be less than 100% due to a number of factors including the

compliance with vaccination, receipt of the full vaccination dose, age of the recipient, and existing infections with these and other forms of HPV.

The cost of prevention and treatment of anogenital warts and cervical HPV-related disease is estimated to be $4 billion or more annually in United States. Approximately $200 million of this amount is attributable to the management of genital warts; approximately $300 to $400 million to invasive cervical cancer; and the remainder to routine cervical cancer screening, the follow-up of abnormal Pap tests, and pre-invasive cervical lesions (MMWR, 2007).

AB 1429 would add coverage for the HPV vaccine to about 1% of the insured population or approximately 27,400 females aged 11 to 26 years in California. Approximately 6,500 additional females are expected to be vaccinated due to this mandate (depending on the number that will be vaccinated prior to the mandate effective date). Subsequently, a clinically significant reduction in treatment of the HPV sequelae over the lifetime of these individuals is expected. However, the most likely reductions in the one-year timeframe of this report may be less treatment of anogenital warts, fewer follow-up Pap tests of infected individuals, and less frequent treatment of CIN 2 and 3. In the absence of data on the number of HPV cases and disease sequelae averted in the one-year timeframe, CHBRP does not include potential cost savings in the year following the mandate in this report. Rather, the long-term cost savings are discussed in the following section.

Long-term cost impacts

HPV vaccination will likely produce several important health benefits, including reductions in CIN 2 and 3, cases of cervical cancer, and cervical cancer deaths. Several cost-effectiveness studies have been published recently examining both the long-terms costs of vaccination as well as the long-term savings associated with reductions in these adverse health events (Sanders and Taira, 2003; Goldie et al., 2004). These studies found that the lifetime costs and benefits of HPV vaccination for a hypothetical cohort of females aged 12 years, where the vaccine is most effective, produces incremental cost-effectiveness ratios (ICERs) of $22,755 and $20,600 per quality-adjusted life-year (QALY) saved. These estimates mean that the net cost, after accounting for all savings associated with the reductions in adverse health events, ranges from about $20,600 to $22,755 per additional QALY saved, using different assumptions on length of immunity and other such details. Although there is no consensus about the most appropriate threshold, policy makers have routinely accepted technologies with estimated ICERs much higher than these.

Costs or Savings for Each Category of Insurer Resulting from the Benefit Mandate

AB 1429 will lead to an estimated increased total expenditure of $4,562,000, or an increase of 0.006% in the year following the mandate. This increased expenditure is attributed to a 0.023% increase and is equivalent to $0.10 in the large group CDI market and 0.029%, or $0.13, in the small group CDI market. In the individual market, the increase is estimated to be in the magnitude of 0.175%, or $0.32 PMPM.

Of the total expenditures, $1,575,000 is attributable to increases in premiums by employers and another $4,066,000 is attributable to increases in share of premiums paid by employees and

premiums paid by individual policy holders (Table 6). An additional $1,328,000 is attributable to member cost sharing not covered by the insurance policy.

The increase in PMPM employer share of premiums is in the magnitude of $0.12 in the large group and $0.13 in the small group CDI markets. An increase of $0.39 PMPM is also estimated in the individual CDI market. Member out-of-pocket expenditures are estimated to increase by $0.02 in the large, $0.04 in the small, and $0.10 PMPM in the individual markets.

No increased costs are projected as a result of AB 1429 for members in DMHC-regulated health plans in various market segments, CalPERS and for publicly insured individuals.

A summary of the projected cost impacts as a result of AB 1429 is summarized in Table 6. The increased expenditures are projected for the year following the mandate and are likely to significantly diminish over time as the percentage of the population subject to the mandate decreases exponentially because they would have been vaccinated.

Table 6. Postmandate Impacts on Per Member Per Month and Total Expenditures by Insurance Plan Type, California, 2007

	Large Group		Small Group		Individual		Cal-PERS	Medi-Cal Managed Care	Medi-Cal Managed Care	Healthy Families Managed Care	Total Annual
	DMHC Regulated	CDI Regulated	DMHC Regulated	CDI Regulated	DMHC Regulated	CDI Regulated	HMO	65 and Over	Under 65 (1)		
Population Subject to the Mandate	10,354,000	363,000	3,086,000	679,000	1,268,000	794,000	791,000	165,000	2,513,000	681,000	20,694,000
Average Portion of Premium Paid by Employer	$0.00	$0.12	$0.00	$0.13	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$1,575,000
Average Portion of Premium Paid by Employee	$0.00	$0.03	$0.00	$0.03	$0.00	$0.39	$0.00	$0.00	$0.00	$0.00	$4,066,000
Total Premium	$0.00	$0.15	$0.00	$0.16	$0.00	$0.39	$0.00	$0.00	$0.00	$0.00	$5,641,000
Member expenses for covered benefits (Deductibles, copays, etc)	$0.00	$0.02	$0.00	$0.04	$0.00	$0.10	$0.00	$0.00	$0.00	$0.00	$1,328,000
Member expenses for benefits not covered	$0.00	–$0.06	$0.00	–$0.07	$0.00	–$0.16	$0.00	$0.00	$0.00	$0.00	–$2,407,000
Total Expenditures	$0.00	$0.10	$0.00	$0.13	$0.00	$0.32	$0.00	$0.00	$0.00	$0.00	$4,562,000
Percentage Impact of Mandate											
Insured Premiums	0.000%	0.037%	0.000%	0.046%	0.000%	0.262%	0.000%	0.000%	0.000%	0.000%	0.008%
Total Expenditures	0.000%	0.023%	0.000%	0.029%	0.000%	0.175%	0.000%	0.000%	0.000%	0.000%	0.006%

Source: California Health Benefits Review Program, 2007.

Notes: The population includes individuals and dependents in California who have private insurance (group and individual) or public insurance (e.g., CalPERS, Medi-Cal, Healthy Families, AIM, MRMIP) under health plans or policies regulated by DMHC or CDI. All population figures include enrollees aged 0 to 64 years and enrollees 65 years or older covered by employment-based coverage. *Key:* CalPERS = California Public Employees' Retirement System; HMO = health maintenance organization and point of service plans; PPO = preferred provider organization and fee-for-service plans.

Impact On Access and Health Service Availability

AB 1429 is not expected to impact access to the HPV vaccine beyond the population currently without this benefit. Similarly, this mandate is not expected to impact the overall availability of the vaccine. Given that the vaccine was recently developed, there is no evidence to date that the supply of this vaccine is restricted or limited. In fact, the vaccine is being heavily promoted by the manufacturer through advertisements in a variety of media. Furthermore, the introduction of a competing vaccine, Cervarix, will further increase the supply of HPV vaccines and may lower its cost.

PUBLIC HEALTH IMPACTS

Present Baseline Health Outcomes

HPV Prevalence and Incidence

HPV is the most common sexually transmitted infection in the United States (Weinstock et al., 2004). It is estimated that more than 80% of sexually active women will be infected with the HPV virus at some point in their lifetime (MMWR, 2007). A systematic review of studies in the last decade analyzing the epidemiology of HPV across different populations found that the prevalence of HPV ranged from 14% to more than 90% and the reported annual incidence ranged from 7% to 20% (Revzina and DiClemente, 2005). The first population-based prevalence of HPV in a representative U.S. sample was published recently, and reported that in 2002-2003, 27% of females aged 14 to 59 years were infected with HPV (Dunne et al., 2007; Weller and Stanberry, 2007).

HPV strains can be categorized as either low risk or high risk in terms of their association with cancer. The current HPV vaccine on the market targets two of the most common low-risk strains (strains 6 and 11) as well as two of the most common high-risk strains (strains 16 and 18). Strains 6 and 11 are responsible for 90% of genital warts and are thought to have a prevalence in females aged 14 to 59 years of 1.3% and 0.1%, respectively (Greer et al., 1995; Dunne et al., 2007). Strains 16 and 18 are responsible for 70% of cervical cancers and have an estimated prevalence in females aged 14 to 59 years of 1.5% and 0.8%, respectively (Bosche et al., 2003; Dunne et al, 2007). It is estimated that 3.4% of females aged 14 to 59 years are currently infected with one of the four strains of HPV that the current FDA-approved vaccine targets (Dunne et al., 2007). In California, this would translate into nearly 400,000 females in this age group currently infected with HPV strains 6, 11, 16, or 18.

Health Consequences of HPV Infection

Most HPV infections are transient and do not lead to any health consequences. Approximately 70% of infections are cleared by the body after 1 year and 90% are cleared within 2 years (Ho et al., 1998). HPV infections that are not cleared by the body may lead to anogential warts, cervical cancer precursors, invasive cervical cancer, other anogenital cancers as well as oral cavity and pharyngeal cancers (MMWR, 2007).

Genital warts

The key clinical manifestation of HPV is the presence of visible genital warts, which appear on the vulva; in or around the vagina or anus; and on the penis, scrotum, groin, or thigh. Genital warts usually appear as soft, moist, pink, or flesh-colored swellings. They can be raised or flat, single or multiple, small or large, and sometimes cauliflower shaped. After sexual contact with an infected person, warts may appear within weeks or months, or not at all. The fact that not all infected persons display visual genital warts affects all the prevalence and incidence statistics presented in this literature review.

It has been estimated that approximately 1% of sexually active men and women in the United States has genital warts (CDC, 2007). Estimates of the prevalence of clinically visible genital warts range from 0.1% to 2.6% (Becker et al., 1987). Among the people who have been identified as having an HPV infection, only about 10% develop warts (CDC, 2007). It is estimated that approximately 500,000 people each year acquire symptomatic genital warts (CDC, 2007). Scientists estimate that as many as 1 million new cases of genital warts are diagnosed in the United States each year (NIH, 2006).

Cancer associated with HPV

While the majority of HPV infections are cleared by the body, those that are not may lead to cancer. Infection with high risk strains that are not cleared by the body may lead to precancerous lesions in the cervix known as cervical intraepithtlial neoplasia (CIN). CIN 1, low-grade CIN, has an estimated annual incidence rate of 1.2 per 1,000 while CIN 2 and 3, high-grade CIN, has an estimated annual incidence rate of 1.5 per 1,000 (Insinga et al., 2004). The age-adjusted cervical cancer incidence rate for California is 8.1 per 100,000 women per year in 2003 (NCI, 2003). The California cancer registry expects 1,465 new cases of cervical cancer in 2007, representing 1% of new cancer cases (ACS, 2006). Nationally, the median age for diagnosis of cervical cancer is 47 (MMWR, 2007)

The most common cancer caused by HPV is cervical cancer—where nearly 100% of all cases of cervical cancer are caused by HPV—but there are many other cancers caused as a result of HPV infection. Other cancers caused by HPV include anal (90% caused by HPV), vulvar (40% caused by HPV), vaginal (40% caused by HPV), penile (40% caused by HPV), oral cavity (specifically tongue and tonsils), and pharynx (<12% caused by HPV) (MMWR, 2007). Of the nearly 100% of cervical cancers related to HPV, about 70% are caused by HPV types 16 or 18. In addition, a high percentage of non-melanoma skin cancers in people with weakened immune systems contain HPV types (ACS, 2006). High-risk HPV types including HPV-16 and HPV-18 have been linked to 80% of anal cancer cases and HPV-16 plays a prominent role in vulvar, vaginal, penile, and oral cancer cases (ACS, 2006; MMWR, 2007).

Cervical cancer mortality

For cervical cancer diagnosed in California, the 5-year survival rates are 92% for localized cancer (the tumor has not spread outside the cervix), 56% for regional cancer (the tumor has spread to the lymph nodes or adjacent tissue), and 17% for distant cancer (the tumor has spread to other parts of the body) (ACS, 2006). Across all three stages, the 5-year survival rate is 72%. It is estimated that in 2007, 400 women will die from cervical cancer in California (ACS, 2006). The age-adjusted death rate from cervical cancer in California in 2002 was 2.4 deaths per 100,000 women (Nasseri et al., 2006).

Cervical cancer screening

Cervical cancer screening is an essential tool in the prevention of cervical cancer. Both the American Cancer Society and the U.S. Preventive Services Task Force recommend screening for cervical cancer at least once every three years starting at age 21 or within three years of onset of sexual activity (USPSTF, 2003; Saslow et al., 2002). In the population of women in California aged 18 years and older, screening for cervical cancer using Pap tests is very high with 86% reporting receiving a Pap test within the last three years, 6% reporting receiving a Pap test more

than three years ago, and 9% reporting never having had a Pap test (CHIS, 2005). In the population of adult women affected by this mandate (women aged 19 to 26 years with health insurance) it is estimated that 68% had a Pap test in the past year (CHIS, 2005).

Table 7. California Cervical Cancer Screening, Incidence, and Mortality

Race/ethnicity	Screening rate, 2005 (% of women 18 and over who received a pap test within 3 years)	Age-adjusted incidence rate, 2002 (per 100,000 women per year)	Age-adjusted death rate, 2002 (per 100,000 women per year)
All races	85.7 (84.8-86.5)	8.1	2.4
White	87.4 (86.4-88.5)	7.3	1.8
Black	87.6 (84.2-91.0)	7.6	3.4
Hispanic	86.4 (84.4-88.4)	14.5	3.8
Asian/Pacific Islander	77.1 (74.2-80.0)	8.4	2.3

Sources:
(1) Screening rates come from the California Health Interview Survey, 2005 (CHIS, 2005).
(2) Overall age-adjusted death rate for all-races and age-adjusted incidence and mortality rates by race/ethnicity come from Nasseri et al., 2006.
(3) The age adjusted incidence rate for all races is from the National Cancer Institute's state cancer profiles (http://statecancerprofiles.cancer.gov/cgi-bin/incidencerates/incidencerates.pl?00&057&00&2&001&1&1&1) and is for year 2003 (NCI, 2003).
Note: The uninsured and women who had a hysterectomy were excluded from the analysis of screening rates. White, black, and Asian/Pacific Islander racial categories exclude Hispanics. Hispanics may be of any race.

Impact of the Proposed Mandate on Public Health

The clinical trials presented in the *Medical Effectiveness* section present the efficacy of the vaccine in preventing persistent infections; genital warts; and CIN 1, 2, and 3. Simulation models have been constructed in order to predict the impact of HPV vaccination on the reduction in lifetime risk of HPV infection, risk of developing CIN, and the risk of developing cervical cancer (Garnett et. al., 2006; Sanders and Taira, 2003; Goldie et al., 2004; Taira et al., 2004, Barnabas et al., 2006; Elbasha et al., 2007; Van de Velde et al., 2007; Kohli et al., 2007). Of these models, only two assessed the impact of a vaccine targeting strains 6,11,16, and 18 (Van de Velde et al., 2007; Elbasha E, 2007). CHBRP selected the results presented in the Van de Velde article to calculate the public health impacts because the results were presented by age at vaccination, allowing us to account for the older age of the population that would be newly covered by this mandate (mean age of 18.3).

In the data modeled by Van de Velde et al. (2007), assuming a 95% efficacy rate of the vaccine and no change in current cervical cancer screening practices, the reduction in a cohort of girls vaccinated at 12 years of age in lifetime HPV infection was estimated at 21%; reduction in CIN

1 was estimated at 24%; reduction in CIN 2 and 3 was 49%; and the reduction in cervical cancer was 61%. These same data were presented for women vaccinated at age 20 years and the lifetime reduction in HPV infection, CIN 1, CIN 2/CIN 3, and cervical cancer was 18%, 18%, 34%, and 56%, respectively (Van de Velde et al., 2007).

Using these estimates of reduction in lifetime risk by the model developed by Van de Velde et al.(2007), CHBRP calculated the reduction in HPV infection and cervical cancer for those newly covered by the mandate. As presented in the *Utilization, Cost, and Coverage Impacts* section, it is estimated that, if the mandate is implemented, among females not currently covered, the number of vaccinated females will be 19,100 by the end of 2008. In absence of a mandate, the number of vaccinations among females not currently covered is estimated to be 12,600 by the end of 2008. This represents an increase of 6,500 vaccinations due to the passage of the mandate. Thus, approximately 1,000 cases of HPV could be averted over the lifetime of the women impacted by AB 1429, thereby preventing almost 30 cases of cervical cancer and 10 cervical cancer-related deaths (see Appendix D for a description of the methods used to calculate these estimates).

Although no models have been developed to quantify the impact, it is likely that a reduction in cases of anal, vulvar, vaginal, penile, or oral cavity and pharynx cancer due to vaccination with an HPV vaccine would occur as a result of this mandate as well.

The calculations presented above represent the effect of one year of vaccination on the lifetime risk of HVP infection, cervical cancer cases, and mortality of those vaccinated. After AB 1429 goes into effect, in each future year the effect of the vaccine will be reduced due to two factors. First, as clinical practice guidelines are implemented and girls are vaccinated routinely at age 11 or 12, there will be fewer and fewer numbers of females who would *not* have been covered (in absence of the mandate) who had not already been vaccinated as children. In other words, there would be less need for mandating coverage for the vaccine as more and more females become routinely vaccinated. Second, due to "herd immunity" as more and more women are vaccinated for HPV types 6, 11, 16, and 18, their prevalence in the population will decrease, thus lessening the effects of the vaccine on those newly vaccinated each year.

The calculations presented here may represent an upper bound in that the data is derived from the total population and is being applied to a population of women with health insurance. Evidence suggests that uninsured women have higher rates of cervical cancer compared to insured women (Ferrante et al., 2000). This being the case, there is still a significant amount of cervical cancer occurring among the insured population—with one study reporting that 85% of late-stage cervical cancer cases are found in women with health insurance coverage (Ferrante et al., 2000). In addition, although these models take into account current screening practices in the general population, this once again includes the uninsured, who are less likely to get Pap screenings at the recommended intervals (Ferrante et al., 2000). To the extent that the population of insured women subject to the mandate has a higher rate of Pap screenings, these models may overestimate the extent to which cervical cancer and related mortality may be reduced due to vaccination.

One further contributing factor to the possible overestimation of the effect of the vaccine in this population is that the models assumed a 95% efficacy rate. While this is consistent with what was found in the clinical trials, as presented in the *Medical Effectiveness* section, it most likely does not represent what would be seen in a real world setting due to imperfect compliance and other factors.

Impact on Community Health Where Gender and Racial Disparities Exist

A literature review was conducted to determine whether there are racial disparities associated with the prevalence and outcomes of HPV infection documented in the academic literature. While HPV infection occurs in both men and women, the health effects of HPV—chiefly cervical cancer—are health issues facing women. Therefore, most of the literature on HPV focuses on women's health.

HPV prevalence by gender and race and ethnicity

Although there is limited data on HPV infection in heterosexual men, a systematic review of 40 publications from 1990 to 2006 estimated that HPV prevalence in men ranged from 1.3% to 72.9% (Dunne et al., 2006). In studies in which multiple anatomic sites or specimens were evaluated, over half of these studies reported over 20% HPV prevalence in men (Dunne et al., 2006). The most common anogential HPV types detected in men were similar to the types commonly detected in women, with type 16 consistently among the most common.

Among women, racial disparities have been reported in the literature with regard to HPV prevalence. Researchers have found that black women are more likely to have HPV compared to white women (Burk et al., 1996; Khan et al., 2005; Stone et al., 2002; Shields et al., 2004). In addition, Hispanic women have also been found to have a higher prevalence of HPV compared to non-Hispanic women (Burk et al., 1996; Peyton et al., 2001). Population-based estimates of HPV prevalence in the United States among females aged 14 to 59 years by race/ethnicity showed that non-Hispanic black women had the highest prevalence rates (39.2%) compared to non-Hispanic white women (24.2%) or Mexican-American women (24.3%) (Dunne et al., 2007).

Clinical genital warts by gender and race and ethnicity

In men, genital warts are less common. If present, they are usually seen on the tip of the penis. They also may be found on the shaft of the penis, on the scrotum, or around the anus (National Institute of Allergy and Infectious Diseases, 2006). Additional research has been conducted on the relationship between circumcision and the appearance of genital warts. A study comparing heterosexual men with and without confirmed sexually transmitted diseases (STDs) in an urban STD clinic showed that uncircumcised men were less likely than circumcised men to have genital wart detectable by clinical examination (Cook, 1993).

The frequency of visible genital warts has been higher among whites than among non-whites in at least two studies. Hypotheses for these differences include racial differences in innate susceptibility, acquired immunity, behavior, or the effects of skin color on detectability of warts (Tanfer et al., 1995; Koutsky et al., 1988).

Cervical cancer incidence and prevalence by race/ethnicity

Nationally, Black women have higher incidence and prevalence rates of cervical cancer compared to all other races (Krieger et al., 1999; Patel et al. 2005; Newmann and Garner, 2005; Morgan et al., 1996; CDC, 2005). Additionally, other minority groups, particularly Hispanic women, have been found to have higher incidence and prevalence rates of cervical cancer compared to non-Hispanic whites (Napoles-Springer et al., 1996; Krieger et al., 1999; CDC, 2005; Patel et al., 2005). In California, the age-adjusted annual incidence rate of cervical cancer among Hispanics in 2002 was estimated as 14.5 per 100,000 women, for Asians as 8.4 per 100,000 women, for non-Hispanic blacks as 7.6 per 100,000 women, and for non-Hispanic whites as 7.3 per 100,000 women (Nasseri et al., 2006).

Stage at diagnosis and cervical cancer mortality by race/ethnicity

Compared to white women, black women have been found to present with more advanced stages of cervical cancer (Morgan et al., 1996; Howell et al., 1999; Leath et al., 2005; Schwartz et al., 2003) and have poorer survival rates (Mundt et al., 1998; Howell et al., 1999; Patel et al., 2005). Some research has found that Hispanic women have poorer survival rates compared to non-Hispanic white women (Napoles-Springer et al., 1996). Blacks have the lowest percentage (45%) of cervical cancer diagnosed at an early stage (*in situ* or localized), followed by Asians and Pacific Islanders (51%), Hispanics (52%), and whites (54%) (Nasseri et al., 2006). Cervical cancer mortality rates vary by race and ethnicity in California. In California, the age-adjusted death rate for Hispanics in 2002 is estimated as 3.8 per 100,000 women, for non-Hispanic blacks as 3.4 per 100,000 women, for Asians as 2.3 per 100,000 women, and non-Hispanic whites as 1.8 per 100,000 women (Nasseri et al., 2006).

Cervical cancer screening by race/ethnicity

In the population of women in California aged 21 years and older, rates of recommended screening for cervical cancer using Pap tests varies across race and ethnicity, with Asians reporting the lowest rate of having a Pap test within the last three years (77%) compared to Latinos (86%), whites (87%), and blacks (88%) (CHIS, 2005).

Vaccination by race/ethnicity

In a study of parents of Californian girls, it was found that there were significant racial/ethnic disparities in terms of the likelihood of vaccinating for HPV infection. Hispanics reported the highest rates of likelihood of vaccinating by age 13 (84%) followed by whites (74%), blacks (61%), and Asians (61%).

It has been suggested that providing coverage for vaccination might be one way to reduce these racial and ethnic disparities in terms of the prevalence of HPV, the prevalence of cervical cancer and cervical cancer mortality (Saslow et al., 2007). The rationale is that it is much easier to try to address disparities in vaccination (only three visits required) than to address disparities in cervical cancer screening, which requires visits every three years over the course of a women's lifetime to be effective (Saslow et al., 2007). It has also been suggested that the women who do not go in for regular Pap screening may be the same women who do not get vaccinated against HPV. Therefore, the extent to which this mandate will reduce these disparities is unknown.

Reduction of Premature Death and the Economic Loss Associated with Disease

Reduction in premature death

HPV is responsible for almost all cervical cancer cases (Walboomers et al., 1999). In California, approximately 400 women are expected to die in 2007 from cervical cancer (ACS, 2006). As presented in the analysis on the impact on community health (section above), vaccination modeling predicts that vaccination could decrease mortality from cervical cancer in a cohort of women vaccinated at age 20 by 56%, assuming current screening practices.[10] As described in the section on *Utilization, Cost, and Coverage Impacts*, it is assumed that premandate, 20% of the females aged 11 to 26 years affected by this mandate would get vaccinated and pay for the cost of vaccination out of pocket. Postmandate, the vaccination rate among this group would increase to 43%. This increase in 6,500 vaccinations could lead to a reduction in lifetime deaths from cancer in this group by 10.

Economic loss

The economic loss associated with cervical cancer consists of the direct costs discussed in the section *Utilization, Cost, and Coverage Impacts* and the indirect costs related to a reduction in productivity due to premature mortality. Based on a review of literature by Insinga et al. (2005), there is limited economic research quantifying these indirect costs. Insinga et al., did conclude that based on available data and given the mortality rates of cervical cancer over the past 30 years, the annual indirect costs of cervical cancer at the national level are likely to be in the billions of dollars and exceed direct medical costs by a factor of several times. A recent analysis in California reported a present value for the lost wages and housekeeping services of women dying from cervical cancer of $351,000 per cervical cancer death in 1998 dollars (Max et al., 2003). Furthermore, this study stated that the 452 deaths reported from cervical cancer in California in 1998 amounted to 12,989 person-years lost, or 28.7 years per death at an overall loss of $159 million to the economy. Lastly, since almost two thirds (64%) of the deaths due to cervical cancer occur among women under age 65, these deaths to younger women represent more than four fifths (82%) of the person-years lost and almost all (97%) of the losses in productivity (Max et al., 2003). CHBRP estimates that as a result of this mandate roughly 10 deaths could be prevented over the lifetime of women vaccinated in the first year, yielding a total savings of 300 person years, valued at approximately 3.5 million dollars (in 1998 dollars).

[10] While the Van de Velde et al., 2007, article does not present information on reduced mortality, other published models predicted similar reductions in cervical cancer and reduction in mortality from cervical cancer (Kohli et al., 2007; Sanders and Taira, 2003). Therefore, we are assuming that the 56% reduction in cervical cancer cases (for women vaccinated at age 20) is also the reduction in cervical cancer deaths.

APPENDICES

Appendix A: Text of Bill Analyzed

AB 1429 was introduced on February 23, 2007, by Assembly Member Noreen Evans. The following language is the amended version of AB 1429 which was forwarded to CHBRP on March 7, 2007. CHBRP analyzed the following version since it contains the amendments that the Bill Author intends to make.

SECTION 1. Section 1367.66 of the Health and Safety Code is amended to read:

1367.66. *(a)* Every individual or group health care service plan contract, except for a specialized health care service plan, that is issued, amended, or renewed, on or after January 1, 2002, and that includes coverage for treatment or surgery of cervical cancer shall also be deemed to provide coverage for an annual cervical cancer screening test upon the referral of the patient's physician and surgeon, a nurse practitioner, or *a* certified nurse midwife, providing care to the patient and operating within the scope of practice ~~otherwise~~ permitted for the licensee.

The coverage for an annual cervical cancer screening test provided pursuant to this section shall include the conventional Pap test, a human papillomavirus screening test that is approved by the federal Food and Drug Administration, and the option of any cervical cancer screening test approved by the federal Food and Drug Administration, upon the referral of the patient's health care provider.

~~Nothing~~

(b) Every individual or group health care service plan contract, except for a specialized health care service plan, that is issued, amended, or renewed on or after January 1, 2008, and that includes coverage for treatment or surgery of cervical cancer shall also be deemed to provide coverage for a ~~cervical cancer~~ human papillomavirus vaccination upon the referral of the patient's physician and surgeon, a nurse practitioner, or a certified nurse midwife, providing care to the patient and operating within the scope of practice permitted for the licensee.

(c) Nothing in this section shall be construed to establish a new mandated benefit or to prevent application of deductible or copayment provisions in an existing plan contract. The Legislature intends in this section to provide that cervical cancer *vaccination and* screening services are deemed to be covered if the plan contract includes coverage for cervical cancer treatment or surgery.

SEC. 2. Section 10123.18 of the Insurance Code is amended to read:

10123.18. (a) Every individual or group policy of health insurance that provides coverage for hospital, medical, or surgical benefits, that is issued, amended, or renewed, on or after January 1, 2002, and that includes coverage for treatment or surgery of cervical cancer shall also be deemed to provide coverage, upon the referral of ~~a~~ *the* patient's physician and surgeon, a nurse practitioner, or a certified nurse midwife, providing care to the patient and operating within the scope of practice ~~otherwise~~ permitted for the licensee, for an annual cervical cancer screening test.

The coverage for an annual cervical cancer screening test provided pursuant to this section shall include the conventional Pap test, a human papillomavirus screening test that is approved

by the federal Food and Drug Administration, and the option of any cervical cancer screening test approved by the federal Food and Drug Administration, upon the referral of the patient's health care provider.

~~Nothing~~

(b) Every individual or group policy of health insurance that provides coverage for hospital, medical, or surgical benefits, that is issued, amended, or renewed, on or after January 1, 2008, and that includes coverage for treatment or surgery of cervical cancer shall also be deemed to provide coverage for ~~a cervical cancer~~ human papillomavirus vaccination upon the referral of the patient's physician and surgeon, a nurse practitioner, or a certified nurse midwife, providing care to the patient and operating within the scope of practice permitted for the licensee.

(c) Nothing in this section shall be construed to require an individual or group policy to cover treatment or surgery for cervical cancer or to prevent application of deductible or copayment provisions contained in the policy or certificate, nor shall this section be construed to require that coverage under an individual or group policy be extended to any other procedures.

~~(b)~~

(d) This section shall not apply to vision only, dental only, accident only, specified disease, hospital indemnity, Medicare supplement, CHAMPUS supplement, long-term care, or disability income insurance. For accident only, hospital indemnity, or specified disease insurance, coverage for benefits under this section shall apply only to the extent that the benefits are covered under the general terms and conditions that apply to all other benefits under the policy or certificate. Nothing in this section shall be construed as imposing a new benefit mandate on accident only, hospital indemnity, or specified disease insurance.

SEC. 3. No reimbursement is required by this act pursuant to Section 6 of Article XIII B of the California Constitution because the only costs that may be incurred by a local agency or school district will be incurred because this act creates a new crime or infraction, eliminates a crime or infraction, or changes the penalty for a crime or infraction, within the meaning of Section 17556 of the Government Code, or changes the definition of a crime within the meaning of Section 6 of Article XIII B of the California Constitution.

Appendix B: Literature Review Methods

Appendix B describes the literature search for studies on the medical effectiveness of the HPV vaccine mandated for coverage by AB 1429.

In making a "call" for each outcome measure, the Medical Effectiveness team and the content expert consider the number of studies as well the strength of the evidence. To grade the evidence for each outcome measured, the team uses a grading system that has the following categories:

- Research design
- Statistical significance
- Direction of effect
- Size of effect
- Generalizability of findings

The grading system also contains an overall conclusion that encompasses findings in the five domains of research design, statistical significance, direction of effect, size of effect, and generalizability of findings. The conclusion is a statement that captures the strength and consistency of the evidence of an intervention's effect on an outcome. The following terms are used to characterize the body of evidence regarding an outcome:

- Clear and convincing evidence
- Preponderance of evidence
- Ambiguous/conflicting evidence
- Insufficient evidence

The conclusion states that there is "clear and convincing" evidence that an intervention has a favorable effect on an outcome if most of the studies included in a review have strong research designs and report statistically significant and clinically meaningful findings that favor the intervention.

The conclusion characterizes the evidence as "preponderance of evidence" that an intervention has a favorable effect if most but not all five criteria are met. For example, for some interventions the only evidence available is from nonrandomized studies. If most such studies that assess an outcome have statistically and clinically significant findings that are in a favorable direction and enroll populations similar to those covered by a mandate, the evidence would be classified as a "preponderance of evidence favoring the intervention." In some cases, the preponderance of evidence may indicate that an intervention has no effect or an unfavorable effect.

The evidence is presented as "ambiguous/conflicting" if none of the studies of an outcome have strong research designs and/or if their findings vary widely with regard to the direction, statistical significance, and clinical significance/size of the effect.

The category “insufficient evidence” of an intervention’s effect is used where there is little if any evidence of an intervention’s effect.

An English language–only literature search with no date limits was conducted in PubMed (138 citations found). Searches in the Cochrane Library (52 citations found), the National Guideline Clearinghouse (15 citations found), the Centre for Reviews and Dissemination (5 citations found), and MicroMedex were also conducted.

Publication types included in the literature search were systematic reviews, meta-analyses, randomized controlled trials, clinical trials, multi-center studies, practice guidelines, and reviews. Internet searches were conducted and focused on several Web sites including the Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices, U.S. Prevention Task Force, American Cancer Society, American Academy of Family Practice, American Academy of Pediatrics, American College of Obstetrics and Gynecology, and Society of Adolescent Medicine.

The *Medical Subject Headings* (MeSH) terms used by the librarian in the PubMed search were:
Adverse Drug Reaction Reporting Systems
Cervarix
Clinical Trials
Clinical Trials, Phase I
Clinical Trials, Phase II
Clinical Trials, Phase III
Clinical Trials, Phase IV
Clinical Trials, Phase IV
Cohort
Cohort studies
Controlled
Controlled Clinical Trials +
Device Approval
Drug Approval
Drug Evaluation
Drug Evaluation, Preclinical
Drug Screening Assays, Antitumor +
Effective
Effectiveness
Efficacy
Episode
Evaluation Studies
First
Gardasil
HPV vaccine
Human Papilloma Virus Vaccines
Human Papillomavirus Vaccine
In process
Investigational New Drug Application

Meta-Analysis
Microbial Sensitivity Tests +
Multicenter Studies
Outcome Assessment
Papillomavirus vaccines
Parasitic Sensitivity Tests
Practice Guideline
Product Surveillance, Postmarketing
Prognos*
Program Evaluation
Quadrivalent HPV
Randomized
Randomized Controlled Trial
Relative
Relative risk
Reproducibility of Results
Risk*
Risks
Specificity
Stud* Clinical Trial
Treatment Failure
Treatment Outcome
Trial
Validate
Validation

At least two reviewers screened the title and abstract of each citation returned by the literature search to determine eligibility for inclusion. Full-text articles were obtained, and reviewers reapplied the initial eligibility criteria.

A large number of publications were initially identified through the literature search. The analysis focused on a comprehensive summary of the most recent evidence-based clinical guidelines for HPV vaccination as well as the most recent clinical trials meeting inclusion criteria.

Due to specific criteria (Phase II and Phase III clinical trials of bivalent and quadrivalent HPV vaccines) and the very recent FDA approval and manufacturer introduction of this vaccine, the literature search resulted in a sparse body of eligible literature that addressed HPV vaccine efficacy and effectiveness. Three clinical trials were included in this analysis.

Appendix C: Cost Impact Analysis: Data Sources, Caveats, and Assumptions

This appendix describes data sources and general and mandate-specific caveats and assumptions used in conducting the cost impact analysis. For additional information on the cost model and underlying methodology, please refer to the CHBRP Web site, http://www.chbrp.org/analysis_methodology/cost_impact_analysis.php.

The cost analysis in this report was prepared by the Cost Team, which consists of CHBRP task force members and staff, specifically from the University of California, Los Angeles, and Milliman Inc. (Milliman). Milliman is an actuarial firm and provides data and analyses per the provisions of CHBRP authorizing legislation.

Data Sources

In preparing cost estimates, the Cost Team relies on a variety of data sources as described below.

Private health insurance

1. The latest (2005) California Health Interview Survey (CHIS), which is utilized to estimate insurance coverage for California's population and distribution by payer (i.e., employment-based, privately purchased, or publicly financed). The biannual CHIS is the largest state health survey conducted in the United States, collecting information from over 40,000 households. More information on CHIS is available at www.chis.ucla.edu.
2. The latest (2006) California Employer Health Benefits Survey is utilized to estimate:
    - Size of firm
    - Percentage of firms that are purchased/underwritten (versus self-insured)
    - Premiums for plans regulated by the Department of Managed Health Care (DMHC) (primarily health maintenance organizations [HMOs])
    - Premiums for policies regulated by the California Department of Insurance (CDI) (primarily preferred provider organizations [PPOs])
    - Premiums for high deductible health plans (HDHP) for the California population covered under employment-based health insurance

This annual survey is released by the California Health Care Foundation/Center for Studying Health System Change (CHCF/HSC) and is similar to the national employer survey released annually by the Kaiser Family Foundation and the Center for Studying Health System Change. More information on the CHCF/HSC is available at www.chcf.org/topics/healthinsurance/index.cfm?itemID=127480.

3. Milliman data sources are relied on to estimate the premium impact of mandates. Milliman's projections derive from the Milliman Health Cost Guidelines (HCGs). The HCGs are a health care pricing tool used by many of the major health plans in the United States (see www.milliman.com/tools_products/healthcare/Health_Cost_Guidelines.php). Most of the data sources underlying the HCGs are claims databases from commercial health insurance plans. The data are supplied by health insurance companies, Blues Cross and Blue Shield

plans, HMOs, self-funded employers, and private data vendors. The data are mostly from loosely managed healthcare plans, generally those characterized as preferred provider plans or preferred provider organizations (PPOs). The HCGs currently include claims drawn from plans covering 4.6 million members. In addition to the Milliman HCGs, CHBRP's utilization and cost estimates draw on other data, including the following:

- The MEDSTAT MarketScan Database, which includes demographic information and claim detail data for approximately 13 million members of self-insured and insured group health plans
- An annual survey of HMO and PPO pricing and claim experience, the most recent survey (2006 Group Health Insurance Survey) contains data from 6 major California health plans regarding their 2005 experience
- Ingenix MDR Charge Payment System, which includes information about professional fees paid for healthcare services, based upon approximately 800 million claims from commercial insurance companies HMOs and self-insured health plans

These data are reviewed for generalizability by an extended group of experts within Milliman, but are not audited externally

4. An annual survey by CHBRP of the seven largest providers of health insurance in California (Aetna, Blue Cross of California, Blue Shield of California, CIGNA, Health Net, Kaiser Foundation Health Plan, and PacifiCare) to obtain estimates of baseline enrollment by purchaser (i.e., large and small group and individual) type of plan (i.e., DMHC- or CDI-regulated), cost-sharing arrangements with enrollees and average premiums. Enrollment in these seven firms represents 82% of enrollees in full service health plans regulated by DMHC and 85% of lives covered by comprehensive health insurance products regulated by CDI.

Public Health Insurance

1. Premiums and enrollment in DMHC and CDI regulated plans by self-insured status and firm size are obtained annually from CalPERS for active state and local government public employees and their family members who receive their benefits through CalPERS. Enrollment information is provided for fully funded, Knox-Keene- licensed health care service plans—which is about 75% of CalPERS total enrollment. CalPERS self-funded plans—approximately 25% of enrollment—are not subject to state mandates. In addition, CHBRP obtains information on current scope of benefits from health plans' evidence of coverage (EOCs) publicly available at www.calpers.ca.gov.
2. Enrollment in Medi-Cal Managed Care (Knox-Keene licensed plans regulated by the DMHC) is estimated based on CHIS and data maintained by the Department of Health Services (DHS). DHS supplies CHBRP with the statewide average premiums negotiated for the Two-Plan Model, as well as generic contracts that summarize the current scope of benefits. CHBRP assesses enrollment information online at www.dhs.ca.gov/admin/ffdmb/mcss/RequestedData/Beneficiary%20files.htm.
3. Enrollment data for other public programs: Healthy Families, Access for Infants and Mothers (AIM), and the Major Risk Medical Insurance Program (MRMIP) are estimated based on CHIS and data maintained by the Major Risk Medical Insurance Board (MRMIB). The basic

minimum scope of benefits offered by participating plans under these programs must comply with all requirements of the Knox-Keene Act, and thus these plans are affected by changes in coverage for Knox-Keene licensed plans. CHBRP does not include enrollment in the Post-MRMIB Guaranteed-Issue Coverage Products as these individuals are already included in the enrollment for individual health insurance products offered by private carriers. Enrollment figures for AIM and MRMIP are included with enrollment for Medi-Cal in presentation of premium impacts. The enrollment information is obtained online at www.mrmib.ca.gov. Average statewide premium information is provided to CHBRP by MRMIB staff.

General Caveats and Assumptions

The projected cost estimates are estimates of the costs that would result if a certain set of assumptions were exactly realized. Actual costs will differ from these estimates for a wide variety of reasons, including:

- Prevalence of mandated benefits before and after the mandate may be different from CHBRP assumptions.
- Utilization of mandated services before and after the mandate may be different from CHBRP assumptions.
- Random fluctuations in the utilization and cost of health care services may occur.

Additional assumptions that underlie the cost estimates presented in this report are:

- Cost impacts are shown only for people with insurance.
- The projections do not include people covered under self-insured employer plans because those plans are not subject to state-mandated minimum benefit requirements.
- Employers and employees will share proportionately (on a percentage basis) in premium rate increases resulting from the mandate. In other words, the distribution of premium paid by the subscriber (or employee) and the employer will be unaffected by the mandate.
- For state-sponsored programs for the uninsured, the state share will continue to be equal to absolute dollar amount of funds dedicated to the program.
- When cost savings are estimated, they reflect savings realized for one year. Potential long-term cost savings or impacts are estimated if existing data and literature sources are available and provide adequate detail for estimating long-term impacts. For more information on CHBRP's criteria for estimating long-term impacts, please see http://www.chbrp.org/analysis_methodology/cost_impact_analysis.php.

There are other variables that may affect costs, but which CHBRP did not consider in the cost projections presented in this report. Such variables include, but are not limited to:

- **Population shifts by type of health insurance coverage.** If a mandate increases health insurance costs, then some employer groups or individuals may elect to drop their coverage. Employers may also switch to self-funding to avoid having to comply with the mandate.

- **Changes in benefit plans.** To help offset the premium increase resulting from a mandate, members or insured may elect to increase their overall plan deductibles or copayments. Such changes would have a direct impact on the distribution of costs between the health plan and the insured person, and may also result in utilization reductions.
- **Adverse Selection.** Theoretically, individuals or employer groups who had previously foregone insurance may now elect to enroll in an insurance plan postmandate because they perceive that it is to their economic benefit to do so.
- **Health plans may react to the mandate by tightening their medical management of the mandated benefit.** This would tend to dampen the CHBRP cost estimates. The dampening would be more pronounced on the plan types that previously had the least effective medical management (i.e., PPO plans).
- **Variation in existing utilization and costs, and in the impact of the mandate, by geographic area and delivery system models.** Even within the plan types CHBRP modeled (HMO, including HMO and POS plans; and non-HMO, including PPO and FFS policies), there are likely variations in utilization and costs by these plan types. Utilization also differs within California due to differences in the health status of the local commercial population, provider practice patterns, and the level of managed care available in each community. The average cost per service would also vary due to different underlying cost levels experienced by providers throughout California and the market dynamic in negotiations between health plans and providers. Both the baseline costs prior to the mandate and the estimated cost impact of the mandate could vary within the state due to geographic and delivery system differences. For the purposes of this analysis, however, CHBRP has estimated the impact on a statewide level.

Bill Analysis–Specific Caveats and Assumptions

- Coverage assumptions
  - CHBRP projects current coverage in California based on the responses of the largest carriers. It is possible that smaller insurance carriers not captured by CHBRP's survey may vary.
- Assumptions underlying utilization impact estimates
  - While the FDA has licensed the vaccine for girls as young as age 9, it is assumed that females aged 11 to 26 years will be obtaining the vaccine since that is the population for which the vaccine has been recommended by ACIP.
  - The actual HPV vaccination rate may differ substantially from those stated in this report for a number of reasons. For example, the intense advertising campaign by the vaccine manufacturers to individuals and providers may lead to high rates of awareness and acceptability of the vaccine. Alternatively, parental concerns over consequences of vaccination (including vaccine safety and moral and behavioral consequences) may lower the acceptability of the vaccine, leading to a lower initial vaccination rate than estimated in this report.
  - This analysis does not take into account potential future uses for an HPV vaccine. For example, there are studies that are currently examining the efficacy of administering

the HPV vaccine to males. If the vaccine is approved and recommended for boys the mandate may lead to increased coverage, utilization and cost that those presented here.

- CHBRP estimates that 45% of those without insurance coverage are likely to be vaccinated compared to those with insurance coverage for this vaccine. This estimate is based on the Rand Health Insurance experiment (Newhouse, 1993) and based on general use of preventive health services in the absence of insurance coverage. However, given the relatively high unit price of HPV vaccine, 45% is likely to represent the upper bound of the vaccination rate for those without such coverage. Information provided on the body of the report on the poverty status of the mandate population indicate that the costs of the vaccine may not be affordable for at least some of those without such coverage.
- The vaccination rates in this report reflect the one-time impact of increased use during the first years a vaccine is available and covered. If the use of the vaccine is widely accepted, and most of the females aged 11 to 26 have been vaccinated, vaccination rates will decrease dramatically in future years, to reflect primarily females entering the recommended age range, or those aged 11 to 12 years. This could occur about four years after the adoption of the mandate. For most CHBRP analyses, the one-year cost projection is based on these long term utilization rates. This mandate is unique because it becomes effective shortly after the mandated service is first available. The premium and cost impact estimates in this report reflect expected short-term costs, and as a result, overstate expected annual costs in the future.

- Assumptions on per-unit costs
  - Per-unit costs were estimated based on the current cost of Gardasil. As stated, the per-unit cost of vaccination may increase if a booster dose is required in five years. In addition, the per-unit cost may be different if another vaccine, such as Cervarix by GlaxoSmithKline is introduced in the market.

Appendix D: Calculations of Cases of Cervical Cancers Averted over the Lifetime of Those Newly Vaccinated

This analysis assumes the following:

- The number of females aged 11 to 26 years who would be newly covered under AB 1429 is 27,400.
- The number of vaccinations in absence of a mandate in the population of females aged 11 to 26 years affected by AB 1429 is 12,600.
- The number of vaccinations postmandate in the population of females aged 11 to 26 years who would be newly covered under AB 1429 is 19,100.
- This translates into 6,500 additional vaccinations as a result of the mandate.

"Cumulative lifetime incidence" at baseline was calculated from data presented in Sanders and Taira (2003), Table 2. For example, in the absence of a vaccination it was assumed that there would be 1,684,954 cases of HPV in a population of 1,988,600 females over the course of their lifetime (Sanders and Taira, 2003). Thus (by dividing these two numbers), CHBRP estimated that the cumulative lifetime incidence rate of HPV in the absence of a vaccination is 84.7%. This is in line with other published estimates (MMWR, 2007). The "reduction in cumulative lifetime incidence if vaccinated" was taken from Van de Velde et al. (2007). This article was chosen because it modeled the effect of Gardasil (the current FDA-approved vaccine on the market) and presented outcomes by age at vaccination. This model adjusted for later age of vaccination (age 20) whereas most available literature present data only for the vaccination of a cohort females aged 12 years. In addition, while less recent literature modeled a vaccine efficacy rate of only 75%, the Van de Velde model used 95% for the base-case calculations, which is much closer to the efficacy rates presented in the *Medical Effectiveness* section of this report. It is important to note that the Van de Velde model assumes no change in current cervical cancer screening practices.

Table D-1. Calculated public health outcomes postmandate

Outcome	Cumulative Lifetime Incidence (Baseline)	Reduction in Cumulative Lifetime Incidence if Vaccinated	Cumulative Lifetime Incidence (if Vaccinated)	Premandate (Cases)	Postmandate (Cases)	Lifetime Cases Averted
HPV Infection	0.847[a]	0.18[b]	0.6945	22,400	21,400	1,000
Cervical Cancer	0.0084[a]	0.56[b]	0.0037	200	170	30
Cervical Cancer Deaths	0.0032[a]	0.56[c]	0.0014	80	70	10

Sources:

a) Sanders and Taira, 2003.

b) Van de Velde et al., 2007.

c) While the Van de Velde et al., 2007, article does not present information on reduced mortality, other published models predicted similar reductions in cervical cancer and reduction in mortality from cervical cancer (Kohli et al., 2007; Sanders and Taira, 2003). Therefore, CHBRP assumes that the 56% reduction in cervical cancer cases (for women vaccinated at age 20) is also the reduction in cervical cancer deaths.

Appendix E: Information Submitted by Outside Parties

In accordance with CHBRP policy to analyze information submitted by outside parties during the first two weeks of the CHBRP review, the following parties chose to submit information.

No information was submitted directly by interested parties for this analysis.

For information on the processes for submitting information to CHBRP for review and consideration, please visit http://www.chbrp.org/recent_requests/index.php.

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A group of faculty and staff undertakes most of the analysis that informs reports by the California Health Benefits Review Program (CHBRP). The CHBRP **Faculty Task Force** comprises rotating representatives from six University of California (UC) campuses and three private universities in California. In addition to these representatives, there are other ongoing contributors to CHBRP from UC. This larger group provides advice to the CHBRP staff on the overall administration of the program and conducts much of the analysis. The CHBRP **staff** coordinates the efforts of the Faculty Task Force, works with Task Force members in preparing parts of the analysis, and coordinates all external communications, including those with the California Legislature. The level of involvement of members of the CHBRP Faculty Task Force and staff varies on each report, with individual participants more closely involved in the preparation of some reports and less involved in others.

As required by the CHBRP authorizing legislation, UC contracts with a certified actuary, Milliman Inc. (Milliman), to assist in assessing the financial impact of each benefit mandate bill. Milliman also helped with the initial development of CHBRP methods for assessing that impact.

The **National Advisory Council** provides expert reviews of draft analyses and offers general guidance on the program to CHBRP staff and the Faculty Task Force. CHBRP is grateful for the valuable assistance and thoughtful critiques provided by the members of the National Advisory Council. However, the Council does not necessarily approve or disapprove of or endorse this report. CHBRP assumes full responsibility for the report and the accuracy of its contents.

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