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CURRENT OPINION

Human Papillomavirus Vaccines: Successes and Future Challenges

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Abstract

Over a decade has passed since the first human papillomavirus (HPV) vaccine was introduced. These vaccines have received unequivocal backing from the scientific and medical communities, yet continue to be debated in the media and within the general public. The current review is an updated examination that the authors made five years ago on some of the key sociocultural and behavioral issues associated with HPV vaccine uptake and acceptability, given the changing HPV vaccine policies and beliefs worldwide. We explore current worldwide HPV vaccination rates, outline HPV vaccine policies, and revisit critical issues associated with HPV vaccine uptake including: risk compensation, perceptions of vaccine safety and efficacy, age of vaccination, and healthcare provider (HCP) recommendation and communication. While public scrutiny of the vaccine has not subsided, empirical evidence supporting its safety and efficacy beyond preventing cervical cancer has amassed. There are conclusive findings showing no link that vaccinated individuals engage in riskier sexual behaviors as a result of being immunized (risk compensation) both at the individual and at the policy level. Finally, HCP recommendation continues to be a central factor in HPV vaccine uptake. Studies have illuminated how HCP practices and communication enhance uptake and alleviate misperceptions about HPV vaccination. Strategies such as bundling vaccinations, allowing nurses to vaccinate via "standing orders," and diversifying vaccination settings (e.g., pharmacies) may be effective steps to increase rates. The successes of HPV vaccination outweigh the controversy, but as the incidence of HPV-related cancers rises, it is imperative that future research on HPV vaccine acceptability continues to identify effective and targeted strategies to inform HPV vaccination programs and improve HPV coverage rates worldwide.

Key Points

We examine key sociocultural and behavioral issues associated with HPV vaccine uptake and acceptability, including risk compensation, perceptions of vaccine safety and efficacy, age of vaccination, and healthcare provider (HCP) recommendation and communication.

There are conclusive findings showing no link that vaccinated individuals engage in riskier sexual behaviors as a result of being immunized (risk compensation).

An HCP recommendation continues to be a central factor in HPV vaccine uptake. Strategies such as bundling vaccinations, allowing nurses to vaccinate via "standing orders," and diversifying vaccination settings (e.g., pharmacies) may be effective steps to increase rates.

The successes of HPV vaccination far outweigh the controversy.

Future research on HPV vaccine acceptability continues to identify effective and targeted strategies to inform HPV vaccination programs and improve HPV coverage rates worldwide.

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1 Background

Five years ago, we published a paper examining myths and misinformation surrounding HPV vaccine [1]. Since that time the HPV vaccine context has changed in several respects: (i) A number of countries are now recommending, funding, and vaccinating both males and females [2, 3]. (ii) A 9-valent vaccine (9vHPV) has been introduced [4]. (iii) An increasing number of countries have implemented publicly funded national HPV vaccination programs for girls and boys [3, 5, 6]. (iv) There are more and more reports demonstrating long-term vaccine effectiveness [7–10], including a recent study showing that HPV vaccine prevents invasive HPV-related cancers beyond cervical cancer [11]. (v) There is an accumulated body of evidence that HPV vaccines are very safe [12–14]. Despite continued empirical evidence of the vaccines' safety and effectiveness, and the broad backing of HPV vaccination from the medical and scientific communities, many countries continue to report that HPV vaccine uptake rates are low or have dropped steeply [18, 44, 50–53, 122], often related to incorrect attributions of harm [15–18, 53, 123].

The intent of this paper, as with our 2013 article [1], is not to provide a systematic review of behavioral science research about HPV vaccination. Rather, it is to provide an updated, targeted commentary that addresses a specific set of topics concerning HPV vaccination that we consider timely and important in the evolving landscape. We revisit and update the issues that were first addressed in our previous publication concerning myths and misinformation about HPV vaccination and discuss whether these issues "can be put to rest" or remain pertinent. In addition, we present and discuss new issues that have surfaced over the last five years and discuss challenges that may arise in the years to come.

Over a decade has passed since the first human papillomavirus (HPV) vaccine, Gardasil®, was licensed in Gabon in 2006. Currently, three HPV vaccines are available: The bivalent vaccine (2vHPV) Cervarix® (GSK, Rixensart, Belgium), the quadrivalent (4vHPV) vaccine, Gardasil® (Merck, Kenilworth, NJ, USA), and the nonavalent (9vHPV) vaccine Gardasil® 9 (Merck). All three vaccines protect against the two oncogenic HPV genotypes, 16 and 18, which are high-risk types, and are responsible for 70% of all cervical cancers and are also associated with other cancer sites e.g., penis, vagina, vulva, anus, oral cavity and oropharynx [7, 19]. 4vHPV and 9vHPV also protect against genotypes 6 and 11, which are responsible for 85% of genital warts [20]. 9vHPV offers protection against five additional high-risk HPV genotypes, 31, 33, 45, 52, and 58, which means that this vaccine can prevent 80–90% of cervical cancers. With the development of this vaccine, "virtual elimination of this disease [cervical cancer] in vaccinated women is likely" [21], particularly in the context of continued cervical cancer-screening programs and wide population vaccine coverage.

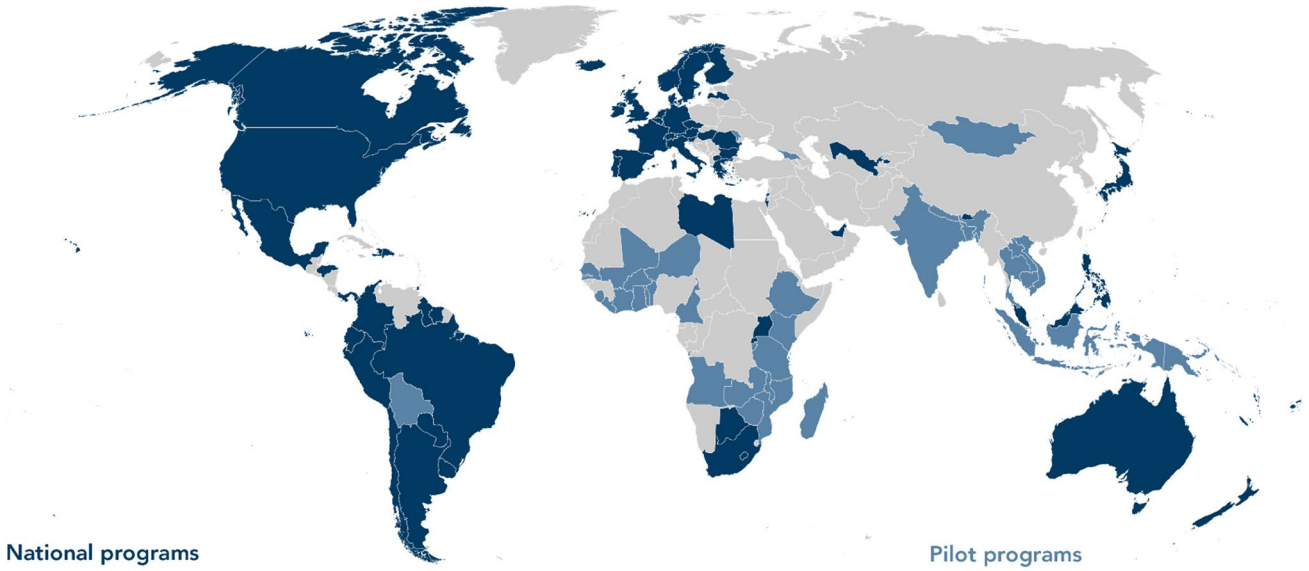
2 Current Worldwide Estimates of HPV Vaccine Uptake Rates

The 4vHPV and 9vHPV has been approved in 129 countries and over 270 million doses of the vaccine have been distributed worldwide [5]. As of June 2017, there were an estimated 90 national publicly funded HPV vaccination programs and 38 pilot programs, with many of these implemented in low- and middle-income countries [22] (see Fig. 1). The most extensive estimates report a worldwide coverage of 6.1% (95% CI 4.9–7.1) among females aged 10–20 years, with a 33.6% coverage (95% CI 25.9–41.7) in more developed regions and a mere 2.7% coverage (95% CI 1.8–3.6) in less developed regions [6].

HPV vaccine uptake rates have varied widely—not only from country to country, but also within the same country or jurisdictions (i.e., state/provincial, regional, local, and territorial differences) [6] due to differing programs, access to services, as well as the attitudes and beliefs towards HPV vaccination of the citizens, policy makers, and/or community leaders in the different areas/regions [2, 23–25]. Australia has been a leader with respect to HPV vaccination, being the first country to introduce an HPV vaccination free of charge for girls (in 2007), followed by boys (in 2013) in a national HPV vaccination program. The program has been deemed highly successful, leading to a decline of up to 92% in cervical HPV types among women aged 18–35 years, a 54% reduction in the incidence of high-grade cervical abnormalities in girls under 18 years of age, and a 90% reduction in genital warts in heterosexual men and women under 21 years of age [26–29]. Virtually every school in Australia has chosen to participate in the program, and rates of 81.5% for one dose and 71.4% for three-dose completion have been reported [30].

In the US, the HPV vaccine is funded nationally by the Vaccines for Children program and by private insurance, and is required to be covered by the Affordable Care Act. In 2017, in the US, 48.6% of adolescents (53.1% of females; 44.3% of males were up to date with the with the HPV vaccination[1] series recommendations, which was a small increase in coverage from the year prior (3.8% increase for females; 6.8% increase for males) [31]. Importantly, substantial variation has been reported by state, with HPV vaccine series

[1] HPV up-to-date rates were defined as those with three or more doses, and those with two doses when the first HPV vaccine dose was initiated before age 15 years and the time between the first and second dose was at least 5 months minus 4 days.



National programs

American Samoa
Andorra
Anguilla
Argentina
Aruba
Australia
Austria
Bahamas
Barbados
Belgium
Belize
Bermuda
Bhutan
Bonaire
Botswana
Brazil
Brunei
Bulgaria
Canada
Cayman Islands
Chile
Colombia
Cook Islands
Curacao
Czech Republic
Denmark
Dominican Republic
Ecuador
Fiji
Finland
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Germany
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Guyana
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Seychelles
Singapore
Slovenia
South Africa
Spain
St. Eustatius
Suriname
Sweden
Switzerland
Trinidad and Tobago
Uganda
United Arab Emirates
United Kingdom
United States
Uruguay
US Virgin Islands
Uzbekistan
Vanuatu

Pilot programs

Angola
Bangladesh
Benin
Bolivia
Burkina Faso
Burundi
Cambodia
Cameroon
Cote d'Ivoire
Ethiopia
Gambia
Georgia
Ghana
Haiti
India
Indonesia
Kenya
Lao PDR
Liberia
Madagascar
Malawi
Mali
Moldova
Mongolia
Mozambique
Nepal
Niger
Papua New Guinea
Sao Tome
Senegal
Sierra Leone
Solomon Islands
Tanzania
Thailand
Togo
Vietnam
Zambia
Zimbabwe

Fig. 1 Global progress in HPV vaccine introduction (June, 2017). (From Cervical Cancer Action. Global maps: global progress in HPV vaccination. 2017. Available at: http://www.cervicalcanceraction.org/comments/comments3.php. Accessed 24 Aug 2017)
Note. Countries were cross referenced with HPVcentre.net for up-to-date status on national programs (as of September 15, 2018)
*According to HPVcentre.net and [47], Niue (planned, supported by Rotary Clubs of Australia and New Zealand) and Samoa (possibly in 2019/20, supported by Asia Development Bank) do not have national programs

completion rates as high as 77.7% for adolescents in Rhode Island and as low as 28.8% and 30% for adolescents in Mississippi and Wyoming, respectively [31].

Canada's vaccination program differs from its US neighbor in two major ways: First, the HPV vaccine is predominantly administered through publicly funded school-based provincial programs across the country with minor variations in the vaccination schedule and age/school-grade of the program across the provinces. In Canada, all ten provinces and three territories have publicly funded school-based HPV vaccination programs for females in place, and all provinces have begun or are in the process of implementing publicly funded school-based HPV vaccination programs for boys [32]. Unlike the US, Canada does not have a national vaccination surveillance program, and each province differs in their data collection procedures, vaccination target age, years reported, and linking registries. For these reasons, a fully accurate national Canadian HPV vaccine uptake rate is not provided [33, 34]. Perhaps the closest national estimate for Canada comes from a recent systematic review and

meta-analysis, which, using a pooled random effects model, found that the HPV vaccination uptake rate in Canada was 55.92% [35].

As is the case in the US, Canada's HPV vaccine rates vary by province and by jurisdiction [36], with HPV vaccine completion rates for females as high as 89.2% in Newfoundland and Labrador (three doses, females) and as low as 39.3% (three doses, females) in the Northwest Territories [36]. A report from Public Health Ontario examining vaccination records for 13-year-old females reported a complete-for-age HPV coverage rate of 61% for the 2015–2016 school year, far from the 90% HPV vaccine coverage goal wanted by the Canadian Immunization Committee [37]. The available data for HPV vaccine uptake rates for Canadian males is limited due to the recent initiation of the programs, but rates as high as 66.0–81.4% (three doses, males) have been reported in the provinces of Prince Edward Island (PEI) and Alberta [38].

Across Europe, all 28 European Union (EU) countries have implemented HPV vaccination [39], where vaccine uptake rates have been reported as low as 10% (three doses, females) in Poland [25, 40], 43% in Luxembourg (three doses, females) [41], 27–83% among the administrative regions of Italy (three doses, females) and as high as 86% (three doses, females) in the UK [29, 42] and 90% (three doses, females) in Flanders, Belgium [43, 44]. Disparities across central and South America have also been reported e.g., Haiti (31%), Brazil (85%), and Bolivia (77%) [25]. This has been largely due to variations in funding (e.g., whether or not funding was supported by the Pan American Health Organization (PAHO) Revolving Fund). Uptake rates in Asian countries are not as easily accessible to report; however, the introduction of HPV vaccination has begun in some Asian cities, e.g., an uptake rate of 87% for two doses in females in Ayutthaya province in Thailand, [45] or is underway, e.g., China was set to introduce HPV vaccination in community health centers across 17 provinces starting in October 2017 [46]; India introduced HPV vaccination in two districts of Punjab state and is set to for statewide introduction in Sikkim in 2018 [47]. Many Western Pacific and South-East Asia Regions have already successfully applied for GAVI funds to either introduce national HPV vaccine programs e.g., Bangladesh, Indonesia, Lao, Myanmar. Solomon Islands and/or plan to introduce the vaccine in the near future (2019–2020) e.g., Cambodia, Mongolia, Niue, Samoa, Singapore [47]. In Israel, universal school-based vaccination programs for middle-school girls were introduced in 2013, and have achieved coverage rates of ~60%. Uptake in Israel has differed across the country, with similar barriers reported elsewhere, e.g. religious beliefs, vaccine cost, and awareness [48, 49]. By October 2014, in Africa and Asia, only 1–2% of females aged 10–20 years received one dose of the HPV vaccine, compared to 53.4% in Northern America, 36.4% in Europe, 41.1% in Oceania, and 22.1% in Latin America and the Caribbean [6].

While HPV vaccination coverage continues to improve in many jurisdictions, some fall-off in vaccination rates has been observed [44]. Drops in coverage have been reported in the Netherlands from 53.4 to 45.5% [50], Denmark (as low as 40%) [51], and Ireland (50% uptake of first the dose in 2016–2017) [52]. These drops can be explained by parents' concerns related to vaccine safety due to misinformation spread by certain lobby groups, often through the use of television and social media [52]. Coordinated efforts of health authorities, civil societies, and media have been proven efficient in reversing declining vaccination rates [52]. A special case is represented by Japan where incorrect attributions of harm to HPV vaccine prompted the government to withdraw support for the vaccination program in 2013 and was followed by a drastic fall in vaccine coverage [53]. This was a parallel situation to that reported in Chile in 2016 where the Court of Talca hosted an application for protection and decided to discontinue local HPV vaccine administration [54]. There are major differences in HPV coverage both at the development level and including considerable differences in the performance of each country's unique program [6]. Substantial opportunities exist to increase HPV vaccine uptake, not only in low- and middle-income countries, which have the highest rates of cervical cancer, but also in some resource-rich settings.

3 The Psychosocial Aspects of HPV Vaccination

From its early beginnings [55–57] and through the years [1, 58, 59], from Japan [53] to Canada [60], the HPV vaccine has stirred up controversy, even if largely undeserved [61]. Early on, challenges arose as the HPV vaccine was associated with sexual activity and there were unfounded claims that HPV vaccination would lead to earlier and/or increased sexual activity in females, which caused high levels of parental concern [62–65]. This claim has now been systematically refuted and disproven [66–68]. Importantly, this controversy appears to have been unique to the HPV vaccine, over and above the classical difficulties that come with the introduction of any vaccine [69], even those—such as the hepatitis B vaccine—that protect against a sexually transmitted infection. It has been said that "the HPV vaccine has been among the most scrutinized and controversial vaccines since its first licensure in 2006" [61].

Over the past five years, there has been a proliferation of studies within the behavioral sciences trying to identify and better understand what influences HPV vaccination intentions and vaccination uptake. As a testament to the exponential growth of literature in this area, there are now

at least 20 systematic reviews examining the acceptability and uptake of HPV vaccination in relation to knowledge, attitudes, beliefs, and behaviors in a vast array of diverse populations [66, 67, 70–87]. This list does not include six published systematic reviews [88–93] focused specifically on interventions aimed to increase (HPV) vaccination coverage, with the most recent examining intervention studies on HPV vaccination completion [93]. While the search strategy, population of interest and data synthesis methods differ across the systematic reviews, by and large there are some common themes and ideas conveyed about how we understand HPV vaccination decision-making.

4 HPV Vaccine: Beyond Cervical Cancer

There have also been several new developments in the understanding of the spectrum of HPV-related diseases, including the established link between HPV and anal and oropharyngeal cancers, and the incidence of HPV+ oropharyngeal cancers is on the rise [94]. In fact, in the US, HPV has overtaken tobacco use as the main cause of oropharyngeal cancer [95]

Squamous cell carcinoma (SCC) is the most frequent malignant tumor of the head and neck, and more than 70% of oropharyngeal SCCs are HPV-associated [96]. There is preliminary evidence showing that the HPV vaccination prevents HPV infection in the oral cavity [97–99], including recent findings showing an 88% reduction of oral HPV16/18/6/11 infections in vaccinated versus unvaccinated men and women in the US after adjusting for age, sex, and race [100]. The authors also estimated the population-level effect of HPV vaccination on the burden of oral HPV16/18/6/11 infections was 17.0% reduction overall, 25.0% in women and 6.9% in men [100]. Moreover, one population with an increased burden of HPV infection may be carried by men who have sex with men (MSM), who have been estimated to have an HPV-related anal cancer incidence rate that is 44 times higher than the general population, as well as HIV-positive MSM who have an incidence rate 60 times higher than that in the population [101, 102]. Taken together, these advances have shifted our understanding of HPV as the "cervical cancer vaccine" to an increasing recognition that HPV does not discriminate and causes multiple diseases/cancers among both genders [3].

5 Risk Compensation

An early HPV vaccine-related concern, promoted by the media, involved fear that vaccinated adolescents would engage in risky and/or earlier onset of sexual behavior following HPV vaccination [103], an issue defined as risk compensation and/or sexual disinhibition. Since our 2013 paper [1], two systematic reviews on this issue were published in 2016, and both reviews concluded that there was no evidence that getting vaccinated against HPV resulted in increased risky sexual behavior measured by both self-report and by biological markers such as STI diagnoses and pregnancies [66, 67]. Several studies published subsequent to the systematic reviews continue to refute the notion that HPV vaccination may lead to decreases in sex-related risk perceptions and increases in sexual risk behaviors [104–106]. A recent study conducted with over 500 Canadian undergraduates not only provided little evidence of risk compensation, it demonstrated that a substantial proportion of HPV unvaccinated Canadian youth are already at elevated risk of HPV-related morbidity and mortality at an early stage of their sexual careers due to their HPV transmission risk sexual behaviors and lack of vaccine protection [68].

Furthermore, a recent difference-in-difference study that examined the concept of risk compensation at the policy level found that US state HPV legislation was not associated with any increased or significant changes in riskier US adolescent sexual behaviors [107]. In fact, the authors found the reverse: sexual intercourse decreased by 0.90 percentage points ($P=0.21$) and recent condom use increased by 0.96 percentage points ($P=0.32$) among adolescents in states that had enacted HPV vaccine legislation compared with states that had not [107], highlighting that HPV legislation might actually promote positive safe-sex behaviors.

Interestingly, while there were some earlier studies reporting that "sexual promiscuity" post-vaccination was a concern for some parents [65], this worry appears to be relatively uncommon [108–111]. In a related vein, a recent US study of NIS-Teen data examined reasons for parental non-initiation of HPV vaccination, comparing 2010–2014 results [112]. The authors found that parental concern that a child was not sexually active was a relatively commonly endorsed reason for non-initiation in 2010 (18%), but this had significantly declined in 2014 to 9%. Similarly, results from a national study of over 3000 parents of 9-to-16-year-old boys across Canada [113] found that only 13% of Canadian parents somewhat or strongly agreed with this statement: "I feel that the HPV vaccine would encourage my son to have sex at an earlier age." Similarly, nearly 75% "somewhat" to "strongly" disagreed that vaccinating their son for HPV would send a message that he would not have to use safe sex practices, with only 11.1% of parents saying that they somewhat to strongly agreed that it would (unpublished data). Correspondingly, in a national study of 3779 parents of 9-to-16-year-old boys and girls across Canada [114], fewer than 7% of parents "somewhat" to "strongly" agreed that if their child received the HPV vaccine she/he may be more likely to have sex in the future.

Taken together, these results suggest that parental concerns about disinhibition may have been exaggerated by media coverage and at this time are likely not a concern for many parents. With a decline in the appearance of these stories in the media along with more balanced reporting (i.e., presenting the scientific evidence that adolescents do not engage in riskier sexual behavior after HPV vaccination), it is likely concerns around this issue will continue to decline. Moreover, HCPs can use the robust evidence against sexual disinhibition/risk compensation to alleviate any lingering parental concerns.

6 Safety and Communication About Safety Data

In our earlier paper [1], we highlighted numerous studies attesting to HPV vaccine safety. Five years later, the safety profiles of the three HPV vaccines have been reviewed extensively, and the research continues to show they are safe, well tolerated, and have adverse effects similar to those experienced with other vaccines [12, 13, 115–118]. The most common adverse effects of the vaccines are soreness (pain), swelling, itching, and redness at the injection site, as well as syncope (fainting) [118]. The safety profiles of the three HPV vaccines are similar and continuously being followed in Canada, the US, and around the world, e.g., via the CDC's Vaccine Adverse Event Reporting System [119] and the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) [120]. While media reports have extensively presented stories regarding adverse effects of the vaccine (real or fatuous; see, e.g., Toronto Star, now rescinded [121]), little has been written in the media regarding the profound effects of *not* being vaccinated, i.e., increased risk of genital warts and HPV-related cancers later in life.

Despite the plethora of scientific evidence, ominous reports of HPV vaccine harm have continued to circulate, having a significant impact on HPV vaccine uptake rates in many countries (e.g., Austria, Columbia, Denmark, Ireland, and Japan). In the Republic of Ireland, a group called Reactions and Effects of Gardasil Resulting in Extreme Trauma (REGRET) demanded an injunction from the High Court for a withdrawal of the vaccine across the country. Vaccination rates dropped to just 51% as a result [122]. In Columbia, a class action lawsuit of over 700 women has been filed alleging that they have been damaged by the HPV vaccine [54]. In Japan, the Health Ministry withdrew its recommendation for 4vHPV, though the vaccine is still available [16, 17, 53, 123]. Tireless efforts by many researchers, clinicians, and advocacy groups worldwide (e.g., Drs. Riko Muranaka and Sharon Hanley from Japan, Dr. Juliette Guichon from Canada) have vigorously worked to counter the scientifically unjustified assertions of vaccine adverse effects and harms [124, 125]. Fortunately, for some countries, the decline was temporary (e.g., Austria and Brazil) [126]; for others there has been some slow recovery (e.g., Ireland [18]). Japan's program has suffered greatly, with HPV vaccination rates plummeting from 70% (in 2013) to less than 1% currently, meaning that substantial numbers of Japanese youth will remain susceptible to HPV-related pre-cancers and cancers for years to come [16, 17, 123].

7 Healthcare Provider's Influence on HPV Vaccine Uptake

The centrality and importance of the HCP was highlighted in our 2013 paper [1]. We also explored the variability in provider recommendation due to time constraints, patient's age, availability of insurance or other coverage, provider's views, and level of comfort, e.g., their own safety and/or efficacy concerns, and hesitancy in discussing sexuality. We had some earlier indications about what might help to increase the impact of a provider's recommendation, e.g., message framing.

To date, the role of the HCP remains largely unchanged, with continued evidence to support that one of the strongest predictors of both HPV vaccine initiation and completion is recommendation from an HCP [71, 82, 87, 127–130]. The lack of an HCP recommendation is similarly an important barrier to HPV vaccination. What we can now add to this is that the quality/type of recommendation matters [131–134]. In two studies examining audio recordings of HCP conversations with parents, HCPs made relatively weak, non-presumptive recommendations for HPV vaccination [132, 133]. The rate of HPV vaccination completion is higher when the HCP makes a consistent, same-day recommendation, and emphasizes cancer prevention [135, 136] in contrast with an inconsistent or without an urgency recommendation [131]. Similarly, research shows that when HCPs are trained to make a presumptive recommendation (i.e., a clear brief statement that assumes parents are ready to vaccinate, also termed "announcements"), modest but significant increases in HPV vaccine initiation rates can be achieved [134]. Another effective strategy is to bundle the HPV vaccine with other vaccinations [132].

HCPs themselves report lack of knowledge, discomfort, and/or can be misinformed by information they received from the internet related to HPV vaccination. Providing additional training to HCPs related to HPV vaccination could help mitigate the different barriers that HCPs report. First and foremost, HCPs need to be made aware of the wide availability of resources such as clinician fact sheets,

toolkits, videos, and e-learning modules that can help them both general information and with their recommendation (e.g., from agencies like the CDC, the WHO, Catalan Institute of Oncology; see Session 4: Materials available for in service training of HCP: https://www.uantwerpen.be/en/projects/hpv-prevention-control-board/meetings-/hpv-romania/). Second, creating an infrastructure that continues to help support HCPs to have these discussions and assist them in making impactful, strong recommendations [132, 134, 137] will be key to improving HPV vaccine uptake. Thirdly, once an HCP feels well equipped, opportunities exist to have HCPs adapt existing resources and materials to their own cultures/locations as well as effectively communicate and advocate with the media/press and amplify key messages through their own and/or institution's social media platforms. The use of social media to promote pro-HPV vaccination messages can be one strategy to refute the misleading yet impactful anti-vaccination messages that are widely available on the web and social media.

One avenue worthy of exploration is who is best suited to provide information on the vaccine recommendation, and who should administer the vaccine. A recent examination of pediatricians' views as part of a randomized controlled trial involving clinical decision support reminders highlighted that half of the physicians pointed to the key role of their nurse(s) in the vaccination setting. Ideally, nurses would be both allowed and encouraged to administer vaccinations without approval from a physician (e.g., via standing orders). This approach has been shown to be more effective in increasing vaccine rates as compared to clinical decision reminders geared toward physicians [138]. Other potential providers may include pharmacists [139], who depending on the healthcare system, could administer directly at the pharmacy.

8 The Age of Vaccination

Across the globe, the age of HPV vaccination has varied widely, with some children being vaccinated as early as 9 years old, and others in high/middle school (12 years and above), and/or up to 18, 21, 24, or 28 years old. Many programs and providers are recommending vaccine initiation at ages 9 or 10 years, as it is optimal that the two-dose series be completed by age 11 years. The child's age has been shown to influence parents' HPV vaccine acceptance, with mixed findings on whether parents are more likely to vaccinate if their child is older or younger. What we do know is that there are qualitative differences between childhood and mid to late adolescence. These periods are marked by changes in social, physical, and neurocognitive statuses. As children pass through puberty (~ 10–14 years old), there are changing notions of privacy, increased behavioral autonomy, and increased parent-child conflict [17]. This raises the issue of what is the optimal age of HPV vaccination.

Medico-legal issues including the capacity of adolescents to consent to medical treatment on their own behalf, parental authority, and confidentiality become particularly pertinent with respect to HPV vaccination involvement. In most countries' legal systems, the legal age of consent tends to coincide with the age of majority, typically 18 years of age [25]. In a growing number of countries, the age of consent for medical treatments is set below the age of majority [25]. Some countries have even fixed the age of consent specifically to allow HPV vaccination at 12 years of age [25].

Since laws regarding HPV vaccination for young people under 18 years vary widely from country to country and even amongst states/provinces/regions, much is often left to the judgment of the healthcare professional as to the maturity of the young person and their capacity to consent, particularly in regions with no school-based vaccination programs [25]. In school-based immunization programs, e.g., Austria, Australia, and Canada, there are different issues at play as the parent may sign the consent form, but the student may refuse immunization and it will not be given or vice versa, i.e., the parent refuses to sign, but the student is judged capable of giving informed consent, is requesting the vaccine, and will be given their immunization. This is further complicated by paradoxes in vaccine policy and adolescent consent laws. While some have stated that parental consent for vaccination may present a significant barrier to improving adolescent vaccine uptake [27], the authors are highlighting that the *ideal age* of HPV vaccination has yet to be established. From a biomedical perspective, vaccination before age 16 years will capitalize on optimal immunogenicity and minimal likelihood of prior HPV infection.

An important point to consider is that vaccinating against HPV in pre-puberty (typically 9–12 years of age) as opposed to during or post puberty is recommended because it provides immunity prior to sexual activity debut (possibly being exposed to HPV transmission) and could be more easily accepted by the child-parent dyad. During puberty, there is an increased likelihood that child-parent conflicts and parents' difficulties in communicating [128] about sexuality with their child could negatively influence HPV vaccine acceptability. Moreover, in publicly funded programs, if vaccination does not occur during the recommended time frame, there are often no publicly funded catch-up programs for young adults (e.g., early twenties and beyond), and the issue of cost often surfaces. For example, for the 40% of unvaccinated Ontarians who are not vaccinated by age 18 years, many do not see HPV vaccine as a priority and cannot afford to pay for the vaccine [68]. These are all important considerations for vaccination programs and policy. Future research may also consider the effectiveness of vaccinating children

prior to 9 years of age and have the HPV vaccine fit in with other early childhood vaccinations.

9 Conclusions

Public scrutiny of the HPV vaccine is indispensable. This prompts researchers, scientists, politicians, and stakeholders to not only continuously evaluate the effectiveness, safety, and overall utility of the HPV vaccine, but also to work hard to provide sound, empirical evidence that the benefits outweigh any potential harms. Unfortunately, much of the work surrounding HPV vaccination that is widely available to the public (e.g., media) has been clouded with myths and misinformation, speculation, and a priori doubts/worries that are presented as empirical science. These controversies and challenges have arisen from misinformation and disregard of scientific evidence, stemming from distrust of institutions, the pharmaceutical industry, and biomedical technologies [140–142]. One such controversy was that of risk compensation, which is no longer a valid argument to prevent HPV legislation [107], and appears to be less and less of a concern among most parents. Nonetheless, continued concerns about the safety of the HPV vaccine linger. With over a decade of extensive high-quality science, and the backing from the medical and research communities, it is very clear that the HPV vaccine is a safe and effective vaccine that is critical for cancer prevention.

In the next two years (by 2020), the highest number of HPV-related cancer deaths in many high-income countries will be oropharyngeal. This draws more and more attention to HPV-associated cancers that affect *both* men and women. Over the next few years, we can also anticipate continued advances with respect to the vaccines themselves, age of vaccination, and dosing schedules. For example, similar to the shift from a three-dose schedule to a two-dose schedule, research is currently underway considering the pairing of the 9vHPV and the 2vHPV as a way to elicit a strong immunity response at an affordable price. In fact, for the 2018–2019 school year, children in the province of Quebec, Canada are set be the first in the world to receive a new mixed vaccination schedule of one dose of 9vHPV and one dose of 2vHPV as part of their national program, which has garnered some new controversy as to whether this offers the best protection [143]. Another example is a current clinical trial looking at whether administering one dose of either 2vHPV or 9vHPV vaccines are as effective as giving two doses of these vaccines to women aged 12–16 years [144].These are additional contributing factors that could increase HPV vaccine uptake rates globally, especially in middle- and low-income countries, which account for 86% of cervical cancer cases worldwide [6].

With over a decade of research behind the HPV vaccine, the tide has shifted and the successes appear to be outweighing the challenges. While this is promising, many individual policies (i.e., males, young adults) for those who could benefit from HPV vaccination are still not being implemented and the individuals are still not receiving the vaccine and/or are not being considered in HPV vaccination programs and in the implementation of country policies, particularly in low-income and lower-middle-income countries. The wide variability of uptake rates across the globe can be explained by differences in policy and socioeconomic disparities, though in many countries the amount and content of social media information (i.e., Twitter; Facebook) has accounted for a greater part of the difference than socioeconomic status. This suggests that the information that we acquire via the media, which in turn shapes our attitudes and opinions, may "give the biggest bang for the buck" in terms of influencing HPV vaccine rates. Using push technology to provide up-to-date information related to HPV vaccination to HCPs could represent an important initiative as one of the major barriers towards HPV vaccination is providers' lack of time [145]. Informing and training pediatricians, general practitioners, and obstetricians/gynecologists is a first step to improve HPV vaccination dose completion in females and males [146]. Importantly, the ideal goal would be to ensure that all HCPs who are providing the HPV vaccination are well trained and confident when providing information to patients. Working within the various media forms to convey the science to the lay public, as well as working to establish strategies with HCPs to provide strong recommendations in the most ideal settings, i.e., school-based programs, standing orders, can ultimately increase HPV vaccination rates and reduce worldwide morbidity and mortality in a meaningful fashion [146].

Compliance with Ethical Standards

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