Two decades of the HPV vaccine: its promise, progress, prospects, projections, and posterity

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Summary

Since its 2006 FDA approval, the Human Papillomavirus (HPV) vaccine has transformed the prevention of cervical, oropharyngeal, and other HPV-associated cancers in the United States. Despite notable progress, with 78.2% of adolescents initiating and 62.9% completing vaccination, support for the vaccine is at a critical point. Because the Department of Health and Human Services (HHS) mainly provides recommendations, state-level action is crucial. Only five states and territories have adopted school-entry HPV vaccination requirements, but with varying enforcement policies. Uptake varies across the U.S., from Massachusetts' 79.8% completion to Mississippi's 39.1%. Evidence shows that school-entry requirements can significantly improve vaccination rates. As we approach the vaccine's twentieth anniversary, maintaining the current gains and achieving the 80% Healthy People 2030 target for series completion demands a multipronged approach. State policies must become more robust, especially if federal support wanes. Preventing HPV-related cancers for future generations depends on continued progress. By prioritizing policy that strengthens prevention and access, states can safeguard this progress.

Keywords: Health policy; HPV vaccine; Human papillomavirus; Cancer

Promise

Human Papillomavirus (HPV) is the most prevalent sexually transmitted infection in the US. A significant portion of adult women and men are positive for HPV (45 and 40%, respectively) at any given time.[1] HPV is the most common sexually transmitted infection in the US and worldwide, with an estimated 42 million Americans already infected with a type of the virus known to cause cancer, and 13 million new infections every year.[2] The ubiquity of this virus has transformed the incidence of these cancers, with more than 90% of cervical cancer and approximately 80% of oropharyngeal cancer cases associated with the virus.[3,4]

HPV types 16 and 18 are the most common high risk variants that are associated with cervical, anal, vulvar, vaginal, penile, and oropharyngeal (OPC) cancers; these variants cause 90% of HPV positive cancers globally.[1,5] Less common variants—types 31, 33, 45, 52, and 58 are also causally associated with these cancers.[5] The first HPV vaccine, a quadrivalent vaccine, was approved by the Food and Drug Administration (FDA) in 2006 for females between 9 and 26 years of age and targeted 4 types of HPV.[5] This vaccine targeted two low risk types (6 and 11) that are associated with genital warts and recurrent respiratory papillomatosis and the two common high risk types (16 and 18).[5] The vaccine was later approved for males in 2009, with routine vaccination of males recommended in 2011. In 2016, a 9-valent vaccine was approved by the FDA, which targets the 4 types covered by the quadrivalent vaccine along with five additional high risk types: 31,33, 45, 52, and 58.[1,5] This vaccine is considered the gold standard in preventing HPV related cancers and received an indication for the prevention of oropharyngeal cancer in 2020.[1] The expansion to males and indication for oropharyngeal cancer prevention are of particular importance. The HPV infection rate among males in the US has been increasing significantly and the infection rate among males is expected to surpass the infection of females.[5] Moreover, the incidence of

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oropharyngeal cancer is much higher in males than in females and the overall OPC incidence has far exceeded the cervical cancer incidence in the US.[5] The US Department of Health and Human Services' Healthy People 2030 outlines an HPV national vaccination completion target of 80%.[6] Reaching this target can have profound implications. For example, a 2019 study found that vaccine coverage of 80% among a female cohort 12 and younger—in comparison to the 30% coverage at the time of the study—is expected to decrease lifetime cervical cancer incidence by 53,300 cases and cervical cancer deaths by 17,100 just among this population.[7]

Progress and prospects

There has been an overall national increase in HPV vaccine initiation and completion nationally. Currently, 78.2% of eligible adolescents between 13 and 17 years of age have received at least one dose of the HPV, with about 62.9% up to date on their vaccine dose.[8] This is below, but approaching, the national target of 80%, as stipulated in the Healthy People 2030 initiative.[3] Table 1 demonstrates the HPV vaccine initiation rate (at least one dose) and completion rate in 13–17-year-olds in 2024 by state and territory.[8] The benefit and spanning impact of the HPV vaccine cannot be understated. Cervical cancer mortality in the US among females under 25 declined significantly between 2016 and 2021, the first population of females broadly protected by the vaccine.[9] A just released study examining cervical precancer trends in the US between 2008 and 2022 found a 79% decrease in lower-grade cervical precancer—cervical intraepithelial neoplasia (CIN) grade 2—incidence among 20–24 year olds, an 80% decreased in higher-grade cervical precancer (CIN grade 3) incidence among 20–24 year olds, and a 37% decrease in higher-grade cervical precancer among 25–29 year olds.[10] These results show the beginning of the massive positive impact of the HPV vaccine, which will continue to pay dividends for years to come if vaccination progress continues. These benefits have been demonstrated internationally, with a 2020 study showing that females in Sweden between 10 and 30 who had been vaccinated for HPV had a significantly reduced risk for invasive cervical cancer.[11] A study from Scotland similarly found that complete HPV vaccination of females between the ages of 14 and 22 or even partial vaccination of females between the ages of 12 and 13 significantly reduced invasive cervical cancer incidence.[12] These international findings suggest that the vaccine is already having a substantial impact on reproductive health, as the reduced incidence in cervical cancer will lead to a reduction in the number of people requiring treatment and excision of cervical lesions. The true impact of the HPV vaccine will be seen in the years to come. At the current rates of vaccination and screening, Australia is

State	HPV initiation (%)	HPV completion (%)
Massachusetts	87.5	79.8
Puerto Rico[a]	91.8	77
Rhode Island[a]	91.3	76.1
District of Columbia[a]	89.3	75.8
Hawaii[a]	89.2	75.6
New Hampshire	83.8	72.2
Virginia[a]	86.9	71.9
Washington	83.5	71.8
Vermont	85.2	71.7
New York	81.7	70.4
North Dakota	82.9	70.4
South Dakota	82.5	70
Maryland	84.5	69.2
Delaware	84.1	69
Minnesota	83.3	67.7
Arizona	81.2	67.4
Ohio	81.8	67.3
Wisconsin	77.7	67.2
Connecticut	78.6	67
Maine	75.6	66.9
North Carolina	80	66.8
New Mexico	82	66.7
Illinois	80.2	66.2
California	82	66
Oregon	81.9	65.8
Louisiana	74.5	65.8
Michigan	80.8	65.6
Georgia	74.5	65.3
Colorado	80.6	64.3
Nebraska	80.1	64.1
Pennsylvania	75	63.3
Kentucky	75	61.1
Alabama	77.7	60.9
Arkansas	80.7	60.3
Montana	75.4	59.8
Iowa	71.6	59.8
Kansas	72.5	59.7
South Carolina	74.6	59.5
Florida	84.2	59
New Jersey	73.1	58.6
Utah	81.8	57.5
Indiana	73.2	56.6
Nevada	71.6	56.1
Idaho	70.7	55.9
West Virginia	72.4	55.6
Tennessee	73	54.3
Missouri	69.4	52.7
Texas	69.9	52.2
Alaska	69.7	51.8
Oklahoma	68	49.7
Wyoming	69.2	47.1
Guam	72.9	43.1
Mississippi	58.6	39.1

[a]States with Vaccine School-Entry Requirements.

Table 1: **2024 US HPV vaccination initiation and completion rates of adolescents ages 13–17.**

expected to eliminate cervical cancer as a public health issue by 2040.[13] The long-term benefits of the HPV vaccine will also extend to OPC, with a decrease in the incidence of OPC among young and middle-aged adults by 2045.[14] We are also seeing the impact of low HPV vaccination. For example, a 2024 study by Adekanmbi et al. found that Texas counties with lower HPV vaccination rates had higher incidence rates of HPV-related cancers.[15]

There is a wide variety of factors affecting HPV vaccine uptake in the US. Counterintuitively, vaccination is lower among adolescents from households with higher incomes compared to those with lower incomes.[16] A 2019 meta-analysis found that Black and Latino adolescents were more likely to initiate the HPV vaccine compared to white adolescents, when using provider-verified vaccination data.[17] Conversely, both Black and Latino adolescents were less likely to complete their HPV vaccinations compared to white adolescents.[17] Rurality also plays a key role in vaccine initiation and completion, with rural populations being significantly less likely to initiate and complete the HPV vaccine regimen.[18] Additionally, there is a gender divide in vaccination rates: males consistently trail females in HPV vaccination rates. Additionally, this trend is shown among 27–45-year-olds, an age group that gained eligibility for the vaccine in 2018.[19] Regional and state differences persist in HPV vaccine initiation and completion (see Figs. 1 and 2). For example, while states like Rhode Island and Massachusetts have over 75% of adolescents between 13 and 17 who have completed the vaccine series, completion is under 55% in southern states such as Mississippi, Oklahoma, and Texas.[8]

Projections and possibilities

HPV vaccine recommendations and uptake in the United States have dramatically evolved since the Food and Drug Administration (FDA) approved the HPV vaccine in 2006.[1,5] The current recommendation is routine vaccination at ages 11–12 years, as part of the early adolescent immunization platform that also includes the tetanus, diphtheria, and pertussis booster (Tdap) and meningococcal ACWY vaccines. HPV vaccination is also routinely recommended for ages 14–26 years and can be initiated as early as nine years of age. The AAP has endorsed routine HPV vaccination for all children ages nine to twelve years of age.[20]

The US Department of Health and Human Services (HHS) oversees federal agencies that approve, recommend, and monitor vaccines, including the Food and Drug Administration (FDA) and Center for Disease Control (CDC).[21] Outside of specific health

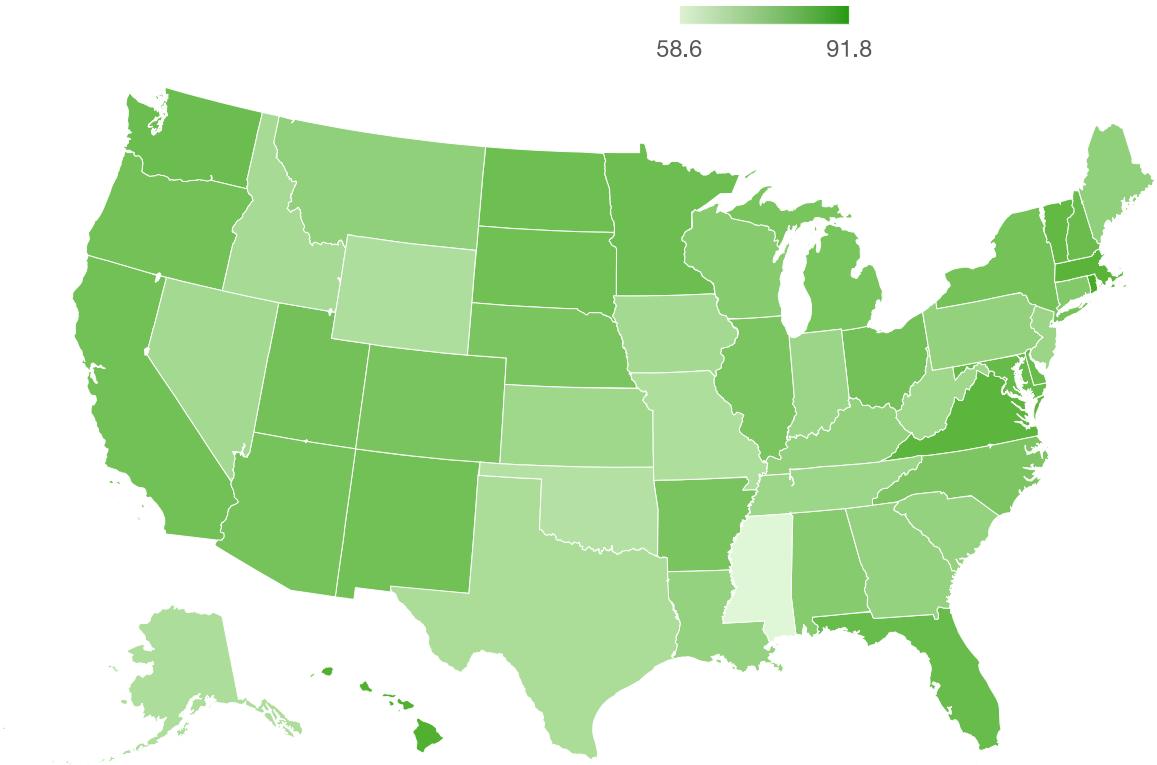

Fig. 1: HPV vaccine initiation rate. 2024 HPV vaccine initiation rate in the US among 13- to 17-year-old adolescents.

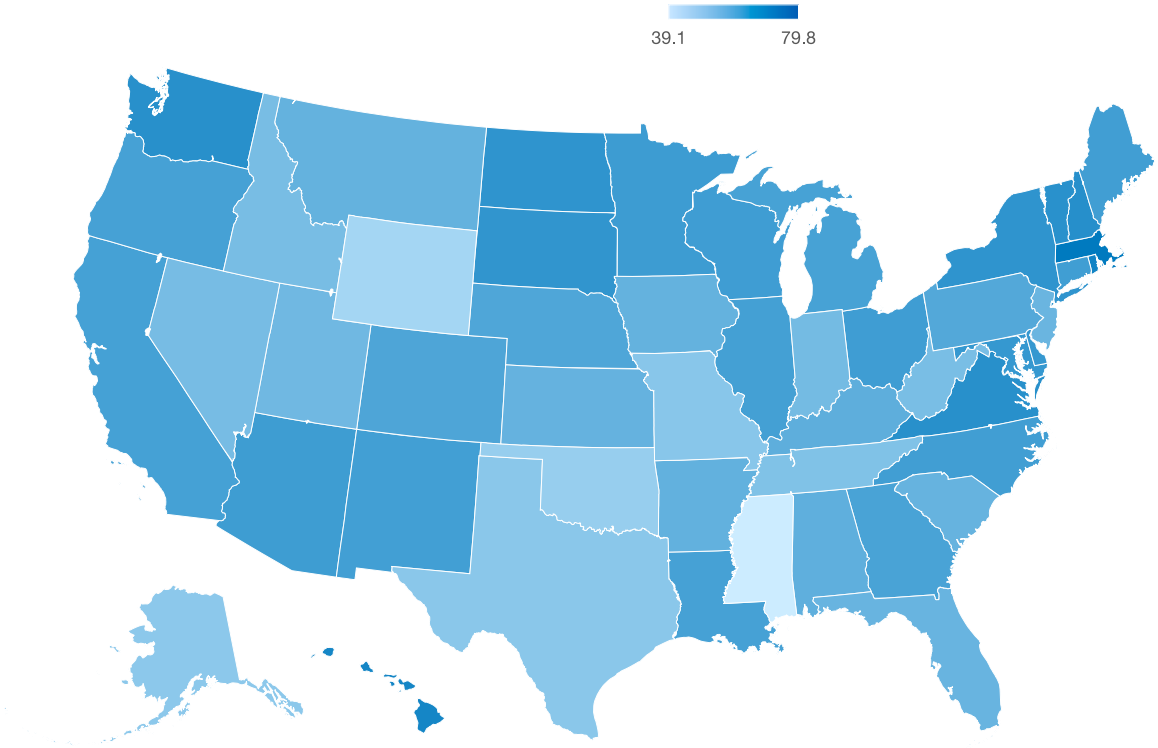

Fig. 2: HPV vaccine completion rate. 2024 HPV vaccine completion rate in the US among 13- to 17-year-old adolescents.

emergencies, HHS cannot implement or rescind vaccine requirements (those decisions rest with the states).[21] It can, however, shape federal policy by approvals and recommendations (see Fig. 3). This is done through two central advisory committees: the Vaccines and Related Biological Products Advisory Committee (VRBPAC) and the Advisory Committee on Immunization Practices (ACIP).[21] The VRBPAC advises the FDA on vaccine approval and regulation; however, the FDA is not required to seek input from the VRBPAC on vaccine approval.[21] Vaccines recommended by the ACIP for individuals 18 years old or younger, once adopted by the CDC, become part of the Vaccines for Children (VFC) program, which provides free vaccines (including HPV) to children whose parents or guardians otherwise cannot afford them.[21] The FDA commissioner, who reports to the Secretary of HHS, can appoint and replace members of the VRBPAC. The Secretary of HHS can appoint and replace members of the ACIP.[21]

Aside from the aforementioned vaccine approval and recommendation processes, vaccine policy lies with the states. Since it was first approved, there has been no national requirement or specifically targeted national policy regarding HPV vaccination.[22,23] The lack of a centralized policy allows each state to set its own policies and requirements. School entry vaccine requirements have long been an effective public health tool for US states to increase vaccine uptake and prevent disease.[24] The utilization of this strategy for HPV has been slow. Forty states, along with Puerto Rico and the District of Columbia, have introduced legislation to include the HPV vaccine in vaccines required for school entry, but only five have successfully implemented a school-entry requirement, and these five states/jurisdictions have had varying levels of enforcement.[25] While there is recent concern about support for the HPV vaccine on the federal level, states have and must continue to serve as the main player in protecting the HPV vaccination and ensuring its continued progress. We, as healthcare providers and advocates, must remain an active part of the public discourse, and advocate for proven, vital science.[26] Ahead of the twentieth anniversary of its approval, the HPV vaccine and HPV-related cancer prevention are threatened due to increasing HPV vaccine hesitancy and skepticism.[27] To ensure continued progress in combatting HPV-associated cancers, we must look towards state policies.

States with school-based HPV vaccine requirements

School-entry requirements have been implemented sparingly across the US (see Table 2). The Virginia General Assembly passed House Bill 2035 in 2007 (which went into effect in 2008), which required HPV

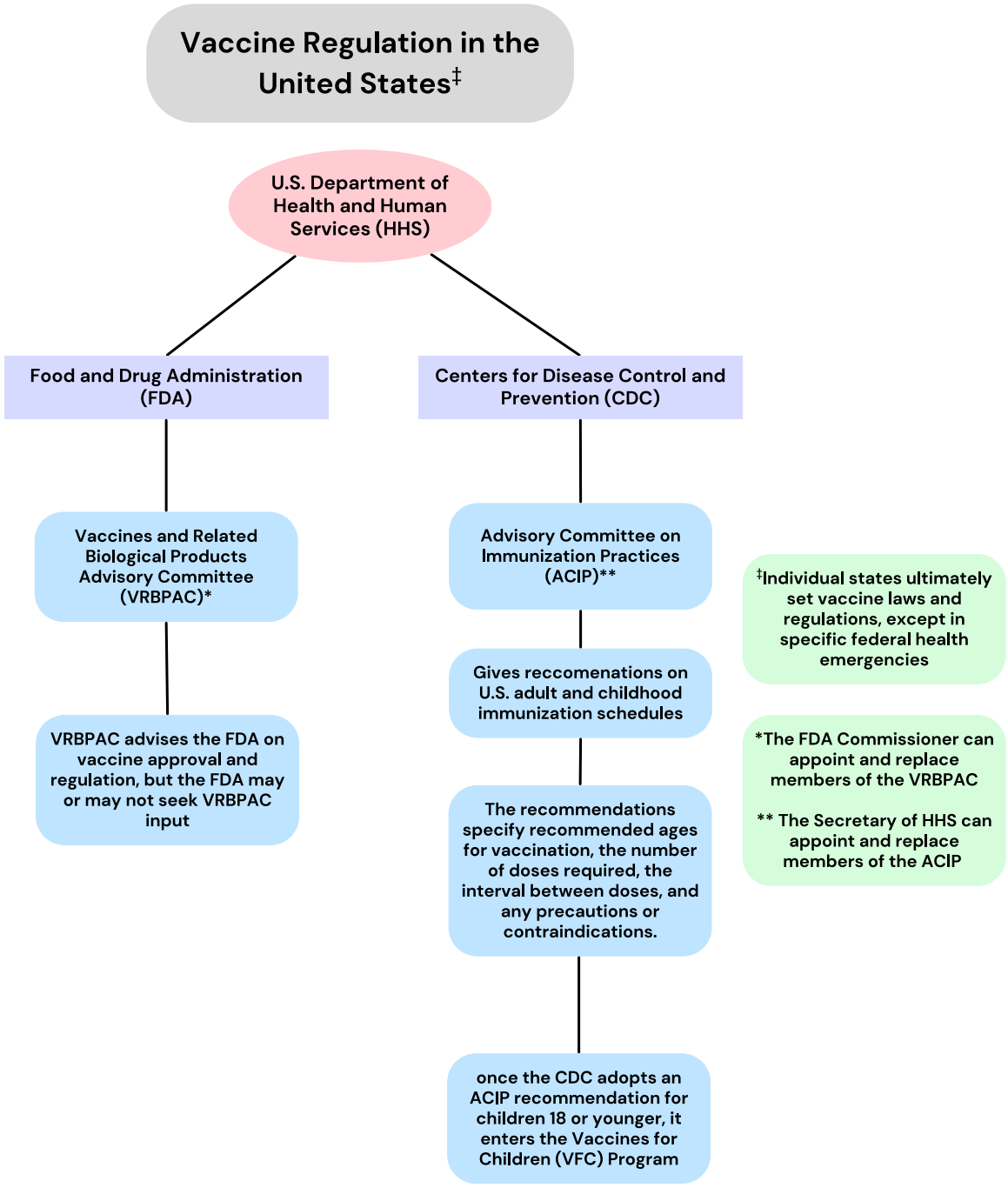

Fig. 3: Infographic of the federal government's role in vaccine policy and regulation.

vaccination for females entering 7th grade, but with no enforcement mechanism.[28] There are several exceptions, including parental objection based on religious belief, provider statement that the vaccine would be detrimental to the child's health, philosophical concerns, or sole parental discretion after reviewing state-approved HPV vaccine material that links HPV to cervical cancer.[29] In 2021, Virginia moved to include males in the HPV vaccine school entry requirement.[30] Virginia's vaccine completion rate is 71.9% and is among the top ten states and territories with the highest vaccine completion rates.[8]

State or territory	Type of vaccine requirement	Year of enactment	Strength of exemptions	HPV initiation (%)	HPV completion (%)
Hawaii	Administrative	2020	Strong Exemption Requirements	89.2	75.6
Puerto Rico	Legislative	2018	Strong Exemption Requirements	91.8	77
Rhode Island	Administrative	2015	Strong Exemption Requirements	91.3	76.1
District of Columbia	Legislative	2009	Lax Exemption Requirements	89.3	75.8
Virginia	Legislative	2008	Lax Exemption Requirements	86.9	71.9

Table 2: **US states and territories with HPV vaccine school requirements.**

The Council of the District of Columbia passed DC Law 17–10 in 2007, which requires female students to receive the HPV vaccine before entering seventh grade. This rule was amended and enacted in 2009 and required the HPV vaccination for all female students starting sixth grade.[27] This rule was amended in 2014 to include males starting sixth grade and led to improved vaccination rates.[31,32] There are multiple exceptions, including parental objection based on religious belief, provider statement that the vaccine would harm the child's health, or sole parental discretion for any reason.[33]

Rhode Island's Department of Health implemented a policy in 2015 that required all students entering seventh grade to receive the HPV vaccine and one dose a year until 9th grade.[29] Rhode Island has few exceptions to their requirement. Parents can opt out with a religious exemption or proof from a medical professional that the child should be exempt for medical reasons.[29] The state has one of the highest HPV vaccine completion rate (76.1%) and initiation rate (91.3%) in the country.[8]

Puerto Rico's Department of Health implemented an HPV vaccine requirement for public school students in 2018.[33,34] Puerto Rico has some of the highest rates of HPV-related cancers, including the highest rate of cervical cancer in all US states and territories.[35] This law intends to combat the growing prevalence of these cancers. Parents can opt out via a sworn religious declaration or a certification that shows the child cannot get the vaccine for medical reasons.[34,35] Their completion rate has now reached 77%.[8]

Most recently, Hawaii implemented Hawaii Administrative Rule 11–157 in 2020 to require HPV vaccination for students entering the seventh grade.[29] Hawaii has few exceptions to their requirement. Parents can opt out with religious exemption or proof from a medical professional that the child should be exempt for medical reasons.[29] Hawaii now has a vaccine completion rate of 75.6%.[8]

Other state policy strategies

There are other strategies that states have taken in HPV vaccine policy, including funding free or reduced-cost vaccines. Rhode Island has a law that covers the cost of any vaccine recommended by the ACIP, including the HPV vaccine.[29] Massachusetts has the Vaccine Purchase Trust Fund, which provides all federally recommended vaccines, including the HPV vaccine, free of charge.[29] New Hampshire funds all recommended vaccines for children through the age of 18, including the HPV vaccine, through their New Hampshire Immunization Program (NHIP).[31] Maine provides the HPV vaccine free of charge for any child ages nine to eighteen through the Universal Childhood Immunization Program.[29] While it is apparent the northeast is a leader in this space, Alaska, Colorado, Illinois, Louisiana, Mississippi, Maryland, Nevada, New Mexico, Ohio, Oklahoma, Oregon, Pennsylvania, and West Virginia have all implemented similar programs that reduce or cover the cost of the HPV vaccine.[23,29] However, a number of states that provide reduced cost or free vaccines such as West Virginia, Oklahoma, and Mississippi still have some of the lowest vaccine completion rates in the country.[8]

In addition, all 50 states and the District of Columbia now have policies that allow pharmacists to administer the HPV vaccine, with variations regarding age eligibility.[36] Oregon additionally allows dentists to administer the vaccine.[29] Allowing older adolescents to consent to the HPV vaccine themselves is another strategy to improve HPV vaccine access.[37] Three states have taken this approach: Illinois and California allow adolescents 12 and older while New York allows adolescents 14 and older to consent to the HPV vaccine without parental consent.[23,37,38] Additionally, the city of Philadelphia allows minors between 11 and 17 to consent for the HPV vaccine without parental consent.[37] Several states have laws that promote education on the HPV vaccine. In Illinois, for example, the Department of Public Health must create programming or strategic plans for HPV vaccination in their state.[23] Colorado, Indiana, Iowa, Michigan, Missouri, Montana, North Dakota, Texas, and Washington all have legislation that supports or requires HPV vaccine education in their states.[23] Finally, some states exclude the HPV vaccine from school vaccination requirements. Arizona, Louisiana, South Carolina, and West Virginia explicitly exclude the HPV vaccine from school requirements.[23]

Prognosis

State-level HPV vaccine policies will play a particularly vital role in protecting the progress of the HPV vaccine in the United States in the coming years. We found substantial variation in both policies and uptake, with rates as high as 79.8% in Massachusetts and as low as 39.1% in Mississippi.[8] Rhode Island, Puerto Rico, and Hawaii have among the most robust HPV vaccine school-entry requirements and associated policies in the country. The limited exemptions can be noted as a differentiator from Virginia and Washington DC.

The effects of these requirements have been overwhelmingly positive. Following its policy, Rhode Island increased the vaccination rate in the state, particularly among adolescent boys, and the policy led to better coverage at an earlier age among girls.[39] Rhode Island may already be seeing a positive impact in terms of cancer prevention. A study published in 2022, examined incidence of cervical precancerous lesions among females in Rhode Island.[40] They found a lower incidence among females between 20 and 29 years age compared to females between 30 and 39 years old.[40] The vaccine initiation rate in the District of Columbia increased substantially, particularly among males following implementation of its requirement.[32] The 2014 rule amendment also expanded the requirement to 6–12th grade and parents were required to opt-out every year, rather than a one-time opt-out.[31] These changes and earlier inclusion of males strengthen the requirement compared to Virginia, and likely have played a role in the higher vaccination rate in the District of Columbia.[31] The District of Columbia now has the fourth highest HPV vaccine completion rate in the country at 75.8%.[8] The initiation and completion rate in Puerto Rico also increased significantly and helped to reduce a previous gender disparity in vaccine uptake.[33] Puerto Rico now has one of the highest HPV vaccine completion rates in the US at 77% second only to Massachusetts.[8] There have not been, to our knowledge, literature published on the impact of Hawaii's requirement on HPV vaccination rates. The state, however, has historically had a completion close to the national average,[41] but now has one of the highest vaccine completion rates in the country (75.6%).[8]

The only school-entry requirement that did not, initially, have a significant impact on HPV vaccination rates was Virginia.[42] This was likely due to the lack of any enforcement mechanism, various exceptions associated with the law, which differentiates it from later requirements like Rhode Island's policy.[25] Additionally, the law only required females to receive the vaccine in the initial 2008 school entry requirement, and males were not included until 2021 when the policy was revised. The state has recently increased its vaccine completion rate and has the seventh highest vaccine completion rate in the country.[8]

Many states fund free or reduced-cost vaccines.[23] Some of these funding related policies are contingent on federal recommendation,[29] and should be adjusted in the scenario where the federal recommendation for the HPV vaccine is revoked. Other factors beyond policy inevitably influence vaccination rates, such as rural and socioeconomic disparities.[18,43,44] Another common issue is misconceptions and misinformation regarding the HPV vaccine among parents and guardians. This is a particular concern in the aftermath of COVID-19 and the associated increase in vaccine hesitancy and misinformation on social media.[45,46] Provider recommendations, funding, and education are all important factors that can improve vaccination rates.[47,48] These findings show the complexity of vaccine accessibility and acceptance, highlighting an opportunity for state HPV-specific policy solutions.

Aside from the vaccine recommendations, federal policy has and will continue to serve an important role in combatting HPV associated cancers. Models from countries that are on track to eliminate cervical cancer, such as Australia, have shown high levels of population coverage for HPV vaccination along with comprehensive preventative screening (i.e., HPV DNA testing and/or Papanicolaou Smears).[13] Robust policies providing individuals with insurance coverage and reducing barriers to access are needed in order for the US to match the success of other countries. Both HPV vaccination and cervical cancer screening rates have been shown to be lower in individuals who are uninsured.[49,50] The Affordable Care Act (ACA) has played a transformative role in addressing this disparity. A recent study found that the ACA led to an increase in HPV vaccination uptake, particularly among underserved minorities.[51]

Rhode Island's intervention could be seen as the gold standard due to its impact in significantly increasing vaccine uptake.[52] This increase in vaccination rate shows the results that ambitious policy can have. This type of policy may vary in its feasibility based on the local political climate.[53,54] It should be noted that several factors likely impact the inclusion and accompanying exemptions of the HPV vaccine in school entry requirements. State-level dynamics impact the viability and specifics of these policies. Moreover, building a wide consensus among stakeholders is vital in creating effective vaccine policy. Respect for individual choice has been a key consensus-building element for effective state HPV vaccine policy, which permits exemptions for religious, medical, and other significant reasons. Public health experts, parents, policymakers, physicians, and other stakeholders alike should be involved in crafting these policies. Politicizing the HPV vaccine school-entry requirements can decrease support for these policies.[55] In these situations, policies geared towards increasing access to and awareness of the HPV vaccine could also be effective.[53,56] These policies include increasing provider recommendation of the vaccine,

community educational campaigns, and allowing the vaccine to given alternative settings such as pharmacies, dental offices, and schools.[56] These strategies may be particularly useful in rural areas where issues like access to care are prevelant.[56]

Posterity

Vaccinations and vaccine policy should be apolitical. The focus should remain on their vital, positive public health impact that results in lives saved and serious illness averted for current and future generations. In the case of this vaccine, the focus should be on preventing HPV related cancers for future generations. Above all, the HPV vaccine is a cancer prevention vaccine. It gives us the opportunity to dramatically alter population level trends of several different cancers. It is a vital tool for us to make the future of the US healthy. A multi-pronged approach that includes strong policy and concurrent countering of HPV vaccine disinformation and hesitancy is required to continue our progress toward the Health People 2030 goal of a national HPV series completion rate of 80%. State vaccine policy has served as an empowering tool towards this national goal and will be all the more critical in the immediate future.

Contributors

JZ contributed to conceptualisation, literature search, figures, and writing–original draft. NOP contributed to conceptualisation, supervision, and writing–review and editing, YD contributed to visualisation, figures, and writing–reviewing & editing. GZ contributed to writing–reviewing & editing. MV contributed to conceptualisation, methodology, supervision, writing–review and editing.

AI use disclosure

Artificial Intelligence was not used in any portion of this paper, including for language or writing assistance.

Declaration of interests

NOP has served as a scientific advisor to Navigating Cancer, has received consulting fees from Merck, and reports receiving grants from the National Institute of Health/National Institute of Dental and Craniofacial Research (K01 DE030916; R01 DE032216; R21 DE032531) outside of this work. GZ has received consulting fees from Merck for work on HPV vaccination, has served on external advisory committees for Moderna (COVID-19 vaccination) and Pfizer (meningococcal vaccination), and has received investigator-initiated grant funding from Merck administered through Indiana University. All others have no conflict of interest to declare.

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