



CALIFORNIA
HEALTH BENEFITS REVIEW PROGRAM

Analysis of Senate Bill 158: Human Papillomavirus Vaccination

A Report to the 2009-2010 California Legislature
April 13, 2009

CHBRP 09-05



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. In 2002, CHBRP was established 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.

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A Report to the 2009-2010 California State Legislature

Analysis of Senate Bill 158: Human Papillomavirus Vaccination

April 13, 2009

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PREFACE

This report provides an analysis of the medical, financial, and public health impacts of Senate Bill 158, a bill to mandate that health plans and insurance policies that include coverage for treatment or surgery of cervical cancer provide coverage for a human papillomavirus (HPV) vaccination upon referral. In response to a request from the California Senate Committee on Health on February 13, 2009, 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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Susan Philip, MPP
Director

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EXECUTIVE SUMMARY

California Health Benefits Review Program Analysis of Senate Bill 158: 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 (SB) 158. In response to a request from the California Senate Health Committee on February 13, 2009, CHBRP undertook this analysis pursuant to the provisions of SB 1704 (Statutes of 2006, Chapter 684) as chaptered in Section 127600, et seq., of the California Health and Safety Code.

SB 158 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. SB 158 would amend current law to require health plans and insurance policies that include coverage for treatment of or surgery for cervical cancer to provide coverage for a human papillomavirus (HPV) vaccination upon referral. SB 158 is intended to prevent cervical cancer and other conditions caused by HPV by requiring health insurance to cover HPV vaccinations approved by the U.S. Food and Drug Administration (FDA).

HPV is the most common sexually transmitted infection in the United States. It is estimated that more than 80% of sexually active women will be infected with HPV at some point in their lifetime. 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. However, cervical cancer is a relatively rare cancer in the United States, 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 two HPV strains that cause 70% of cervical cancers and the two HPV strains that cause 90% of genital warts. Materials in support of another HPV vaccine, Cervarix by GlaxoSmithKline, have been submitted to the FDA for approval. 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 under review by the FDA.
- A full course of the quadrivalent HPV vaccine requires the injection of three doses of the vaccine over a six-month period.
- All clinical trials of the quadrivalent and bivalent HPV vaccines published to date were sponsored by their manufacturers.

- While the quadrivalent HPV vaccine is recommended for females aged 11 to 26 years, the three major clinical trials on the vaccine limited enrollment to females aged 15 to 26 years.
- The only trial to enroll girls younger than 15 has only published results on the vaccine's efficacy one year following vaccination. Long-term efficacy in this population is unknown.
- Interim results from the largest clinical trial of the quadrivalent vaccine published to date indicate that **among females who complete all three doses of the vaccine and were not previously exposed to HPV 16 or 18**, the vaccine provides for reductions in precancerous cervical lesions of 98% for lesions caused by the HPV types 16 and 18. However, the efficacy of the vaccine against precancerous lesions associated with all types of HPV has not been reported for this population.
- Interim results of the largest clinical trial of the quadrivalent vaccine published to date indicate that the vaccine is less effective among females who have not completed all three doses of the vaccine and/or were exposed to HPV prior to vaccination. Analyses that included all women who received at least one dose of the vaccine regardless of prior exposure to HPV report that the vaccine provides for the following reductions in precancerous cervical lesions:
 - 44% reduction in precancerous lesions caused by the HPV types **targeted** by the vaccine, and
 - 17% reduction in precancerous lesions regardless of associated HPV type, **including those not targeted** by the vaccine. Of note, the overall effect of vaccination on what many experts consider to be the most proximal cervical cancer precursor lesion (carcinoma *in situ*, or cervical intraepithelial neoplasia grade 3) was not statistically significant.
- Interim results from the largest clinical trial of the quadrivalent vaccine suggest that the vaccine prevents precancerous vaginal and vulvar lesions. As with cervical cancer lesions, the vaccine is less effective among females who do not receive all three doses of the vaccine or are exposed to HPV prior to vaccination.
- The quadrivalent vaccine provides protection against anogenital warts, but findings from the clinical trials do not indicate what proportion of females enrolled in the trials were concerned about their anogenital warts.
- The approved quadrivalent vaccine appears safe at 5 years postvaccination with minimal side effects such as transient injection-site discomfort common to many vaccines.
- Duration of protection is unknown beyond five years. Ongoing Phase 3 trials are monitoring durability to assess the need for a future booster vaccination.
- Because the vaccine does not provide complete protection against all types of HPV associated with cervical cancer, Papanicolaou (Pap) tests remain recommended to ensure that precancerous cervical lesions are detected and treated early.

Utilization, Cost, and Coverage Impacts

Coverage

- About 21,340,000 enrollees are in health plans or policies subject to SB 158. This includes approximately 3,348,000 females aged 11 to 26 years.
- An estimated 99.5% of enrollees currently have coverage for HPV vaccination. If the mandate were to become law, an additional 17,000 or 0.5% would gain coverage.

Utilization

- An HPV vaccine has been available since June 2006. Utilization rates for new vaccines are dynamic within the first few years of availability, and are likely to be higher at onset and to diminish over time as pent-up demand decreases and equilibrium is achieved.
- CHBRP estimates that by 2010, and before SB 158 would go into effect, approximately 33.0% of insured females aged 11 to 26 years would have been vaccinated for HPV. CHBRP estimates that among the newly covered population of insured females, 19.0% of those aged 11 to 18 years and 13% of those aged 19 to 26 years would be vaccinated in 2010 and after the implementation of SB 158.
- An additional 2,500 or 1.4% of insured females aged 11 to 26 years are estimated to receive the HPV vaccine in 2010 after SB 158 is implemented.

Costs

- The expenditures presented in this report are projected for the year following the implementation of the mandate and are likely to diminish over time as more older females are vaccinated. Over time (assuming that vaccination guidelines remain the same) primarily girls aged 11 to 12 years would obtain the vaccine on an ongoing basis. However, some girls older than 12 may receive HPV vaccination in their later teens due to various considerations preventing early vaccination.
- The unit cost of vaccination using Gardasil, the only HPV vaccine currently approved by the FDA, is estimated at \$468 for those covered by private insurance, which includes the cost of the three-dose vaccine and the cost of administration of the vaccine.
- The increase in expenditures is limited to health policies regulated by the California Department of Insurance (CDI) in the individual and the large group market segments. This is because these are the market segments that currently have gaps in coverage for female enrollees aged 11 to 26 years.
- The overall increase in expenditures due to SB 158 is estimated at \$1,625,000, or 0.0019%, in total California health care expenditures in the year following the mandate.
- The increase in premium expenditures is \$1,357,000, or 0.0228%, in the individual market and \$84,000, or 0.0002%, in the large group market.

- Employee share of premiums is expected to increase by \$24,000, or 0.0002%.
- Out-of-pocket costs in the form of copayments and deductibles are expected to increase by \$345,000, or 0.0054%.
- Because plans regulated by the Department of Managed Health Care (DMHC), CalPERS, and other public managed care programs currently have coverage for the vaccine, no cost increases are expected for these plans due to SB 158.
- Existing studies indicate that HPV vaccination, primarily of females aged 12 years, is cost-effective. Estimated cost-effectiveness ratio of vaccination ranges from \$2,964 to \$43,600 per quality-adjusted life year gained for 12-year-old girls. This means \$2,964 to \$43,600 in vaccinations would have to be spent to save a quality-adjusted life-year.

Public Health Impacts

- HPV is the most common sexually transmitted infection in the United States, with over 80% of sexually active women infected at some point in their lifetime. It is estimated that 3.4% of females aged 14 to 59 years are infected with one of the four strains of HPV that the current FDA-approved vaccine targets.
- Models predict that vaccinating a cohort of 12-year-old girls would result in a reduction in cervical cancer cases by 36% to 62% over the course of the lifetime of the cohort. Catch-up vaccination of older females is predicted to have a lower efficacy rate due to higher rates of prior exposure in this group. Thus, assuming 2,500 additional females get vaccinated in the first year after passage of the mandate, between 8 and 13 cases of cervical cancer could be prevented.
- In subsequent years, after catch-up vaccinations are complete, the number of additional females getting vaccinated as a result of the mandate would decrease to approximately 350, preventing one to two cases of cervical cancer over the lifetime of these females.
- It is possible that a reduction in cases of anal, vulvar, vaginal, penile, or oral cavity and pharynx cancer due to HPV vaccination 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. Over time, as researchers are able to assess differences in the vaccination rates across racial and ethnic groups, the potential for the HPV vaccine to reduce disparities in health outcomes related to HPV infection will be clearer. Therefore, the extent to which this mandate would reduce these disparities is unknown.
- CHBRP estimates that, as a result of this mandate, three to five deaths could be prevented over the lifetime of women vaccinated in the first year, yielding a total savings of 80 to 140 person years, valued at an amount between \$1.3 and \$2.2 million.

Table 1. Summary of Coverage, Utilization, and Cost Impacts of SB 158

	Before Mandate	After Mandate	Increase/ Decrease	Change After Mandate
Coverage				
Total population in plans subject to state regulation (a)	21,340,000	21,340,000	0	0%
Total population in plans subject to SB 158	21,340,000	21,340,000	0	0%
Number of females aged 11 to 26 in plans subject to SB 158				
Covered	3,331,000	3,348,000	17,000	0.5%
No coverage	17,000	-	-17,000	-100%
Percentage of females aged 11 to 26 in plans subject to SB 158				
Covered	99.5%	100.0%	0.5%	0.5%
No coverage	0.5%	0.0%	-0.5%	-100%
Utilization and cost				
Number of females aged 11 to 26 vaccinated annually	181,100	183,600	2,500	1.4%
Average per unit cost (commercial plans)	\$468	\$468	-	0%
Expenditures				
Premium expenditures by private employers for group insurance	\$50,546,207,000	\$50,546,291,000	\$84,000	0.0002%
Premium expenditures for individually purchased insurance	\$5,944,229,000	\$5,945,586,000	\$1,357,000	0.0228%
Premium expenditures by individuals with group insurance, CalPERS, Healthy Families, AIM or MRMIP (b)	\$13,475,994,000	\$13,476,018,000	\$24,000	0.0002%
CalPERS employer expenditures (c)	\$3,161,160,000	\$3,161,160,000	\$0	0.0000%
Medi-Cal state expenditures	\$4,112,865,000	\$4,112,865,000	\$0	0.0000%
Healthy Families state expenditures	\$643,247,000	\$643,247,000	\$0	0.0000%
Individual out-of-pocket expenditures for HPV vaccine such as deductibles and copayments	\$6,384,077,000	\$6,384,422,000	\$345,000	0.0054%
HPV vaccination expenditures paid by individuals not covered for HPV vaccine	\$185,000	\$0	-\$185,000	-100%
Total annual expenditures	\$84,267,964,000	\$84,269,589,000	\$1,625,000	0.0019%

Source: California Health Benefits Review Program, 2009.

Notes: (a) This population includes privately insured (group and individual) and publicly insured (e.g., CalPERS, Medi-Cal, Healthy Families, AIM, MRMIP) individuals enrolled in health insurance products regulated by DMHC or CDI. Population includes enrollees aged 0 to 64 years and enrollees 65 years or older covered by employment sponsored insurance.

(b) Premium expenditures by individuals include employee contributions to employer-sponsored health insurance and member contributions to public insurance.

(c) Of the CalPERS employer expenditures, about 59% would be state expenditures for CalPERS members who are state employees, however CHBRP estimates no impact of the mandate on CalPERS employer expenditures.

Key: CalPERS = California Public Employees' Retirement System.

INTRODUCTION

Cervical cancer was once the number one cause of cancer death among women in the United States. However, the use of the Papanicolaou (Pap) test to routinely screen for cervical cancer has reduced cervical cancer to the 14th most frequent cause of cancer-related death in women in the United States (American Cancer Society, 2008; Saslow et al., 2002). Because cervical cancer is caused by certain strains of the human papillomavirus (HPV) and because HPV is the most common form of sexually transmitted infection, there has been significant interest in developing a vaccine that would protect against those HPV strains that lead to the development of cervical cancer.

Background on SB 158

Senate Bill (SB) 158 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. SB 158 would amend current law to require health plans and insurance policies that include coverage for treatment of or surgery for cervical cancer to provide coverage for HPV vaccination upon referral. SB 158 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).

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 158. In response to a request from the California Senate Health Committee on February 13, 2009, CHBRP undertook this analysis pursuant to the provisions of SB 1704 (Statutes of 2006, Chapter 684) as chaptered in Section 127600, et seq., of the California Health and Safety Code.

HPV and Its Disease Burden

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.

HPV is the most prevalent 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 HPV at some point in their lifetime (CDC, 2004). A systematic review of studies in the last decade analyzing the epidemiology of the infection found that HPV prevalence ranged widely depending on the population studied—ranging from 14% to more than 90% (Revzina and DiClemente, 2005). The first population-based prevalence estimate of HPV in a representative U.S. sample reported that in 2002 to 2003, 27% of females aged 14 to 59 years were infected with HPV and

3.4% are currently infected with the types of HPV most frequently associated with the development of anogenital warts, high-grade cervical lesions, and cervical cancer. (types 6, 11, 16, or 18) (Dunne et al., 2007; Weller and Stanberry, 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.

Most HPV infections are asymptomatic, transient, and do not lead to any health consequences. Approximately 70% of infections are cleared by the body after one year and 90% within two years (Ho et al., 1998). However, some infections may persist. HPV infections that are not cleared by the body may lead to anogenital warts, cervical cancer precursors, invasive cervical cancer, other anogenital cancers, or oral cavity and pharyngeal cancers, depending on the viral type (Markowitz et al., 2007). 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 HPV types 16 and 18 are associated with high-grade cervical lesions 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). Cervical cancer is responsible for approximately 1,500 new cases and 400 deaths annually in California (CCR, 2008). Table 2 presents information about the health burden of HPV-related diseases.

Table 2. HPV-Related Diseases

HPV Types	Condition	Percentage of Cases Due to HPV 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 6 and 11	Cervical intraepithelial neoplasia (CIN) (a)	5%	Common
Types 16 and 18		25%	
Types 16 and 18	CIN 2 and 3 (a)	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
Multiple types	Vulvar cancer	40%	3,870 new cases and 870 deaths in U.S. annually
Multiple types	Penile, vaginal, urethral, vulvar, head, and neck cancers	Varying percentage	Various (c)

Source: California Health Benefits Review Program, 2009.

Notes: (a) CIN 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, 2008 (c) Markowitz et al., 2007; Munk et al., 1997. (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.

Genital warts

The key clinical manifestation of certain HPV types 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 of the prevalence and incidence statistics presented in this literature review.

Among the people who have been identified as having an HPV infection, only about 10% develop warts (CDC, 2007a). It has been estimated that approximately 1% of sexually active men and women in the United States have genital warts at any one time (CDC, 2007a). Estimates of the prevalence of clinically visible genital warts range from 0.1% to 2.6% (Becker et al., 1987). It is estimated 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

As mentioned, 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 intraepithelial 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 8.4 per 100,000 females per year in 2005 (NCI, 2005). The California Cancer Registry predicted 1,480 new cases of cervical cancer in 2009, representing 1% of new cancer cases (CCR, 2008).

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 and pharynx (<12% caused by HPV) (Markowitz et al., 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 16 and 18 have been linked to 80% of anal cancer cases and type 16 plays a prominent role in vulvar, vaginal, penile, and oral cancer cases (ACS, 2006; Markowitz et al., 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 2009, 410 women will die from cervical cancer in California (CCR, 2008).

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 and effective tool in the prevention of cervical cancer. There is a preponderance of evidence that, among asymptomatic women who are sexually active and have not had a hysterectomy, screening with conventional testing methods (i.e., Pap test) reduces the incidence of cervical cancer, because this test can detect precancerous lesions. Treatment of precancerous lesions can prevent a woman from developing cervical cancer. In addition, Pap tests can reduce morbidity and mortality from cervical cancer by detecting cancerous lesions at an early stage at which treatment is most likely to be successful (USPSTF, 2003).

Both the American Cancer Society (ACS) and the USPSTF recommend screening for cervical cancer at least once every three years starting at age 21 or within three years of onset of sexual activity (Saslow et al., 2002; USPSTF, 2003). In the population of females in California aged 18 years and older, screening for cervical cancer using Pap tests is 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 8% reporting never having had a Pap test (CHIS, 2007).

Background on the HPV Vaccine

On June 8, 2006, the 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 two HPV strains (16 and 18) that cause 70% of cervical cancers and two (6 and 11) that cause 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. Data in support of the approval of another HPV vaccine, Cervarix, was submitted to the FDA in March 2007 by its manufacturer, GlaxoSmithKline. This bivalent vaccine protects against the two HPV strains (16 and 18) that cause 70% of cervical cancers. While approved for use in Europe and Australia, Cervarix has not yet been approved by the FDA for use in the United States.

HPV vaccination

The rate at which young women and girls with health insurance have been vaccinated to date is affected by many factors including, awareness of the HPV vaccine's availability and uses, and compliance with current recommendations. As will be discussed further in the *Utilization, Cost, and Coverage Impacts* section of this report, awareness of HPV in California has increased dramatically since 2006, with a majority of teens and young women reporting that they would be interested in receiving the vaccine. The most frequent reason cited for not getting the vaccine was lack of sufficient knowledge about the vaccine followed by worry about its safety. The actual HPV vaccination rate, however, is lower: with 19% of insured females aged 11 to 26 years

having had received at least one dose of the vaccine, based on CHBRP's analysis of the 2007 California Health Information Survey (CHIS).

Current California Law

Under current law, health plans regulated under the Health and Safety Code by the Department of Managed Health Care (DMHC) and insurers regulated under the Insurance Code by the California Department of Insurance (CDI) in California are required to:

- cover comprehensive preventive care for children aged 16 years and younger for group policies, and
- *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, 2009).¹

Current California law also requires that health plans regulated by the DMHC cover “preventive health services,” which would include childhood and adult immunizations.² Health insurers regulated by the CDI are not required to cover or offer coverage for adult immunizations.

California law also requires that health plans and insurers provide coverage for cervical cancer screenings such as the Pap and HPV tests. SB 158 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*. SB 158 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.

California State Programs

Access to the Vaccine for Children Program

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

- **Private insurance:** As will be discussed in further detail in the *Utilization, Cost, and Coverage Impacts* 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 Medi-Cal, are uninsured, or are 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

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).

program pays for the HPV vaccine. The administration fees associated with the medical office visit are paid by the Medi-Cal program.

- The 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. Unless they are American Indian or Alaska Native, these children do not qualify for the VFC program since their household incomes exceed Medi-Cal eligibility requirements.

Access to the Vaccine for Adults

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 Impacts* 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.

Other California public programs include Access for Infants and Mothers (AIM); Family Planning, Access, Care and Treatment (Family PACT); and the Cervical Cancer Screening program. AIM is a health insurance program for low- to middle-income pregnant women who do not have insurance coverage. AIM tends to cover the same level of benefits as Knox-Keene³ licensed DMHC-regulated plans. However, there would likely be virtually no utilization for AIM enrollees since the HPV vaccine is not recommended during pregnancy. Family PACT is not an insurance program but instead provides comprehensive family planning services to low-income women and men who are underinsured or uninsured and who are ineligible for Medi-Cal. Vaccines are not part of family planning services provided by Family PACT. California's Cervical Cancer Screening program is also not an insurance program, but rather an initiative to provide free access to Pap tests and pelvic exams for qualifying women over the age of 25. Vaccines are not part of the screening services provided by the Cervical Cancer Screening program⁴.

Legislative Activity in Other States

The HPV vaccine has been the focus of much state-level debate across the country since it has been developed and approved by the FDA. Discussion has centered on the issues of vaccine safety and cost, parental choice, and the morality of requiring a vaccine against a virus that is sexually transmitted.

While policymakers and advocates have sought to mandate that girls aged 11 to 12 years be administered the vaccine before they enter the sixth or seventh grade, such legislation remains controversial. To date, 25 states, including California and the District of Columbia, have introduced school-entry mandate legislation (NCSL, 2009; Women in Government, 2008). Texas, through a gubernatorial executive order, made the vaccine mandatory for school-aged

³ 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

⁴ Personal communication, Monica Wagoner, California Department of Public Health, March 2009.

girls with some exceptions; however, the Legislature ultimately overturned the order. The Virginia Legislature passed a school vaccine requirement in 2007. The following year, however, the state legislature considered a bill to remove that requirement. Because the bill to remove the requirement failed, Virginia remains the only state to have enacted the school mandate. However, a number of states are introducing legislation mandating health insurance coverage of the vaccine: To date, 19 states have done so, and 5 have enacted such legislation: Colorado, Iowa, Nevada, New Mexico, and Rhode Island (NCSL, 2009; Women in Government, 2008).

MEDICAL EFFECTIVENESS

This section of the report describes the role of HPV in the development of cervical cancer and other diseases; summarizes clinical guidelines for vaccination against HPV; and reviews findings from randomized controlled trials (RCTs) that have been conducted to assess the efficacy of the quadrivalent vaccine (Gardasil) that has been approved by the FDA, and the bivalent vaccine (Cervarix) that is under review by the FDA.

Natural Course of HPV Infection

As discussed in the *Introduction*, exposure to HPV usually results from sexual activity with an infected partner. Most HPV infections are asymptomatic, transient infections that do not affect health. However, some HPV infections persist and can lead to anogenital warts, precancerous cervical lesions, invasive cervical cancer, and other types of cancer.

Precancerous cervical lesions are often initially detected by the Pap test. Abnormalities of cervical cells may indicate the presence of 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. CIN 3 and adenocarcinoma in situ are the most important precursors of invasive cervical cancer. However, not all CIN 2 and CIN 3 lesions progress to cancer: up to 40% of CIN 2 lesions will regress over two years (Castle et al., 2009). Where cervical cancer develops, the progression 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 HPV vaccines. Documenting prevention of CIN 2 and CIN 3 provide some 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 given the time required for such cancers to develop.

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. The appearance of antibodies following vaccine administration is evidence of 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 the two types of HPV that cause 70% of cervical cancers (types 16 and 18) and the two types of HPV that cause 90% of anogenital warts (types 6 and 11). A bivalent vaccine (Cervarix) targeted against HPV types 16 and 18 is currently under review by the FDA. The targeted virus types were chosen because of their importance in causing human disease, as illustrated in Table 2.

Current Vaccination Recommendations

Following FDA approval of the quadrivalent HPV vaccine, several professional and governmental organizations issued immunization guidelines on its use. These guidelines are summarized in Table 3. 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 those aged 13 to 26 years, and vaccination in some situations for those as young as age 9. The ACS only recommends vaccination through age 18, citing insufficient evidence of benefit for females 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 (Markowitz et al., 2007). The USPFTS has not issued its own recommendation on the HPV vaccine because it refers clinicians to ACIP for immunization guidelines.

All organizations recommend that women and their health care providers continue to follow current cervical cancer screening guidelines, including use of 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 females, as they will experience the most significant outcome of high-risk HPV infection: cervical cancer. No clinical trials in males have been completed, although some are underway.

Table 3. Summary of the Most Recent HPV Vaccine Guidelines

Organization	Year Issued	Patient Age	Recommended Schedule	Comment
American Academy of Family Physicians (AAFP)	2009	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 Academy of Pediatrics (AAP)	2009	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 College of Obstetricians and Gynecologists (ACOG)	2006	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)	2006	The SAM fully endorses the ACIP recommendations for the three-dose HPV vaccine.		
U.S. Preventive Services Task Force (USPSTF)	Defers to the ACIP for vaccine-related recommendations.			

Sources: AAFP, 2009a; AAFP, 2009b; AAP, 2009; ACOG, 2006; Markowitz et al., 2007 (ACIP); SAM, 2006; Saslow et al., 2007 (ACS).

Literature Review Methods

The literature search for SB 158 was an update of the literature search CHBRP performed in 2007 for a similar bill (AB 1429). The search was limited to RCTs published in English from January 2007 to present. Studies were identified through searches of MEDLINE (PubMed), the Cochrane Database of Systematic Reviews, the Cochrane Register of Controlled Clinical Trials, Web of Science, and EconLit. In addition, Web sites maintained by the following organizations were searched: Agency for Healthcare Research and Quality, Institute for Clinical Systems Improvement, International Network of Agencies for Health Technology Assessment, National Health Service Centre for Reviews and Dissemination, National Guidelines Clearinghouse, National Institute for Health and Clinical Excellence, National Institutes of Health, Scottish Intercollegiate Guideline Network, the U.S. Preventive Services Task Force, and the World Health Organization.

The search yielded a total of 225 citations. Seven additional articles pertinent to the medical effectiveness review were identified, retrieved, and reviewed. An article published in 2005 was subsequently retrieved to provide a more thorough assessment of the results of a phase 2 trial⁵ of the quadrivalent vaccine, Gardasil (Villa et al., 2005). Findings from these articles were integrated with findings from the three articles that were included in the literature review for CHBRP's report on AB 1429. These eleven articles include eight articles that summarize the results of four clinical trials of the quadrivalent HPV vaccine and three articles that report results of two clinical trials of the bivalent HPV vaccine.

Several additional articles regarding these clinical trials were excluded for several reasons. Two articles were excluded that reported pooled findings for subsets of the women enrolled in the clinical trials of the quadrivalent vaccine who resided in Asian-Pacific and Latin American nations (Perez et al., 2008; Tay et al., 2008). Two articles that presented pooled results from the three clinical trials of the quadrivalent vaccine with a clinical trial of a monovalent vaccine that has not been approved by the FDA were excluded because the effects of the quadrivalent vaccine could not be separated from the effects of the monovalent vaccine (Ault et al., 2007; Barr et al., 2008). In addition, an article regarding a clinical trial of the bivalent vaccine that enrolled women in Costa Rica infected with HPV at the time of enrollment was excluded because the trial was intended to assess whether the HPV vaccine could be used to treat rather than prevent HPV infection and associated conditions (Hildesheim et al., 2007).

A more thorough description of the methods used to conduct the medical effectiveness review and the process used to grade the evidence for each outcome measure is presented in *Appendix B: Literature Review Methods*. *Appendix C* includes tables that describe the studies that CHBRP reviewed and their findings.

⁵ Phase 2 trials are RCTs that are conducted to obtain preliminary data regarding the effectiveness of a vaccine in protecting persons against a specific disease(s) or condition(s) and to ascertain common short-term side effects and risks associated with a vaccine. They are closely monitored and typically enroll several hundred people. FDA, 2009.

Outcomes Associated with HPV Vaccination

RCTs reviewed in this report address vaccine-related prevention of short-term outcomes such as antibody development following vaccination, prevention of persistent HPV infections, reductions in CIN 2 and CIN 3 lesions (representing an interruption of the pathway toward cervical cancer), adenocarcinoma in situ (AIS), vaginal intraepithelial neoplasia (Val), vulvar intraepithelial neoplasia (VIN), and anogenital warts.

Study Findings

All clinical trials of both the quadrivalent and the bivalent HPV vaccines that have been published to date were sponsored by the vaccines' manufacturers. No results of independent clinical trials have been published.

FDA-Approved Vaccine: Gardasil (Quadrivalent Vaccine)

The results of four clinical trials of Gardasil, the FDA-approved, quadrivalent (types 6/11/16/18) HPV vaccine, have been published in the peer-reviewed literature. A single Phase 2 trial and two Phase 3 trials,⁶ the FUTURE I trial and the FUTURE II trial, have assessed the safety and efficacy of the vaccine in females aged 15 to 26 years (specific age ranges vary across the three trials). To date, only interim results have been published from the Phase 3 trials. A Phase 2 trial has assessed safety and short-term efficacy in girls and boys aged 9 to 15 years. Because the FDA has not approved the quadrivalent vaccine for administration in boys, CHBRP only reviewed findings from this trial for girls.

Phase 2 trials

Both interim and final results of the Phase 2 trials of the quadrivalent vaccine have been published (Villa et al., 2005; Villa et al., 2006). This trial enrolled 552 females aged 16 to 23 years from Brazil, Scandinavia, and the United States who were not pregnant, had no previous abnormal Pap tests, and a lifetime history of four or fewer male sexual partners. 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. The initial peer-reviewed publication from this trial (Villa et al., 2005) reported efficacy against persistent infection or disease associated with HPV types 6, 11, 16, or 18 three years after vaccination. The second peer-reviewed publication from this trial combined data analyzed for the initial peer-reviewed publication with data on a subset of subjects (241 females) who were followed for 5 years following vaccination (Villa et al., 2006).

The peer-reviewed publication on the final results of the trial reported that subjects receiving the quadrivalent vaccine showed an antibody response to all four HPV types in magnitudes at or

⁶ Phase 3 trials are conducted if preliminary evidence obtained from Phase 2 trials suggests that a vaccine is effective. The objectives of Phase 3 trials are to amass further information about effectiveness and safety that is used to assess whether the benefits of a vaccine outweigh the harms and to extrapolate research findings to the population to which the vaccine would be marketed. Phase 3 trials usually enroll several hundred to several thousand people (FDA, 2009).

above those seen among persons naturally infected. The subset of 468 persons who received all three doses of the vaccine and were negative for HPV 16 and 18 at the beginning of the trial through one month after the third dose was administered (i.e., the per-protocol population) experienced 95.8% efficacy (95% CI, 83.3% to 99.5%) against persistent infection from HPV 6, 11, 16, and 18. The authors reported a 100% efficacy for prevention of CIN 1, 2, and 3 due to HPV 6, 11, 16, and 18. A test of statistical significance was not performed because only three women (all in the placebo group) had a CIN outcome. 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 associated with HPV type 6, 11, 16, and 18, although the clinical importance of this finding is uncertain because the authors did not assess whether subjects were bothered by their genital warts. Statistical testing was not conducted due to the small number of cases.

The article also reported results of a modified intent-to-treat analysis⁷ that included subjects who only received one or two doses of the quadrivalent vaccine and, thus, may not have been fully protected against infection with HPV types 6, 11, 16, and 18. For the 510 subjects included in the modified intent-to-treat analysis, observed efficacy against persistent infection with these types of HPV decreased slightly to 93.5% (95% CI, 82.5%-98.3%). The authors reported 100% efficacy for prevention of CIN 1, 2, and 3 and genital warts associated with these types of HPV for the modified intent-to-treat population. As in the per-protocol analysis, all CIN cases were combined, although only CIN 2 and CIN 3 are considered precancerous. Findings regarding efficacy against precancerous lesions associated with other types of HPV were not reported.

Results of the Phase 2 trial of safety and efficacy of the quadrivalent vaccine in boys and girls aged 9 to 15 years were published in 2007 (Reisinger et al., 2007). To date, this is the only trial published in a peer-reviewed journal that has assessed the efficacy of the vaccine for girls under age 15. This clinical trial enrolled 1,781 boys and girls from 10 Asian-Pacific, European, Latin American, and North American countries who had never had a sexual partner. This trial only assessed the quadrivalent vaccine's effect on immunogenicity for one year after receipt of the third and final dose of the vaccine. It did not examine efficacy for CIN or genital warts. The authors reported seroconversion rates for girls separately for the four types of HPV against which the quadrivalent vaccine offers protection. The seroconversion rates were 97.9% for HPV 6, 99.2% for HPV 11, 99.8% for HPV 16, and 91.5% for HPV 18. Efficacy was highest for the youngest girls enrolled in the trial.

Phase 3 trials

Interim results from two Phase 3 trials of the quadrivalent vaccine have been published. The FUTURE I trial enrolled 5,455 females aged 16 to 24 years from 16 countries who were not pregnant, had no abnormal Pap tests, no history of genital warts, and a lifetime history of four or fewer sexual partners (Garland et al., 2007). The FUTURE II trial enrolled 10,565 females aged 15 to 26 years from 13 countries who met the same inclusion criteria as in the FUTURE I trial,

⁷A pure intent-to-treat analysis includes all patients assigned to a given treatment, regardless of whether they actually received any part of it. The modified intent-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.

except that those who had a history of genital warts were not excluded (FUTURE II Study Group, 2007).

Interim findings of the FUTURE I trial were published in May 2007 after CHBRP had completed its report on AB 1429 (Garland et al., 2007). The article presented findings regarding the efficacy of the quadrivalent vaccine three years after administration of the third and final dose of the vaccine. The authors reported efficacy for a **per-protocol population** that consisted of subjects who received all three doses of the quadrivalent vaccine and were seronegative and HPV DNA negative for at least one of the four types of HPV addressed by the vaccine at the time they enrolled in the trial, and who remained HPV DNA negative for the same HPV type through one month after the third dose of the vaccine. They also assessed efficacy for an **intent-to-treat population** that included all subjects who received at least one dose of the quadrivalent vaccine regardless of whether they had infection or disease associated with any of the four types of HPV addressed by the vaccine at the time they enrolled in the trial. Findings for the intent-to-treat population are more generalizable to the population to whom SB 158 would apply because it includes females with and without exposure to HPV prior to vaccination.

For the per-protocol population, the efficacy of the quadrivalent vaccine against HPV types 6, 11, 16, and 18 was 100% (95% CI, 81% to 100%) for CIN 2, 100% (95% CI, 76% to 100%) for CIN 3, and 100% (95% CI, 15% to 100%) for AIS. The wide confidence interval for AIS reflects the small number of cases (n = 6, all in the control group). Efficacy for CIN 1, 2, and 3 and AIS combined associated with HPV types 6, 11, 16, and 18 was 98% (95% CI, 92% to 100%) for this population (Garland et al., 2007).

The quadrivalent vaccine was much less effective for the intent-to-treat population that included females with prior exposure to HPV. For the intent-to-treat population, the efficacy of the vaccine against CIN 1, 2, and 3 and AIS combined was 55% (95% CI, 40% to 66%). However, for this population there were no statistically significant differences between the intervention and control groups (i.e., the vaccine and placebo groups) in rates of CIN 3 and AIS, the strongest precursors of invasive cervical cancer. These findings suggest that the vaccine offers greater protection to women who were not exposed to HPV prior to vaccination than to those who have been exposed (Garland et al., 2007).

Interim findings from the FUTURE II trial with regard to the efficacy of the quadrivalent vaccine three years after the final vaccination were similar to those of the FUTURE I trial (FUTURE II Study Group, 2007). The most important findings from the FUTURE II trial are summarized in Table 4. CHBRP highlights findings from this trial because it is the largest trial of the quadrivalent vaccines for which results have been published.

Table 4. Major Findings from the FUTURE II Trial of the Quadrivalent HPV Vaccine (Gardasil): Efficacy Against Cervical Lesions Three Years After Vaccination

Population	HPV Types	Outcome	Finding
Per-protocol population ⁸	HPV types 6, 11, 16, and 18	CIN 2, CIN 3, and AIS	98% (95% CI, ⁹ 86% to 100%)
		CIN 2	100% (95% CI, 86% to 100%)
		CIN 3	97% (95% CI, 79% to 100%)
		AIS	100% (95% CI, <0% to 100%)
Intent-to-treat population ¹⁰	HPV types 6, 11, 16, and 18	CIN 2, CIN 3, and AIS	44% (95% CI, 26% to 58%)
		CIN 2	57% (95% CI, 38% to 71%)
		CIN 3	45% (95% CI, 23% to 61%)
		AIS	28% (95% CI, <0% to 82%)
	Any type of HPV	CIN 2, CIN 3, and AIS	17% (95% CI, 1% to 31%)
		CIN 2	22% (95% CI, 3% to 38%)
		CIN 3	21% (95% CI, <0% to 38%)
		AIS	17% (95% CI, <0% to 84%)

Source: FUTURE II Study Group, 2007.

For the per-protocol population¹¹ enrolled in the FUTURE II trial, the efficacy of the quadrivalent vaccine against lesions associated with HPV types 16 and 18 was 100% (95% CI, 86% to 100%) for CIN 2, 97% (95% CI, 79% to 100%) for CIN 3, and 100% (95% CI, <0% to 100%) for AIS. As with the FUTURE I trial, the wide confidence interval for AIS reflects the small number of cases (n = 1, in the control group). The rates of protection for CIN 2, CIN 3, and AIS combined were 98% (95% CI, 86% to 100%) in the per-protocol population (FUTURE II Study Group, 2007).

As in the FUTURE I trial, the FUTURE II trial found that the quadrivalent vaccine was much less effective in the intent-to-treat population that included females with prior exposure to HPV than in the per-protocol population. For this population, the efficacy of the vaccine against HPV

⁸ The per-protocol population consisted of females aged 15 to 26 years who received all three doses of the quadrivalent vaccine and were seronegative and HPV DNA negative for at least one of the four types of HPV addressed by the vaccine at the time they enrolled in the trial, and who remained HPV DNA negative for the same HPV type through one month after the third dose of the vaccine.

⁹ CI = confidence interval.

¹⁰ The intent-to-treat population consisted of females who received at least one dose of the quadrivalent vaccine regardless of whether they had infection or disease associated with any of the four types of HPV addressed by the vaccine at the time they enrolled in the trial.

¹¹ The populations included in the interim per-protocol and intent-to-treat analyses for the FUTURE II trial were identical to those analyzed for the interim analysis of the FUTURE I trial (FUTURE II Study Group, 2007).

types 16 and 18 was 57% (95% CI, 38% to 71%) for CIN 2, 45% (95% CI, 23% to 61%) for CIN 3, and 28% (95% CI, <0% to 82%) for AIS. The rate of protection for CIN 2, CIN 3, and AIS combined was 44% (95% CI, 26% to 58%) in the intent-to-treat population (FUTURE II Study Group, 2007).

Several articles have reported findings regarding the efficacy of the quadrivalent vaccine in protecting women from infection with types of HPV that the vaccine does not target (i.e., HPV types other than types 6, 11, 16, and 18). Such findings are important because HPV types 6, 11, 16, and 18 cause only 70% of cervical cancers; the other 30% of cervical cancers are caused by other types of HPV. Collectively, the findings reported in these articles indicate that the quadrivalent vaccine does not provide much protection against cervical lesions associated with HPV types other than 6, 11, 16, and 18. The interim results of the FUTURE I trial indicate that for the intent-to-treat population, the efficacy of the vaccine for CIN 1, 2, and 3 and AIS associated with any type of HPV of was 20% (95% CI, 8% to 31%) (Garland et al., 2007). In the FUTURE II trial (FUTURE II Study Group, 2007), the efficacy for CIN 2 and 3 and AIS associated with any type of HPV was 17% (95% CI, 1% to 31%). However, neither study found a statistically significant difference in rates of CIN 3 and AIS—the lesions that are the strongest precursors of cervical cancer—between females receiving the vaccine and the placebo.

Two subsequent articles report the results of pooled analyses of findings from the FUTURE I and FUTURE II trials regarding the efficacy of the quadrivalent vaccine for HPV types other than 6, 11, 16, and 18. Brown and colleagues (2009) report that efficacy against CIN 2 and 3 and AIS associated with HPV types other than 6, 11, 16, and 18 was 32.5% (95% CI = 6.0%, 51.9%) among women who received at least one dose of the vaccine and had not been exposed to any of the types of HPV targeted by the quadrivalent vaccine or to any of 10 other HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, and 59). Wheeler and colleagues (2009) found no statistically significant difference in the rate of CIN 2, CIN 3, and adenocarcinoma in situ combined between all subjects who received at least one dose of the vaccine or the placebo regardless of whether they were infected with any of the types of HPV targeted by the quadrivalent vaccine or to any of 10 other HPV types.

Another article published in a peer-reviewed journal pooled findings from the Phase 2 trial and the Phase 3 trials to examine the efficacy of the quadrivalent vaccine in preventing high-grade vaginal and vulvar lesions associated with HPV types 6, 11, 16, and 18 for three years after vaccination (Joura et al., 2007). If not treated, such lesions can lead to vaginal or vulvar cancer. Vaginal and vulvar cancers occur less frequently than cervical cancers but there are no screening programs to detect them (unlike the Pap test for cervical cancer and precancerous lesions). Thus, the quadrivalent vaccine could be helpful in preventing vaginal and vulvar cancers associated with these types of HPV. For the per-protocol population¹² enrolled in the three trials, the efficacy of the vaccine against vaginal intraepithelial neoplasia (Val) grades 2 and 3 and vulvar intraepithelial neoplasia (VIN) grades 2 and 3¹³ associated with HPV types 16 and 18 was 100% (95% CI, 72% to 100%). Consistent with findings for cervical lesions, the vaccine was less

¹² The populations included in the interim per-protocol and intent-to-treat analyses for this combined analysis of results from the Phase 2 trial, the FUTURE I trial, and the FUTURE II trial were identical to those analyzed for the interim analysis of the FUTURE I trial (FUTURE II Study Group, 2007).

¹³ Vaginal intraepithelial neoplasia (Val) and vulvar intraepithelial neoplasia (VIN) are rated using criteria similar to those used to grade cervical lesions. Val 2 and 3 and VIN 2 and 3 are considered precancerous lesions.

effective in the intent-to-treat population. In that population the efficacy of the vaccine against Val 2 and 3 and VIN 2 and 3 associated with HPV types 16 and 18 was 71% (95% CI, 37% to 88%).

Vaccine under review: Cervarix

As stated previously, the manufacturer of a bivalent vaccine (Cervarix) has filed a new drug application with the FDA. This vaccine targets HPV types 16 and 18 only. As indicated previously, these are the two types of HPV that cause 70% of cervical cancers. Should the FDA grant approval, a choice of vaccines would become available to consumers and their physicians. Therefore, CHBRP decided to present information about the effectiveness of this vaccine. Interim and final results of a single randomized controlled Phase 2 trial for the unapproved bivalent vaccine have been reported (Harper et al., 2004; Harper et al., 2006). Interim results for an ongoing Phase 3 trial (Paavonen et al., 2007) have also been reported in the peer-reviewed medical literature.

Phase 2 trial

The Phase 2 trial of the bivalent vaccine enrolled 1,113 females aged 15 to 25 years from Canada, Brazil, and the United States. The subjects had no previous abnormal Pap test or ablative or excisional treatment of the cervix, were not undergoing treatment for genital warts, tested negative for 14 high-risk HPV types, and reported a lifetime history of no more than six sexual partners. The initial peer-reviewed publication (Harper et al., 2004) reported efficacy 27 months after vaccination. The second peer-reviewed publication combined data analyzed for the initial peer-reviewed publication with data on a subset of subjects (776 females) who were followed for 4.5 years following vaccination (Harper et al., 2006).

The peer-reviewed publication of the final results of the trial (Harper et al., 2006) reported that among females in the intervention group (i.e., those who received the bivalent vaccine and not the placebo), antibody levels following vaccination were 14- to 17-fold above those seen with natural infection. Efficacy was 96.0% (95% CI, 75.2%-99.9%) for persistent HPV 16 and 18 infections in the 799 subjects who received all three doses of the vaccine and were negative for HPV 16 or 18 at the beginning of the trial and at the time the third dose was administered (i.e., the per-protocol population). Slightly lower efficacy was found in the 951 subjects included in a modified intent-to-treat population (i.e., subjects who had received at least one dose of the vaccine and were negative for HPV 16/18 at the beginning of the trial). In the intent-to-treat population the bivalent vaccine provided a 94.4% reduction (95% CI, 78.2%-99.4%) in persistent infections from HPV 16 and 18. The intent-to-treat analysis showed 100% protection against CIN 2 and 3 lesions due to HPV 16/18 (95% CI, -7.7%-100%). This finding was not statistically significant at conventional levels ($p > .05$); the wide confidence interval reflects the fact that there were few occurrences of CIN 2 and 3 ($n=5$). Finding regarding efficacy against precancerous lesions associated with other types of HPV were not reported.

Phase 3 trial

Interim results of a Phase 3 trial of the bivalent vaccine were published in 2007 (Paavonen et al., 2007). The mean length of follow-up for persons for whom findings were reported in the peer-reviewed publication was 14.8 months after the third dose of the vaccine was dispensed. The Phase 3 trial, known as the PATRICIA trial, enrolled 18,525 females aged 15 to 25 years from

14 Asian-Pacific, European, Latin American, and North American countries who were not pregnant or breastfeeding and who did not have a history of colposcopy, chronic disease, autoimmune disease, or immunodeficiency. Some of the women and girls enrolled in this trial had been infected with HPV prior to enrollment. Inclusion of these persons makes the results of the Phase 3 study more generalizable to the population to which SB 158 would apply than the results of the Phase 2 trial.

Despite the inclusion of some persons who had HPV infection at the time they enrolled in the trial, the authors reported that the bivalent vaccine was associated with high levels of protection against HPV and cervical lesions. There was an 80.4% (95% CI = 70.4%, 87.4%) reduction in persistent infection with HPV 16 and 18 six months following vaccination and a 90.4% (97.9% CI = 53.4%, 99.3%) reduction in CIN 2+ lesions associated with HPV 16 or 18. Findings for CIN 3 and adenocarcinoma in situ were not reported separately from findings for CIN 2. The interim results of the Phase 3 trial also suggest that the bivalent vaccine offers little protection against types of HPV that the vaccine does not target (i.e., types other than HPV 16 and 18). The authors found no statistically significant difference between the intervention and control groups in the rates of persistent infection with other types of HPV six months after vaccination (Paavonen et al., 2007). This finding is consistent with the findings for the quadrivalent vaccine.

Side Effects and Safety

Undesirable side effects of Gardasil include local site reactions and fever, headache, and nausea. In the clinical trials, these occurred in similar frequency in the treatment and placebo groups (ACS, 2006). At five years postvaccination, no serious adverse health events were attributable to the vaccine. Although five women who became pregnant within 30 days of Gardasil vaccination delivered children with congenital abnormalities vs. 0 cases in the placebo group—a statistically significant difference—the anomalies were of several types, and expert review judged these cases to not be related to the vaccine (Markowitz et al., 2007). 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 (Markowitz et al., 2007). However, the vaccine is not recommended for use in pregnancy.

Conclusion

Extant literature provides a consistent picture of the quadrivalent 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 would reduce cancer incidence. 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 are limited to a select group of females who had no prior evidence of HPV infection and were compliant with the vaccination regimen. The effectiveness of the quadrivalent vaccine in females 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 (30% versus 70%).

In addition, the duration of immunity beyond five years is still unknown. Villa and colleagues (2006) report that among females who received Gardasil, vaccine-induced antibody titers are at or above those occurring from naturally acquired infection at five years postimmunization. Continual monitoring of vaccine recipients in Phase 3 and Phase 4 postlicensure studies will be critical to detecting a possible reduction in immunity and determining the need for a booster vaccination.

As noted above, all organizations that have issued recommendations for use of the quadrivalent HPV vaccine also recommend that women and their health care providers continue to follow current cervical cancer screening guidelines, including the Pap test. There is strong evidence that performing cervical cancer screening at recommended intervals and promptly treating high-grade cervical lesions can prevent morbidity and mortality from cervical cancer (USPSTF, 2007).

Females who receive the quadrivalent vaccine should continue to obtain Pap tests because the vaccine offers little protection against cervical cancers caused by the types of HPV it does not target (i.e., types other than 6, 11, 16, and 18). These types of HPV are associated with 30% of cervical cancers. Furthermore, women exposed to HPV types 16 or 18 prior to vaccination may be susceptible to cancer as well. As previously discussed, the interim results of the FUTURE I trial indicate that for the intent-to-treat population¹⁴ the efficacy of the vaccine for CIN 1, 2, and 3 and AIS combined regardless of the type of HPV with which it was associated was 20% (95% CI, 8% to 31%) (Garland et al., 2007). In the FUTURE II trial (FUTURE II Study Group, 2007), the efficacy for CIN 2 and 3 and AIS combined regardless of HPV type was 17% (95% CI, 1% to 31%). In addition, neither trial found a statistically significant effect on CIN 3 and adenocarcinoma in situ, the strongest precursors to cervical cancer. In addition, clinical trials have not reported the efficacy of vaccination on cervical lesions regardless of HPV type among females who received all three doses of the vaccine and who were not exposed to HPV prior to vaccination.

¹⁴ For both the FUTURE I and FUTURE II trials, the intent-to-treat population consisted of subjects who received at least one dose of the vaccine regardless of whether they had infection or disease associated with any of the four types of HPV addressed by the quadrivalent vaccine at the time they enrolled in the trial

UTILIZATION, COST, AND COVERAGE IMPACTS

SB 158 would apply to health care service plans licensed by the DMHC, and regulated under the California Health and Safety Code. SB 158 would also apply to health insurance policies regulated by the CDI, subject to the California Insurance Code. SB 158 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.

SB 158 would require:

- All Knox-Keene 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 SB 158. For further details on the underlying data sources and methods, please see *Appendix D*.

Present Baseline Cost and Coverage

Current Coverage of the Mandated Benefit

Coverage of the commercially insured population subject to the mandate

Approximately 21,340,000 individuals in California are enrolled in health plans or policies that would be affected by this legislation. This includes an estimated 3,348,000 females aged 11 to 26 years.

A survey of the seven largest health plans and insurers in California, representing 96% of the privately insured market, was conducted by CHBRP to examine current coverage levels for HPV vaccination for the population of females aged 11 to 26 years. Six out of seven health plans and insurers responded to the survey representing 88% of the total market and including 77% of the privately insured enrollees in the CDI-regulated market and 91% in the DMHC-regulated market.

The results of CHBRP's coverage survey of health plans indicate that all enrollees in DMHC-regulated plans have coverage for the HPV vaccine (Table 5). Among those enrolled in CDI-regulated products, 96.6% of the large group market, 100% of the small group market, and 88.2% of the individual market have coverage for this vaccine. These coverage gaps are restricted to those female enrollees aged 11 to 26 years in CDI-regulated individual policies and female enrollees aged 17 to 26 years in CDI-regulated group policies. Overall, 99.5% of the

insured population of females aged 11 to 26 years in California has coverage for the HPV vaccine.

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 that report coverage of HPV vaccination stated that they cover this benefit following the existing national guidelines (as discussed in the *Medical Effectiveness* section), or per internally developed guidelines that are consistent with national guidelines, which recommended the coverage of the HPV vaccine for all females aged 11 to 26 years.

Table 5. Current Coverage of Females aged 11 to 26 for the HPV Vaccine by Market Segment, California 2009

DMHC-regulated plans	
Large group	100%
Small group	100%
Individual	100%
All	100%
CDI-regulated policies	
Large group	96.9%
Small group	100%
Individual	88.2%
All	94.4%
CalPERS	100%
Medi-Cal	100%
Healthy Families	100%
MRMIP	100%
AIM	100%
Total	99.5%

Source: California Health Benefits Review Program, 2009

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.

Availability of the HPV vaccine in the absence of coverage

As discussed in the *Introduction*, 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. However, the manufacturer, 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. It is unknown how much this program is used for the HPV vaccine.

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. Utilization rates for such new vaccines are dynamic within the first few years of availability. Initial vaccination rates are likely to be high at onset due to intensive advertising by vaccine manufacturer and media campaigns. These rates are likely to diminish over time as pent-up demand decreases because many would have already been vaccinated. In a few more years, vaccination rates would reflect primarily females who reach the eligible ages for vaccination each year. If the current analyses were conducted several years from now, the one-year utilization and cost projection by CHBRP would have reflected those stable vaccination rates. Given the potential changes in vaccination rates after 2010, the premium and cost impact estimates in this report reflect expected short-term utilization and costs, and as a result, may overestimate expected annual costs in the future.

The rate of vaccination is impacted by awareness of HPV and compliance with provider recommendations. Awareness of HPV in California has increased dramatically from 2006 (Grant et al., 2009). The great majority of teen girls (76%) and young adult women (60%) reported they would be interested in receiving the HPV vaccine. A smaller percentage (57%) of parents of age-eligible girls reported an interest in getting the HPV vaccine for their daughters. The most frequent reason cited for not getting the vaccine was lack of sufficient knowledge about the vaccine followed by worry about its safety (Grant et al., 2009). At least one study of pediatricians indicated the majority intended to recommend the vaccine to their patients (Ishibashi et al., 2008); however, studies of actual rates of recommendation were not available during preparation of this report.

The rates of awareness and interest in receiving the vaccine are higher than the self-reported vaccination rate of HPV. Overall, 19% of insured females aged 11 to 26 years had received at least one dose of the vaccine, based on CHBRP's analysis of the 2007 CHIS. This rate differed by age group and was higher among teens aged 12 to 17 (25%) and lowest among young adults aged 18 to 26 years (13%). CHBRP estimates that by 2010, and before SB 158 would go into effect, approximately 33% of covered females aged 11 to 26 and 15% of females aged 11 to 26 years without coverage for HPV vaccination would have been vaccinated in the prior years.

The overall vaccination rates are assumed to be similar among the group (large and small) and individual privately insured market segments. The 2010 cumulative vaccination rates for specific programs including CalPERS, Healthy Families, Medi-Cal Managed Care, Access for Infants and Mothers (AIM), and Major Risk Medical Insurance Program (MRMIP) populations are not calculated because these programs currently cover HPV vaccination and are therefore not impacted by SB 158.

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 priced at \$138 per

dose, for a cost of \$413 for the full three-dose series in 2010.¹⁵ An additional cost of \$55 for administration of the vaccine in the commercial insurance market is estimated, leading to a full unit cost of \$468 for HPV vaccination.

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. All state-funded public programs already cover HPV vaccination for 100% of their enrollees and would thus not be impacted by SB 158.

The unit price of the vaccine does not include cost estimates for booster shots should they be necessary in the future. This is because durability of the vaccine beyond the first 5 years of vaccination 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 \$156 (\$138 for a single dose and \$18 for the administration fee). However, these costs would not be reflected in premiums until at least 5 years after the first wave of the vaccine (mid-2011).

The baseline cost associated with the mandate given current utilization and unit price of the vaccine are presented in Table 6.

The Extent to Which Costs Resulting from Lack of Coverage are Shifted to Other Payers, Including Both Public and Private Entities

Currently, 17,000 insured 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). In the absence of HPV coverage, CHBRP estimates that approximately 3.6% of those aged 11 to 18 years and 0.6% of those aged 19 to 26 years would have been vaccinated for HPV in 2010 (See *Appendix D* for further detail.). For females without HPV vaccination coverage, this translates to approximately \$185,000 in 2010 for the entire cost of the vaccine in the absence of SB 158. An undetermined portion of these costs may have been shifted to other entities as follows.

As discussed previously, children and adults without coverage for this vaccine who meet financial eligibility requirements may be able to receive the vaccine through other public (VFC program for low-income children) and private programs (Merck's program for low-income adults). Analysis of the 2007 California CHIS reveals that of the population of females aged 11 to 26 years insured by CDI-regulated plans who are not pregnant, 52% live in families earning 300% of the federal poverty level (FPL) or above and are most likely to afford the costs of HPV vaccination. The remaining 48% (64% are aged 11 to 18 and 36% are aged 19 to 26 years) may qualify for these other programs.

CalPERS, Medi-Cal, and Healthy Families programs are estimated to currently cover 100% of their enrollees for the HPV vaccine.

¹⁵ VFC/CDC Vaccine price list. Available at www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm. Accessed Feb 5, 2009.

Public Demand for Coverage

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 158. Currently, the largest public self-insured plan—CalPERS preferred provider organization (PPO)—includes coverage for vaccinations according to 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.¹⁶

Impacts of Mandated Coverage

How Would Changes in Coverage Related to the Mandate Affect the Benefit of the Newly Covered Service and the Per-Unit Cost?

Impact on supply and on the health benefit

SB 158 would lead to an increase of 0.5% in coverage of HPV vaccination, among insured females aged 11 to 26. Intensive direct-to-consumer advertising campaigns to raise awareness of HPV and increase HPV vaccination occurred at the introduction of the vaccine in June 2006 and continued into 2008. These campaigns led to an initial surge in vaccination rates, but are likely to have diminished by 2010. A small surge in media and advertising campaigns due to SB 158 is possible but unlikely to lead to supply constraints due to the projected number of individuals who may receive the vaccine post SB 158.

Impact on per-unit cost

CHBRP assumes that there would be no impact on the per-unit costs of the HPV vaccine due to SB 158.

Post-mandate coverage

SB 158 would have a minimal impact on coverage for the HPV vaccine because 99.5% 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 0.5% of the total insured female population aged 11 to 26. More specifically, SB 158 would increase the population of females aged 11 to 26 years with HPV vaccination coverage by 17,000, or 0.5%, concentrated in the CDI-regulated market.

How Would Utilization Change as a Result of the Mandate?

Calculation of the annual vaccination rate in 2010, after SB 158 goes into effect, take into account vaccinations that have occurred *prior* to the mandate's effective date. This rate does not take into account individuals who may receive the vaccine outside a conventional office visit,

¹⁶ Personal communication with the California Labor Federation and member organizations on January 29, 2007.

such as health fairs and other community outreach activities by community-based organizations. The rate of increase in vaccination is assumed to be the same between the group 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. CHBRP estimates that among the newly covered population of insured females, 19% of those aged 11 to 18 and 13% of those aged 19 to 26 years would be vaccinated in 2010. CHBRP estimates the increase in the number of females vaccinated, among those not currently covered, to be 2,500 by the end of 2010.

The only HPV vaccine currently on the market, Gardasil, was 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, organizations aiming to reduce HPV infections, including the CDC have raised awareness of the vaccine. Existing data indicate a high level of awareness of HPV prior to SB 158. An increase in the level of ongoing campaigns in California due to SB 158 is possible. However, such an increase is not anticipated to change the existing vaccination rates significantly among the population with current coverage for the HPV vaccine.

The advertising and public health campaigns were also targeted to physicians, though evidence of increased physician recommendations for HPV vaccinations is not available. 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 receive this vaccination with existing coverage.

To What Extent Would 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 due to SB 158. 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 would remain proportional to the increase in premiums and amount to \$468,000.

CHBRP estimates that members currently without coverage for the HPV vaccine collectively pay \$185,000 for the vaccine above their share of premiums. After the implementation of SB 158, these individuals would instead pay for any increases in their share of premiums as well as out-of-pocket costs of the vaccine including deductibles and copayments.

Impact of the Mandate on Total Health Care Costs

Changes in total expenditures

The overall increase in expenditures due to SB 158 is limited to policies regulated by the CDI in the large and individual market segments. CHBRP estimates that total expenditures would increase by \$1,625,000, or 0.0019%. The increase in expenditures includes \$84,000, or 0.0002%,

in premium expenditures by private employers providing group insurance; \$1,357,000, or 0.0228%, in premium expenditures for individually purchased insurance; \$24,000, or 0.0002%, in premium expenditures by individuals with group insurance; \$345,000, or 0.0054%, in individual out-of-pocket expenditures, including deductibles and copayments; and no increase in CalPERS, Medi-Cal or Healthy Families state, or CalPERS individual out-of-pocket expenditures.

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 (Markowitz et al., 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 (Markowitz et al., 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 not included in the current vaccine.

The cost of prevention and treatment of anogenital warts and cervical HPV-related disease is estimated to be \$4 billion or more annually in the 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 preinvasive cervical lesions (CDC, 2007).

SB 158 would add coverage for the HPV vaccine to about 17,000 females aged 11 to 26 years in California. Approximately 2,500 females are expected to be vaccinated in 2010 due to this mandate. Subsequently, a clinically significant reduction in treatment of the HPV sequelae over the lifetime of these individuals may be expected. However, the most likely reductions during a one-year timeframe may be less treatment of anogenital warts, fewer follow-up Pap tests of infected individuals, and less frequent treatment of CIN 2 and 3. Potential reductions in other treatments may also result. The long-term costs impacts are further discussed below.

Impact on long-term costs

HPV vaccination will likely produce several important health benefits, including reductions in CIN 2 and 3, cases of cervical cancer, and cervical cancer deaths. Multiple cost-effectiveness studies have been published recently examining both the long-term costs of vaccination as well as the long-term savings associated with reductions in the adverse health events. These studies

found that the lifetime costs and benefits of HPV vaccination for hypothetical cohorts of females aged 12 years, where the vaccine is most effective, varies considerably depending on important assumptions such as length of immunity, types of viruses considered, vaccination of age groups older than 12 years and gender, rate of vaccination, and reductions in disease sequelae, among others. CHBRP examined cost-effectiveness studies of currently available or in-development vaccines in studies that are based on U.S. screening patterns and U.S. dollars.

Existing studies estimate a cost-effectiveness ratio of vaccination ranging from \$2,964 to \$43,600 per quality-adjusted life year (QALY) gained, depending on model assumptions. In other words, for every QALY saved, \$2,964 to \$43,600 in vaccinations would be spent. These estimates represent the net cost, after accounting for all savings associated with the reductions in adverse health events. There is no consensus about the most appropriate threshold, though policymakers have routinely accepted technologies with estimated costs per QALY higher than these amounts. One study by Kim and Goldie (2008) included additional information for catch-up vaccination of females aged 13 to 26, as currently recommended by national guidelines and who will gain coverage under SB 158. The cost per QALY estimates for including catch-up vaccination of females aged 13 to 26 in addition to a cohort of 12 year-old-females was estimated at \$152,700. Alternative estimates are provided by Kim and Goldie (2008) in the event that that level of immunity from the available vaccine is shorter than lifetime. The cost per QALY for reduction of lifetime immunity to requiring a booster at 10 years was estimated at \$83,300. The cost per QALY in the event of reduction of lifetime immunity to immunity that waned at 10 years was estimated at \$144,100.

Impacts for Each Category of Payer Resulting from the Benefit Mandate

Changes in expenditures and PMPM amounts by payer category

The impact of SB 158 on total expenditures and PMPM premium amounts for each payer category are displayed in Table 7.

- In the large-group CDI-regulated market, total expenditures would increase by 0.0048% (\$0.0236 PMPM) and premiums would increase by 0.0051% (\$0.0224 PMPM).
- In the individual CDI-regulated market, total expenditures would increase 0.0576% (\$0.1213 PMPM) and premiums would increase 0.0644% (\$0.1089 PMPM).

No increased costs are projected as a result of SB 158 for enrollees in the CDI-regulated small group market, DMHC-regulated health plans, CalPERS, or in other public programs. The increased expenditures are projected for the year following the mandate and are likely to diminish rapidly over time as those who are newly covered either become vaccinated or reach age 26, after which the vaccine is not recommended.

Changes in coverage as a result of premium increases

SB 158 would lead to an increase of less than 1% in premiums among the CDI-regulated group and individual plans. Thus, CHBRP does not anticipate a measurable 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.

Impact of changes in private coverage on public programs

CHBRP estimates that the mandate would produce no measurable impact on enrollment in public insurance programs or on utilization of covered benefits in the public sector.

Impact on Access and Health Service Availability

Based on a review of the DMHC's Independent Medical Review (IMR) database, as of March 16, 2009, there was one IMR case related to the HPV vaccine—a request for its use in the treatment of a nasal papilloma. The denial by the health plan in this case was upheld as it was considered an experimental use not approved by the FDA. Given no other IMR cases related to the HPV vaccine, access does not appear to be an issue in the DMHC-regulated market. The CDI's Consumer Complaints Report data does not allow for retrieval of information by medical condition, therefore it is unknown whether enrollees in the CDI-regulated market have faced access barriers due to health insurers denials.

SB 158 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 has been heavily promoted by the manufacturer through advertisements in a variety of media. Furthermore, the introduction of a competing vaccine, Cervarix, in the foreseeable future will further increase the supply of HPV vaccines and may lower its cost.

Table 6. Baseline (Pre-Mandate) Per Member Per Month Premiums and Total Expenditures by Market Segment, California, 2009

	DMHC-Regulated							CDI-Regulated			Total Annual
	Large Group	Small Group	Individual	CalPERS (b)	Medi-Cal (c)		Healthy Families	Large Group	Small Group	Individual	
				HMO	Managed Care 65 and Over	Managed Care Under 65	Managed Care				
Total Population in Plans Subject to State Regulation (a)	11,100,000	2,844,000	966,000	820,000	159,000	2,366,000	715,000	400,000	932,000	1,038,000	21,340,000
Total Population in Plans Subject to SB 158	11,100,000	2,844,000	966,000	820,000	159,000	2,366,000	715,000	400,000	932,000	1,038,000	21,340,000
Average portion of premium paid by employer	\$279.83	\$246.48	\$0.00	\$321.26	\$239.00	\$128.09	\$74.97	\$341.25	\$288.13	\$0.00	\$58,443,353,000
Average portion of premium paid by employee	\$69.94	\$71.52	\$330.89	\$56.69	\$0.00	\$0.71	\$10.22	\$97.61	\$54.11	\$169.28	\$19,440,350,000
Total Premium	\$349.77	\$318.00	\$330.89	\$377.95	\$239.00	\$128.80	\$85.19	\$438.86	\$342.24	\$169.28	\$77,883,703,000
Member expenses for covered benefits (Deductibles, copays, etc.)	\$18.90	\$24.61	\$54.10	\$19.49	\$0.00	\$0.59	\$2.32	\$53.72	\$124.95	\$41.39	\$6,384,077,000
Member expenses for benefits not covered	\$0.00	\$0.00	\$0.00	\$0.00	\$0.00	\$0.00	\$0.00	\$0.00	\$0.00	\$0.01	\$185,000
Total Expenditures	\$368.67	\$342.62	\$385.00	\$397.44	\$239.00	\$129.39	\$87.51	\$492.58	\$467.19	\$210.68	\$84,267,965,000

Source: California Health Benefits Review Program, 2009.

Notes: (a) This population includes privately insured (group and individual) and publicly insured (e.g., CalPERS, Medi-Cal, Healthy Families, AIM, MRMIP) individuals enrolled in health insurance products regulated by the DMHC or CDI. Population includes enrollees aged 0 to 64 years and enrollees 65 years or older covered by employment sponsored insurance.

(b) Of these CalPERS members, about 59% or 483,800 are state employees.

(c) Medi-Cal state expenditures for members under 65 years of age include expenditures for the Major Risk Medical Insurance Program (MRMIP) and the Access for Infants and Mothers (AIM) program. Medi-Cal state expenditures for members over 65 years of age include those with Medicare coverage.

Table 7. Impacts of the Mandate on Per Member Per Month Premiums and Total Expenditures by Market Segment, California, 2009

	DMHC-Regulated							CDI-Regulated			Total Annual
				CalPERS (b)	Medi-Cal (c)		Healthy Families				
	Large Group	Small Group	Individual	HMO	Managed Care 65 and Over	Managed Care Under 65	Managed Care	Large Group	Small Group	Individual	
Total Population in Plans Subject to State Regulation (a)	11,100,000	2,844,000	966,000	820,000	159,000	2,366,000	715,000	400,000	932,000	1,038,000	21,340,000
Total Population in Plans Subject to SB 158	11,100,000	2,844,000	966,000	820,000	159,000	2,366,000	715,000	400,000	932,000	1,038,000	21,340,000
Average portion of premium paid by employer	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0174	\$0.0000	\$0.0000	\$84,000
Average portion of premium paid by employee	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0050	\$0.0000	\$0.1089	\$1,381,000
Total Premium	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0224	\$0.0000	\$0.1089	\$1,465,000
Member expenses for covered benefits (Deductibles, copays, etc.)	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0027	\$0.0000	\$0.0266	\$345,000
Member expenses for benefits not covered	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	-\$0.0015	\$0.0000	-\$0.0143	-\$185,000
Total Expenditures	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0000	\$0.0236	\$0.0000	\$0.1213	\$1,624,000
Percentage Impact of Mandate											
Insured Premiums	0.0000%	0.0000%	0.0000%	0.0000%	0.0000%	0.0000%	0.0000%	0.0051%	0.0000%	0.0644%	0.0019%
Total Expenditures	0.0000%	0.0000%	0.0000%	0.0000%	0.0000%	0.0000%	0.0000%	0.0048%	0.0000%	0.0576%	0.0019%

Source: California Health Benefits Review Program, 2009.

Notes: (a) This population includes privately insured (group and individual) and publicly insured (e.g., CalPERS, Medi-Cal, Healthy Families, AIM, MRMIP) individuals enrolled in health insurance products regulated by the DMHC or CDI. This population includes enrollees aged 0 to 64 years and enrollees 65 years or older covered by employment sponsored insurance. (b) Of these CalPERS members, about 59% or 483,800 are state employees. (c) Medi-Cal state expenditures for members under 65 years of age include expenditures for the Major Risk Medical Insurance Program (MRMIP) and the Access for Infants and Mothers (AIM) program. Medi-Cal state expenditures for members over 65 years of age include those with Medicare coverage

PUBLIC HEALTH IMPACTS

The Impact of the Proposed Mandate on the Health of the Community

The clinical trials presented in the *Medical Effectiveness* section describe the efficacy of the vaccine in preventing persistent infections; genital warts; and CIN 1, 2, and 3. These trials have not been going on long enough to directly assess the impact of HPV vaccination on the development of cervical cancer or related mortality. Many simulation models have been constructed in order to predict these longer-term impacts. CHBRP conducted a literature search to identify models predicting the reduction in cervical cancer cases given current screening practices in the United States. This search yielded nine studies: Chesson et al., 2008; Elbasha et al., 2007; Goldhaber-Fiebert et al., 2007; Goldie et al., 2003; Goldie et al., 2004; Hughes et al., 2002; Kim and Goldie, 2008; Kulasingam and Myers, 2003; and Taira et al., 2004.

The smallest impact reported in the literature was a 36% reduction in cervical cancer over the course of a lifetime of a cohort of 12-year-old girls (Goldhaber-Fiebert et al., 2007). The largest impact, reported by Taira et al. (2004) was a 62% reduction. This same study reported that the first cohort of 12-year-old girls vaccinated would experience a 46% reduction in lifetime cervical cancer, while the first cohort of 24-year-old women receiving a catch-up vaccination would experience a 35% reduction in cervical cancer (Taira et al., 2004).

Using these estimates of reduction in lifetime risk, CHBRP calculated the reduction in cervical cancer for those newly covered by the mandate. As presented in the *Utilization, Cost, and Coverage Impacts* section, it is estimated that SB 158 would increase utilization of the HPV vaccine by 2,500 among females aged 11 to 26 years newly covered for HPV vaccination. Thus, CHBRP estimates that between 8 and 13 cases of cervical cancer could be prevented as a result of SB 158. It is possible that a reduction in a few cases of anal, vulvar, vaginal, penile, or oral cavity and pharynx cancer due to vaccination with an HPV vaccine could occur as a result of this mandate as well.

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). In addition, although these models take into account current screening practices in the general population, these screening rates include the uninsured, who are less likely to get Pap tests 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 tests, 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 assume a 90% efficacy rate against infection with HPV types 6, 11, 16, and 18. 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 the impact that would be seen in

a real world setting due to imperfect compliance and other factors. In addition, it is not yet clear what the duration of protection is for the HPV vaccine, or if booster shots will be needed at some point in the future.

The Impact on the Health of the Community 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

A systematic review of 40 publications from 1990 to 2006 demonstrated that estimates of HPV prevalence in men varied greatly—ranging from 1.3% to 72.9% depending on the population studied (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 anogenital HPV types detected in males were similar to the types commonly detected in females, with type 16 consistently among the most common. Comparing HPV prevalence rates between males and females found that prevalence rates among females were twice as high as those among males (Stone et al., 2002).

Among females, racial disparities have been reported in the literature with regard to HPV prevalence. Researchers have found that black females are more likely to have HPV compared to white females (Burk et al., 1996; Shields et al., 2004; Stone et al., 2002). 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 females had the highest prevalence rates (39.2%) compared to non-Hispanic white (24.2%) or Mexican American females (24.3%) (Dunne et al., 2007).

Cervical Cancer Incidence and Prevalence by Race/Ethnicity

Nationally, black females have higher incidence and prevalence rates of cervical cancer compared to all other races (Morgan et al., 1996; Patel et al., 2005; USCSWG, 2009). Additionally, other minority groups, particularly Hispanics, have been found to have higher incidence and prevalence rates of cervical cancer compared to non-Hispanic whites (Napoles-Springer et al., 1996; USCSWG, 2009). In California, the age-adjusted annual incidence rate of cervical cancer among Hispanics was estimated as 14.4 per 100,000 females, for Asians as 8.3 per 100,000 females, for non-Hispanic blacks as 8.7 per 100,000 females, and for non-Hispanic whites as 7.0 per 100,000 females (Hofer et al., 2008).

Stage at Diagnosis and Cervical Cancer Mortality by Race/Ethnicity

Compared to white females, black females have been found to present with more advanced stages of cervical cancer (Howell et al., 1999; Leath et al., 2005; Morgan et al., 1996; Schwartz et al., 2003) and have poorer survival rates (Howell et al., 1999; Mundt et al., 1998; Patel et al., 2005). Some research has found that Hispanic females have poorer survival rates compared to

non-Hispanic white females (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. The age-adjusted death rate for Hispanics in 2002 is estimated as 3.8 per 100,000 females, for non-Hispanic blacks as 3.4 per 100,000 females, for Asians as 2.3 per 100,000 females, and non-Hispanic whites as 1.8 per 100,000 females (Nasseri et al., 2006).

Cervical cancer screening by race/ethnicity

In the population of insured females in California aged 18 years and older, rates of screening for cervical cancer using Pap tests in the past 3 years varies by race and ethnicity, with Asians reporting the lowest rate of having a Pap test within the last three years (74%) compared to Hispanics (87%), non-Hispanic whites (88%), and non-Hispanic blacks (90%) (CHIS, 2007). Asian women also reported the highest rates of never having been screened with the Pap test—19% compared to 4% to 9% for other racial and ethnic groups (CHIS, 2007).

Vaccination by race/ethnicity

There are no statistically significant differences in the rates at which insured females aged 12 to 26 years report receiving the HPV vaccine (Table 8). 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). Alternatively, it has also been suggested that due to disparities in vaccination rates, the HPV vaccine will actually widen the disparities in cervical cancer already seen, where the lowest risk population of white females will differentially take up the vaccine (Goldhaber-Fiebert et al., 2008). Over time, as researchers are able to accurately assess the differences in vaccination rates across different racial and ethnic groups, the potential for the HPV vaccine to reduce disparities in health outcomes related to HPV infection will be clearer. Given the uncertainty about the impact of the HPV vaccine on racial/ethnic disparities in the prevalence of HPV, the prevalence of cervical cancer, and cervical cancer mortality, the extent to which this mandate will reduce these disparities is unknown.

Table 8. California Cervical Cancer Screening, Incidence, and Mortality and HPV Vaccination

Race/ethnicity	Age-adjusted incidence rate (1)	Age-adjusted death rate (2)	Pap Screening Rate (3)	Vaccination Rate (4)
All races	7.0	2.4	85.8 (84.9-86.8)	18.6 (16.5-20.7)
Hispanic	14.4	3.8	86.9 (84.4-89.4)	14.2 (10.1-18.2)
Non-Hispanic white	7.0	1.8	88.2 (87.2-89.3)	21.3 (18.0-24.6)
Non-Hispanic black	8.7	3.4	89.5 (86.6-92.3)	20.1 (11.8-28.5)
Asian	8.3	2.3	74.2 (70.7-77.6)	18.1 (12.1-24.1)

Sources:

(1) The age adjusted incidence rate for all races is from NCI, 2005. Incidence by race/ethnicity comes from Hofer et al., 2008. Rates are presented per 100,000 females.

(2) Age-adjusted death rates in 2002 for all races and by race/ethnicity come from Nasser et al., 2006. Rates are presented per 100,000 females.

(3) Screening rates come from the California Health Interview Survey, 2007 (CHIS, 2007). This rate is for insured women 18 and over who received a Pap test within 3 years. The uninsured and women who had a hysterectomy were excluded from the analysis of screening rates.

(4) Self-reported vaccination rates come from CHIS, 2007. This rate is for insured females aged 12 to 26 years.

The Extent to Which the Proposed Service Reduces Premature Death and the Economic Loss Associated with Disease

Premature Death

HPV is essentially responsible for all cervical cancer cases (Walboomers et al., 1999). In California, approximately 410 women are expected to die in 2009 from cervical cancer (CCR, 2008). As presented above, vaccination modeling predicts that increases in HPV vaccination as a result of SB 158 could result in fewer cases of cervical cancer diagnoses and related deaths. As described in the section on *Utilization, Cost, and Coverage Impacts*, it is estimated that an additional 2,500 vaccinations would occur as a result of SB 158. This could lead to a decrease in the number of cervical cancer cases by 8 to 13 cases—preventing 3 to 5 deaths from cervical cancer over the lifetime of those vaccinated. Although not quantified in this report, it is also possible that increased vaccination could lead to a reduction in other HPV-associated cancers such as cancer of the vagina, vulva, and anus. Across the United States, the average years of potential life lost (YPPPL) for each cervical cancer death is 27.6 and the average YPPPL for each HPV-associated cancer death is 21.8 (Ekwueme et al., 2008).

Economic Loss

The economic loss associated with cervical cancer consists of direct medical costs and the indirect costs related to a reduction in productivity due to premature mortality. An analysis conducted in California reported a present value for the lost wages and housekeeping services of women dying from cervical cancer of \$445,000 per cervical cancer death converted to 2007

dollars (Max et al., 2003). Furthermore, this study stated that the 452 deaths reported from cervical cancer in California in 1998 amounted to 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 as a result of cervical cancer and almost all (97%) of the losses in productivity (Max et al., 2003).

CHBRP estimates that as a result of this mandate, three to five deaths could be prevented over the lifetime of women vaccinated in the first year, yielding a total savings of 80 to 140 person years, valued at between \$1.3 and \$2.2 million.

Long-Term Public Health Impacts

All of the impacts discussed in this section are expected to occur in the long-term over the course of the lifetime of newly vaccinated girls and women. As presented in the *Medical Effectiveness* section, it is also expected that vaccination could improve interim health outcomes through the reduction in HPV infection, CIN diagnoses, and genital warts. Although both vaccination and screening and treatment for HPV infections will lead to a reduction in cervical cancer cases, vaccination additionally leads to a reduction in medical procedures such as colposcopy, used in the treatment of HPV infections. In subsequent years, after catch-up vaccinations are complete, the number of additional women getting vaccinated as a result of the mandate would decrease to approximately 350, preventing one to two cases of cervical cancer a year.

APPENDICES

Appendix A: Text of Bill Analyzed

BILL NUMBER: SB 158 INTRODUCED
BILL TEXT

INTRODUCED BY Senator Wiggins

FEBRUARY 12, 2009

An act to amend Section 1367.66 of the Health and Safety Code, and to amend Section 10123.18 of the Insurance Code, relating to health care coverage.

LEGISLATIVE COUNSEL'S DIGEST

SB 158, as introduced, Wiggins. Health care coverage: human papillomavirus vaccination.

Existing law, under the Knox-Keene Health Care Service Plan Act of 1975, provides for the licensure and regulation of health care service plans by the Department of Managed Health Care and makes a willful violation of the act a crime. Existing law also provides for the regulation of health insurers by the Department of Insurance. Under existing law, health care service plan contracts and health insurance policies that include coverage for the treatment or surgery of cervical cancer are deemed to provide coverage for an annual cervical cancer screening test, upon the referral of specified persons.

This bill would require those plan contracts and insurance policies to also provide coverage for the human papillomavirus vaccination, as specified.

Because a willful violation of the bill's requirements by a health care service plan would be a crime, the bill would impose a state-mandated local program.

The California Constitution requires the state to reimburse local agencies and school districts for certain costs mandated by the state. Statutory provisions establish procedures for making that reimbursement.

This bill would provide that no reimbursement is required by this act for a specified reason.

Vote: majority. Appropriation: no. Fiscal committee: yes. State-mandated local program: yes.

THE PEOPLE OF THE STATE OF CALIFORNIA DO ENACT AS FOLLOWS:

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 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.

(b) Every individual or group health care service plan contract, except for a specialized health care service plan contract, that is issued, amended, or renewed on or after January 1, 2010, and that includes coverage for treatment or surgery of cervical cancer shall also be deemed to provide coverage for a human papillomavirus vaccination upon the referral of the patient's physician and surgeon, a nurse practitioner, or certified nurse midwife, providing care to the patient and operating within the scope of practice otherwise permitted for the licensee.

~~Nothing~~

(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 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 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.

(b) Every individual or group policy of health insurance that is issued, amended, or renewed, on or after January 1, 2010, and that includes coverage for treatment or surgery of cervical cancer shall also be deemed to provide coverage for a human papillomavirus vaccination upon the referral of a 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.

~~Nothing~~

(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 methods used in the medical effectiveness literature review for SB 158, a bill that would require health plans regulated by the DMHC and health insurance policies issued by insurance companies regulated by the CDI that include coverage for treatment or surgery of cervical cancer to provide coverage for a HPV vaccination upon referral.

The literature search for SB 158 was limited to studies published in English from January 2007 to present. The timeframe for the search was truncated because CHBRP conducted a search of the literature on the effectiveness of prenatal care services published prior to 2007 for a report it issued in 2007 regarding a similar bill (AB 1429). Pertinent studies retrieved during the previous literature search are discussed in this report along with studies obtained from the new search.

The following databases that index peer-reviewed literature were searched: PubMed, the Web of Science, EconLit, the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Register of Controlled Clinical Trials). Web sites maintained by the following organizations that publish systematic reviews and evidence-based guidelines were searched: Agency for Healthcare Research and Quality (including the U.S. Preventive Services Task Force), Centers for Disease Control and Prevention, Institute for Clinical Systems Improvement, International Network of Agencies for Health Technology Assessment, National Guideline Clearinghouse, National Health Service Centre for Reviews and Dissemination, National Institute for Health and Clinical Excellence, National Institutes of Health, the Scottish Intercollegiate Guideline Network, and the World Health Organization.

The literature search yielded a total of 225 citations. At least two reviewers screened the title and abstract of each citation returned by the literature search to determine eligibility for inclusion. The reviewers obtained the full text of articles that appeared to be eligible for inclusion in the review and reapplied the initial eligibility criteria. Seven additional articles pertinent to the medical effectiveness review were identified, retrieved, and reviewed. An article published in 2005 was subsequently retrieved to provide a more thorough assessment of the results of a Phase 2 trial of the quadrivalent vaccine (Gardasil) (Villa et al., 2005). Findings from these eight articles were integrated with findings from the three articles that were included in the literature review for CHBRP's report on AB 1429.

The eleven articles reviewed include eight articles that summarize the results of four clinical trials of the quadrivalent HPV vaccine and three articles that report results of two clinical trials of the bivalent HPV vaccine (Cervarix). Several additional articles regarding these clinical trials were excluded for several reasons. Two articles were excluded that reported pooled findings for subsets of the women enrolled in the clinical trials of the quadrivalent vaccine who resided in Asian-Pacific and Latin American nations (Perez et al., 2008; Tay et al., 2008). Two articles that presented pooled results from the three clinical trials of the quadrivalent vaccine with a clinical trial of a monovalent vaccine that has not been approved by the FDA were excluded because the effects of the quadrivalent vaccine could not be separated from the effects of the monovalent vaccine (Ault et al., 2007; Barr et al., 2008). In addition, an article regarding a clinical trial of the bivalent vaccine that enrolled women in Costa Rica infected with HPV at the time of enrollment

was excluded because the trial was intended to assess whether the HPV vaccine could be used to treat rather than prevent HPV infection and associated conditions (Hildesheim et al., 2007).

In making a “call” for each outcome measure, the 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 these five domains. 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 are well-implemented randomized controlled trials (RCTs) 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 or from small RCTs with weak research designs. 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 has an unfavorable effect.

The evidence is presented as “ambiguous/conflicting” 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.

Search Terms

The Medical Subject Headings (MeSH) terms and keywords used in the PubMed and Cochrane Library searches for SB 158 were as follows.

MeSH Terms

Adolescent
Adult
Adverse Drug Reaction Reporting Systems
African continental ancestry group
Antibodies, viral/blood/immunology
Asian Americans/ statistics & numerical data
California/epidemiology
Cohort studies
Cost benefit analysis
Cost savings
Costs and cost analysis
Delivery of health care
Ethnic groups
European continental ancestry group
Evidence-based practice
Female
Genital diseases, female/ prevention & control/ virology
Genital neoplasms, female/epidemiology/ prevention & control
Health services accessibility
Health status disparities
Hispanic Americans
Human Papillomavirus 6/drug effects//immunology/pathogenicity
Human Papillomavirus 11/drug effects//immunology/pathogenicity
Human Papillomavirus 16/drug effects/immunology/pathogenicity
Human Papillomavirus 18/drug effects/immunology/pathogenicity
Human Papillomavirus Vaccine, L1 type 16, 18 [Substance Name]
Immunization schedule
Incidence
Mass immunization/standards/utilization
Mass screening/economics
Models, economic
Papillomaviridae/ immunology
Papillomavirus infections/complications/ epidemiology/prevention & control
Papillomavirus vaccines/ administration & dosage/adverse effects/economics
Patient acceptance of health care
Poverty
Prevalence
Product surveillance, postmarketing

Prospective studies
Public health
Quality-adjusted life years
Quality of life
Safety
Sexually transmitted diseases/prevention & control
Sexually transmitted diseases, viral/complications/ethnology/prevention & control
Socioeconomic factors
Survival rate
Treatment failure
Treatment outcome
Uterine cervical neoplasms/epidemiology/ ethnology/prevention & control/virology
Vaccination/economics/standards/utilization
Warts/ prevention & control/trends/virology

Publication Type:

Clinical Trial (including Clinical Trials, Phase I Clinical Trials, Phase II Clinical Trials, Phase III Clinical Trials, Phase IV Clinical Trials)
Comparative Studies
Controlled Clinical Trial
Evaluation Studies
Meta-Analysis
Multicenter Study
Practice Guideline
Randomized Controlled Trial

Subset:

Systematic Reviews

Keywords used to search PubMed, the Cochrane Library, EconLit, Web of Science and relevant web sites

Acceptance, access, ACS, adolescent*, ADRRS, Adverse Drug Reaction Reporting Systems, Adverse event*, American Academy of Family Physicians, American Academy of Pediatrics, American Cancer Society, American College of Obstetrics and Gynecology, blacks, CDC, Center for Diseases Control, Cervarix, cervical cancer, comparative, comparison, cost*, cost benefits analysis, cost effective*, cost saving*, disparit*, effective*, efficacy, ethnic*, evidence-Based, female, Future I, Future II, Gardasil, genital disease*, genital warts, HPV, HPV infection*, HPV vaccine*, human papillomavirus, human papilloma virus, human papillomavirus infection, human papilloma virus infection, immunization, model*, National Vaccine Information Center, phrase, post market*, poverty, practice guideline*, Quality-adjusted life years, quality of life, safety, sexually transmitted disease*, side effect*, socioeconomic*, survival rate, survivor*, treatment failure, treatment outcome, vaccine*,

* indicates that the term was truncated to retrieve articles in which multiple variations on the term appeared.

Combinations of MeSH terms and keywords were used to search Business Sources Complete, EconLit, Web of Science and the web.

Appendix C: Description of Studies on the Medical Effectiveness of Vaccines for the Human Papillomavirus

Appendix C describes the studies on the medical effectiveness of human papillomavirus (HPV) vaccines. For each study, Table C-1 presents the citation and information about the type of study, relationship(s) assessed, population studied, and location at which a study was conducted. Table C-2 summarizes findings from these studies. These tables include studies that were reviewed for the report CHBRP issued on AB 1429, a similar bill introduced in 2007, as well as studies published since that report was issued. The new studies are indicated in bold in the tables below.

Table C-1. Characteristics of Published Studies on the Medical Effectiveness of Human Papillomavirus Vaccines

Vaccine	Citation	Trial(s)	Type of Trial ¹⁷	Intervention and Control Groups	Population Studied	Location
Gardasil	Villa et al., 2005	Phase 2 trial	Level I: well-implemented RCT	Quadrivalent HPV vaccine vs. placebo	552 women aged 16-23 yrs. who were not pregnant, had no previous abnormal Pap tests, and a lifetime history of ≤ 4 male sexual partners	Brazil, Finland, Norway, Sweden, United States
	Villa et al., 2006	Phase 2 trial	Level I: well-implemented RCT	Quadrivalent HPV vaccine vs. placebo	241 women aged 16-23 yrs.; same inclusion criteria as Villa et al., 2005	Brazil, Finland, Norway, Sweden,
	Garland et al., 2007	FUTURE I trial	Level I: well-implemented RCT	Quadrivalent HPV vaccine vs. placebo	5,455 women aged 16-24 yrs. who were not pregnant, had no abnormal Pap tests, no history of genital warts, and a lifetime history of ≤ 4 sexual partners	16 countries
	Future II Study Group, 2007	FUTURE II trial	Level I: well-implemented RCT	Quadrivalent HPV vaccine vs. placebo	10,565 women aged 15-26 yrs. – same inclusion criteria as Villa et al., 2005	13 countries

¹⁷ Level I = Well-implemented 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 group, time series analyses, and cross-sectional surveys; Level IV = Case series and case reports; Level V = Clinical/practice guidelines based on consensus or opinion.

Table C-1. Characteristics of Published Studies on the Medical Effectiveness of Human Papillomavirus Vaccines (Cont'd)

Vaccine	Citation	Trial(s)	Type of Trial¹⁸	Intervention and Control Groups	Population Studied	Location
	Joura et al., 2007	FUTURE I, FUTURE II, and Phase 2 trials	Level I: pooled analysis of 3 well-implemented RCTs	Quadrivalent HPV vaccine vs. placebo	18,174 women aged 16-26 yrs. – same inclusion criteria as Villa et al., 2005	24 Asia-Pacific, European, Latin American, and North American countries
	Brown et al., 2009	FUTURE I and FUTURE II trials	Level I: pooled analysis of 2 well-implemented RCTs	Quadrivalent HPV vaccine vs. placebo	17,622 women aged 15-26 yrs. – same inclusion criteria as Garland et al., 2007	Multiple countries – names not reported
	Wheeler et al., 2009	FUTURE I and FUTURE II trials	Level I: pooled analysis of 2 well-implemented RCTs	Quadrivalent HPV vaccine vs. placebo	17,622 women aged 15-26 yrs. – same inclusion criteria as Garland et al., 2007	Multiple countries – names not reported

¹⁸ Level I = Well-implemented 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 group, time series analyses, and cross-sectional surveys; Level IV = Case series and case reports; Level V = Clinical/practice guidelines based on consensus or opinion.

Table C-1. Characteristics of Published Studies on the Medical Effectiveness of Human Papillomavirus Vaccines (Cont'd)

Vaccine	Citation	Trial(s)	Type of Trial ¹⁹	Intervention and Control Groups	Population Studied	Location
	Reisinger et al., 2007	No name stated	Level I: well-implemented RCT	Quadrivalent HPV vaccine vs. placebo	1,781 boys and girls aged 9-15 yrs. who had never had a sexual partner ²⁰	10 Asian-Pacific, European, Latin American, and North American countries
Cervarix	Harper et al., 2004	Phase 2 Trial	Level I: well-implemented RCT	Bivalent HPV vaccine vs. placebo	1,113 women aged 15-25 yrs. who had no previous abnormal Pap test or ablative or excisional treatment of the cervix, were not undergoing treatment for genital warts, tested negative for 14 high-risk HPV types, and had reported a lifetime history of ≤6 sexual partners	Brazil, Canada, United States
	Harper et al., 2006	Phase 2 Trial	Level I: well-implemented RCT	Bivalent HPV vaccine vs. placebo	776 women aged 15-25 yrs. – same inclusion criteria as Harper et al., 2004	Brazil, Canada, United States
	Paavonen et al., 2007	PATRICIA	Level I: well-implemented RCT	Bivalent HPV vaccine vs. Hepatitis A vaccine	18,525 women aged 15-25 yrs. who were not pregnant or breastfeeding, did not have a history of colposcopy, did not have a history of chronic disease, autoimmune disease, or immunodeficiency	14 Asian-Pacific, European, Latin American, and North American countries

¹⁹ Level I = Well-implemented 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 group, time series analyses, and cross-sectional surveys; Level IV = Case series and case reports; Level V = Clinical/practice guidelines based on consensus or opinion.

²⁰ Only results for girls are reported in Table C-2a, because the Food and Drug Administration (FDA) has only approved administration of Gardasil to females.

Table C-2a. Findings from RCTs on the Efficacy of the Gardasil HPV Vaccine

Citation	Outcome	Research Design ²¹	Length of Follow-Up	Statistical Significance ²²	Direction of Effect	Size of Effect	Generalizability
Villa et al., 2005, 2006 (Phase 2 trial)	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	<ul style="list-style-type: none"> Level I: 2 studies (follow-up studies with two different lengths of follow-up) 	<ul style="list-style-type: none"> Follow-up study 1 = 3 yrs. Follow-up study 2 = 5 yrs. 	<ul style="list-style-type: none"> Statistically significant 	<ul style="list-style-type: none"> Protection for females receiving quadrivalent vaccine 	<ul style="list-style-type: none"> Prevention of persistent HPV 6/11/16/18 infection—95.8% (95% CI = 83.3%, 99.5%) in the per protocol population²³ and 93.5% (95% CI = 82.5%, 98.3%) in the intent-to-treat population²⁴ Prevention of genital warts—100% (95% CI = <0.0%, 100.0%) in both the per protocol and intent-to-treat populations Prevention of HPV 16/18 related CIN 1, 2, and 3—100% (95% CI = <0.0%, 100.0%) in the per protocol population and 100% (95% CI = 30.8%, 100.0%) in the intent-to-treat population 	<ul style="list-style-type: none"> Somewhat generalizable in that the primary study analyses focused on persons with no prior HPV infection and who were compliant with the 3-shot regimen

²¹ 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.

²² Findings presented are from an analysis that combined results from the three-year and five-year follow-up studies (Villa et al., 2006).

²³ Defined as women who received all three doses of the vaccine.

²⁴ Defined as women who received at least one dose of the vaccine.

Table C-2a. Findings from RCTs on the Efficacy of the Gardasil HPV Vaccine (Cont'd)

Citation	Outcome	Research Design	Length of Follow-Up	Statistical Significance	Direction of Effect	Size of Effect	Generalizability
Garland et al., 2007 (FUTURE I trial)	External anogenital & vaginal lesions and cervical lesions (CIN grade 1+) related to HPV 6/11/16/18	<ul style="list-style-type: none"> Level I = 1 study 	<ul style="list-style-type: none"> 3 yrs. 	<ul style="list-style-type: none"> Statistically significant 	<ul style="list-style-type: none"> Protection for females receiving quadrivalent vaccine 	<ul style="list-style-type: none"> Prevention of external anogenital and vaginal lesions associated with HPV 6/11/16/18—100% (95% CI = 94%, 100%) in the per-protocol population²⁵ and 73% (95% CI, 58%, 83%) in the intent-to-treat population²⁶ Prevention of cervical lesions associated with HPV 6/11/16/18—100% (95% CI = 94%, 100%) in the per-protocol population and 55% (95% CI = 40%, 66%) in the intent-to-treat population 	<ul style="list-style-type: none"> More generalizable than the Phase 2 Gardasil trial because the intent-to-treat analysis includes women infected with HPV prior to enrollment in the trial

²⁵ Defined as women who received all three doses of the vaccine who did not have abnormal cervical cytology and who were seronegative and HPV DNA negative for at least one of the four types of HPV addressed by the quadrivalent vaccine (i.e., HPV 6, 11, 16, and 18) at the time they enrolled in the trial and who remained HPV DNA negative for the same HPV type through one month after the third dose of the vaccine.

²⁶ Defined as all women who received at least one dose of the vaccine regardless of whether they had infection or disease associated with HPV 6, 11, 16, or 18 at the time they enrolled in the trial.

Table C-2a. Findings from RCTs on the Efficacy of the Gardasil HPV Vaccine (Cont'd)

Citation	Outcome	Research Design	Length of Follow-Up	Statistical Significance	Direction of Effect	Size of Effect	Generalizability
FUTURE II Study Group, 2007b (FUTURE II trial)	High-grade cervical lesions (CIN 2 or 3) and adenocarcinoma in situ (AIS) related to HPV 16/18	<ul style="list-style-type: none"> Level I = 1 study 	<ul style="list-style-type: none"> 3 yrs. 	<ul style="list-style-type: none"> Statistically significant 	<ul style="list-style-type: none"> Protection for females receiving quadrivalent vaccine 	<ul style="list-style-type: none"> Prevention of high-grade cervical lesions and AIS related to HPV 16/18—98% (95% CI = 86%, 100%) in the per-protocol population²⁷ and 44% (95% CI, 26%, 58%) in the intent-to-treat population²⁸ 	<ul style="list-style-type: none"> More generalizable than the Phase 2 Gardasil trial because the intent-to-treat analysis includes women infected with HPV prior to enrollment in the trial
Joura et al., 2007 (FUTURE I, FUTURE II, and Phase 2 trials)	High-grade vaginal and vulvar interepithelial neoplasia (Val N2-3 and VIN 2-3) related to HPV 16/18	<ul style="list-style-type: none"> Level I = 1 study 	<ul style="list-style-type: none"> 3 yrs. 	<ul style="list-style-type: none"> Statistically significant 	<ul style="list-style-type: none"> Protection for females receiving quadrivalent vaccine 	<ul style="list-style-type: none"> Prevention of Val N2-3 and VIN 2-3 related to HPV 16/18—100% (95% CI = 72%, 100%) in the per-protocol population²⁹ and 71% (95% CI, 37%, 88%) in the intent-to-treat population³⁰ 	<ul style="list-style-type: none"> More generalizable than the Phase 2 Gardasil trial because the intent-to-treat analysis includes women infected with HPV prior to enrollment in the trial

²⁷ Defined as women who received all three doses of the vaccine who were seronegative and HPV DNA negative for HPV 16 or HPV 18 at the time they enrolled in the trial and who remained HPV DNA negative for the same HPV type through one month after the third dose of the vaccine.

²⁸ Defined as all women who received at least one dose of the vaccine regardless of whether they had infection or disease associated with HPV 16 or HPV 18 at the time they enrolled in the trial.

²⁹ Defined as women who received all three doses of the vaccine who were seronegative and HPV DNA negative for HPV 16 or HPV 18 at the time they enrolled in the trial and who remained HPV DNA negative for the same HPV type through one month after the third dose of the vaccine.

³⁰ Defined as all women who received at least one dose of the vaccine regardless of whether they had infection or disease associated with HPV 16 or HPV 18 at the time they enrolled in the trial.

Table C-2a. Findings from RCTs on the Efficacy of the Gardasil HPV Vaccine (Cont'd)

Citation	Outcome	Research Design	Length of Follow-Up	Statistical Significance	Direction of Effect	Size of Effect	Generalizability
Brown et al., 2009 (FUTURE I and FUTURE II trials)	High-grade cervical interepithelial neoplasia (CIN 2 or 3) or AIS related to the HPV types other than 6/11/16/18 for which testing is available (i.e., HPV types not targeted by the quadrivalent vaccine)	<ul style="list-style-type: none"> Level I = 1 study 	<ul style="list-style-type: none"> 3.6 yrs. 	<ul style="list-style-type: none"> Statistically significant 	<ul style="list-style-type: none"> Protection for females receiving quadrivalent vaccine 	<ul style="list-style-type: none"> Prevention of high-grade cervical lesions and AIS related to HPV types other than 6/11/16/18—32.5% (95% CI = 6.0%, 51.9%) Efficacy primarily due to reductions in infection with HPV types 31, 33, 52, and 58 	<ul style="list-style-type: none"> Somewhat generalizable in that the authors analyze outcomes for persons with no prior HPV infection and who were compliant with the 3-shot regimen
Wheeler et al., 2009 (FUTURE I and FUTURE II trials)	Cervical lesions (CIN 1+) or AIS related to the HPV types not targeted by the quadrivalent vaccine	<ul style="list-style-type: none"> Level I = 1 study 	<ul style="list-style-type: none"> 3.6 yrs. 	<ul style="list-style-type: none"> Statistically significant 	<ul style="list-style-type: none"> Protection for females receiving quadrivalent vaccine 	<ul style="list-style-type: none"> Prevention of high-grade cervical lesions and AIS related to HPV types other than 6/11/16/18—15.1% (95% CI = 6.0%, 23.4%) 	<ul style="list-style-type: none"> More generalizable than Brown et al., 2009 because the population studied includes persons with prior exposure to HPV as well as those with no prior exposure

Table C-2a. Findings from RCTs on the Efficacy of the Gardasil HPV Vaccine (Cont'd.)

Citation	Outcome	Research Design	Length of Follow-Up	Statistical Significance	Direction of Effect	Size of Effect	Generalizability
Reisinger et al., 2007 ³¹	Seroconversion rates for HPV 6/11/16/18 1 yr. after completion of vaccination regimen	<ul style="list-style-type: none"> • Level I = 1 study 	<ul style="list-style-type: none"> • 18 months 	<ul style="list-style-type: none"> • Statistically significant 	<ul style="list-style-type: none"> • Protection for females receiving quadrivalent vaccine 	<ul style="list-style-type: none"> • Seroconversion rates for each of the four types of HPV against which the vaccine is designed to protect—97.9% for HPV 6, 99.2% for HPV 11, 99.8% for HPV 16, and 91.5% for HPV 18 • Strongest response in the youngest subjects 	<ul style="list-style-type: none"> • Somewhat generalizable—only trial to enroll persons under age 15 yrs.

³¹ Only results for girls are reported because the FDA has only approved administration of Gardasil to females.

Table C-2b. Findings from RCTs on the Efficacy of the Cervarix HPV Vaccine

Citation	Outcome	Research Design ³²	Length of Follow-Up	Statistical Significance ³³	Direction of Effect	Size of Effect	Generalizability
Harper et al., 2004, 2006 (Phase 2 trial)	Persistent HPV infection 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	<ul style="list-style-type: none"> Level I: 2 studies (initial study and a follow-up study) 	<ul style="list-style-type: none"> Initial study = 27 months Follow-up study = 4.5 yrs. 	<ul style="list-style-type: none"> Statistically significant 	<ul style="list-style-type: none"> Protection for females receiving bivalent vaccine 	<ul style="list-style-type: none"> Immune response 14- to 17-fold higher than from natural infections, in the according-to-protocol population Prevention of persistent HPV 16/18-related infection at 6 months—96.0% (95% CI = 75.2%, 99.9%) in the according-to-protocol population³⁴ and 94.4% (95% CI = 78.2%, 99.4%) in the intent-to-treat population³⁵ Prevention of HPV 16/18-related CIN 2/3 lesions—100% (95% CI = -7.7%, 100%) in the intent-to-treat population 	<ul style="list-style-type: none"> Somewhat generalizable in that the primary study analyses focused on women with no prior HPV infection and who were compliant with the three-shot regimen

³² 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.

³³ Findings presented are from an analysis that combined results from the initial and follow-up studies of outcomes at 4.5 years (Harper et al., 2006).

³⁴ Defined as women who received all three doses of the vaccine.

³⁵ Defined as women who received at least one dose of the vaccine.

Table C-2b. Findings from RCTs on the Efficacy of the Cervarix HPV Vaccine (Cont'd)

Citation	Outcome	Research Design ⁽¹⁾	Length of Follow-Up	Statistical Significance	Direction of Effect	Size of Effect	Generalizability
Paavonen et al., 2007 (PATRICIA trial)	Persistent HPV infection, CIN grade 1+, CIN grade 2+ related to HPV 16/18; persistent HPV infection related to HPV types other than 16/18 (i.e., HPV types not targeted by the quadrivalent vaccine)	<ul style="list-style-type: none"> Level I: 1 study 	<ul style="list-style-type: none"> 14.8 months 	<ul style="list-style-type: none"> Statistically significant for outcomes related to HPV 16/18 Not statistically significant for persistent infection related to other HPV types 	<ul style="list-style-type: none"> Protection against outcomes related to HPV 16/18 for females receiving bivalent vaccine No difference in persistent infection related to other HPV types 	<ul style="list-style-type: none"> Prevention of persistent HPV 16/18-related infection at 6 months—80.4% (95% CI = 70.4%, 87.4%) Prevention of HPV 16/18-related CIN 1+ lesions—89.2% (97.9% CI = 59.4%, 98.5%) Prevention of HPV 16/18-related CIN 2+ lesions—90.4% (97.9% CI = 53.4%, 99.3%) Prevention of persistent infection related to other HPV types at 6 months—9% (95% CI = -5.1%, 21.2%) 	More generalizable than the Phase 2 Cervarix trial because the study population includes women infected with HPV prior to enrollment in the trial

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

This appendix describes data sources, as well as 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 at 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 that provides data and analyses per the provisions of CHBRP's 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 (2007) California Health Interview Survey (CHIS), which is used 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 approximately 53,000 households. More information on CHIS is available at www.chis.ucla.edu/
2. The latest (2008) California Employer Health Benefits Survey is used 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] and Point of Service Plans [POS]),
 - premiums for policies regulated by the California Department of Insurance (CDI) (primarily preferred provider organizations [PPOs] and fee-for-service plans [FFS]), and
 - premiums for high-deductible health plans (HDHPs) for the California population covered under employment-based health insurance.

This annual survey is currently released by the California Health Care Foundation/National Opinion Research Center (CHCF/NORC) and is similar to the national employer survey released annually by the Kaiser Family Foundation and the Health Research and Educational Trust. Information on the CHCF/NORC data is available at: www.chcf.org/topics/healthinsurance/index.cfm?itemID=133543.

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/expertise/healthcare/products-tools/milliman-care-guidelines/index.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 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 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 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 (2008 Group Health Insurance Survey) contains data from seven major California health plans regarding their 2007 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 applicability 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, Anthem 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 96.0% of the privately-insured market: 98.0% of privately insured enrollees in full-service health plans regulated by DMHC and 82% of lives privately insured health insurance products regulated by the CDI.

Public Insurance

5. 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 covering non-Medicare beneficiaries—comprise 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.
6. Enrollment in Medi-Cal Managed Care (Knox-Keene licensed plans regulated by DMHC) is estimated based on CHIS and data maintained by the Department of Health Care Services (DHCS). DHCS 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 <http://www.dhcs.ca.gov/dataandstats/statistics/Pages/BeneficiaryDataFiles.aspx>.

7. 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 Managed 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-MRMIP 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. 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:

- 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.
- 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 products subject to state-mandated health insurance benefits.
- Cost impacts are only for the first year after enactment of the proposed mandate
- 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 the 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

- Several recent studies have examined the effect of private insurance premium increases on the number of uninsured (Chernew et al., 2003; Hadley, 2006; Glied and Jack, 2003). Chernew et al. estimate that a 10% increase in private premiums results in a 0.74 to 0.92 percentage point decrease in the number of insured, while Hadley (2006) and Glied and Jack (2003) estimate that a 10% increase in private premiums produces a 0.88 and 0.84 percentage point decrease in the number of insured, respectively. The price elasticity of demand for insurance can be calculated from these studies in the following way. First, take the average percentage point decrease in the number of insured reported in these studies in response to a 1% increase in premiums (about -0.088), divided by the average percentage of insured individuals (about 80%), multiplied by 100%, i.e., $(\{-0.088/80\} \times 100) = -0.11$). This elasticity converts the *percentage point* decrease in the number of insured into a *percentage* decrease in the number of insured for every 1% increase in premiums. Because each of these studies reported results for the large-group, small-group, and individual insurance markets combined, CHBRP employs the simplifying assumption that the elasticity is the same across different types of markets. For more information on CHBRP's criteria for estimating impacts on the uninsured 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 and 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, health plan members 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 (i.e., high levels of patient cost sharing result in lower utilization of health care services). CHBRP did not include the effects of such potential benefit changes in its analysis.
- Adverse selection: Theoretically, individuals or employer groups who had previously foregone insurance may now elect to enroll in an insurance plan post-mandate 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 point of service (POS) plans—and non-HMO—including PPO and fee for service (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 purposes of this analysis, however, CHBRP has estimated the impact on a statewide level.

Bill Analysis–Specific Caveats and Assumptions

- 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 HPV vaccination rates in this report are based on self-reported data from the 2007 CHIS survey and may differ from actual rates. Self-reported data may overstate vaccination rates that are identified from patient chart review. However chart review studies were not available at the time of this report. Also, survey data are subject to sampling and other forms of error and variations in HPV vaccination rates are possible.
 - 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 the 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 indicates 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. CHBRP assumes that by 2010 the number of females aged 11 to 26 years with HPV vaccination would have increased thus reducing the number of unvaccinated individuals. Therefore, the annual vaccination rates are anticipated to drop over time. For most CHBRP analyses, the one-year cost projection is based on long-term utilization rates. This mandate is unique because it becomes effective within 3 to 4

years after the mandated service is first available, requiring projection of vaccination rates in 2010. 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 later required. In addition, the per-unit cost may be different if another vaccine, such as Cervarix by GlaxoSmithKline, is introduced in the market.

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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California Health Benefits Review Program Committees and Staff

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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