National- and state-level impact and cost-effectiveness of nonavalent HPV vaccination in the United States

David P. Durham[a,1], Martial L. Ndeffo-Mbah[a], Laura A. Skrip[a], Forrest K. Jones[a], Chris T. Bauch[b], and Alison P. Galvani[a]

[a]Center for Infectious Disease Modeling and Analysis, Yale School of Public Health, Yale University, New Haven, CT 06511; and [b]Department of Applied Mathematics, University of Waterloo, Waterloo, ON N2L 3G1, Canada

Edited by Burton H. Singer, University of Florida, Gainesville, FL, and approved March 11, 2016 (received for review August 20, 2015)

Every year in the United States more than 12,000 women are diagnosed with cervical cancer, a disease principally caused by human papillomavirus (HPV). Bivalent and quadrivalent HPV vaccines protect against 66% of HPV-associated cervical cancers, and a new nonavalent vaccine protects against an additional 15% of cervical cancers. However, vaccination policy varies across states, and migration between states interdependently dilutes state-specific vaccination policies. To quantify the economic and epidemiological impacts of switching to the nonavalent vaccine both for individual states and for the nation as a whole, we developed a model of HPV transmission and cervical cancer incidence that incorporates state-specific demographic dynamics, sexual behavior, and migratory patterns. At the national level, the nonavalent vaccine was shown to be cost-effective compared with the bivalent and quadrivalent vaccines at any coverage despite the greater per-dose cost of the new vaccine. Furthermore, the nonavalent vaccine remains cost-effective with up to an additional 40% coverage of the adolescent population, representing 80% of girls and 62% of boys. We find that expansion of coverage would have the greatest health impact in states with the lowest coverage because of the decreasing marginal returns of herd immunity. Our results show that if policies promoting nonavalent vaccine implementation and expansion of coverage are coordinated across multiple states, all states benefit both in health and in economic terms.

HPV | vaccination | cervical cancer | model | migration

Human papillomavirus (HPV) is the most prevalent sexually transmitted infection in the United States (1). Although more than 100 types of HPV have been identified, HPV-16 and HPV-18 are responsible for 66% of cervical cancers (2). Two vaccines, Gardasil (4vHPV) and Cervarix (2vHPV), were approved by the Food and Drug Administration in 2006 and 2009, respectively. Both of these vaccines are highly efficacious against HPV-16 and HPV-18 and are partially efficacious against other non–vaccine-targeted oncogenic serotypes (2, 3). Licensed in 2014, Gardasil-9 (9vHPV) is a new vaccine that elicits immunity to five additional oncogenic serotypes, extending protection to 80% of cervical cancers (2, 4). In 2007, the Centers for Disease Control and Prevention (CDC) recommended HPV vaccination for all girls and women aged 9–26 y (5). In 2011, this recommendation was extended to males to reduce transmission (3). In 2015, the CDC recommended that females aged 11–26 y be vaccinated with any of the three available vaccines and that males aged 11–21 y receive either 4vHPV or 9vHPV (2). Although CDC contract and private sector prices vary, the new vaccine, at a per-dose cost of $126, is approximately $13 more costly than 4vHPV and $18 more costly than 2vHPV (*SI Appendix*).

HPV vaccination has been recommended nationwide with funding to enhance coverage provided by the CDC Prevention and Public Health Fund (PPHF) (6). Vaccine cost, the availability of subsidies, and the supplementing of federal support with state and local funds have been shown to increase coverage significantly (7). Although some states have taken no action to promote HPV vaccination, others have adopted measures that range from mandating HPV vaccination as a prerequisite for school attendance to permitting vaccination in pharmacies (8–10).

Migration among states generates complex interdependency among state-specific policies, but the impact of the variation in policy implementation and resulting vaccination coverage on HPV epidemiology has not been previously evaluated. To project the long-term impact of these dynamics, we developed a geographically explicit model of HPV transmission and cervical cancer progression, incorporating 10 oncogenic serotypes, demographics, age and gender-specific sexual behavior, and interstate and international migration. We found that switching to 9vHPV dominates 2vHPV/4vHPV, producing greater health benefits at the same or lower societal cost. Furthermore, because of the decreasing marginal returns of vaccination that arise through herd immunity, expansions in coverage are predicted to avert up to 66% more cervical cancers and deaths if targeted in states with the lowest coverage as compared with those states with the greatest coverage. However, as a result of migration between states, 29–84% of the long-term health benefit of a state's vaccination will be realized beyond its borders. We find that all states will achieve greater reductions in both the incidence of and expenditure for cervical cancer if vaccination policies are coordinated among states.

Results

Accounting for interstate migration and current heterogeneous state vaccination rates that range from 20–57% full-series coverage for girls (Fig. 1) and 9–43% full-series coverage for boys (6), we quantified the public health impact of switching from 2vHPV/4vHPV to 9vHPV nationwide. From the national perspective, we

Significance

Vaccination protects against human papilloma virus (HPV)-induced cervical cancer, but coverage varies markedly across the United States. The nonavalent vaccine produces greater health benefits than the bivalent and quadrivalent vaccines at a lower societal cost. Because of the impact of herd immunity, any expansion in coverage will be much more effective in reducing cancer incidence and healthcare costs if targeted in those states with the lowest coverage. Because of interstate migration and the long duration between HPV infection and resultant cervical cancer, much of the benefit of vaccination will be realized beyond a state's borders. Therefore, both cervical cancer incidence and expenditure can be substantially reduced if the states coordinate policies to promote expansion of coverage, particularly for the new nonavalent vaccine.

Author contributions: D.P.D., M.L.N.-M., C.T.B., and A.P.G. designed research; D.P.D., M.L.N.-M., L.A.S., and F.K.J. performed research; D.P.D. contributed new reagents/analytic tools; D.P.D., M.L.N.-M., and L.A.S. analyzed data; and D.P.D., L.A.S., C.T.B., and A.P.G. wrote the paper.

Conflict of interest statement: D.P.D. and A.P.G. have consulted for and received research funding from Merck and from Sanofi Pasteur. C.T.B. has consulted for and received research funding from GlaxoSmithKline Vaccines. These entities played no role in the research presented here.

This article is a PNAS Direct Submission.

[1]To whom correspondence should be addressed. Email: david.durham@yale.edu.

This article contains supporting information online at www.pnas.org/lookup/suppl/doi:10.1073/pnas.1515528113/-/DCSupplemental.

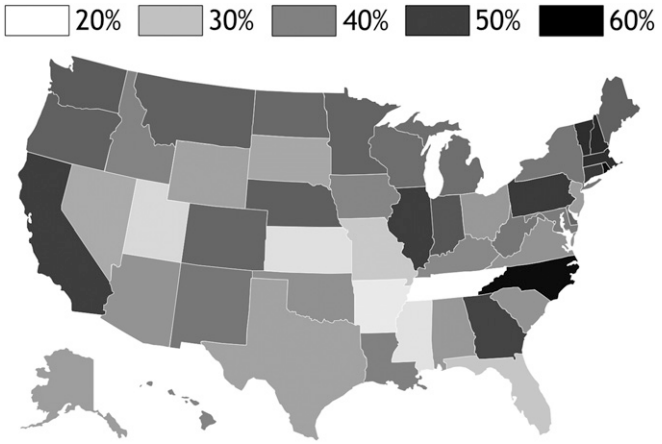

Fig. 1. Current state-specific full-schedule HPV vaccination among adolescent girls (age 13–17 y) in 2014.

found that 9vHPV would avert more cervical cancer cases and deaths than 2vHPV/4vHPV through 2050 for any coverage (Fig. 2). In particular, vaccination with 2vHPV/4vHPV sustained at current state-specific coverages was projected to reduce cervical cancer incidence by 63% [95% confidence interval (CI) 50–73%] and mortality by 43% (95% CI 22–58%). Switching to 9vHPV while maintaining current coverage would achieve more substantial reductions, decreasing incidence by 73% (95% CI 62–81%) and mortality by 49% (95% CI 30–62%) (Table 1).

We quantified the cost-effectiveness both of expanded coverage and of switching to 9vHPV. Specifically, we calculated the quality-adjusted life years (QALYs) gained, vaccination costs, and total societal costs across a range of scenarios. We found that 9vHPV dominates 2vHPV/4vHPV, producing greater health benefits for the same or lower societal cost. For example, completely switching to 9vHPV at current coverages would yield 65,000 QALYS. To gain 65,000 QALYs using 2vHPV/4vHPV, in contrast, would require vaccination of an additional 11% of the population—an increase from 39.7% to 50.7% for girls and from 21.6% to 32.6% for boys. This expansion in 2vHPV/4vHPV coverage would cost $2.7 billion more, from a societal perspective, than using 9vHPV at current coverage, to achieve the same benefit (Fig. 3 *A* and *B*).

To quantify the robustness of the cost-effectiveness of 9vHPV to parameter uncertainty, we conducted a probabilistic sensitivity analysis across a range of societal willingness-to-pay (WTP) per QALY gained parameters (11). Switching completely to 9vHPV and expanding coverage to an additional 20% of the adolescent population in each state would be very cost-effective at a WTP of $53,000 [the 2015 US per capita gross domestic product (GDP)]. Switching to 9vHPV and vaccinating an additional 40% of the adolescent population would be cost-effective at a WTP of $106,000 per QALY, whereas universal coverage with 9vHPV would be cost-effective at a WTP of $159,000 per QALY (three times the 2015 US per capita GDP) (Fig. 3*C*). Strategies that did not include switching to 9vHPV would not be cost-effective at any WTP.

Increases in coverage between 2013 and 2014 were observed in several jurisdictions that received resources from the CDC PPHF to provide educational outreach to physicians, parents, and adolescents and for other measures (6). This experience suggests that additional resources may be necessary to increase uptake further as coverage rises (12). To quantify the impact of increasing investment on the cost-effectiveness of 9vHPV, we considered three scenarios (concave, convex, and linear) of rising marginal vaccination costs. We calibrated these scenarios to the observed improvements in HPV coverage among jurisdictions receiving support from the PPHF (6, 12). We found that the cost-effectiveness of 9vHPV was robust for all these scenarios of increasing marginal vaccination costs (*SI Appendix*).

We evaluated the impact from the national perspective of heterogeneity in state-specific coverage on vaccination outcomes and cost-effectiveness. Specifically, we calculated the HPV-associated cervical cancer incidence, mortality, and incremental cost-effectiveness ratio (ICER) of national and state-specific expansions in coverage. We focused on 9vHPV, given its favorability compared with 2vHPV/4vHPV (Fig. 3). We compared a coordinated national increase in coverage of 10% for all states with a unilateral increase of 10% for each state individually (including Washington, DC) while every other state remained unchanged (Fig. 4). A coordinated national increase of 10% was projected to avert 12 cancers and 1.8 deaths per 10,000 vaccines administered, at an ICER of $40,000 per QALY. In contrast, for states with low coverage such as Mississippi, Kansas, Arkansas, and Tennessee, 10% increases in vaccination were projected to avert up to 20 cancers and three deaths per 10,000 vaccines administered at an ICER of $13,500 per QALY. For states with high coverage, such as California, Pennsylvania, and Rhode Island, a 10% expansion in vaccination would avert as few as 9.3 cancers and 1.4 deaths per 10,000 vaccines at an ICER of $56,400 per QALY (Fig. 4 *A*–*C*). Thus, the effectiveness of expanded coverage in any one state is inversely proportional to the adolescent female coverage that already has been achieved in that state. This result indicates that, because of herd immunity, the marginal benefit of vaccination decreases as coverage increases. Consequently, the United States as a whole will achieve the greatest improvements in health outcomes if expansions to coverage are targeted first toward states with the lowest coverage.

Because of the lengthy duration between the average age of vaccination and the onset of cervical cancer, a substantial number of women will have moved to another state before the health benefits of vaccination are realized. Consequently, 16–71% of the cervical cancers averted by expansion of coverage within an individual state will occur within that state's borders, and the remainder of cases will be averted in other states (Fig. 4*D*). As a result, states with low emigration rates such as Michigan, Wisconsin, Ohio, Texas, and Alabama exercise much greater control over health outcomes within their borders, whereas states with high emigration rates such as Hawaii, Wyoming, and Alaska are effectively subsidizing health outcomes in other states.

We found that for each state the per capita cost of switching to 9vHPV ranges from −$1.84 (cost-saving) to $4.40 (Fig. 5*A*). If all states switch to 9vHPV, the cost per state would fall to between −$4.65 and $2.16 (Fig. 5*B*), yielding a savings of between $0.55 and $4.42 per capita (Fig. 5*C*). Likewise, for a unilateral switch the corresponding health improvements would range from 0.54 to 3.1 QALYs per 10,000 population (Fig. 5*D*). If all states switched to 9vHPV, the health outcome for each state would rise to 1.2–4.1 QALYs per 10,000 population (Fig. 5*E*), a gain of 0.3–1.9 QALYs per 10,000 (Fig. 5*F*). These results indicate that, although all states benefit from cooperation, states with high emigration rates benefit the most (Fig. 5 *C* and *F*).

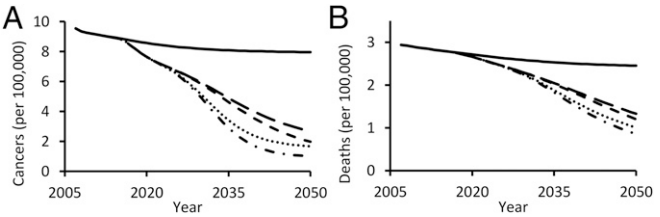

Fig. 2. Impact through 2050 of no vaccination (solid line), 2vHPV/4vHPV continued at current adolescent coverage (long dashed line), 9vHPV at current coverage (short dashed line), 2vHPV/4vHPV at 100% coverage (dotted line), and 9vHPV at 100% coverage (dashed and dotted line) on annual HPV-associated cervical cancers (*A*) and annual HPV-associated cervical cancer mortality (*B*).

Table 1. HPV-associated cervical cancer incidence and mortality in 2050

Scenario	2050 outcomes (95% CI)		2050 reduction in outcomes relative to no vaccination (95% CI)	
	Incidence	Mortality	Incidence, %	Mortality, %
No vaccination	15,947 (12,246–20,808)	4,912 (3,765–6,420)	NA	NA
2vHPV/4vHPV at current coverage	5,795 (4,883–6,948)	2,779 (2,332–3,358)	63 (50–73)	43 (22–58)
9vHPV at current coverage	4,209 (3,491–5,177)	2,499 (2,072–3,012)	73 (62–81)	49 (30–62)
Maximum achievable under 2vHPV/4vHPV	3,353 (2,860–4,020)	2,067 (1,826–2,390)	79 (72–85)	58 (44–68)
Maximum achievable under 9vHPV	1,927 (1,581–2,449)	1,727 (1,494– 2,014)	88 (83–91)	65 (53–74)

Maximum achievable outcomes correspond to 100% adolescent coverage.

Discussion

Our results indicate that switching to 9vHPV is cost-effective for any coverage. 9vHPV vaccination at current state-specific coverages yields the same health benefit as does covering an additional 11% of adolescents with 2vHPV/4vHPV at a cost that is $2.7 billion less. Because of nonlinearities of transmission dynamics, expanding coverage in states with the lowest coverage will be much more effective in reducing nationwide cervical cancer than expanding coverage in states with the highest coverage. Thus, our results suggest that, to have the greatest impact, resources provided to improve HPV coverage, such as those made available by the CDC PPHF, should be targeted at the states with the lowest coverage.

Nationally funded but locally targeted programs to promote vaccination are particularly appropriate, given that considerable interstate migration is likely to occur between the average age of vaccination and the average age of onset of cervical cancer that vaccination is averting. Consequently, much of the health and economic benefits of an HPV vaccination program within a state will be realized beyond that state's borders. From both national and state-specific perspectives, these dynamics generate strong public health and economic incentives for coordinated vaccination efforts.

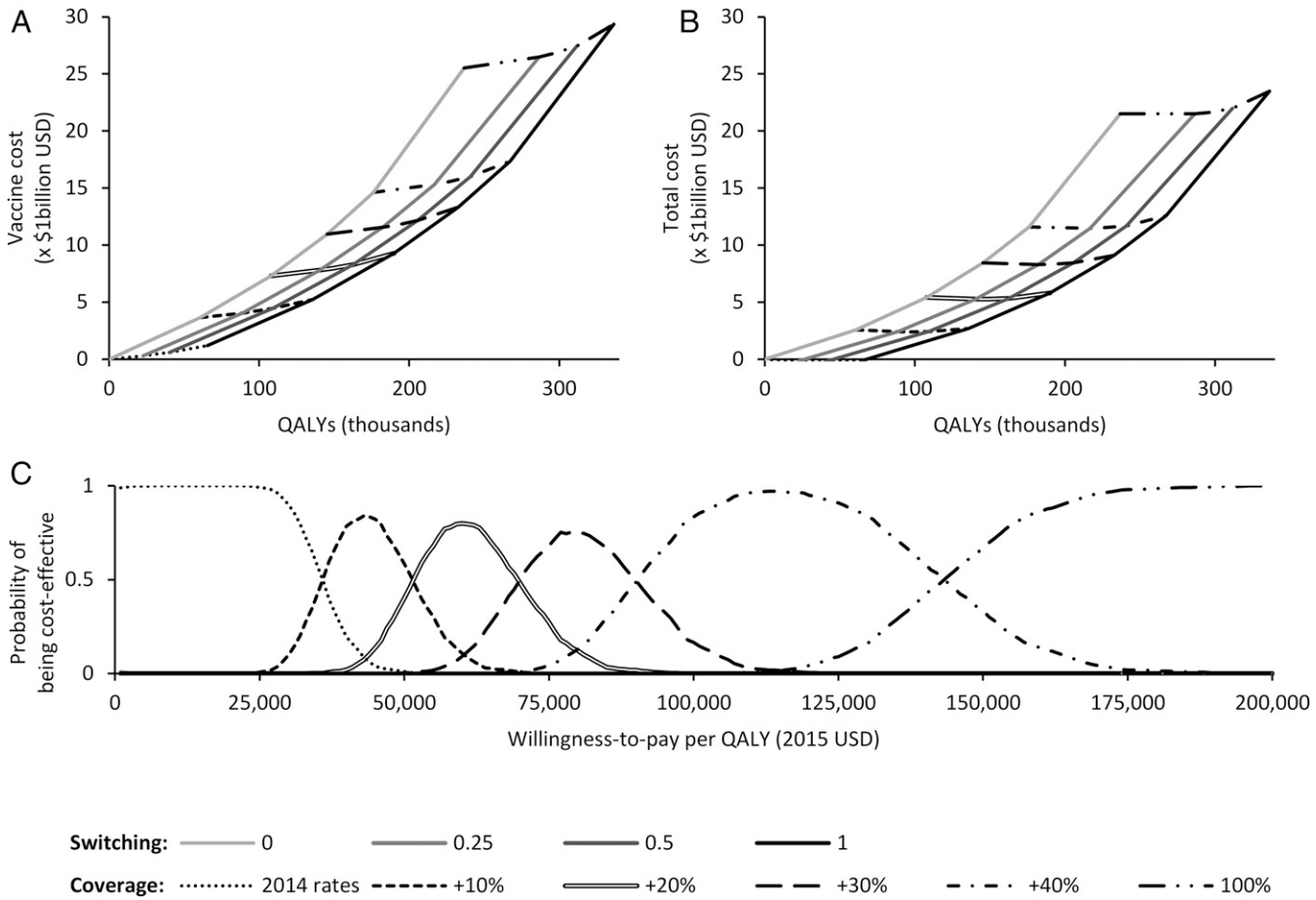

Fig. 3. (*A* and *B*) QALYs gained and vaccination cost (*A*) and QALYs gained and total societal cost (including both vaccination and medical costs) (*B*) associated with a proportion switching to the nonavalent vaccine of 0, 0.25, 0.5, or 1 (vertical contours). (*C*) The probability that vaccination is cost-effective, as a function of WTP per QALY gained. Adolescent vaccination was evaluated at current coverage (dotted line), with an additional 10% (short dashed line), 20% (double line), 30% (long dashed line), and 40% (dashed and dotted line) of the population vaccinated, and at 100% adherence (dashed and double-dotted line).

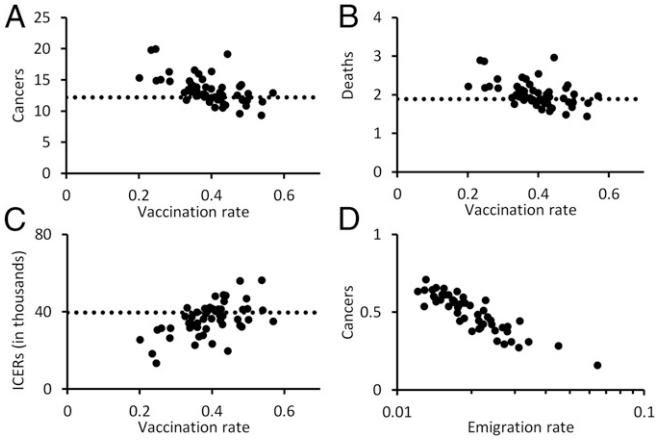

Fig. 4. (*A–C*) Impact of a national 10% expansion in vaccination coverage above current levels with 9vHPV (horizontal dotted lines) compared with a unilateral 10% expansion by each state (circles) on the nationwide cumulative cancers averted through 2050 per 10,000 vaccines administered (*A*), the nationwide cumulative deaths averted through 2050 per 10,000 vaccines administered (*B*), and the incremental cost-effectiveness ratio (*C*). (*D*) Of those cancers averted by a unilateral 10% increase in coverage, the proportion that occurs within the borders of the state in which coverage is increased is negatively log-linear with the state emigration rate.

In practice, actions taken to promote vaccination involve multiple stakeholders at a combination of the national, state, and local levels as well as private insurance markets that cover multiple states. Although vaccination uptake has been stymied by factors such as vaccine price, concerns that immunization might encourage adolescent sexual behavior, and physician reluctance to recommend the vaccine (8, 13), lessons can be learned from the significant increases in coverage that have been observed in Georgia, Illinois, Montana, North Carolina, and Washington, DC (6). These successes have been attributed to resources provided by the CDC PPHF and to multipronged strategies combining cancer and vaccination initiatives, public outreach, and physician training (6). Complementary approaches to increase coverage include allowing pharmacists to immunize children and implementing reminder systems to prompt physicians to offer the vaccine (13–15). In addition, states that supplement federal and private sector measures with local funding have been able to achieve significantly greater HPV coverage (7).

All HPV models are limited by epidemiological and clinical uncertainty, particularly with respect to HPV and vaccine-induced immunity. We assumed no interactions among HPV types. Cohort studies have found some evidence of interactions among types for women with abnormal cytology but not for the general population (16, 17), although models have shown that type interactions may exist in the general population at levels that are difficult to detect (18, 19). However, type interactions and postvaccination type replacement is of less concern for the nonavalent vaccine that targets most oncogenic types than for the bivalent or quadrivalent vaccines (20).

Recent studies have indicated that fewer than three doses may be sufficient to confer protection against HPV, although the duration of such protection is unknown (21–24). Because the possibility of one- or two-dose vaccination schedules is promising but inconclusive, we conservatively assumed that the full three doses are necessary to achieve lasting protection against any serotype. Should future clinical trials of lower dose schedules demonstrate enduring protection comparable to that achieved by a three-dose schedule (25), vaccination would be even more effective and cost-effective than shown in our projections. In addition, our findings that a vaccine dose has the greatest impact in states with lower coverage and that every state benefits from cooperative vaccination policies are direct consequences of interstate migration and therefore are robust to assumptions of dose efficacy.

Despite ongoing research, considerable empirical uncertainty remains regarding the natural history of HPV infection and the factors that affect the progression to cervical intraepithelial neoplasia (CIN). For our model we parameterized the rates of HPV progression, cross-protection, and clearance from the control arm of the PATRICIA clinical trial (26, 27). Although these data are currently the most detailed estimates available, they are potentially biased by not representing a random sample of the US population and by having been collected from clinical observations at regular follow-up appointments. However, any such biases do not affect our projections significantly, as demonstrated by our model validation.

Finally, because of limited data, our model does not differentiate between the sexual behavior and vaccination decision-making of individuals who move to another state and individuals who do not leave their home state. Some migrants may, after moving, maintain sexual relationships in their previous state which would introduce cross-state transmission. Individual-based models may be used to incorporate heterogeneity in sexual risk behavior and vaccination decision-making explicitly (12, 28, 29). Such individual-level heterogeneity may interact dynamically with heterogeneities in state-specific screening or vaccination. Our differential-equation model, although accounting for variance in the number of sexual partners, does not explicitly model individual heterogeneity in sexual risk behavior. However, any such effect will be minor relative to the magnitude of within-state transmission.

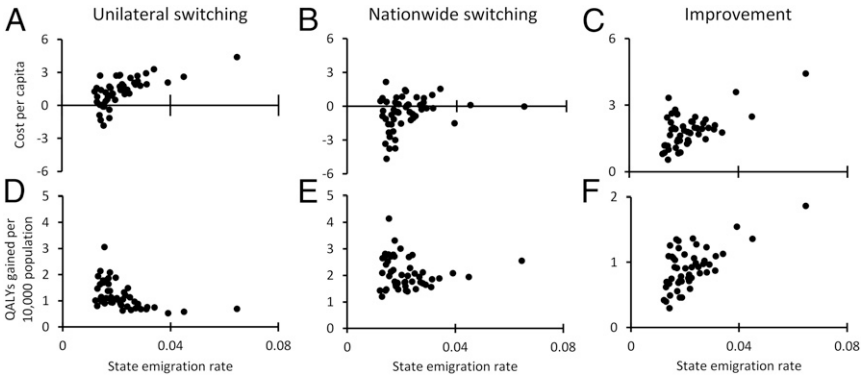

Fig. 5. From the perspective of each state: Cost per capita (*A–C*) and QALYs gained per 10,000 population (*D–F*) if the state unilaterally switches to 9vHPV (*A* and *D*) or all states switch to 9vHPV (*B* and *E*). *C* and *F* show the improvement in each outcome if all states switch to 9vHPV compared with each state unilaterally switching to 9vHPV.

Considerable public health improvements and cost savings can be achieved by switching to 9vHPV. Because of these cost savings and the difficulty of achieving high coverage among adolescents, health agencies may consider prioritizing switching to 9vHPV while expanding coverage. Moreover, any increases in coverage would produce the greatest benefits if these increases occur in states that presently have low coverage. If vaccination coverage and switches to the nonavalent vaccine are coordinated across states, every state will reduce cervical cancer incidence and deaths as well as expenditure.

Methods

Overview. We developed an age-structured compartmental model of HPV infection, cervical cancer, vaccination, and interstate migration for 50 states as well as Washington, DC. We specified 24 age groups: 11 y and younger, each year of age from 12 through 26 y, 5-y increments for ages 27 y through 46 y, 10-year increments for ages 47 y through 76 y, and 77 y and older. We parameterized state-specific birth and age-specific death rates from the US National Vital Statistics Reports (30, 31) and initialized the population based upon age, gender, and state profiles from the American Community Survey (32). The annual number of international immigrants to each state was parameterized by combining estimates of age, gender, and state-specific legal immigration as well as illegal immigration (Dataset S1).

To calculate the probability that an individual will emigrate between states, we extracted the age- and state-specific 5-y migration rates from the 2000 US Census (33). These 5-y migration rates are less sensitive than single-year migration rates to return migration, in which an individual returns to a state within a few years, and to onwards migration, in which an individual moves among several states over a brief period (34). We obtained the interstate migration matrix from the American Community Survey, combining data from 2005–2013 to compensate for short-term migratory trends (32) (Dataset S1).

Sexual Mixing. We represented sexual partnerships through direct contact mixing, based upon age- and gender-specific rates of partnership formation estimated from the National Survey for Family Growth (35). To estimate age-specific mixing between men and women, we combined data from adolescent behavior surveys (36), young adult surveys (37), and marriage trends (38) (Dataset S1). We modeled frequency-dependent heterosexual HPV transmission as the product of the per partner transmission rate, the age- and gender-specific rate of partnership formation, the age distribution of sexual partners, and the age-specific proportion of partners who are infected (*SI Appendix*).

Epidemiology. We represented men and women as susceptible, infected, recovered, or vaccinated against HPV, distinguishing between 2vHPV, 4vHPV, and 9vHPV. Equations and detailed parameter tables are provided (*SI Appendix*, Table S1). We parameterized the type-specific HPV clearance rate in women and the type-specific antibody protection against reinfection from the control arm of the PATRICIA clinical trial (26, 39), the type-specific clearance rate in men from the HIM cohort study (40), the type-specific probability of developing antibodies from the Slovenian HPV prevalence survey (41), and the type-specific rate of antibody decay from the Finnish Family HPV study (42).

Building on previous cervical cancer progression models (43, 44), we assumed that HPV infection leads to CIN grades 2 (CIN-2) or 3 (CIN-3) at serotype-specific rates (39). CIN-2 and CIN-3 are detected at state- and age-specific rates of cervical screening, estimated from the Behavioral Risk Factor Surveillance System, incorporating test sensitivity (45, 46). If untreated, CIN-2 may progress to CIN-3, and either CIN-2 or CIN-3 may progress to local cervical cancer (LCC) (45–47). In addition, CIN-2 and CIN-3 may regress spontaneously (47, 48). Undiagnosed LCC progresses to regional cervical cancer (RCC), and undiagnosed RCC progresses to distant cervical cancer (DCC) with mortality increasing at each stage (44). LCC, RCC, and DCC may be detected at incrementally higher rates, with diagnosed cancers subject to treatment and cure at progressively lower rates. We assumed the risk of developing CIN-2, CIN-3, or cervical cancer to be independent of age (47, 49).

We independently modeled HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, and 58. We assumed that HPV types do not interact. Because concurrent HPV infections increase the cervical cancer risk approximately linearly (39, 50), we summed cervical cancer incidence and mortality across the 10 types.

Calibration. We defined uncertainty distributions for each model parameter from the epidemiological and clinical literature. We then used Markov Chain Monte Carlo simulation to calibrate our model without the vaccination component to prevaccine era serotype-specific female-age seroprevalence, male seroprevalence, cervical cancer incidence, and ratio of female–male transmission to male–female transmission. To obtain serotype-specific parameter estimates and posterior distributions for the female–male and the male–female transmission rates, we conducted this calibration procedure for each of the 10 HPV types (*SI Appendix*).

Validation. To validate our model, we compared model-predicted cervical cancer incidence with the state-specific estimates over the period 2003–2006. We found close agreement between our model and the data, with the empirical estimate falling within the 95% CI of our model predictions for 48 of 51 states (*SI Appendix*).

Vaccine Efficacy. We parameterized type-specific and cross-protective efficacies for 2vHPV, 4vHPV, and 9vHPV from the corresponding phase III clinical trials (4, 51–55). Because 9vHPV has been shown to be immunogenic in males (56) but efficacy estimates of 9vHPV in males are not yet available, we used the same efficacy for both males and females. Clinical trials and statistical projections have demonstrated sustained efficacy with no detectable waning for both 2vHPV and 4vHPV (57–59). Although recent studies suggest that protective efficacy may be conferred by incomplete vaccine regimens, the long-term efficacy for a subdose vaccine regimen is presently inconclusive (21–24). Therefore, we conservatively assumed that the full three-dose regimen is required to protect against HPV.

To model vaccination coverage, we initialized age- and state-specific rates of vaccination among men and women. We conservatively assumed no further catch-up vaccination among adults and modeled adolescent vaccination before sexual debut at state-, age-, and gender-specific rates. We incorporated a scale-up period in adolescent vaccination from 2008 to 2014, the most recent year for which data were available (6, 10, 60–64). State-specific coverage and series completion among girls ranged from 20% to 57%, with a median of 40% full-series coverage in New Mexico (Fig. 1). For our base case, we assumed that adolescent vaccination continued at 2014 coverage (6, 60–62). Before the availability of 9vHPV in 2015, we assumed that all vaccinated males received 4vHPV and that 50% of vaccinated females received 2vHPV and the others received 4vHPV (3).

Cost-Effectiveness. We calculated the net present value costs and effectiveness associated with each vaccination strategy from the societal perspective at both the national and at the state level, assuming an annual 3% discount rate, from 2015 to 2050 (65). To calculate costs, we summed the cost of vaccination with administration, assuming $129 per dose for 2vHPV, $135 per dose for 4vHPV, and $148 per dose of 9vHPV (*SI Appendix*, Table S1), as well as treatment costs for CIN-2, CIN-3, LCC, RCC, and DCC (66, 67). To quantify effectiveness, we considered the total QALYs under each scenario, assigning established weights to CIN-2, CIN-3, LCC, RCC, and DCC (66, 67).

We compared the health and economic impact of varying adolescent coverage and the degree to which vaccine providers switch from 2vHPV/4vHPV to 9vHPV. We considered six coverages: (*i*) current state-specific rates; increases of (*ii*) 10%, (*iii*) 20%, (*iv*) 30%, and (*v*) 40% in the fraction of the population covered; and (*vi*) 100% adolescent coverage. For each coverage, we also considered the proportion switching to 9vHPV as (*i*) none, (*ii*) 0.25, (*iii*) 0.5, and (*iv*) complete switching. We computed the QALYs gained, vaccination costs, and total societal costs for each of the 24 scenarios (*SI Appendix*).

Data analysis and visualization were aided by Daniel's XL Toolbox (68).

ACKNOWLEDGMENTS. This research was funded by NIH Grants 2 U01 GM087719 and 5 U01 GM105627, by James S. McDonnell Foundation Grant 220020114, and by the Canadian Institutes of Health Research Grant 450024. Simulations were run on the Yale University Biomedical High Performance Computing Center, which is supported by NIH Grants RR19895 and RR029676-01.

1. Dunne EF, et al. (2007) Prevalence of HPV infection among females in the United States. *JAMA* 297(8):813–819.
2. Petrosky E, et al.; Centers for Disease Control and Prevention (CDC) (2015) Use of 9-valent human papillomavirus (HPV) vaccine: Updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep* 64(11):300–304.
3. Dunne EF, et al.; Centers for Disease Control and Prevention (CDC) (2011) Recommendations on the use of quadrivalent human papillomavirus vaccine in males–Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep* 60(50):1705–1708.
4. Joura EAEA, et al.; Broad Spectrum HPV Vaccine Study (2015) A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med* 372(8):711–723.
5. Markowitz LE, et al.; Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices (ACIP) (2007) Quadrivalent human papillomavirus vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 56(RR-2):1–24.

6. Reagan-Steiner S, et al. (2015) National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 Years–United States, 2014. *MMWR Morb Mortal Wkly Rep* 64(29):784–792.
7. Dorell CG, Markowitz LE, Hariri S, Stokley S, Yankey D (2013) 16. The Role of State Human Papillomavirus (HPV) Vaccine Financing and Legislative Policies on HPV Vaccination Rates Among Girls, 13-17 Years, National Immunization Survey-Teen, 2008 and 2010. *J Adolesc Health* 52(2):S28.
8. Colgrove J, Abiola S, Mello MM (2010) HPV vaccination mandates–lawmaking amid political and scientific controversy. *N Engl J Med* 363(8):785–791.
9. Laugesen MJ, et al. (2014) Early policy responses to the human papillomavirus vaccine in the United States, 2006-2010. *J Adolesc Health* 55(5):659–664.
10. Dorell C, Stokley S, Yankey D, Cohn A, Markowitz L (2010) National, state, and local area vaccination coverage among adolescents aged 13-17 years—United States, 2009. *MMWRMorb Mortal Wkly Rep* 59(32):1018–1023.
11. Barton GR, Briggs AH, Fenwick EA (2008) Optimal cost-effectiveness decisions: The role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). *Value Health* 11(5):886–897.
12. Ryser MD, McGoff K, Herzog DP, Sivakoff DJ, Myers ER (2015) Impact of coverage-dependent marginal costs on optimal HPV vaccination strategies. *Epidemics* 11:32–47.
13. Gilkey MB, Malo TL, Shah PD, Hall ME, Brewer NT (2015) Quality of physician communication about human papillomavirus vaccine: Findings from a national survey. *Cancer Epidemiol Biomarkers Prev* 24(11):1673–1679.
14. Brewer NT, Chung JK, Baker HM, Rothholz MC, Smith JS (2014) Pharmacist authority to provide HPV vaccine: Novel partners in cervical cancer prevention. *Gynecol Oncol* 132(Suppl 1):S3–S8.
15. Stokley S, et al. (2013) Human papillomavirus vaccination coverage among adolescent girls, 2007-2012, and postlicensure vaccine safety monitoring, 2006-2013 - United States. *MMWR Morb Mortal Wkly Rep* 62(29):591–595.
16. Yang Z, Cuzick J, Hunt WC, Wheeler CM (2014) Concurrence of multiple human papillomavirus infections in a large US population-based cohort. *Am J Epidemiol* 180(11):1066–1075.
17. Dickson EL, Vogel RI, Bliss RL, Downs LS, Jr (2013) Multiple-type human papillomavirus (HPV) infections: A cross-sectional analysis of the prevalence of specific types in 309,000 women referred for HPV testing at the time of cervical cytology. *Int J Gynecol Cancer* 23(7):1295–1302.
18. Durham DP, Poolman EM, Ibuka Y, Townsend JP, Galvani AP (2012) Reevaluation of epidemiological data demonstrates that it is consistent with cross-immunity among human papillomavirus types. *J Infect Dis* 206(8):1291–1298.
19. Lía Murall C, McCann KS, Bauch CT (2014) Revising ecological assumptions about Human papillomavirus interactions and type replacement. *J Theor Biol* 350:98–109.
20. Safaeian M, Rodriguez AC (2014) Invited commentary: Multiple human papillomavirus infections and type replacement-anticipating the future after human papillomavirus vaccination. *Am J Epidemiol* 180(11):1076–1081.
21. Safaeian M, et al.; CVT Group (2013) Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. *Cancer Prev Res (Phila)* 6(11):1242–1250.
22. Kahn JA, Bernstein DI (2013) HPV vaccination: Too soon for 2 doses? *JAMA* 309(17):1832–1834.
23. Kreimer AR, et al.; Costa Rica Vaccine Trial and PATRICIA study groups (2015) Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: Combined analysis of data from the Costa Rica Vaccine and PATRICIA trials. *Lancet Oncol* 16(7):775–786.
24. Dobson SRM, et al. (2013) Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: A randomized clinical trial. *JAMA* 309(17):1793–1802.
25. Kreimer AR, Sherman ME, Sahasrabuddhe VV, Safaeian M (2015) The case for conducting a randomized clinical trial to assess the efficacy of a single dose of prophylactic HPV vaccines among adolescents. *J Natl Cancer Inst* 107(3):dju436.
26. Castellsagué X, et al. (2014) Risk of newly detected infections and cervical abnormalities in women seropositive for naturally acquired human papillomavirus type 16/18 antibodies: Analysis of the control arm of PATRICIA. *J Infect Dis* 210(4):517–534.
27. Wilson L, et al. (2014) Seroprevalence of 8 oncogenic human papillomavirus genotypes and acquired immunity against reinfection. *J Infect Dis* 210(3):448–455.
28. Van de Velde N, et al. (2012) Population-level impact of the bivalent, quadrivalent, and nonavalent human papillomavirus vaccines: A model-based analysis. *J Natl Cancer Inst* 104(22):1712–1723.
29. Brisson M, et al. (2016) Health and Economic Impact of Switching from a 4-Valent to a 9-Valent HPV Vaccination Program in the United States. *J Natl Cancer Inst* 108(1):djv282.
30. Arias E (2012) United States life tables, 2008. *Natl Vital Stat Rep* 61(3):1–63.
31. Martin JA, et al. (2012) Births: Final data for 2010. *Natl Vital Stat Rep* 61(1):1–72.
32. US Census Bureau (2016) American Community Survey Public Use Microdata Sample. Available at https://www.census.gov/programs-surveys/acs/data/pums.html. Accessed December 3, 2015.
33. US Census Bureau (2003) Census 2000 Public Use Microsdata Sample. Available at www.census.gov/main/www/cen2000.html. Accessed December 3, 2015.
34. Rogers A, Little J, Raymer J (2010) *The Indirect Estimation of Migration: Methods for Dealing with Irregular, Inadequate, and Missing Data* (Springer Science & Business Media) Available at: https://books.google.com/books?hl=en&lr=&id=vhKbjxhpvKYC&pgis=1. Accessed March 19, 2015.
35. National Center for Health Statistics (2015) National Survey of Family Growth, 2011–2013. Available at www.cdc.gov/nchs/nsfg/nsfg_2011_2013_puf.htm. Accessed December 3, 2015.
36. Kaestle CE, Morisky DE, Wiley DJ (2002) Sexual intercourse and the age difference between adolescent females and their romantic partners. *Perspect Sex Reprod Health* 34(6):304–309.
37. Martinez G, Chandra A, Abma J, Jones J, Mosher W (2006) Fertility, contraception, and fatherhood: Data on men and women from Cycle 6 (2002) of the National Survey of Family Growth. *Natl Cent Heal Stat Vital Heal Stat* 23(26):1–142.
38. Goodwin PY, Mosher WD, Chandra A (2010) Marriage and cohabitation in the United States: A statistical portrait based on cycle 6 (2002) of the National Survey of Family Growth. *Vital Health Stat 23* 23(28):1–45.
39. Jaisamrarn U, et al.; HPV PATRICIA Study Group (2013) Natural history of progression of HPV infection to cervical lesion or clearance: Analysis of the control arm of the large, randomised PATRICIA study. *PLoS One* 8(11):e79260.
40. Giuliano AR, et al. (2011) Incidence and clearance of genital human papillomavirus infection in men (HIM): A cohort study. *Lancet* 377(9769):932–940.
41. Faust H, et al. (2013) Serum antibodies to human papillomavirus (HPV) pseudovirions correlate with natural infection for 13 genital HPV types. *J Clin Virol* 56(4):336–341.
42. Syrjänen S, et al. (2009) Dynamics of human papillomavirus serology in women followed up for 36 months after pregnancy. *J Gen Virol* 90(Pt 6):1515–1526.
43. Elbasha EH, Dasbach EJ, Insinga RP (2007) Model for assessing human papillomavirus vaccination strategies. *Emerg Infect Dis* 13(1):28–41.
44. Campos NG, et al. (2014) An updated natural history model of cervical cancer: Derivation of model parameters. *Am J Epidemiol* 180(5):545–555.
45. Gage JC, et al. (2014) Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. *J Natl Cancer Inst* 106(8):dju153.
46. Arbyn M, et al. (2012) Evidence regarding human papillomavirus testing in secondary prevention of cervical cancer. *Vaccine* 30(Suppl 5):F88–F99.
47. McCredie MRE, et al. (2008) Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: A retrospective cohort study. *Lancet Oncol* 9(5):425–434.
48. Moscicki A-B, et al. (2010) Rate of and risks for regression of cervical intraepithelial neoplasia 2 in adolescents and young women. *Obstet Gynecol* 116(6):1373–1380.
49. Rodríguez AC, et al. (2010) Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: Critical role of duration of infection. *J Natl Cancer Inst* 102(5):315–324.
50. Chaturvedi AK, et al.; CVT Group (2011) Human papillomavirus infection with multiple types: Pattern of coinfection and risk of cervical disease. *J Infect Dis* 203(7):910–920.
51. Lehtinen M, et al.; HPV PATRICIA Study Group (2012) Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol* 13(1):89–99.
52. Ault KA; Future II Study Group (2007) 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. *Lancet* 369(9576):1861–1868.
53. Brown DR, et al. (2009) 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. *J Infect Dis* 199(7):926–935.
54. Wheeler CM, et al.; HPV PATRICIA Study Group (2012) Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. *Lancet Oncol* 13(1):100–110.
55. Giuliano AR, et al. (2011) Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *N Engl J Med* 364(5):401–411.
56. Castellsagué X, et al. (2015) Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine* 33(48):6892–6901.
57. Naud PS, et al. (2014) Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: Final analysis of a long-term follow-up study up to 9.4 years post-vaccination. *Hum Vaccin Immunother* 10(8):2147–2162.
58. Villa LL, et al. (2006) High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *Br J Cancer* 95(11):1459–1466.
59. David M-P, et al. (2009) Long-term persistence of anti-HPV-16 and -18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: Modeling of sustained antibody responses. *Gynecol Oncol* 115(3, Suppl):S1–S6.
60. Dorell C, et al.; Centers for Disease Control and Prevention (CDC) (2012) National and state vaccination coverage among adolescents aged 13-17 years–United States, 2011. *MMWR Morb Mortal Wkly Rep* 61(34):671–677.
61. Robinette Curtis C, et al.; Centers for Disease Control and Prevention (CDC) (2013) National and state vaccination coverage among adolescents aged 13-17 years–United States, 2012. *MMWR Morb Mortal Wkly Rep* 62(34):685–693.
62. Elam-Evans LD, et al.; Immunization Services Division, National Center for Immunization and Respiratory Diseases; Centers for Disease Control and Prevention (CDC) (2014) National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years–United States, 2013. *MMWR Morb Mortal Wkly Rep* 63(29):625–633.
63. Stokley S, Dorell C, Yankey D (2009) National, state, and local area vaccination coverage among adolescents aged 13-17 years - United States, 2008. *MMWR Morb Mortal Wkly Rep* 58(36):997–1001.
64. Dorell C, Stokley S, Yankey D, Liang JL, Markowitz L (2011) National and state vaccination coverage among adolescents aged 13 through 17 years—United States, 2010. *MMWR Morb Mortal Wkly Rep* 60:1117–1123.
65. Gold MR, Siegel JE, Russell LB, Weinstein MC, eds (1996) *Cost-Effectiveness in Health and Medicine* (Oxford Univ Press, New York).
66. Chesson HW, Ekwueme DU, Saraiya M, Dunne EF, Markowitz LE (2011) The cost-effectiveness of male HPV vaccination in the United States. *Vaccine* 29(46):8443–8450.
67. Kim JJ, Goldie SJ (2008) Health and economic implications of HPV vaccination in the United States. *N Engl J Med* 359(8):821–832.
68. Kraus D (2014) Consolidated data analysis and presentation using an open-source add-in for the Microsoft Excel® spreadsheet software. *Medical Writing* 23(1):25–28.