CALIFORNIA
HEALTH BENEFITS REVIEW PROGRAM

Issue Brief:
Immunization Mandates, Benchmark Plan Choices, and Essential Health Benefits

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EXECUTIVE SUMMARY

The Affordable Care Act of 2010 (ACA) includes provisions that require coverage for new federal benefit mandates as well as a provision that requires coverage of "essential health benefits" (EHBs) for most health insurance products sold in the individual and small-group markets, including the qualified health plans (QHPs) that will be sold through state health benefit exchanges. EHBs have yet to be defined in California, but when coverage for EHBs is required in 2014, some current state benefit mandates could exceed EHBs. The ACA requires the state to defray the costs of requiring QHPs to provide coverage that exceeds EHBs.[1] Therefore, there is significant interest in whether any state benefit mandates that could exceed EHBs are present in California.

In this issue brief, the California Health Benefits Review Program (CHBRP) provides an example of how state benefit mandates could exceed EHBs and how evidence-based analysis may inform discussions of whether to keep or repeal state benefit mandates that exceed EHBs, specifically looking at immunization coverage requirements.

Benefit Mandate Coverage Requirements that Could Exceed Essential Health Benefits: Immunization Coverage Requirements

The ACA requires coverage for immunizations recommended by the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (CDC ACIP) *after an interval of not less than one year*.[2] Plans regulated by the California Department of Managed Health Care (DMHC) are required to cover CDC ACIP-recommended immunizations for all ages *from the time the recommendation is made*.[3] Policies regulated by the California Department of Insurance (CDI) are required to cover CDC ACIP-recommended immunizations for enrollees aged 18 years and younger *from the time the recommendation is made*.[4]

The U.S. Department of Health and Human Services (HHS) has proposed that each state define its own EHBs for 2014 and 2015 by selecting one of a set of specified benchmark plan options. The choice of benchmark plan is expected to dictate which state benefit mandates, if any, will be included in the state's EHBs. Depending on the benchmark plan selected in California to help define EHBs in 2014 and 2015, the time difference in when coverage is required for immunizations could result in cases where current state benefit mandates could exceed EHBs for the first year following a newly recommended immunization.

- If California selects a benchmark plan regulated by DMHC, no state immunization benefit mandates would exceed EHBs.
- If California selects a benchmark plan regulated by CDI, DMHC immunization coverage requirements would exceed EHBs for enrollees aged 19 years and older.

[1] Affordable Care Act Section 1311(d)(3)(B)
[2] Affordable Care Act Section 1001, modifying Section 2713 of the Public Health Service Act
[3] California Health and Safety Code Sections 1345(b), 1367.35, and 1367.3
[4] California Insurance Code (IC) Section 10123.5 requires coverage of CDC ACIP-recommended immunizations for children aged 16 years and younger. IC Section 10123.55 requires policies to offer to coverage CDC ACIP recommended immunizations for adolescents aged 17 and 18 years. For the purposes of this analysis, CHBRP is assuming a requirement to offer coverage is the same as a requirement to cover, and therefore could exceed EHBs.

- If California selects a benchmark plan subject only to federal regulation, both DMHC and CDI immunization coverage requirements would exceed EHBs.

As can be seen above, depending on under whose regulation the selected benchmark plan falls—DMHC regulation, CDI regulation, or federal regulation—a differing set of benefit mandates would be included in EHBs.

While California has not yet selected a benchmark plan to define EHBs, this issue brief will focus on the latter possibility in which EHBs are defined by a nongrandfathered[5] benchmark plan subject to federal regulation only, and therefore not subject to any state benefit mandates. In this case, DMHC- and CDI-enforced benefit mandate coverage requirements for immunizations could exceed EHBs by requiring coverage of CDC ACIP-recommended immunizations from the time the recommendation is made as opposed to after an interval of not less than one year. To illustrate this, this issue brief will use a *hypothetical scenario* of a specific vaccine previously recommended by CDC ACIP in 2007 being recommended as a new vaccine in 2012.

Evidence-Based Analysis: Quadrivalent Human Papillomavirus Vaccine

In 2007, CDC ACIP recommended the quadrivalent human papillomavirus vaccine (quadrivalent vaccine) for females aged 11 to 12 years, with catch-up vaccinations recommended for females aged 13 to 26 years (Markowitz et al., 2007). Using a *hypothetical scenario* of the quadrivalent vaccine being recommended as a new vaccine in 2012 (under CDC ACIP's initial recommendation of the vaccine in 2007), this issue brief explores the evidence on medical effectiveness, as well as the 2012 cost, utilization, and public health impacts associated with coverage of the quadrivalent vaccine in the first year following the CDC ACIP recommendation.[6] Although it is not clear as of now what portion of enrollees in the small-group and individual markets in 2012 will be in QHPs in 2014, **CHBRP hopes this brief will provide an example of how evidence-based analysis may inform discussions of whether to keep or repeal state benefit mandates that could exceed EHBs**.

Background on the Human Papillomavirus

There are more than 100 types of human papillomavirus (HPV), of which 40 are known to infect the anogenital epithelium. Exposure to these 40 HPV types usually results from sexual contact with an infected partner. HPV is the most prevalent sexually transmitted infection in the U.S. (Weinstock et al., 2004). It is estimated that about 80% of sexually active females will acquire HPV infection during their lifetime, and more than 50% of adolescents will acquire HPV within two years of becoming sexually active (Rambout et al., 2007). Most of these HPV infections are asymptomatic transient infections that resolve naturally and do not affect health. However, some

[5] A grandfathered health plan is defined as "A group health plan that was created—or an individual health insurance policy that was purchased—on or before March 23, 2010. Grandfathered plans are exempted from many changes required under the Affordable Care Act. Plans or policies may lose their 'grandfathered' status if they make certain significant changes that reduce benefits or increase costs to consumers" (www.healthcare.gov/glossary/g/grandfathered-health.html).

[6] It is important to note that the medical effectiveness as well as the cost and public health impacts to California in the first 12 months following a CDC ACIP recommendation of a new vaccine may be dramatically different than those presented here for the quadrivalent vaccine. The medical effectiveness as well as the cost and public health impacts would change depending on the target disease/condition and the characteristics of the vaccine itself (e.g., vaccine efficacy, target population).

HPV infections persist and can lead to anogenital warts, precancerous cervical lesions, and various cancers, including invasive cervical cancer in females.

Medical Effectiveness

The *Medical Effectiveness* analysis resulted in the following findings and conclusions:

- Prevention of high-risk HPV is expected to reduce incidence of cervical, vaginal, and vulvar cancer because infection with HPV is a necessary step in the path to these cancers (although most HPV infections do not proceed to cancer).
- The HPV vaccine works by exposing the immune system to nonliving virus-like particles so that antibodies against a virus 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 a person is later exposed to the real virus of the same type, the antibodies attack the virus and prevent infection.
- The quadrivalent vaccine targets two types of HPV that cause 70% of cervical cancers, types 16 and 18, and two types of HPV that cause 90% of anogenital warts, types 6 and 11. A full course of the quadrivalent vaccine requires the injection of three 0.5-mL doses of the vaccine intramuscularly over a six-month period.
- There is clear and convincing evidence from clinical trials of the quadrivalent vaccine that, when all three doses of the quadrivalent vaccine are given to previously uninfected females under ideal conditions, the vaccine yields antibody production and provides 90% to 100% protection against precancerous cervical, vaginal, and vulvar lesions and genital warts due to HPV types 6, 11, 16, and 18 for up to five years following vaccination.
- These findings are limited to a select group of females who had no prior evidence of infection with high-risk HPV types and were compliant with the three-dose vaccination regimen.
- Efficacy is much lower among females infected with high-risk HPV prior to vaccination.
- There are no statistically significant differences between females receiving the quadrivalent vaccine and a placebo in rates of precancerous cervical, vaginal, and vulvar lesions associated with high-risk HPV types other than the four the vaccine targets. Those other high-risk HPV types are associated with 30% of cervical cancers in the U.S.
- The impact of the vaccine on cervical, vaginal, and vulvar cancer morbidity and mortality is unknown because of the long latency between infection with high-risk HPV and development of cancer.

Benefit Coverage, Utilization, and Cost

Of the approximately 16.4 million Californians with privately purchased health insurance in California, 5.5 million have privately purchased health insurance in the small-group and individual markets. Small-group and individual market plans and policies will be required to cover EHBs, so state benefit mandates could exceed EHBs for these two markets.

Of the 16.4 million Californians with privately purchased health insurance, there are approximately 2.1 million female enrollees aged 11 to 26 years with required coverage for the quadrivalent vaccine, of which 588,730 are in the small-group and individual markets (28.5%).

In the hypothetical scenario of the quadrivalent vaccine being recommended as a new vaccine in 2012, among enrollees in privately purchased small-group and individual market plans and policies with required coverage for the quadrivalent vaccine that could exceed EHBs, CHBRP estimates 124,459 females would receive the vaccine. CHBRP estimates:

- 100,971 females aged 11 to 18 years would receive the quadrivalent vaccine, and, assuming completion of the three-dose series, a total of 302,914 doses would be dispensed to this population; and
- 23,488 females aged 19 to 26 years would receive the quadrivalent vaccine, and, assuming completion of the three-dose series, a total of 70,464 doses would be dispensed to this population.[7]

Total expenditures in the small-group and individual markets due to required coverage for the quadrivalent vaccine in the first year following a CDC ACIP recommendation would be approximately $74 million, assuming enrollees are vaccinated for the full three-dose series. This is 0.09% of total statewide costs, including expenditures for all privately purchased plans and policies across all health insurance markets. The first year is the only year in which state benefits could exceed EHBs, and therefore, the only year in which the state would be required to cover excess health expenditures (this is because, as noted above, the federal benefit mandate requires coverage for immunizations but after an interval of not less than one year as opposed to immediately). This figure represents a likely upper bound of estimated expenditures that the state could be asked to defray because only a portion of the quadrivalent vaccines would be provided to enrollees in QHPs purchased through the Exchange.

Public Health Impacts

The public health analysis offers an evidence-based method to help policymakers assess the "value" the state would realize from paying for "additional health" (e.g., for state benefit mandates that exceed EHBs). In this hypothetical scenario, CHBRP estimates that, despite the high prevalence of HPV infection, a small number of HPV-related diseases would be prevented by requiring coverage for the quadrivalent vaccine in the first 12 months following the CDC ACIP recommendation. CHBRP estimates that of the 124,459 females with state benefit coverage exceeding the federal mandate who receive the quadrivalent vaccine, about:

- 1,400 cases of genital warts could be prevented over the lifetime of this hypothetical cohort; and
- 60 hypothetical cases of grade 2 and 3 precancerous cervical lesions (known as cervical intraepithelial neoplasia, or CIN) could be prevented within the first year of the adoption of the CDC ACIP recommendation.

[7] Not all enrollees complete the full three-dose series. However, for this analysis CHBRP made the assumption that females who obtained the quadrivalent vaccine received all three doses. Therefore, these estimates are upper bound estimates of treatment completion adherence.

CHBRP did not estimate the vaccine's effect on preventing cervical cancer due to a lack of clinical evidence on this long-term outcome.

CHBRP's estimated public health outcomes represent an upper bound because vaccine effectiveness in "real world" situations tends to be less than that observed in carefully controlled studies. Moreover, the duration of protection from the vaccine is unknown, as is whether HPV types not targeted by the vaccine will substitute in causing disease (including cancer) as HPV types 16 and 18 are eliminated. Finally, we assumed that all persons beginning the series received all three doses. This is unlikely in practice, and persons not adhering to the full three-dose vaccine series will have reduced protection.

These estimates for HPV-related morbidity do not apply to other diseases and their associated vaccines. The number of cases prevented for other diseases for which future vaccines may be recommended will differ depending on the particular disease prevalence, infection rate, population affected, and vaccine effectiveness.

Conclusion

As California moves toward selecting its benchmark plan and defining EHBs for the state, CHBRP recommends using evidenced-based analysis, similar to what is provided in this issue brief, to help inform discussions of whether to keep or repeal state benefit mandates that could exceed EHBs. Evidenced-based analysis can provide decision-makers with a more comprehensive understanding of the impacts of state benefit mandates that exceed EHBs—not only potential costs, but also reviews of the medical effectiveness evidence and estimates of the mandate's public health impacts for Californians.

INTRODUCTION

In March 2010, the federal government passed the Patient Protection and Affordable Care Act (P.L.111-148) and the Health Care and Education Reconciliation Act (P.L. 111-152). These laws, together referred to as the Affordable Care Act (ACA), include a number of provisions that would directly and indirectly prompt changes in health care delivery, finance, and coverage, and that would affect benefits covered by California health insurance products. Specifically, the ACA includes provisions that require coverage for new federal benefit mandates and that require coverage of "essential health benefits" (EHBs) for most health insurance products sold in the individual and small-group markets, including the qualified health plans (QHPs) that will be sold through state health benefit exchanges.

The California Health Benefits Review Program (CHBRP), a program established in 2002, responds to requests from the California State Legislature for independent evidence-based analysis of the medical, financial, and public health impacts of proposed health insurance benefit mandates and repeals.[8] CHBRP makes no recommendations regarding bills, but instead aims to support decision-makers by providing evidence-based analyses.

While EHBs have yet to be defined in California, when coverage for EHBs will be required in 2014, some state benefit mandates could exceed EHBs. The ACA requires the state to defray the costs of requiring QHPs to provide coverage that exceeds EHBs.[9] Therefore, there is significant interest in whether any state benefit mandates that could exceed EHBs are present in California. **CHBRP offers this issue brief as an example of how state benefit mandates could exceed EHBs and how evidence-based analysis may inform discussions of whether to keep or repeal state benefit mandates that exceed EHBs.**

CHBRP recommends assessing the medical effectiveness, cost, and public health impacts of each state benefit mandate that seems to exceed EHBs in order to determine the value of the "excess" benefit coverage. This issue brief follows that recommendation. Focusing on California state benefit mandate coverage requirements for immunizations, this brief addresses how these state benefit mandates could exceed EHBs and provides an example of an evidence-based analysis of one vaccine.

Specifically, this brief provides:

- A general discussion on state and federal benefit mandates and EHBs;
- A discussion of how California state benefit coverage requirements could exceed EHBs, focusing on required coverage for immunizations; and
- Using a *hypothetical scenario* of a previously recommended vaccine being recommended as a new vaccine in 2012, an analysis of the evidence on medical effectiveness and the 2012 cost, utilization, and public health impacts associated with this specific vaccine.

[8] Additional information about the program is available on CHBRP's website: www.chbrp.org.
[9] Affordable Care Act Section 1311(d)(3)(B)

State Benefit Mandates, Federal Benefit Mandates, and Essential Health Benefits

As defined by CHBRP's authorizing statute,[10] a health insurance benefit mandate law can require health insurance products to provide coverage or offer to cover[11] any of the following: (1) screening, diagnosis, or treatment of a specific disease or condition; (2) specific types of health care treatments or services; and/or (3) services by specific types of health care providers. A mandate can also specify that benefit coverage be provided with specified terms that may affect cost sharing, prior authorization requirements, or other aspects of benefit coverage.

State Benefit Mandates

Uniquely, California has a bifurcated system of regulation for health insurance subject to state benefit mandates. The California Department of Managed Health Care (DMHC) regulates health care service plans, which offer benefit coverage to their enrollees through health plan contracts. The California Department of Insurance (CDI) regulates health insurers, which offer benefit coverage to their enrollees through health insurance policies. California state benefit mandates only apply to health insurance regulated at the state level by either DMHC or CDI. Because of this bifurcated system of regulation, California has two sets of state benefit mandates. CHBRP is currently aware of 48 benefit mandate laws enforced by DMHC and 46 enforced by CDI. The sets of mandates enforced by DMHC and CDI are similar but not identical. To see a list of benefit mandates current in California, see CHBRP's document, *Current Mandates: Health Insurance Benefit Mandates in California State Law*.[12]

Federal Benefit Mandates

Federal benefit mandates can be similar to state benefit mandates in the tests, treatments, and services they require coverage for and in the plans and policies subject to the mandate. However, federal benefit mandates can apply more broadly than state benefit mandates. For example, federal benefit mandates may apply to Medicare or to self-insured plans, which are not subject to state benefit mandates. There were federal benefit mandates in place prior to the passage of the ACA, and the ACA added federal benefit mandates that apply to most DMHC-regulated plans and CDI-regulated policies in the individual and group markets in California.

CHBRP is aware of ten federal benefit mandates, six of which were enacted by the ACA.[13] One of the federal benefit mandate requirements in the ACA requires coverage of specified preventive health services without cost sharing.[14] This includes coverage of immunizations that have a recommendation from the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (CDC ACIP).[15] The ACA specifies that coverage of this

[10] Available at: www.chbrp.org/documents/authorizing_statute.pdf.
[11] The majority of health insurance benefit mandates in California are "mandates to cover" particular service(s), treatment(s), health condition(s) or provider type(s) in all products, but there are also a number of "mandates to offer." CHBRP's list of California state benefit mandates includes information on which mandates are "mandates to cover" and which are "mandates to offer," available at: www.chbrp.org/publications.html.
[12] Available at: www.chbrp.org/publications.html.
[13] CHBRP's document *Health Insurance Benefit Mandates in California State Law* lists the federal benefit mandates currently known to CHBRP, and is available at:www.chbrp.org/publications.html.
[14] Affordable Care Act Section 1001, modifying Section 2713(a) of the Public Health Service Act
[15] A list of the immunizations recommended by the CDC ACIP is available here: www.cdc.gov/vaccines/pubs/ACIP-list.htm.

preventive service will be required but only after an interval of not less than one year after the CDC ACIP makes a recommendation.[16] This federal benefit mandate will be a focus of this issue brief.

Essential Health Benefits and Their Interaction with State and Federal Benefit Mandates

Starting in 2014, health insurance plans or policies within a state's exchange and many outside a state's exchange are required by the ACA to cover EHBs. The ACA will require nongrandfathered[17] small-group and individual market plans and policies—including but not limited to QHPs sold through an exchange—to cover EHBs. Most QHPs in California (like the rest of California's small-group and individual market plans and policies) will be regulated by DMHC or CDI. Therefore, each QHP will be subject either to the set of state benefit mandates enforced by DMHC or to the set enforced by CDI. In 2014, QHPs subject to both state and federal benefit mandates must meet the most demanding requirement. However, the ACA requires the state to defray the costs of requiring QHPs to provide coverage that exceeds EHBs.[18,19] The U.S. Department of Health and Human Services (HHS) has not yet offered guidance on how such cost calculations would be made.

The ACA offers a list of 10 categories that broadly define EHBs.[20] To further define EHBs for 2014 and 2015, HHS has proposed that each state select a benchmark plan (CCIIO, 2011). HHS has suggested that a benchmark plan subject to state benefit mandates would, in effect, make the state benefit mandates fall "within" EHBs and so not exceed them. Based on the options provided by HHS, the chosen benchmark plan may be *subject to* or *not subject to* state and/or federal benefit mandates.[21] HHS guidance offers four sets of choices for defining EHBs:

- The largest plan by enrollment in any of the three largest *small-group insurance products* in the state's small-group market, which would be subject to either DMHC-enforced benefit mandates or CDI-enforced benefit mandates;
- Any of the largest three *state employee health benefit plans* by enrollment, which could be a DMHC-regulated California Public Employees' Retirement System (CalPERS) Health

[16] Affordable Care Act Section 1001, modifying Section 2713(b) of the PHSA

[17] A grandfathered health plan is defined as "A group health plan that was created—or an individual health insurance policy that was purchased—on or before March 23, 2010. Grandfathered plans are exempted from many changes required under the Affordable Care Act. Plans or policies may lose their 'grandfathered' status if they make certain significant changes that reduce benefits or increase costs to consumers" (www.healthcare.gov/glossary/g/grandfathered-health.html).

[18] Affordable Care Act Section 1311(d)(3)(B)

[19] It is important to note that the state may place additional requirements on plans and policies in California outside of mandated benefit laws. For example, through a combination of law and regulation, DMHC-regulated plans regulated are required to cover a set of "minimum benefits" or "basic health care services." This set of requirements is broad enough to interact with many benefit mandate laws.

[20] The list of 10 categories as defined in Section 1302(b) of the ACA includes: (1) Ambulatory patient services; (2) Emergency services; (3) Hospitalization; (4) Maternity and newborn care; (5) Mental health and substance use disorder services, including behavioral health treatment; (6) Prescription drugs; (7) Rehabilitative and habilitative services and devices; (8) Laboratory services; (9) Preventive and wellness services and chronic disease management; and (10) Pediatric services, including oral and vision care.

[21] All states have benchmark plan options that include plans *subject to* and plans *not subject to* the state's benefit mandates. Health insurance plans *not subject* to a state's state benefit mandates include all self-insured plans and polices, which are subject only to federal law.

Maintenance Organization (HMO) plan subject to DMHC-enforced benefit mandates or a CalPERS Preferred Provider Plan (PPO) subject only to federal benefit mandates;

- Any of the largest three national *Federal Employee Health Benefits Plan (FEHBP)* options by enrollment, most of which are subject only to federal benefit mandates; or
- The *largest insured commercial non-Medicaid HMO* operating in the state, which is likely a DMHC-regulated plan subject to DMHC-enforced benefit mandates.

A chosen benchmark plan could include no state benefit mandates or could include some but not all of a state's benefit mandates. If a state chooses a benchmark plan *not subject* to state benefit mandates, state benefit mandates could require QHPs (and other small-group and individual market plans) to exceed EHBs. If a state chooses a benchmark plan *subject* to most of the state's benefit mandates, benefit mandate laws may address only some markets (e.g., the individual but not the small-group market), so some plans and policies might still be subject to state benefit mandates that exceed EHBs. Table 1 identifies California's options and highlights what benefit mandates would be included in each option.

In California, the state's bifurcated system of health insurance regulation increases the complexity of possible benchmark plan options. As can be seen in Table 1, the possible benchmark plans in California will all be subject to federal benefit mandates. However, the benchmark plan may also be subject to either DMHC-enforced benefit mandates or CDI-enforced benefit mandates, but not to both. As stated earlier, DMHC-enforced benefit mandates and CDI-enforced benefit mandates are similar but not identical. Therefore, California's benchmark plan options may be subject to the set of state benefit mandates enforced by DMHC, to the set of state benefit mandates enforced by CDI, or to neither. For a more detailed discussion of the possible interactions of benchmark plan options, EHBs, and state benefit mandates, see CHBRP's document *Issue Brief: Interaction between California's State Benefit Mandates and the Affordable Care Act's "Essential Health Benefits*."[22]

Because no benchmark plan has been selected in California yet, this analysis will consider three possible definitions for EHBs as they are likely to be defined by state and federal benefit mandates. This analysis assumes the selected benchmark option will not be a grandfathered plan or policy. For this brief, the important question is whether the chosen benchmark plan would or would not be subject to state benefit mandates that require coverage of immunizations, and how these mandates could interact with the federal benefit mandate requiring coverage of immunizations.

[22] Available at: www.chbrp.org/publications.html.

Table 1. How the Chosen Benchmark Plan Option Will Influence the Definition of Essential Health Benefits in California for 2014 and 2015

Benchmark Plan Option	Essential Health Benefits
Federally regulated plan (a)—benchmark plan options: • State employee health benefits plan—CalPERS PPO • FEHBP	Defined as including: • Benefit coverage required by federal benefit mandates, including required coverage of CDC ACIP-recommended immunizations after an interval of not less than one year
DMHC-regulated plan (a)—benchmark plan options: • Small-group insurance product • State employee health benefits plan—CalPERS HMO • Largest insured commercial non-Medicaid HMO	Defined as including: • Benefit coverage required by federal benefit mandates, including required coverage of CDC ACIP-recommended immunizations after an interval of not less than one year; ***and*** • DMHC-enforced benefit mandates (b)
CDI-regulated policy (a)—benchmark plan options: • Small-group insurance product	Defined as including: • Benefit coverage required by federal benefit mandates, including required coverage of CDC ACIP-recommended immunizations after an interval of not less than one year; ***and*** • CDI-enforced benefit mandates (c)

Source: California Health Benefits Review Program, 2012.
Notes: (a) Assumes a nongrandfathered plan or policy.
(b) DMHC-enforced benefit mandates are in the California Health and Safety Code.
(c) CDI-enforced benefit mandates are in the California Insurance Code.
Key: CalPERS=California Public Employees' Retirement System; CDC ACIP=Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices; CDI=California Department of Insurance; DMHC=Department of Managed Health Care; EHBs=Essential Health Benefits; FEHBP=Federal Employee Health Benefits Plan; HMO=Health Maintenance Organization; and PPO=Preferred Provider Organization.

HOW STATE BENEFIT MANDATES COULD EXCEED ESSENTIAL HEALTH BENEFITS: IMMUNIZATION COVERAGE REQUIREMENTS

Benefit mandates can include numerous test, treatments, and services. Benefit mandates are further complicated by terms and conditions of coverage, including which markets are subject to the benefit mandate and which are excluded, what cost sharing requirements are allowed or not allowed for the benefit mandate, what age range is subject to the benefit mandate, and in what timeframe the benefit mandate is required to be covered. While state benefit mandates could exceed EHBs in the tests, treatments, and services they require, this issue brief focuses on state benefit mandates that could exceed EHBs not in the tests, treatments, or services required, but in the further details of the required terms and conditions of coverage.

How State Benefit Mandated Coverage for Immunizations Could Exceed Essential Health Benefits

The ACA requires coverage for preventive services, including coverage of CDC ACIP-recommended immunizations after an interval of not less than one year.[23] EHBs, as defined by a nongrandfathered plan or policy, regardless of the benchmark plan selected, will include this federal benefit mandate for immunizations coverage. Both DMHC and CDI have benefit mandates that require coverage of immunizations as well, but they are not identical in the coverage they require, both when compared to each other and when compared to the federal benefit mandate requirement.

For DMHC-regulated plans, the Health and Safety Code (H&SC) requires coverage of CDC ACIP-recommended immunizations for children aged 16 years and younger, and requires plans to offer to cover CDC ACIP-recommended immunizations for children aged 17 and 18 years.[24] Further, DMHC requires coverage of "basic health care services," which includes coverage of childhood and adult immunizations.[25] Therefore, all enrollees in DMHC-regulated plans, regardless of age, have coverage for CDC ACIP-recommended immunizations from the time CDC ACIP makes its recommendation. These H&SC regulations are in Appendix A.

CDI-regulated policies are not required to cover basic health care services, but the California Insurance Code (IC) requires policies to cover CDC ACIP-recommended immunizations for children aged 16 years and younger, and requires plans to offer to cover CDC ACIP-recommend immunizations for children aged 17 and 18 years.[26] Therefore, enrollees in CDI-regulated policies aged 16 years and younger have coverage for CDC ACIP-recommended immunizations from the time CDC ACIP makes its recommendation, and for enrollees aged 17 and 18 years

[23] Affordable Care Act Section 1001, modifying Section 2713 of the Public Health Service Act
[24] Health and Safety Code Sections 1367.35 and 1367.3
[25] Basic health care services includes a preventive health services category that requires coverage of childhood and adult immunizations [Health and Safety Code Section 1345(b)]. Basic health care services are not "traditional" benefit mandate laws. However, DMHC-regulated plans are required to cover this set of "minimum benefits." As the state is required to defray the costs of requiring benefit coverage in "excess" of EHBs, this brief assumes the state would need to defray the costs of requiring coverage for basic health care services.
[26] California Insurance Code 10123.5 and 10123.55

coverage is required to be offered from the time CDC ACIP makes its recommendation.[27] These IC regulations are in Appendix A.

State benefit mandates require coverage of CDC ACIP-recommended vaccines from the time the recommendation is made, whereas the federal benefit mandate requires coverage after an interval of not less than one year following the recommendation. As discussed in the bullets below and illustrated in Table 2, depending on the benchmark plan, this time difference in when coverage is required could result in cases where state benefit mandates could exceed EHBs for the first year following a newly recommended immunization.

- If EHBs were defined by a benchmark plan subject to federal benefit mandates only, if a QHP were a DMHC-regulated plan or a CDI-regulated policy, as is likely to be the case, the state would be expected to defray the cost of requiring immunization coverage in the first year following a CDC ACIP recommendation.
- If the EHBs were defined by a CDI-regulated policy, a DMHC-regulated QHP would exceed the EHBs for a specific population—those aged 19 years and older—and the state would be expected to defray the cost of requiring coverage in the first year following a CDC ACIP recommendation for this group of enrollees.
- If EHBs were defined by a DMHC-regulated plan, no state immunization benefit mandates would exceed EHBs.

While California has not yet selected a benchmark plan to define EHBs, **to illustrate how state benefit mandates could exceed EHBs, this issue brief will focus on the first possibility where EHBs are defined by a nongrandfathered benchmark plan that is subject to federal regulation and therefore includes only federal benefit mandates and no state benefit mandates**.

[27] For the purposes of this analysis, CHBRP is assuming a requirement to offer coverage is the same as a requirement to cover, and therefore could exceed EHBs.

Table 2. How State Benefit Mandates Could Exceed the Essential Health Benefits in California for 2014 and 2015—Required Coverage for Immunizations

Benchmark Plan Option	Essential Health Benefits	California H&SC 1345(b), 1367.35, and 1367.3 requirements: DMHC-regulated plans must cover CDC ACIP-recommended immunizations for all ages at the time CDC ACIP makes its recommendation	California IC 10123.5 and 10123.55 requirements: CDI-regulated polices must cover, or offer to cover, CDC ACIP-recommended immunizations for enrollees aged 18 and under at the time CDC ACIP makes its recommendation
Federally regulated plan (a)—benchmark plan options: • State employee health benefits plan (CalPERS PPO) • FEHBP	Defined as including: • Benefit coverage required by federal benefit mandates, including required coverage of CDC ACIP-recommended immunizations after an interval of not less than one year	Exceeds EHBs	Exceeds EHBs
DMHC-regulated plan (a)—benchmark plan options: • Small-group insurance product • State employee health benefits plan (CalPERS HMO) • Largest insured commercial non-Medicaid HMO	Defined as including: • Benefit coverage required by federal benefit mandates, including required coverage of CDC ACIP-recommended immunizations after an interval of not less than one year; ***and*** • DMHC-enforced benefit mandates, including basic health care services coverage requirements (b)	Within EHBs	Within EHBs
CDI- regulated policy (a)—benchmark plan options: • Small-group insurance product	Defined as including: • Benefit coverage required by federal benefit mandates, including required coverage of CDC ACIP-recommended immunizations after an interval of not less than one year; ***and*** • CDI-enforced benefit mandates (c)	Exceeds EHBs—for enrollees aged 19 years and older	Within EHBs

Source: California Health Benefits Review Program, 2012.
Notes: (a) Assumes a nongrandfathered plan or policy.
(b) DMHC-enforced benefit mandates are in the California Health and Safety Code (H&SC).
(c) CDI-enforced benefit mandates are in the California Insurance Code (IC).
Key: CalPERS=California Public Employees' Retirement System; CDC ACIP=Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices; CDI=California Department of Insurance; DMHC=Department of Managed Health Care; EHBs=Essential Health Benefits; FEHBP=Federal Employee Health Benefits Plan; H&SC=California Health & Safety Code; HMO=Health Maintenance Organization; IC=California Insurance Code; and PPO=Preferred Provider Organization.

Evidence-Based Analysis: Quadrivalent Human Papillomavirus Vaccine

If EHBs were defined by a nongrandfathered benchmark plan that is subject to federal benefit mandates only, including required coverage of CDC ACIP-recommended immunizations after an interval of not less than one year, QHPs subject to either DMHC- or CDI-enforced state benefit mandate coverage requirements could exceed EHBs in the first year after an immunization is recommended by CDC ACIP.

In 2007, and again in 2009, CHBRP was asked to analyze bills requiring coverage for human papillomavirus (HPV) vaccines.[28] CHBRP is using findings from these previous reports to present a *hypothetical scenario* of what could happen if a new vaccine were to be recommended by CDC ACIP. Specifically, **this analysis presents the hypothetical scenario of the Gardasil quadrivalent HPV vaccine (quadrivalent vaccine), as initially recommended by CDC ACIP in 2007, being recommended as a new vaccine in 2012**.

In 2007, CDC ACIP recommended the quadrivalent vaccine for females aged 11 to 12 years, with catch-up vaccinations recommended for females aged 13 to 26 years (Markowitz et al., 2007). CHBRP is aware that several changes have taken place since CDC ACIP's initial recommendation of the quadrivalent vaccine. Since 2007, a second HPV vaccine has been approved by the U.S. Food and Drug Administration and recommended by CDC ACIP. Additionally, CDC ACIP recommended that males aged 11 to 26 years receive the quadrivalent vaccine. While CHBRP acknowledges these changes, CHBPR is only using CDC ACIP's first recommendation in 2007 of the quadrivalent vaccine as a hypothetical example for this analysis. Table 3 presents the benefit mandate coverage requirements for DMHC, CDI, and on the federal level for immunizations, as well as specifically for the quadrivalent vaccine as first recommended by CDC ACIP.

Although it is not clear as of now what portion of enrollees in the small-group and individual markets in 2012 will be in QHPs in 2014, using the hypothetical scenario of the quadrivalent vaccine being recommended as a new vaccine in 2012, the following pages of this issue brief explore the evidence on medical effectiveness, as well as the 2012 cost, utilization, and public health impacts associated with immediate coverage of the quadrivalent vaccine. Important to note, the medical effectiveness as well as the cost and public health impacts to California in the first 12 months following a CDC ACIP recommendation of a new vaccine may be dramatically different from those presented here depending on the target disease/condition and the characteristics of the new vaccine (e.g., vaccine efficacy, target population). However, **CHBRP hopes this brief will provide an example of how evidence-based analysis may inform discussions of whether to keep or repeal state benefit mandates that exceed EHBs**.

[28] These two CHBRP reports on the human papillomavirus vaccination, Assembly Bill 1429 (2007) and Senate Bill 158 (2009), are available at: www.chbrp.org/docs/index.php?action=view.

Table 3. State and Federal Benefit Mandate Required Coverage for CDC ACIP Recommended Vaccines and for the Initial CDC ACIP Recommendation for the Quadrivalent Human Papillomavirus Vaccine

California Required Coverage for Immunizations				Federal Required Coverage for Immunizations: ACA Section 1001 modifying Section 2713 of the PHSA	
DMHC-Regulated Plans		CDI-Regulated Policies			
Required Coverage for CDC ACIP-Recommended Vaccines	**Required Coverage for the Quadrivalent HPV Vaccine (a)**	**Required Coverage for CDC ACIP-Recommended Vaccines**	**Required Coverage for the Quadrivalent HPV Vaccine (a)**	**Required Coverage for CDC ACIP-Recommended Vaccines**	**Required Coverage for the Quadrivalent HPV Vaccine (a)**
• Required to cover from time of CDC ACIP recommendation, all ages (b)	• Required to cover from time of CDC ACIP recommendation, aged 11-26 years	• Required to cover from time of CDC ACIP recommendation, aged 0-16 years (c) • Required to offer from time of CDC ACIP recommendation, aged 17-18 years (d)	• Required to cover from time of CDC ACIP recommendation, aged 0-16 years • Required to offer from time of CDC ACIP recommendation, aged 17-18 years	• Required to cover after an interval of not less than 1 year from time of the CDC ACIP recommendation, all ages	• Required to cover after a minimum interval of 1 year from time of CDC ACIP recommendation, aged 11-26 years

Source: California Health Benefits Review Program, 2012.
Notes: (a) This analysis reflects the initial CDC ACIP recommendation for the quadrivalent vaccine in 2007, and not future recommendations made in regards to HPV vaccination.
(b) California Health and Safety Code Section 1345(b), 1367.35, and 1367.3.
(c) California Insurance Code Section 10123.5.
(d) California Insurance Code Section 10123.55. For the purposes of this analysis, CHBRP is assuming a requirement to offer coverage is the same as a requirement to cover, and therefore a requirement to offer coverage can exceed EHBs.
Key: ACA=Affordable Care Act; CDC ACIP=Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices; CDI=California Department of Insurance; DMHC=Department of Managed Health Care; HPV=Human Papillomavirus; and PHSA=Public Health Service Act.

BACKGROUND ON HUMAN PAPILLOMAVIRUS AND RELATED MORBIDITY AND MORTALITY

Natural Course of Human Papillomavirus Infection

There are more than 100 types of HPV, of which 40 are known to infect the anogenital epithelium (e.g., the surface tissue of the anogenital tracts) (Sheinfeld-Gorin et al., 2011). Exposure to these 40 HPV types usually results from sexual contact with an infected partner. The virus infects cervical and other cells inciting an immune response. Most of these HPV infections are asymptomatic transient infections that resolve naturally and do not affect health (CDC, 2012). However, some HPV infections persist and can lead to anogenital warts, precancerous cervical lesions, and various cancers, including invasive cervical cancer (CDC, 2012).

Human Papillomavirus Infection Prevalence and Incidence

HPV is the most prevalent sexually transmitted infection in the U.S. (Weinstock et al., 2004). It is estimated that about 80% of sexually active females will acquire anogenital HPV infection during their lifetime, and more than 50% of adolescents will acquire HPV within two years of becoming sexually active (Rambout et al., 2007). The CDC reports that the prevalence of high-risk HPV (e.g., involving carcinogenic types) in adolescents aged 14 to 19 years was 35% and in persons aged 20 to 29 years was 29% (CDC, 2011) based on sentinel surveillance for cervical infection in 26 clinics around the U.S. (2003-2005). A U.S. population-based survey showed the prevalence of high-risk HPV (e.g, involving carcinogenic types) was about 25% in females aged 14 to 19 years and 43% for those aged 20 to 24 years; prevalence for low-risk HPV (e.g., involving noncarcinogenic types) was about 22% and 37%, respectively (CDC, 2011). Estimates of HPV prevalence and incidence differ by geographic region, age group, and frequency of sexual activity (including number of partners). About 90% of anogenital HPV infections resolve naturally within two years (CDC, 2012).

Health Consequences of Human Papillomavirus Infection

Anogenital Warts

Anogenital warts related to low-risk HPV serotypes may appear within weeks, months, or not at all following exposure (CHBRP, 2009). The CDC estimates that about 10% of persons with HPV infection develop warts, and about 1% of sexually active persons have genital warts at any one time (CDC, 2011). HPV types 6 and 11 are responsible for about 90% of anogenital warts (CDC, 2011). Another study, based on a national health survey, reported that 7.2% of sexually active females aged 18 to 59 years reported ever being diagnosed with genital warts between 1999-2004 (Dinh et al., 2008).

Cancers and Precancerous Lesions

Certain HPV types are associated with development of cancer, the most common of which is cervical cancer, although carcinogenic HPV types are also associated with anal, vulvar, vaginal, and penile cancers and with approximately 25% of head and neck cancers (Sheinfield-Gorin et al., 2011). HPV types 16 and 18 are responsible for approximately 70% of cervical cancers and 25% to 60% of precancerous cervical lesions (known as cervical intraepithelial neoplasia [CIN]) (ACS, 2008) (Table 4). CIN is often initially detected by the Papanicolaou (“Pap”) test.

Abnormalities of cervical cells may indicate the presence of CIN, which is confirmed with cervical biopsy and graded 1, 2, or 3, indicating progressive severity of the abnormalities. CIN 3 and adenocarcimona *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.

Table 4. U.S. and California Health Burden Attributable to the Human Papillomavirus

Condition	HPV Types	Percentage of Cases Due to Specified HPV Types	Health Burden		
			Occurrence (U.S. or California as specified)	**California Cancer Incidence** (f) (cases per 100,000)	**California Cancer Mortality** (f) (cases per 100,000)
Anogenital warts	Types 6 and 11	90% (b)	Approximately 10% lifetime risk (U.S.) (c)	--	--
CIN 1 (a)	Types 6 and 11 Types 16 and 18	5% 25% (b)	Common (U.S.)	--	--
CIN 2 and 3 (a)	Types 16 and 18	52% (d)	Annual incidence 1.5% (e) (U.S.)	--	--
Cervical cancer	Types 16 and 18	70% (b)	1,503 new cases and 440 deaths in California annually (f)	8.3	2.4
Anal cancer	Types 16 and 18	80% to 90% (b)	1055 new cases and 96 deaths in California annually (f)	3.0	0.3
Vaginal, urethral, vulvar, head, and neck cancers	Multiple types	Varying percentage (b)	--	Varying rates	Varying rates

Source: California Health Benefits Review Program, 2012.
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 considered precancerous, some of which may lead to cervical cancer.
(b) Markowitz et al., 2007.
(c) CDC, 2011
(d) Clifford et al., 2003.
(e) Insinga et al., 2004.
(f) CCR, 2011
Key: CIN=cervical intraepithelial neoplasia; and HPV=human papillomavirus.

Racial/Ethnic Disparities in Human Papillomvirus Infection, Cervical Disease, and Vaccination

Human Papillomavirus Infection: U.S.

Nationally, black females are more likely to have HPV infection compared to white females (Burk et al., 1996; Shields et al., 2004; Stone et al., 2002). Other estimates of HPV prevalence in

the U.S. among females aged 14 to 59 years 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, Prevalence, and Mortality: California

In California, Hispanic females have the highest incidence and mortality rates of cervical cancer as compared with non-Hispanics (Table 5). California's experience is similar to national rates where Hispanic females have been found to have higher incidence and prevalence rates of cervical cancer (Napoles-Springer et al., 1996) and lower survival rates (Howell et al., 1999; Mundt et al., 1998) compared to non-Hispanic whites. Although Asian females in California have the second highest cervical cancer incidence rate, their mortality rates are similar to those of black females (Table 5). White females in California have the lowest incidence and mortality rates of cervical cancer.

Human Papillomavirus Vaccination Rates: California

In 2007, the year of the CDC ACIP recommendation, there were no statistically significant racial/ethnic differences in the rates at which insured females aged 11 to 26 years reported receiving the HPV vaccine (CHIS, 2012) (Table 5). The impact of the vaccine on reducing disparities in HPV-related health outcomes is unknown.

Table 5. California Cervical Cancer: Incidence, Mortality, and Quadrivalent Human Papillomavirus Vaccination Rates

Race/Ethnicity	**Age-Adjusted Incidence Rate** (a) (cases/100,000 females/y)	**Age-Adjusted Death Rate** (a) (cases/100,000 females/y)	**Quadrivalent Vaccination Rate 2007** (b) (%)
All races	8.3	2.4	18.6 (16.5-20.7)
Hispanic	11.6	3.5	14.2 (10.1-18.2)
Non-Hispanic white	6.7	1.9	21.3 (18.0-24.6)
Non-Hispanic black	6.9	2.3	20.1 (11.8-28.5)
Asian	8.2	2.2	18.1 (12.1-24.1)

Source: California Health Benefits Review Program, 2012.
Notes: (a) CCR, 2011. Age-adjusted rates are presented per 100,000 females.
(b) Self-reported vaccination rates come from CHIS, 2007. These rates are for insured females aged 12 to 26 years combined who answered the question "Have you ever received the HPV vaccine or HPV shots?" Uptake rate for insured females of all races varied by age: 25% of those aged 12 to17 years obtained the vaccine and 13% of those aged 18 to 26 years obtained the vaccine.

MEDICAL EFFECTIVENESS

The Medical Effectiveness review describes how the quadrivalent vaccine works, discusses findings from randomized controlled trials (trials) that have been conducted to assess the efficacy of the vaccine for prevention of HPV-associated disease among females, and summarizes information regarding the safety of the vaccine. This analysis focuses on the initial CDC ACIP recommendation in 2007 for vaccination of females. Therefore, while CDC ACIP has since recommended this vaccine for males and has recommended a second vaccine, the bivalent vaccine (Cervarix), these additional CDC ACIP recommendations are not addressed.

Mechanism of Action for the Human Papillomavirus 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 a person is later exposed to the real virus of the same type, the antibodies attack the virus and prevent infection.

The quadrivalent vaccine targets the two types of high-risk HPV that cause 70% of cervical cancers, types 16 and 18, and the two types of high-risk HPV that cause 90% of anogenital warts, types 6 and 11. A full course of the quadrivalent vaccine requires the injection of three 0.5-mL doses of the vaccine intramuscularly over a six-month period. CDC ACIP recommends that the second dose be administered 2 months after the first dose and the third dose 6 months after the first dose.

Research Approach and Methods

Literature Review Methods

The literature search for this issue brief updates a literature search CHBRP performed in 2009. The search yielded a total of 354 citations. Fourteen additional articles pertinent to the medical effectiveness review were identified, retrieved, and reviewed. Findings from these articles were integrated with findings from the seven articles on the efficacy of the quadrivalent vaccine that were included in the literature review CHBRP conducted in 2009. A more thorough description of the methods used to conduct the medical effectiveness review is presented in Appendix B.

Outcomes Associated with Human Papillomavirus Vaccination

Trials of vaccine efficacy typically report the percentage difference in the rates at which events against which the vaccine is expected to provide protection occur in the groups receiving the vaccine and the placebo. The trials reviewed in this report address vaccine-related prevention of short-term outcomes such as antibody development following vaccination, prevention of persistent infection with high-risk HPV types, prevention of anogenital warts, and reductions in precancerous lesions of the cervix, vagina, and vulva, which are known as cervical intraepithelial neoplasia (CIN), cervical adenocarcinoma in situ (AIS), vaginal intraepithelial neoplasia (ValN), and vulvar intraepithelial neoplasia (VIN). These lesions are rated on a scale from 1 to 3. Lesions graded as 3 are the most likely to develop into cervical, vaginal, or vulvar cancer if left untreated. AIS is a precancerous lesion found in the glandular tissue of the cervix. The medical

effectiveness review focuses on the efficacy of the quadrivalent vaccine against CIN 2 and 3, AIS, ValN 2 and 3, and VIN 2 and 3. Documenting prevention of these lesions provides some evidence of protection against later cervical, vaginal, or vulvar cancer because prevention of these precancerous lesions represents an interruption of the path toward development of cancer.

Impact on morbidity and mortality from cervical, vaginal, or vulvar cancer is not discussed because none of the articles included in the review address these outcomes. Effects on these outcomes will not be known for several decades because these forms of cancer develop slowly following infection with high-risk HPV types.

Study Findings

The medical effectiveness review summarizes the final, overall results of five trials of the efficacy of the quadrivalent vaccine. Researchers conducting these trials have generally taken two analytic approaches.

- **"Per-protocol"** analyses examine data for females who completed all three doses of the vaccine and who were negative for HPV 6, 11, 16, and 18—the four types of high-risk HPV associated with cervical, vaginal, and vulvar cancer and anogenital warts that are targeted by the quadrivalent vaccine—prior to administration of the vaccine through one month after the third dose was administered. The advantage of a per-protocol analysis is that it includes only subjects who completed the treatment and were not infected with high-risk types of the HPV virus prior to or at the time of enrollment in a trial. Thus, a per-protocol analysis provides an estimate of the maximum efficacy of the quadrivalent vaccine. The disadvantage of a per-protocol analysis is that it overestimates the quadrivalent vaccine's efficacy because they only assess the vaccine's impact on a subset of the females enrolled in the trials.
- **"Intention-to-treat"** analyses examine data for all females regardless of their HPV status at any time during the trial and whether or not they received all three doses of the vaccine. The advantage of an intention-to-treat analysis is that it provides estimates of efficacy for all females enrolled in the trials. The disadvantage of an intention-to-treat analysis is that it underestimates the maximum efficacy of the treatment because it includes persons who did not complete the treatment and persons who previously contracted high-risk HPV types. Intention-to-treat is considered the most appropriate analysis for assessing the likely impact of the quadrivalent vaccine on the population of females for which it is recommended.

Researchers have also published findings from additional sub-group analyses that assessed efficacy for females who resided in a subset of the countries in which the trials were conducted or who had a particular HPV status.[29]

[29] Four articles have been published that summarize findings for females age 15 to 26 years who were enrolled in Phase 2 and Phase 3 trials who reside in specific subsets of the nations in which the trials were conducted (Lazcano-Ponce et al.,2009; Majewski et al., 2009; Perez et al., 2008; Tay et al., 2008). Researchers also published findings from some of these clinical trials for "modified intent-to-treat" populations. Four articles reported findings for females who were not infected with high-risk HPV types prior to enrollment in the trial and who received one or more doses of the vaccine (Brown et al., 2009; Castellsagué et al., 2011; Muñoz, et al., 2010; Villa et al., 2006). Haupt and colleagues (2011) reported findings for females who were infected with HPV 16 or 18 at the time of enrollment in the trials. Olsson and colleagues (2009) presented findings for females for whom there was evidence of prior infection with a high-risk HPV type but whose infection had cleared by the time they enrolled in the trials.

Table C-1 in Appendix C presents major findings from the Phase 2 and Phase 3 clinical trials of the quadrivalent vaccine from both per-protocol and intention-to-treat analyses. The paragraphs below summarize findings from intention-to-treat analyses because they are the most generalizable to the general population of females for whom the vaccine is recommended.

Findings for Females Aged 9 to 15 Years

To date only one trial published in a peer-reviewed journal has assessed the efficacy and safety of the quadrivalent vaccine among females aged 15 years and younger (Reisinger et al., 2007). This trial enrolled females aged 9 to 15 years who were not sexually active.[30] The only outcome assessed was the vaccine's effect on the body's ability to produce antibodies to prevent infection with high-risk HPV for one year after receipt of the third and final dose of the vaccine. The authors reported seroconversion rates (e.g., rates at which antibodies to HPV are detected in a person's blood) separately for the four types of high-risk HPV against which the quadrivalent vaccine offers protection. The seroconversion rates for females 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 females enrolled in the trial.

Findings for Females Aged 15 to 26 Years

Researchers have published findings from pooled analyses of the end-of-trial results from three trials of the efficacy of the quadrivalent vaccine against among females aged 15 to 26 years for:

- High-risk HPV types the vaccine targets (HPV Types 6, 11, 16, and 18);
- High-risk HPV types not targeted by the vaccine (HPV Types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59); and
- All high-risk HPV types.

The mean length of follow-up post vaccination was 3.5 years. Findings for the high-risk HPV types the vaccine targets indicate how well the vaccine prevents the infections it is intended to prevent. Findings for all high-risk HPV types provide the best estimates of overall protection against infection with high-risk HPV, which are important for assessing whether females who are vaccinated should continue to be screened for cervical cancer.

HPV Types 6, 11, 16, and 18

Kjaer and colleagues (2009) published a pooled analysis of final, end-of-trial results for three trials of the quadrivalent vaccine that enrolled females aged 15 to 26 years.[31] The intention-to-treat analysis found that for disease associated with high-risk HPV types 6, 11, 16, and 18, the

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Joura and colleagues (2012) reported findings for females who had an excisional procedure for precancerous cervical lesions or were diagnosed with genital warts, precancerous vaginal lesions, or precancerous vulvar lesions during the trial.

[30] This trial also enrolled males aged 9 to 15 years but CHBRP only reviewed findings for females because the CDC ACIP initially recommended that the quadrivalent vaccine be administered only to females

[31] Final results of the Phase 2 trial were reported by Villa and colleagues (2006). Interim results of the Phase 3 trials were reported by Garland and colleagues (2007) and the FUTURE II Study Group (2007). These results are discussed in detail in CHBRP's report on SB 158 (CHBRP, 2009).

efficacy of the vaccine against CIN 2, CIN 3, and AIS combined was 51.5% (95% CI, 40.6% to 60.6%). This means that females who received the quadrivalent vaccine were approximately half as likely to be diagnosed with CIN 2, CIN 3, or AIS associated with these high-risk HPV types as females who received the placebo.[32] The authors also reported that females in the intervention group who were vaccinated at a younger age were less likely to develop CIN 2, CIN 3, or AIS.

Consistent with findings for cervical lesions, the intention-to-treat analyses found that the quadrivalent vaccine provides protection against precancerous vaginal lesions, vulvar lesions, and anogenital warts associated with high-risk HPV types 6, 11, 16, and 18 (Kjaer et al., 2009). The efficacy of the vaccine against ValN 2 and 3 and VIN 2 and 3 associated with these high-risk HPV types was 79.0% (95% CI, 56.4% to 91.0%).

HPV Types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59

Wheeler and colleagues (2009) assessed the efficacy of the quadrivalent vaccine against infection with 10 high-risk HPV types that can cause cervical cancer but which the quadrivalent vaccine does not target (e.g., HPV types 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59). Such findings are important because HPV types 16 and 18 cause only 70% of cervical cancers; the other 30% of cervical cancers are caused by other high-risk HPV types. The intention-to-treat analysis found no statistically significant difference between females who received the quadrivalent vaccine and the placebo in the rate of CIN 2, CIN 3, and AIS combined associated with the HPV types assessed in this study. In other words, females who received the quadrivalent vaccine were no less likely to be diagnosed with CIN 2, CIN 3, or AIS associated with the high-risk HPV types not targeted by the quadrivalent vaccine than females who received the placebo.

All HPV Types

Muñoz and colleagues (2010) reported findings regarding the efficacy of the quadrivalent vaccine against infection with any high-risk HPV type. These analyses provide the best overall estimates of the protection the quadrivalent vaccine provides to the general population of females against conditions caused by high-risk HPV types. The intention-to-treat analyses found that the quadrivalent vaccine had an efficacy of rate of 19.0% (95% CI, 7.7% to 28.9%) against CIN 2, CIN 3, and AIS combined.[33] The efficacy rate for VaIN 2 and 3 or VIN 2 and 3 was 50.7% (95% CI, 22.5% to 69.3%).

[32] The efficacy rates for CIN 2 and CIN 3 individually were 55.7% and 45.1%, respectively, and were statistically significant. The efficacy rate for AIS was not statistically significant due to the small number of cases (n = 6 in the intervention group and n = 15 in the control groups) (Kjaer et al., 2009).

[33] The efficacy rates for CIN 2 and CIN 3 individually were 19.3% and 16.4%, respectively, and were statistically significant. The efficacy rate for AIS was not statistically significant due to the small number of cases (n = 6 in the intervention group and n = 16 in the control groups) (Muñoz et al, 2010).

Collectively, findings from the three trials that enrolled females aged 15 to 26 years suggest that the quadrivalent vaccine provides some protection against CIN 2, CIN 3, AIS, ValN 2, ValN 3, VIN 2, and VIN 3 but is not 100% effective. The vaccine only provides protection against the four high-risk HPV types it targets and does not prevent high-grade precancerous lesions associated with other high-risk HPV types. Efficacy is lower in the general population of females in this age group than among those who were not infected with high-risk HPV prior to vaccination. This finding suggests that the quadrivalent vaccine is likely to provide the greatest benefit when administered prior to onset of sexual activity.

Findings for Females Aged 24 to 45 Years

One trial has examined the efficacy of the quadrivalent vaccine among females aged 24 to 45 years (Castellsagué et al., 2011; Muñoz et al, 2009). This trial enrolled 3,819 females with no history of cervical disease, genital warts, HIV, or other conditions that suppress the immune system and who were not pregnant at the time of enrollment. Females were monitored for an average of four years following vaccination. Neither the intention-to-treat nor the per-protocol analyses found a statistically significant difference in the rate of CIN 2, CIN 3, and AIS combined associated with the four high-risk HPV types toward which the vaccine is targeted (Castellsagué et al., 2011). Efficacy against other high-risk HPV types was not reported.

Side Effects and Safety

In its recommendation statement regarding use of the quadrivalent vaccine among females, the CDC ACIP cited findings regarding side effects and safety from the FDA's package insert for the vaccine (Markowitz et al., 2007). These findings were based on detailed safety data on females aged 9 to 23 years enrolled in five trials of the vaccine. Two subsequent articles reported end-of-trial data from these trials on side effects and safety of the quadrivalent vaccine. Block and colleagues (2010) reported that the most common side effects were pain (81%), swelling (24%), and rash (24%). There were no statistically significant differences in serious, systemic adverse events between females who received the quadrivalent vaccine and females who received the placebo. The researchers who conducted the trials determined that six serious systemic adverse events that occurred among 5 of the 11,778 females who received the quadrivalent vaccine were related to the vaccine. These conditions were recurrent vaginal hemorrhage, bronchospasm, gastroenteritis, ulcerative colitis, and a combination of hypertension and headache. One female who received the quadrivalent vaccine experienced joint movement impairment and pain that lasted for five months post vaccination. In both the vaccine and placebo groups, 2% of subjects experienced conditions that could indicate an autoimmune condition. The researchers determined that none of the 18 deaths that occurred among trial participants were related to participation in the trials. Garland and colleagues (2009) summarized end-of-trial data on pregnancy outcomes. They found that no statistically significant difference in rates of live births, fetal death, miscarriage, and congenital abnormalities between females who received the vaccine and females who received the placebo.

Two studies have reported findings from the CDC's Vaccine Adverse Events Reporting System (VAERS) regarding side effects and safety of the quadrivalent vaccine (Slade et al., 2009; Souayah et al., 2010). Findings from VAERS are especially important because this surveillance system captures information on adverse events experienced by all persons in the U.S. who

receive the quadrivalent vaccine, which can facilitate detection of rare but serious adverse events. The VAERS data are likely lower bound estimates of the prevalence of adverse events associated with the quadrivalent vaccine because reporting is voluntary.

Slade and colleagues (2009) reported findings from VAERS for the first 2.5 years after the FDA approved the quadrivalent vaccine (June 2006 through December 2008). The vaccine's manufacturer reported that 23 million doses of the quadrivalent vaccine were distributed in the U.S. during this time period. According to the authors, there were 12,424 reports of adverse events. The most common adverse events were fainting (1,896 cases), local site reaction (1,741 cases), dizziness (1,572 cases), nausea (1,164 cases), and headache (937 cases). Six percent of adverse events (772 cases) were considered serious. The most common adverse events classified as serious[34] were headache (150 cases), nausea (119 cases), dizziness (96 cases), and fainting (93 cases). Souayah and colleagues (2010) analyzed findings from VAERS regarding incidence of Guillain-Barré Syndrome between June 2006 and September 2009. The authors found that 34 persons developed Guillain-Barré Syndrome within six weeks of vaccination, the generally accepted interval for determining whether a case of Guillain-Barré Syndrome is associated with vaccination. The average weekly reporting of Guillain-Barré Syndrome within six weeks of vaccination was higher for the quadrivalent vaccine than for the influenza vaccine and the meningococcal vaccine.

Medical Effectiveness Conclusions

There is clear and convincing evidence from trials of the quadrivalent vaccine that, when all three doses of the quadrivalent vaccine are given to previously uninfected females under ideal conditions, the vaccine yields antibody production and provides 90% to 100% protection against CIN 2 and 3, AIS, ValN 2 and 3, and VIN 2 and 3 due to HPV types 6, 11, 16, and 18 for up to five years following vaccination. Because infection with high-risk HPV is a necessary step in the path to cervical, vaginal, and, vulvar cancer (although most infections with high-risk HPV types do not proceed to cancer), it is assumed that prevention of infection with high-risk HPV types would reduce cancer incidence. However, this reduction will not be evident for several decades because of the long latency between infection and cervical, vaginal, and vulvar cancer. In addition, the duration of immunity beyond five years post immunization is unknown.

The best performance of the quadrivalent vaccine is limited to the high-risk HPV types targeted by the vaccine and to a select group of females who had no prior evidence of high-risk HPV infection and were compliant with the vaccination regimen. Efficacy is lower among females infected with high-risk HPV prior to vaccination. In addition, high-risk HPV types not included in the vaccine will continue to cause CIN 2 and 3, AIS, ValN 2 and 3, and VIN 2 and 3 that, if untreated, could develop into cervical, vaginal, or vulvar cancer.

All organizations that have issued recommendations for use of the quadrivalent vaccine also recommend that females and their health care providers continue to follow current cervical

[34] The authors' used criteria set forth in FDA regulations to classify adverse events as "serious." An adverse event was considered serious if it was life threatening; resulted in death, permanent disability, congenital anomaly, hospitalization, or prolonged hospitalization; or medical or surgical intervention was needed to preclude one of these outcomes (Slade et al., 2009, pg. 751).

cancer screening guidelines, including the Pap test (AAFP, 2012a; AAFP, 2012b; AAP, 2012; ACOG, 2006; Markowitz et al., 2007; SAHM, 2011; Saslow et al., 2007). There is strong evidence that performing cervical cancer screening at recommended intervals and treating high-grade cervical lesions can prevent morbidity and mortality from cervical cancer (Vesco et al., 2011).

BENEFIT COVERAGE, UTILIZATION, AND COST IMPACTS

As discussed in the *How State Benefit Mandates Could Exceed Essential Health Benefits* section, CHBRP is presenting the hypothetical scenario of the quadrivalent vaccine being recommended as a new vaccine in 2012 to show how California benefit mandate coverage requirements for immunizations could exceed EHBs in the first year following a CDC ACIP recommendation of a new vaccine. If EHBs were defined as including only federal benefit mandates, which require coverage for CDC ACIP-recommended vaccines after an interval of not less than one year as opposed to immediately, current California state benefit mandates could exceed EHBs. The state would be required to defray the costs of "excess" coverage for QHPs sold in the Exchange.

This section will present, first, estimates of the benefit coverage, utilization, and costs across all markets (large-group, small-group, and individual) for privately purchased health insurance were the quadrivalent vaccine to be recommended as a new vaccine in 2012. This section will then specifically look at the benefit coverage, utilization, and costs in the small-group and individual market where California requirements for coverage of immunizations could exceed EHBs. This analysis looks at California's health insurance market in 2012 in order to give a sense of how these current state benefit mandates could exceed EHBs in 2014, acknowledging that the health insurance market in 2014 may look dramatically different than the health insurance market in 2012.

For this analysis, CHBRP is using CDC ACIP's initial recommendation of the quadrivalent vaccine—coverage for females aged 11 to 26 years (Markowitz et al., 2007). CHBRP assumes that CDC ACIP recommended the quadrivalent vaccine on January 1, 2012, that all DMHC-regulated plans would have to cover it immediately for all enrollees, and that all CDI-regulated policies would have to cover it immediately for enrollees aged 18 years and younger. The cost analysis provides the resulting increase in 2012 premiums by estimating the utilization rate for females in plans and policies with required coverage for the quadrivalent vaccine and the average cost per vaccination.

- **Utilization estimates**: The hypothetical 2012 quadrivalent vaccine utilization rates among females with coverage for the vaccine were based on the observed utilization rates in 2007, the first year the vaccine was recommended. Vaccine utilization rates from the 2007 California Health Interview Survey (CHIS) indicated 25% of females aged 12 to 17 years and 13% of females aged 18 to 26 years obtained one or more doses of the quadrivalent vaccine in 2007 (CHIS, 2007). For this analysis, CHBRP made the assumption that females who obtained one or more doses of the quadrivalent vaccine received all three. However, not all enrollees complete the three-dose series. Therefore the utilization estimates are upper bound estimates of treatment adherence compliance.
- **Cost estimates**: The average cost per vaccination was estimated based on 2012 cost levels. For large-group plans and policies, employers and their employees would pay for the additional premium costs. The additional premium for small-group and individual plans and policies, however, would be the responsibility of the state, since coverage of the quadrivalent vaccine would not be included in the EHBs until after an interval of not less than one year.

For further details on the underlying data sources and methods, please see Appendix D at the end of this document.

Benefit Coverage, Utilization, and Cost for Privately Purchased Health Insurance, 2012

Coverage of the Quadrivalent Vaccine

In 2012, approximately 16.4 million Californians have privately purchased health insurance regulated by DMHC or CDI, and therefore subject to state benefit mandates (Table 6). Coverage of the quadrivalent vaccine was assumed to be 100% for all privately purchased DMHC-regulated plans in the large-group, small-group, and individual markets, as required by current California state law. Current California state law requires CDI-regulated policies in the large-group, small-group, and individual markets to provide immunizations coverage for enrollees aged 18 years and younger.[35] Therefore, coverage of the quadrivalent vaccine for enrollees in privately purchased CDI-regulated policies aged 19 to 26 years was assumed to be 0%.

Utilization Levels for the Quadrivalent Vaccine

Were the quadrivalent vaccine to be recommended as a new vaccine in 2012, CHBRP estimates that approximately 2.1 million females aged 11 to 26 years with privately purchased health insurance in the large-group, small-group, and individual markets would have required coverage for the quadrivalent vaccine. CHBRP estimates that 321,245 females aged 11 to 18 years would receive the quadrivalent vaccine, and, assuming completion of the three-dose series, a total of 963,734 doses would be dispensed to this population. CHBRP estimates that 100,721 females aged 19 to 26 years would receive the quadrivalent vaccine, and, assuming completion of the three-dose series, a total of 302,164 doses would be dispensed to this population (Table 6).

Per-Unit Cost

The average per-unit cost for the full three-dose quadrivalent vaccine series, including both the cost of the vaccine and the estimated professional cost of vaccination administration, is $479, according to 2011 Medispan data.[36]

Required Immunization Coverage that Could Exceed Essential Health Benefits

Of the approximately 16.4 million Californians with privately purchased health insurance in California, 5.5 million have privately purchased health insurance in the small-group and individual markets. Small-group and individual market plans and policies will be required to cover EHBs, so state benefit mandates could exceed EHBs for these two markets.

Of the 16.4 million Californians with privately purchased health insurance, there are approximately 2.1 million female enrollees aged 11 to 26 years with required coverage for the

[35] CDI-regulated policies are required to cover CDC ACIP-recommended immunizations for enrollees aged 16 years and younger, and are required to offer to cover CDC ACIP-recommend immunizations for enrollees aged 17 and 18 years. For the purposes of this analysis, CHBRP is assuming a requirement to offer coverage is the same as a requirement to cover, and therefore could exceed EHBs.

[36] While the CDC ACIP recommendation is one dose at 0, 2, and 6 months, enrollees may receive fewer doses at a lower cost. Thus, the average per-unit cost for the full series represents an upper bound.

quadrivalent vaccine, of which 588,730 are in the small-group and individual markets and so have coverage that could exceed EHBs in this hypothetical scenario (28.5%).

Utilization that Could Exceed Essential Health Benefits

CHBRP estimates that 100,971 females aged 11 to 18 years in the small-group and individual market would receive the quadrivalent vaccine, and, assuming completion of the three-dose series, a total of 302,914 doses would be dispensed to this population. CHBRP estimates that 23,488 females in privately purchased DMHC-regulated plans aged 19 to 26 years would receive the quadrivalent vaccine, and, assuming completion of the three-dose series, a total of 70,464 doses would be dispensed to this population. Therefore:

- Of the 963,734 doses of the quadrivalent vaccine received by females aged 11 to 18 years in privately purchased plans and policies across all health insurance markets, 31.4% would be provided to enrollees in the small-group and individual markets and could exceed EHBs; and
- Of the 302,164 doses of the quadrivalent vaccine received by females aged 19 to 26 years in privately purchased DMHC-regulated plans across all health insurance markets, 23.3% would be provided to enrollees in the small-group and individual markets and could exceed EHBs (Table 6).

CHBRP made the assumption for this analysis that an enrollee that receives at least one dose of the quadrivalent vaccine will receive all three doses. Because the quadrivalent vaccine is administered in three doses over the course of at least six months, not all enrollees will necessarily return to receive all three doses nor will they necessarily receive all three doses in the first year. Therefore, the estimated total number of doses received by utilizing members is an upper bound.

Total Health Care Costs that Could Exceed Essential Health Benefits

Total expenditures in the small-group and individual markets due to required coverage for the quadrivalent vaccine in the first year following a CDC ACIP recommendation would be approximately $74 million (Table 6). This is 0.09% of total statewide costs, including all privately purchased plans and policies across all health insurance markets.

This estimate is an upper bound in terms of what costs the state might be required to defray, both because of the upper bound estimates of treatment adherence completion, as well as because, in 2014, the small-group and individuals markets will be divided, with some portion sold inside the Exchange and some portion sold outside the Exchange. Although plans and policies outside the Exchange will be required to cover EHBs, the state is only required to defray the costs of "excess" coverage for QHPs sold in the Exchange.

Table 6. Privately Purchased Health Insurance: Benefit Coverage, Utilization, and Cost of the Quadrivalent Human Papillomavirus Vaccine, 2012

	Large-Group, Small-Group, and Individual Market (a)	Small-Group and Individual Market (b)	Percent of Privately Purchased Health Insurance Related to Required Benefit Coverage that Could Exceed EHBs (c)
Benefit Coverage			
Total enrollees with privately purchased health insurance	16,400,000	5,473,000	--
Total enrollees with privately purchased health insurance subject to state-level immunization coverage requirements	16,400,000	5,473,000	--
Percentage of enrollees with state-level required coverage for the quadrivalent vaccine			
Females 11-18	100.0%	100.0%	100%
Females 19-26 (d)	79.6%	50.6%	63.6%
Number of enrollees with state-level required coverage for the quadrivalent vaccine			
Females 11-18	1,311,202	412,128	31.4%
Females 19-26 (d)	757,304	176,602	23.3%
Total females 11-26	2,068,507	588,730	28.5%
Utilization			
Number of enrollees receiving the quadrivalent vaccine			
Females 11-18	321,245	100,971	31.4%
Females 19-26 (d)	100,721	23,488	23.3%
Total females 11-26	421,966	124,459	29.5%
Number of doses of vaccine received by enrollees who received the quadrivalent vaccine (e)			
Females 11-18	963,734	302,914	31.4%
Females 19-26 (d)	302,164	70,464	23.3%
Total Females 11-26	1,265,898	373,378	29.5%
Cost			
Average cost for 3-dose quadrivalent vaccine	$479	$479	--
Expenditures			
Premium expenditures by private employers for group insurance	$60,311, 299,000	$37,479,000	0.062%
Premium expenditures for individually purchased insurance	$7,568,369,000	$24,418,000	0.323%
Premium expenditures by persons with privately purchased group insurance (f)	$13,645,816,000	$12,237,000	0.090%
Total Expenditures	$81,531,484,000	$74,134,000	0.091%

Source: California Health Benefits Review Program, 2012

Notes: (a) Excludes enrollees with publicly purchased health insurance (DMHC-regulated plans purchased by CalPERS, MRMIB, or DHCS).
(b) Excludes enrollees with publicly purchased health insurance (DMHC-regulated plans purchased by CalPERS, MRMIB, or DHCS), and excludes all privately purchased large-group market insurance.
(c) The percent of privately purchased coverage benefit, utilization, and cost attributed to the small-group and individual markets that could exceed EHB requirements.
(d) Excludes CDI-regulated policies because current California state law only requires CDI-regulated policies in the large- and small-group and individual markets to provide coverage for enrollees 18 years and younger.
(e) The quadrivalent vaccine is administered in three doses. Not all enrollees complete the recommended three-dose series. However, CHBRP makes the assumption in this analysis that enrollees who obtain the quadrivalent vaccine will receive all three doses. These estimates are upper bound estimates of treatment completion adherence.
(f) Premium expenditures by enrollees include employee contributions to employer-sponsored health insurance.
Key: EHBs=essential health benefits.

PUBLIC HEALTH

This public health impact analysis uses the quadrivalent vaccine as an example of the possible marginal health impacts on Californians for state-required coverage of immunizations up to 12 months earlier than federally required coverage. CHBRP presents an evidence-based public health impact model to which HPV data are applied. The quantitative results presented here will not translate to future vaccines for HPV or other conditions; the costs and public health impacts to California in the first 12 months following a CDC ACIP recommendation for a new vaccine may vary dramatically according to the prevalence and immediacy of the target disease/condition (e.g., cancer prevention vs. flu epidemic) and characteristics of the vaccine itself. However, the general method should prove useful for future vaccines.

This hypothetical scenario serves as an example of an evidence-based approach to assessing the "additional beneficial health outcomes" California "buys" when a state benefit mandate exceeds EHBs.

Public Health Model to Assess Impact of New Vaccine

CHBRP identified the number of insured enrollees in the small-group and individual markets regulated by DMHC and CDI for whom CDC ACIP recommends the quadrivalent vaccine. Using published data on vaccine uptake rates, CHBRP estimated the number of enrollees from this population who would obtain the quadrivalent vaccine in the first year following the CDC ACIP recommendation (thus exceeding the federal coverage mandate). CHBRP then estimated, using published data, the number of cases for three adverse outcomes that would be prevented among those receiving the quadrivalent vaccine. The adverse outcomes addressed are HPV infection, anogenital warts, and CIN2 and 3 lesions.

What Are the Health Impacts of Covering the Quadrivalent Human Papillomavirus Vaccine Immediately Following the CDC ACIP Recommendation?

The quadrivalent vaccine was recommended by CDC ACIP in 2007 for females aged 11 to 26 years (Markowitz et al., 2007); thus, CHBRP uses the rates of vaccine uptake and HPV-related health outcomes from 2007. In this example, CHBRP assumes the average risk for infection over one year among unvaccinated persons is 20% (Muñoz, 2010). Vaccine efficacy for prevention of HPV infection differs according to outcome, as described below.

CHBRP's estimated public health outcomes represent an upper bound because vaccine effectiveness in "real world" situations tends to be less than that observed in carefully controlled studies. Moreover, the duration of protection from the vaccine is unknown, as is whether HPV types not targeted by the vaccine will substitute in causing disease (including cancer) as HPV types 16 and 18 are eliminated. Finally, CHBRP assumed that all persons beginning the vaccine series receive all three injections on schedule in the first year following the CDC ACIP recommendation. This is unlikely to be true in practice, and actual level of protection will be reduced accordingly.

Estimated Health Impacts

Size of Population Protected

Of the estimated 124,459 females in the small-group and individual market who would obtain the quadrivalent vaccine within a year of the CDC ACIP recommendation, we estimate that 35% of this population already would have been infected (CDC, 2011), and thus would receive no protection from the vaccination. This leaves a hypothetical cohort of 80,898 susceptible females who could be potentially protected from some HPV infection by receiving the quadrivalent vaccine.

Hypothetical Cases of Human Papillomavirus Infections Prevented in the First Year Following CDC ACIP Recommendation

CHBRP estimates that the population of 80,898 susceptible females would experience, in the absence of vaccination, a 20% cumulative incidence[37] of HPV infection in the year following the CDC ACIP recommendation, **yielding 16,180 hypothetical cases of HPV infection *of all types*** (including those covered by the quadrivalent vaccine).

Hypothetical Cases of Anogenital Warts Prevented in the First Year Following CDC ACIP Recommendation

There is about a 10% lifetime risk of being diagnosed with genital warts (CDC, 2011); therefore about 1,618 cases of genital warts would develop in the hypothetical cohort of 16,180 females with HPV infection (due to all types). Of the 1,618 cases, about 90% are caused by HPV 6 and 11 (CDC, 2011), which are included in the quadrivalent vaccine; therefore, **about 1,383 to 1,456 cases of genital warts would be prevented over a lifetime, assuming 95%-100% vaccine efficacy** (1618*0.9*0.95).

Hypothetical Cases of CIN 2 and 3 Prevented in the First Year Following CDC ACIP Recommendation

Annual incidence of CIN 2 and 3 is about 1.5%, and about 50% of cases (see Table 4) are due to HPV types 16 or 18, which are covered by the vaccine. Therefore, of the 16,180 cases of HPV infection due to all types, about 243 cases of CIN 2 or 3 would occur. **About 60 cases of CIN 2 or 3 (0.50*243 cases*0.515) are caused by vaccine-covered types and, therefore, might be prevented in the first year following the recommendation by CDC ACIP** (assuming 51.5% efficacy of the quadrivalent vaccine in the interion-to-treat population per Kjaer et al., 2009 [see *Medical Effectiveness* section]).

Cervical Cancer

Cancers caused by HPV take many years to develop post-infection. For example, cervical cancer incidence rates are about 4/100,000 in females aged 25 to 29 years and increases to about 15/100,000 beginning at age 35 (CCR, 2011). As noted in the *Medical Effectiveness* section, although there is clear and convincing evidence that the vaccine reduces precancerous lesions

[37] This estimate is based on study that reported that teens have a 50% likelihood of HPV infection within two years of sexual debut, or 25% per year (Rambout, et al., 2007). Additionally, there is an 80% lifetime HPV prevalence for sexually active females. Therefore, CHBRP chose 20% as a reasonable estimate for this hypothetical scenario.

(which are necessary to developing cancer), no cancer outcomes have been reported in the clinical literature due to the relatively recent approval of the vaccine. **Due to a lack of clinical evidence of the quadrivalent vaccine's efficacy in cervical cancer prevention, CHBRP cannot estimate the number of cases of cervical cancer prevented**.

Premature Death and Economic Loss

HPV-related cancers contribute to premature death and economic loss. For example, Ekwueme et al. estimated that the average years of potential life lost (YPPL) for each cervical cancer death is 27.6 and an average of 21.8 YPPL for each HPV-cancer associated death (Ekwueme et al, 2008). Economic loss (lost wages and housekeeping services) attributable to cervical cancer was about $445,000 (updated to 2007 dollars) per cancer death in California (Max et al., 2003). Max also estimated that California's economy lost about $159 million due to cervical cancer deaths in 1998 (Max et al., 2003).

CONCLUSION

California has not yet selected a benchmark plan that will help define EHBs for the state in 2014 and 2015. Depending on under whose regulation the selected benchmark plan falls—federal regulation, DMHC regulation, or CDI regulation—a differing set of benefit mandates will be included in the EHBs. This issue brief focused on the scenario of a benchmark plan being subject only to federal regulation, thus including only federal benefit mandates and no state benefit mandates, and showed how state benefit mandates could exceed EHBs. However, while DMHC-enforced benefit mandates and CDI-enforced benefit mandates are similar, they are not identical. If California selects a DMHC-regulated plan or a CDI-regulated policy, there may still be state benefit mandates enforced by the other regulator (including immunization coverage requirements) that would exceed EHBs and for which the state would be required to defray the costs.

As California moves toward selecting its benchmark plan and defining EHBs for the state, CHBRP recommends using evidenced-based analysis, similar to what is provided in this issue brief, to help inform discussions of whether to keep or repeal state benefit mandates that could exceed EHBs. Evidenced-based analysis can provide decision-makers with a more comprehensive understanding of the impacts of state benefit mandates that exceed EHBs—not only potential costs, but also reviews of the medical effectiveness evidence and estimates of the mandate's public health impacts for Californians.

APPENDICES

Appendix A: California Benefit Mandates for Immunization Coverage

California Health and Safety Code: DMHC-Regulated Plans[38]

1345. (b) "Basic health care services" means all of the following:
(1) Physician services, including consultation and referral.
(2) Hospital inpatient services and ambulatory care services.
(3) Diagnostic laboratory and diagnostic and therapeutic radiologic services.
(4) Home health services.
(5) Preventive health services.
(6) Emergency health care services, including ambulance and ambulance transport services and out-of-area coverage. "Basic health care services" includes ambulance and ambulance transport services provided through the "911" emergency response system.
(7) Hospice care pursuant to Section 1368.2.

1367.35. (a) On and after January 1, 1993, every health care service plan that covers hospital, medical, or surgical expenses on a group basis shall provide benefits for the comprehensive preventive care of children 16 years of age or younger under terms and conditions agreed upon between the group subscriber and the plan. Every plan shall communicate the availability of these benefits to all group contractholders and to all prospective group contractholders with whom they are negotiating. This section shall apply to each plan that, by rule or order of the director, has been exempted from subdivision (i) of Section **1367**, insofar as that section and the rules thereunder relate to the provision of the preventive health care services described in this section.
(b) For purposes of this section, benefits for the comprehensive preventive care of children shall comply with both of the following:
(1) Be consistent with both of the following:
(A) The Recommendations for Preventive Pediatric Health Care, as adopted by the American Academy of Pediatrics in September of 1987.
(B) The most current version of the Recommended Childhood Immunization Schedule/United States, jointly adopted by the American Academy of Pediatrics, the Advisory Committee on Immunization Practices, and the American Academy of Family Physicians, unless the State Department of Health Services determines, within 45 days of the published date of the schedule, that the schedule is not consistent with the purposes of this section.
(2) Provide for all of the following:
(A) Periodic health evaluations.

[38] As of January 31, 2012

(B) Immunizations.
(C) Laboratory services in connection with periodic health evaluations.

1367.3. (a) On and after January 1, 1993, every health care service plan that covers hospital, medical, or surgical expenses on a group basis shall offer benefits for the comprehensive preventive care of children. This section shall apply to children 17 and 18 years of age, except as provided in paragraph (4) of subdivision (b). Every plan shall communicate the availability of these benefits to all group contractholders and to all prospective group contractholders with whom they are negotiating. This section shall apply to a plan which, by rule or order of the director, has been exempted from subdivision (i) of Section **1367**, insofar as that section and the rules thereunder relate to the provision of the preventive health care services described herein.

(b) For purposes of this section, benefits for the comprehensive preventive care of children shall comply with both of the following:

(1) Be consistent with both of the following:

(A) The Recommendations for Preventive Pediatric Health Care, as adopted by the American Academy of Pediatrics in September of 1987.

(B) The most current version of the Recommended Childhood Immunization Schedule/United States, jointly adopted by the American Academy of Pediatrics, the Advisory Committee on Immunization Practices, and the American Academy of Family Physicians, unless the State Department of Health Services determines, within 45 days of the published date of the schedule, that the schedule is not consistent with the purposes of this section.

(2) Provide for the following:

(A) Periodic health evaluations.

(B) Immunizations.

(C) Laboratory services in connection with periodic health evaluations.

(D) For health care service plan contracts within the scope of this section that are issued, amended, or renewed on and after January 1, 1993, screening for blood lead levels in children at risk for lead poisoning, as determined by a physician and surgeon affiliated with the plan, when the screening is prescribed by a physician and surgeon affiliated with the plan. This subparagraph shall be applicable to all children and shall not be limited to children 17 and 18 years of age.

California Insurance Code: CDI-Regulated Policies[39]

10123.5. (a) On or after January 1, 1993, every insurer issuing group disability insurance which covers hospital, medical, or surgical expenses shall provide benefits for the comprehensive preventive care of children 16 years of age or younger under such terms and conditions as may be agreed upon between the group policyholder and the insurer. Every insurer shall communicate the availability of such benefits to all group policyholders and to all prospective group policyholders with whom they are negotiating.

(b) For purposes of this section, benefits for the comprehensive preventive care of children shall comply with both of the following:

(1) Be consistent with both of the following:

(A) The Recommendations for Preventive Pediatric Health Care, as adopted by the American Academy of Pediatrics in September of 1987.

(B) The most current version of the Recommended Childhood Immunization Schedule/United States, jointly adopted by the American Academy of Pediatrics, the Advisory Committee on Immunization Practices, and the American Academy of Family Physicians, unless the State Department of Health Services determines, within 45 days of the published date of the schedule, that the schedule is not consistent with the purposes of this section.

(2) Provide for the following:

(A) Periodic health evaluations.

(B) Immunizations.

(C) Laboratory services in connection with periodic health evaluations.

10123.55. (a) On or after January 1, 1993, every insurer issuing group disability insurance which covers hospital, medical, or surgical expenses shall offer benefits for the comprehensive preventive care of children 17 and 18 years of age under such terms and conditions as may be agreed upon between the group policyholder and the insurer. Every insurer shall communicate the availability of these benefits to all group policyholders and to all prospective group policyholders with whom they are negotiating.

(b) For purposes of this section, benefits for the comprehensive preventive care of children shall comply with both of the following:

(1) Be consistent with both of the following:

(A) The Recommendations for Preventive Pediatric Health Care, as adopted by the American Academy of Pediatrics in September of 1987.

(B) The most current version of the Recommended Childhood Immunization Schedule/United States, jointly adopted by the American Academy of Pediatrics, the Advisory Committee on Immunization Practices, and the American Academy of Family Physicians, unless the

[39] As of February 3, 2012

State Department of Health Services determines, within 45 days of the published date of the schedule, that the schedule is not consistent with the purposes of this section.

(2) Provide for the following:

(A) Periodic health evaluations.

(B) Immunizations.

(C) Laboratory services in connection with periodic health evaluations.

Appendix B: Literature Review Methods

The literature search for this issue brief updates literature searches CHBRP performed in 2007 and 2009 for two bills (Assembly Bill (AB) 1429 and Senate Bill (SB) 158) that would have mandated that DMHC-regulated health plans and CDI-regulated health insurance policies provide coverage for HPV vaccines. The search was limited to randomized controlled trials (trials) published in English from January 2009 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 medical effectiveness review was limited to articles that presented findings from trials that assessed efficacy of administering the vaccine to general populations of females per the regimen recommended by CDC ACIP (e.g, three 0.5-mL doses of the vaccine intramuscularly over a six-month period with the second dose be administered 2 months after the first dose and the third dose 6 months after the first dose.) Studies that compared the safety and efficacy of different dosing regimens for the quadrivalent vaccine were excluded (Krajden et al., 2011; Neuzil et al., 2011; Zimmerman et al., 2010). A study that examined the effectiveness of the quadrivalent vaccine among persons with the human immunodeficiency virus (HIV) was also excluded because the experience of persons with HIV may not be reflective of the general population of females in the age group for which the vaccine is recommended (Levin et al., 2010). Two articles that presented pooled results from three clinical trials of the quadrivalent vaccine with a clinical trial of a monovalent vaccine that has not been approved by the FDA were also 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).

The search yielded a total of 354 citations. Fourteen additional articles pertinent to the medical effectiveness review were identified, retrieved, and reviewed. Findings from these articles were integrated with findings from the seven articles on the efficacy of the quadrivalent vaccine that was included in the literature review for CHBRP's report on SB 158.

The articles included in the medical effectiveness review present findings from two Phase 2 clinical trials and three Phase 3 clinical trials of the quadrivalent vaccine. Phase 2 trials are clinical trials 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. 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).

One Phase 2 trial assessed safety and short-term efficacy in females aged 9 to 15 years (Reisinger et al., 2007).[40] One Phase 2 trial and two Phase 3 trials evaluated the safety and efficacy of the vaccine in females aged 15 to 26 years (FUTURE II Study Group, 2007; Garland et al., 2007; Villa et al., 2006). Finally, one Phase 3 trial examined safety and efficacy among females aged 24 to 45 years (Castellsagué et al., 2011). These five trials were conducted at multiple sites in Asia, Europe, North America, South America, and the South Pacific. All were sponsored by the vaccine's manufacturer.

[40] This trial also enrolled males aged 9 to 15 years but CHBRP only reviewed findings for females because the CDC ACIP initially recommended that the quadrivalent vaccine be administered only to females.

Appendix C: Summary Findings on Medical Effectiveness

Table C-1 describes the characteristics and summarizes the final, overall results from the five Phase 2 and Phase 3 randomized controlled trials that have been conducted to assess the efficacy of the quadrivalent vaccine.

Table C-1. Major Findings from Clinical Trials of the Quadrivalent Human Papillomavirus Vaccine

Citation	Sample Size	Length of Follow-Up	Age Group	HPV Types	Analytic Approach	Outcome	Efficacy
Reisinger et al., 2007	1,781	1 year	9-15 years	HPV 6, 11, 16, 18	Per-protocol (a)	Serocon-version rates	Ranged from 91.5% for HPV, 18 to 99.8% for HPV 16
Kjaer et al., 2009	18,174 (combined data from 3 trials)	Mean = 3.5 years	16-26 years	HPV 6, 11, 16, 18	Per-protocol	CIN 2/3 or AIS	98.2% (95% CI 93.3% to 99.8%)
Kjaer et al., 2009	18,174	Mean = 3.5 years	16-26 years	HPV 6, 11, 16, 18	Intention-to-treat (b)	CIN 2/3 or AIS	51.5% (95% CI, 40.6% to 60.6%)
Kjaer et al., 2009	18,174	Mean = 3.5 years	16-26 years	HPV 6, 11, 16, 18	Per-protocol	VaIN 2/3 or VIN 2/3	100.0% (95% CI, 82.6% to 100.0%)
Kjaer et al., 2009	18,174	Mean = 3.5 years	16-26 years	HPV 6, 11, 16, 18	Intention-to-treat	VaIN 2/3 or VIN 2/3	79.0% (95% CI, 56.4% to 91.0%).
Muñoz et al., 2010	17,622 (combined data from 2 trials)	Mean = 3.5 years	16-26 years	All	HPV negative	CIN 2/3 or AIS	42.7% (95% CI, 23.7% to 40.0%)
Muñoz et al., 2010	17,622	Mean = 3.5 years	16-26 years	All	Intention-to-treat	CIN 2/3 or AIS	19.0% (95% CI, 7.7% to 28.9%)
Muñoz et al., 2010	17,622	Mean = 3.5 years	16-26 years	All	HPV negative	VaIN 2/3 or VIN 2/3	77.1% (95% CI, 47.1% to 91.5%)
Muñoz et al., 2010	17,622	Mean = 3.5 years	16-26 years	All	Intention-to-treat	VaIN 2/3 or VIN 2/3	50.7% (95% CI, 22.5% to 69.3%)
Castellsagué et al., 2011	3,819	Median = 4 years	24-45 years	HPV 6, 11, 16, 18	Per-protocol	CIN 2/3 or AIS	83.4% (95% CI: -37.6%- to 99.6%)
Castellsagué et al., 2011	3,819	Median = 4 years	24-45 years	HPV 6, 11, 16, 18	Intention-to-treat	CIN 2/3 or AIS	22.4% (95% CI: -42.5% to 58.3%)

Sources: Castellsagué et al., 2011; Kjaer et al., 2009; Muñoz et al., 2010; Reisinger et al., 2007
Notes: (a) Defined as females enrolled in the trial who received all three doses of the vaccine or placebo and who were not infected with HPV from the first day of the trial through the first day of the seventh month of the trial.
(b) Defined as all females enrolled in the trial for whom data were available regardless of the number of doses of the vaccine or placebo received and regardless of whether they were infected with HPV prior to the trial or at any point during the trial.
Key: AIS=cervical adenocarcinoma in situ; CI=confidence interval; and CIN=cervical intraepithelial neoplasia; HPV=Human Papillomavirus; ValN=vaginal intraepithelial neoplasia; and VIN=vulvar intraepithelial neoplasia.

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 website at www.chbrp.org/costimpact.html.

The cost analysis in this report was prepared by the members of cost team, which consists of CHBRP task force members and contributors from the University of California, San Diego, and the University of California, Los Angeles, as well as the contracted actuarial firm, Milliman, Inc. (Milliman). Milliman 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.

Health insurance

1. The latest (2009) California Health Interview Survey (CHIS), which is used to estimate health insurance for California's population and distribution by payer (e.g, employment-based, individually purchased, or publicly financed). The biennial CHIS is the largest state health survey conducted in the United States, collecting information from approximately 50,000 households. More information on CHIS is available at www.chis.ucla.edu.

2. The latest (2011) California Employer Health Benefits Survey is used to estimate:

   - size of firm,
   - percentage of firms that are purchased/underwritten (versus self-insured),
   - premiums for health care service plans regulated by the Department of Managed Health Care (DMHC) (primarily health maintenance organizations [HMOs] and Point of Service Plans [POS]),
   - premiums for health insurance 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 with 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/publications/2010/12/california-employer-health-benefits-survey.

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 health care 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 (2010 Group Health Insurance Survey) contains data from seven major California health plans regarding their 2010 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.

- The California Health Interview Survey (2007).

Issue Brief Specific Caveats, Assumptions, and Limitations

To determine utilization rates, the rates of HPV immunization were assumed to be the same for all market segments and were determined using and CHIS 2007 data, checked against Milliman health outcomes data. The rates are differentiated by age group and coverage as follows:

HPV immunization rates in the first year following recommended status for enrollees with coverage:

- Ages 11 to 18 = 0.245
- Ages 19 to 26 = 0.133

Utilization assumptions

1. CHBRP estimates immediate coverage without delay.
2. After the recommendation is made, DMCH-regulated health plans will have to cover the costs for females aged 11 to 26 years and CDI-regulated policies will have to cover the costs for females aged 11 to 18 years.

Costs assumptions

1. The cost of the vaccine and its administration is the actual discounted price negotiated by health plans/policies with providers.

2. Although adherence to the three-dose series does not always occur, costs figures assume the administration of the three recommended doses.

Limitations

1. Utilization figures from coverage before the mandate used in this brief may not correspond to the actual enrollee response to mandate repeals.
2. The HPV vaccine came onto the market on June 8, 2006, but was not elevated to recommended status until March 23, 2007. Because of this, despite the vaccine being available and utilized during the first quarter of 2007, the assumed immunization rates in the first year following recommended status may be less than what is documented in existing literature.

REFERENCES

American Academy of Family Physicians (AAFP). *Recommended Adult Immunization Schedule United States, 2012*. 2012a. Available at www.aafp.org/online/etc/medialib/aafp_org/documents/clinical/immunization/adultsched07-08.Par.0001.File.dat/2012AdultImmSchedulecolor.pdf. Accessed May 14, 2012.

American Academy of Family Physicians (AAFP). *Recommended Immunization Schedule for Persons Aged 7 Through 18 Years United States, 2012*, 2012b. Available at: www.aafp.org/online/etc/medialib/aafp_org/documents/clinical/immunization/adolescenimmsched.Par.0001.File.dat/7to18adolescentImmunizationSchedule2012.pdf. Accessed May 14, 2012.

American Academy of Pediatrics (AAP) Committee on Infectious Diseases. Policy statement: HPV vaccine recommendations. *Pediatrics*. 2012; 129:602-605.

American Cancer Society (ACS). Cancer Facts and Figures 2008. 2008 Available at . Accessed May 2012.

American College of Obstetricians and Gynecologists Committee on Adolescent Health Care and the ACOG Working Group on Immunization (ACOG). ACOG committee opinion number 344: Human papillomavirus vaccination. *Obstetrics and Gynecology*. 2006;108:699-705.

Ault KA, FUTURE II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *The Lancet*. 2007;369:1861-1868.

Barr et al. Impact of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like particle vaccine in a sexually active population of North American women. *American Journal of Obstetrics and Gynecology*. 2008;198: 261.e1-261.e11.

Block SL, Brown DR, Chatterjee A, et al., Clinical Trial and Post-Licensure Safety Profile of a Prophylactic Human Papillomavirus (Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine. Pediatric *Infectious Disease Journal.* 2010; 29:95-101.

Brown DR, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV; Types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. *Journal of Infectious Disease*. 2009;199:926-935.

Burk RD, Ho GY, Beardsley L, Lempa M, Peters M, Bierman R. Sexual behavior and partner characteristics are the predominant risk factors for genital human papillomavirus infection in young women. *Journal of Infectious Disease*. 1996;174(4):679-689.

California Cancer Registry, Cancer Inquiry System (CCR). Reference Year=2007. Based on October 2011 Quarterly Extract (Released October 27, 2011). Available at: http://www.cancer-rates.info/ca/index.php. Accessed May 2012.

California Health Benefits Review Program (CHBRP). (2009). *Analysis of Senate Bill 158: Human Papillomavirus Vaccination*. Report to California State Legislature. Oakland, CA: CHBRP. 09-05.

California Health Interview Survey (CHIS). 2007 California Health Interview Survey. Los Angeles, CA: UCLA Center for Health Policy Research. 2007. Available at: http://www.chis.ucla.edu/. Accessed May 2012.

Castellsagué X, Munoz N, Pitisuttithum P, et al., End-of-study safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women 24-45 years of age. *British Journal of Cancer*. 2011;105:28-37.

Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. *Obstetrics and Gynecology*. 2009;113:18-25.

Center for Consumer Information and Insurance Oversight (CCIIO). Essential Health Benefits Bulletin. 2011. Available at: http://cciio.cms.gov/resources/files/Files2/12162011/essential_health_benefits_bulletin.pdf. Accessed December 16, 2011.

Centers for Disease Control and Prevention. *Sexually Transmitted Diseases. Genital HPV infection - fact sheet.* Updated February 2012. Available at: http://www.cdc.gov/std/hpv/stdfact-hpv.htm. Accessed May 2012.

Centers for Disease Control and Prevention: *Division of STD Prevention. Sexually transmitted disease surveillance, 2010.* November 2011. Available at: http://www.cdc.gov/std/stats10/surv2010.pdf. Accessed May 2012.

Clifford GM. Smith JS, Aguado T, and Franceschi S. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. *British Journal of Cancer*. 2003; (89):101-105.

Dinh EF, Sternberg M, Markowitz LE. Genital warts among 18- to 59-year olds in the United States, National Health and Nutrition Examination Survey, 1994-2004. *Sexually Transmitted Disease*s. 2008;35(4):357-60.

Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS, Markowitz LE. Prevalence of HPV infection among females in the United States. *The Journal of the American Medical Association*. 2007;297(8):813-9.

Ekwueme DU, Chesson HW, Zhang KB, Balamurugan A. Years of potential life lost and productivity costs because of cancer mortality and for specific cancer sites where human papillomavirus may be a risk factor for carcinogenesis – United States, 2003. *Cancer*. 2008. 113(10):2937-2945.

Food and Drug Administration (FDA). *The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective.* 2009. Available at: www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143534.htm. Accessed May 1, 2012.

FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *New England Journal of Medicine.* 2007;356:1915-1927.

Garland SM, Ault KA, Gall SA, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: A combined analysis of five randomized controlled trials. *Obstetrics and Gynecology*. 2009; 114:1179-1188.

Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *New England Journal of Medicine.* 2007;356:1928-1943.

Haupt RM, Sings HL. The Efficacy and Safety of the Quadrivalent Human Papillomavirus 6/11/16/18 Vaccine Gardasil. *Journal of Adolescent Health.* 2011; 49:467-475.

Howell EA, Chen YT, Concato J. Differences in cervical cancer mortality among black and white women. *Obstetrics & Gynecology*. 1999;94(4):509-515.

Insinga RP, Glass AG, Rush BB. Diagnoses and outcomes in cervical cancer screening: a population-based study. *American Journal of Obsterics and Gynecology*. 2004 Jul;191(1):105-13.

Joura, EA, Garland SM, Paavonen J, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. *BMJ.* 2012; 344:e1401.

Kjaer SK, Sigurdsson K, Iversen OE, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. *Cancer Prevention Research (Phila).* 2009; 2:868-878.

Krajden M, Cook D, Yu A, et al. Human Papillomavirus 16 (HPV 16) and HPV 18 Antibody Responses Measured by Pseudovirus Neutralization and Competitive Luminex Assays in a Two- versus Three-Dose HPV Vaccine Trial.*Clinical and Vaccine Immunology.* 2011;18:418-423.

Lazcano-Ponce E, Perez G, Cruz-Valdez A, et al. Impact of a quadrivalent hpv6/11/16/18 vaccine in Mexican women: public health implications for the region. *Archives of Medical Research.* 2009; 40:514-24.

Levin MJ, Moscicki AB, Song LY, et al. Safety and Immunogenicity of a Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) Vaccine in HIV-Infected Children 7 to 12 Years Old. Jaids-*Journal of Acquired Immune Deficiency Syndrome.* 2010; 55:197-204.

Majewski S, Bosch F, Dillner J, et al. The impact of a quadrivalent human papillomavirus (types 6, 11, 16, 18) virus-like particle vaccine in European women aged 16 to 24. *Journal of the European Academy of Dermatology and Venereology.* 2009;23:1147-55TN: NCT00092495/ClinicalTrials.gov NCT00092534/ClinicalTrials.gov.

Markowitz LE, Dunne EF, Saraiya M, Lawson HW, Chesson H, Unger ER. Quadrivalent human papillomavirus vaccine: Recommendations of the Advisory Committee on Immunization Practices. *Morbidity and Mortality Weekly Recommendation Report*. 2007;56:1-24.

Max W, Rice DP, Sung HY, Michel M, Breuer W, Zhang X. The economic burden of gynecologic cancers in California, 1998. *Gynecologic Oncology*. 2003;88(2):96-103.

Muñoz N, Kjaer SK, Sigurdsson K, et al. Impact of Human Papillomavirus (HPV)-6/11/16/18 Vaccine on All HPV-Associated Genital Diseases in Young Women. *Journal of the National Cancer Institute*. 2010;10:325-339.

Muñoz N, Manalastas R, Pitisuttithum P, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. *The Lancet.* 2009;373:1949-57.

Mundt AJ, Connell PP, Campbell T, Hwang JH, Rotmensch J, Waggoner S. Race and clinical outcome in patients with carcinoma of the uterine cervix treated with radiation therapy. *Gynecologic Oncology*. 1998;71(2):151-158.

Napoles-Springer A, Perez-Stable EJ, Washington E. Risk factors for invasive cervical cancer in Latino women. *Journal of Medical Systems*. 1996;20(5):277-293.

Neuzil KM, Canh DG, Thiem VD, et al. Immunogenicity and Reactogenicity of Alternative Schedules of HPV Vaccine in Vietnam A Cluster Randomized Noninferiority Trial. *The Journal of the American Medical Association*. 2011; 305:1424-1431.

Olsson SE, Kjaer SK, Sigurdsson K, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. *Human Vaccines*. 2009; 5:696-704.

Perez G, Lazcano-Ponce E, Hernandez-Avila M, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like-particle vaccine in Latin American women. *International Journal of Cancer*. 2008;122:1311-1318.

Rambout L, Hopkins L, Hutton B, Fergusson D. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. *CMAJ*. 2007;177(5)469-479.

Reisinger KS, Block SL, Lazcano-Ponce E, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. *The Pediatric Infectious Disease Journal.* 2007;26:201-209.

Saslow D, Castle P, Cox T, et al. American Cancer Society guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA: A Cancer Journal for Clinicians.* 2007;57:7-28.

Sheinfeld Gorin SN, Glenn BA, Perkins RB. The human papillomavirus (HPV) vaccine and cervical cancer: uptake and next steps. *Advance Therapy*. 2011; 28(8):615-639.

Shields TS, Brinton LA, Burk RD, Wang SS, Weinstein SJ, Ziegler RG, et al. A case-control study of risk factors for invasive cervical cancer among U.S. women exposed to oncogenic types of human papillomavirus. *Cancer Epidemiology Biomarkers & Prevention*. 2004;13(10):1574-1582.

Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *The Journal of the American Medical Association*. 2009;302:750-757.

Society for Adolescent Health and Medicine (SAHM). *Human Papillomavirus (HPV) Vaccine: An Updated Position Statement of the Society for Adolescent Health and Medicine*. 2011. Available at: www.adolescenthealth.org/Position_Statements/613/2530.htm. Accessed May 14, 2012.

Souayah N, Michas-Martin PA, Nasar A, et al. Guillain-Barre syndrome after Gardasil vaccination: Data from Vaccine Adverse Event Reporting System 2006-2009. *Vaccine*, 2011; 29:886-889.

Stone KM, Karem KL, Sternberg MR, et al. Seroprevalence of human papillomavirus type 16 infection in the United States. *Journal of Infectious Disease*. 2002;186(10):1396-1402.

Tay EH, Garland S, Tang G, et al. Clinical trial experience with prophylactic HPV 6/11/16/18 VLP vaccine in young women from the Asia-Pacific region. *International Journal of Gynecology and Obstetrics*. 2008; 102:275-83.

Vesco KK, Whitlock EP, Eder M, et al. Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 86. AHRQ Publication No. 11-05156-EF-1. Rockville, MD: Agency for Healthcare Research and Quality, 2011. Available at: www.uspreventiveservicestaskforce.org/uspstf11/cervcancer/cervcanceres.pdf. Accessed May 14, 2012.

Villa LL, Costa RL, Petta CA, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years follow-up. *British Journal of Cancer*. 2006;95:1459-1466.

Weinstock H, Berman S, Cares W Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. *Perspectives on Sexual and Reproductive Health*. 2004;36:6-10.

Wheeler CM, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV; Types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16-26 years. *Journal of Infectious Disease*. 2009;199:936-944.

Zimmerman RK, Nowalk MP, Chyongchiou JL, et al. Randomized trial of an alternate human papillomavirus vaccine administration schedule in college-aged women. *Journal of Women's Health*. 2010;19:1441-1447.

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A group of faculty and staff undertakes most of the analysis that informs reports by the California Health Benefits Review Program (CHBRP). The CHBRP **Faculty Task Force** comprises rotating representatives from six University of California (UC) campuses and three private universities in California. In addition to these representatives, there are other ongoing contributors to CHBRP from UC. This larger group provides advice to the CHBRP staff on the overall administration of the program and conducts much of the analysis. The **CHBRP staff** coordinates the efforts of the Faculty Task Force, works with Task Force members in preparing parts of the analysis, and coordinates all external communications, including those with the California Legislature. The level of involvement of members of the CHBRP Faculty Task Force and staff varies on each report, with individual participants more closely involved in the preparation of some reports and less involved in others. As required by CHBRP's authorizing legislation, UC contracts with a certified actuary, Milliman Inc., to assist in assessing the financial impact of each legislative proposal mandating or repealing a health insurance benefit. 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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