

Human Papillomavirus (HPV) Vaccine: A Gendered Innovation

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Introduction

As a medical student, Leana Wen visited her student health center for an annual check-up and Pap test. Four weeks later, her Pap results came back positive for cervical cancer. After undergoing several excisional procedures,¹ Wen was declared cancer-free. At age 27, her cervical cancer re-emerged, and Wen underwent a more invasive procedure called cervical conization, which involved removing a portion of her cervix along with the cancerous tissue. On November 2018, Dr. Leana Wen, a cervical cancer survivor, activist, and proponent of preventative medicine, became the first physician in 50 years to assume the role of President of Planned Parenthood (Wen, 2019).

Around the same time that Dr. Wen was fighting her second battle with cervical cancer, Academy award-winning actor Michael Douglas was diagnosed with Stage 4 oropharyngeal cancer (Christensen, 2013). He received an aggressive eight-week course of chemotherapy and radiation therapy, during which he lost 45 pounds. Although physicians declared him cancer-free, he recognizes that the cancer may return. Wen has been vocal and transparent about her journey against cervical cancer; however, Douglas kept his condition hidden from the public for three years (Shoard, 2013). In 2013, he decided to share his story to raise awareness about his cancer.

Both Wen and Douglas fought cancers caused by human papilloma virus (HPV), a ruthless virus that affects more than 79 million people in the United States (*STD Facts - Human Papillomavirus (HPV)*, 2022). HPV, the most common sexually transmitted infection worldwide, infects up to 85% of women and 91% of men with sexual partners (Chesson et al., 2014). All sexes can transmit the virus to people of the same or different sex. HPV causes a variety of cancers including cervical, oropharyngeal, urethral, bladder, anal, penile, vaginal, and vulvar cancers as well as genital warts; therefore, HPV-associated cancers can affect people of all sexes (Burd, 2003; *HPV Infection / Human Papillomavirus (HPV)*, 2021). The Centers for Disease Control and Prevention (CDC) estimates on

¹ Leana Wen's cervical cancer excisional procedure is called Loop Electrosurgical Excision Procedure (LEEPs), which are "short procedures which use a small electrical wire loop to remove the abnormal cells."

average 31,500 people—19,400 females and 12,100 males—are diagnosed with HPV-attributable cancers each year (Gargano et al., 2022). Often times, HPV-associated cancers manifest decades after viral exposure, making early detection difficult.



FIGURE 1. CDC HPV Vaccine Poster

Because HPV, a predominantly silent infection, is not readily detected using traditional viral diagnostic tests, vaccination is key. As one of two licensed vaccines² that protect against virally-induced cancers (*Vaccines That Can Help Prevent Cancer*, 2020), the HPV vaccine immunizes individuals (*GARDASIL®9 (Human Papillomavirus 9-Valent Vaccine, Recombinant) for Health Care Professionals*, 2022; *Human Papillomavirus (HPV) Information for Parents*, 2021) against up to seven high-risk viral strains known to cause cancers in all sexes and two low-risk strains responsible for most genital warts. The CDC has identified six reasons why people should receive the vaccine (*6 Reasons to Get HPV Vaccine for Your Child*, 2018), including the high prevalence of HPV (~80%) in the community, high vaccine efficacy (HPV-associated cancers decreased by 71% in teenage females), superiority of cancer prevention over treatment, efficiency of vaccine administration (can be given at the same time as the meningitis vaccine), and the “safe, effective, and long-lasting protection” conferred by the vaccine. Figure 1 summarizes the most significant reason why the CDC encourages the vaccine (*Top 10 Tips to Improve HPV Vaccine Rates | CDC*, 2017) (*HPV Vaccine Safety and Effectiveness Data*, 2021).

Although HPV vaccines prevent cancers in people of all sexes, vaccination rates, especially in non-female sexes, remain low due to stigma surrounding the vaccine and the requirement of 3 doses for full coverage. Based on survey data collected by the CDC, ≥ 1 dose vaccine coverage in 2016 for females ages 19-26 was 48.5% compared to 13.5% of males in the same age group (Lewis & Markowitz, 2018). Only a few countries outside of the U.S. recommend the vaccine to males due to false

² The Hepatitis B vaccine protects against virally-induced liver cancers (hepatocellular carcinomas).

assumptions about the vaccine's cost effectiveness, and most countries do not have recommendations for transgender individuals (Stanley, 2014). Disparity of vaccine administration rates between female and non-female sexes may also arise due to limited health and biomedical research on the impacts of the HPV vaccine on male, transgender, and intersex individuals.

This paper will address gendered gaps in HPV vaccination rates by analyzing the lack of “Health and Biomedical Research” on non-female cells, animal models, and individuals as well as economic and political “Factors Intersecting with Sex and Gender” that restrict vaccine access to non-female individuals. Additionally, this paper will address the female-oriented “Language and Visual Representation” surrounding the vaccine and conclude with innovations that promote a de-gendered HPV vaccine that is accessible to people of all sexes.

Designing Health and Biomedical Research

Biomedical research on both the virus and the vaccine has prioritized women. From laboratory research on cells/tissues to animal models, non-female samples are often excluded until Phase III clinical trials. By applying the method of “Designing Health and Biomedical Research,” this paper reveals the limitations of using non-representative samples.

Pre-clinical studies on the virus and vaccine fail to sufficiently consider sex and rely too heavily on female animal models. Even the most recent HPV studies published in *Nature* do not mention the sex of the cells or tissue samples used in experiments (Schiffman et al., 2016). A medical review article titled “Animal models of papillomavirus pathogenesis” does not specify the sex of the experimental animals, including mice, cattle, and rabbits, used in HPV vaccine research (Campo, 2002). A study that investigated HPV tumorigenesis *in-vitro* (cells/tissues) and *in-vivo* (animal models) used a mouse fibroblast cell line from only female BALB/c mice (Hernández et al., 2000). Additionally, most pre-clinical studies focus on the association between HPV and cervical cancer, as evidenced by sparse literature on other HPV-associated cancers. On PubMed, 18,327 articles are on HPV and cervical cancers, 2475 on oropharyngeal cancers, and only 840 are on penile cancers.

Epidemiological studies investigating the vaccine's effect in non-female individuals also lag behind those of women. In a review of six long-term studies on the quadrivalent vaccine, four studies were conducted on female subjects, two studies only included male subjects, and none included transgender or intersex individuals. Of the four long-term studies on women, only one case of cervical cancer emerged. One of the two longitudinal studies conducted on males focused primarily on men who have sex with men (MSM). In the MSM study, five vaccinated individuals developed anal cancer. Although the vaccine protected against anal cancers, it was more successful at preventing cervical cancer (Vincenzo et al., 2014). Limited data on the vaccine's protective effects against anal

cancers and genital warts initially delayed vaccine recommendations for men. Even today, additional long-term epidemiological studies on HPV-associated non-cervical diseases are needed.

HPV vaccine surveillance on coverage and adverse effects focuses mainly on women. Even in countries with female-only HPV vaccination programs, monitoring the vaccine's impact on males will provide a more accurate representation of herd immunity (population level resistance to the spread of infectious diseases due to sufficiently high levels of immunity in individuals) (*Vaccine Glossary of Terms*, 2020). Regular cervical screening programs for women helped improve HPV vaccine surveillance; however, males do not undergo routine HPV-associated cancer screenings (Brotherton et al., 2016). In general, HPV diagnostic measures for non-female individuals are extremely limited and depend on the presence of genital warts; therefore, research on novel diagnostic measures for detecting HPV in non-female individuals can significantly improve HPV vaccine surveillance and allow policymakers, pharmaceutical companies, and physicians to make more informed decisions.

Analyzing Factors Intersecting With Sex and Gender

The U.S. is one of few countries that offer the HPV vaccine to all sexes. Countries that have only licensed the vaccine to females argue that vaccinating all sexes would not be cost effective. However, this paper demonstrates that the health and economic burdens of HPV-induced cancers, which impact all sexes, heavily outweigh the economic investment towards a gender-neutral vaccine. Changes in global health policy can encourage countries with female-only vaccine programs to adopt gender-neutral recommendations.

Even in the U.S., which has high screening rates and low cancer rates, the economic burden of non-cervical HPV-diseases ranges from \$160 million to \$1.6 billion.³ With the inclusion of cervical cancers, the economic burden of all HPV-attributable diseases is higher. The HPV vaccine can offset these extraordinary costs because it not only has the ability to prevent cancers and genital warts, but it also prevents transmission of the virus (Palefsky & Cox, 2021). The CDC specifically recommends the vaccine to high-risk groups including men who have sex with men and all immunocompromised individuals (e.g. HIV/AIDS patients), who have a higher chance of transmitting the virus (*HPV Vaccine / Human Papillomavirus (HPV)*, 2021). When non-female individuals are excluded from national HPV vaccine recommendations, certain high-risk individuals cannot receive proper preventative care, which leads to higher rates of infection. Therefore, countries with female-only HPV vaccine policies should shift to more gender-neutral policies.

³ The majority of the costs were from treatments for diseases caused by HPV strains 6 and 11, which are covered by the HPV quadrivalent (Gardasil 4) and nonavalent (Gardasil 9) vaccines.

Unlike the CDC, the World Health Organization (WHO) states “young adolescent girls, ages 9-14” as the primary target group for the HPV vaccine, recommends vaccine schedules only for females, and fails to mention vaccine recommendations for male, transgender, or intersex individuals (*Immunization, Vaccines and Biologicals*, 2022). By establishing new vaccine guidelines for all sexes ages 9-45, the WHO can influence countries to implement gender-neutral vaccine programs.

Rethinking Language and Visual Representation



FIGURE 2. a) Cervarix Bivalent Vaccine. b) Gardasil 4. c) Gardasil 9. The design of the boxes has changed over the years to become more gender neutral. The name Cervarix is no longer used and the colors have shifted from pink to green.

Pharmaceutical companies and public health departments contribute to lower vaccination rates in non-female individuals by reinforcing the female bias with their branding and marketing strategies. For example, the HPV vaccine is commonly labeled as a preventative measure against cervical cancer instead of all HPV-associated cancers. A bivalent vaccine licensed in October 2009 called Cervarix includes the word “cervix” in its name (*Pinkbook | HPV | Epidemiology of Vaccine Preventable Diseases*, 2021). A pink-colored box with a flower in the middle encases the Cervarix vaccine (Figure 2a). The packaging for Gardasil 4, a quadrivalent vaccine licensed in June 2006, uses magenta fonts and pink/light-blue colors (Figure 2b). Gardasil 9’s packaging encompasses a more gender-neutral tone with blue and green colors and fonts (Figure 2c).

Female-oriented packaging designs may be an artifact of delayed HPV vaccine recommendations for males compared to females. For example, the FDA first introduced Gardasil 4 in June 2006 for females ages 9-26; three years later, on October 2009, the FDA licensed it for males of the same age group. The FDA approved Gardasil 9, the most updated HPV vaccine, for females ages 9-26 on December 2014, males ages 9-15 on December 2014, and males ages 16-26 on December 2015. Only females ages 9-26 can receive Cervarix (Daley et al., 2017).



FIGURE 3. a) CDC advertisement featuring female model. b) Screenshot of Merck’s video advertisement featuring male model. These two images demonstrate a shift from a female-focused campaign to a more gender-neutral one.

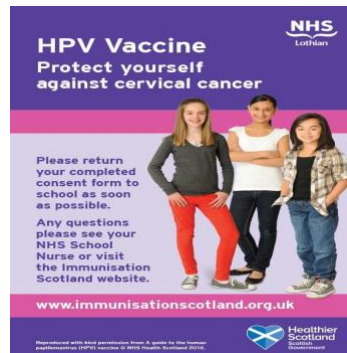


FIGURE 4. UK’s National Health Service (NHS) Female-Oriented HPV Vaccine Advertisement. This poster demonstrates how countries outside of the U.S. focus on a female-centered campaign.

HPV vaccine advertisements in the U.S. more often feature female adolescents than males (Figure 3a). Recent advertisements and infographics have started to include gender-neutral representation, including a Merck video advertisement featuring both an unvaccinated girl and boy who are diagnosed with HPV-associated cancers (Figure 3b) (*Merck Ad for HPV Vaccine Is Tough on Parents*, 2016). However, most countries outside of the U.S. that have licensed the vaccine to females only feature females in their advertisements (Figure 4). Both the CDC and Merck advertisements in Figure 3 target parents, while the NHS female-only advertisement places the burden on the adolescent girl to receive the HPV vaccine. The language used in the NHS advertisement may imply that the female is responsible for protecting herself against cervical cancer and other HPV-associated cancers, although all sexes can transmit the virus. By propagating female-oriented visual representations, these countries impede future transitions toward a gender-neutral vaccine.

Even the more gender-neutral U.S. advertisements perpetuate the male-female dichotomy and exclude transgender and intersex individuals. Developing more inclusive language and visual representations will encourage individuals of all sexes to receive the vaccine.

Gendered Innovations

The HPV vaccine protects people of all sexes against a variety of cancers; therefore, the vaccine ought to be represented as gender-neutral. Dr. Leana Wen has been a large supporter of a gender-neutral HPV vaccine, and the Planned Parenthood website specifically recommends the vaccine to all sexes ages 9-45 (*HPV Vaccine | What Is the HPV Vaccination*, 2022). Michael Douglas helped shape the language surrounding HPV by sharing

his story as a male individual diagnosed with HPV-associated cancer. Wen and Douglas are two individuals who have exemplified gendered innovations for the HPV vaccine.

In addition to individual efforts to promote a gender-neutral vaccine, more comprehensive health and biomedical research should be conducted on non-female cells, animal models, and individuals. To better understand the vaccine, basic science research on the virus and its pathophysiology should be investigated in all sexes. Comparing immune responses by sex may provide insight into vaccine immunogenicity and lead to novel treatments for HPV-associated diseases (Frazer, 2004). Longitudinal and epidemiological studies should analyze the effects of the vaccine in all sexes. By demonstrating long-term vaccine efficacy in a diverse sample population, more people will trust the vaccine.

Global health institutions including the WHO need to include male, transgender, and intersex individuals in their HPV vaccine recommendations. As of May 2018, fourteen African countries offer the vaccine to girls, and no countries offer the vaccine to boys (Chido-Amajuoyi et al., 2018; Kuehn, 2019). Reasons for the low number of HPV vaccination campaigns in Africa include challenges in identifying the target population and difficulty engaging multiple stakeholders to integrate the HPV vaccine into existing school health vaccine vaccination programs (Kuehn, 2019). Very few Asian countries (e.g. Malaysia, Bhutan) have HPV vaccine programs, and most are exclusively for women (Muhamad et al., 2018). Therefore, widescale policy changes are necessary to ameliorate the significant economic costs of HPV-associated diseases and to protect all sexes from the virus.

Advertisements and infographics need to incorporate male, female, transgender, and intersex individuals. Additionally, this paper proposes that the HPV vaccine should not be labeled as a vaccine for cervical cancer but instead as a vaccine that protects against epithelial cancers and genital warts. By doing so, people will view the HPV vaccine just like any other licensed vaccine, which are all gender neutral.

Conclusion

The HPV vaccine serves as an example of how methods of sex and gender analysis promote gendered innovations that have the potential to save lives. De-gendering the vaccine will protect people of all sexes against numerous HPV-attributable diseases. Chido-Amajuoyi et al. published in the *Lancet*, “If countries attain 80% HPV vaccination rates in both men and women, HPV-associated cancers could be eliminated.” If vaccines are only administered to females, this goal would be unattainable. Shifts have started to occur in how the HPV vaccine is presented to the public including in advertisements (e.g. Merck) targeting both females and males and the presentation of the packaging to become more gender-neutral; however, there is room for improvement, so all genders including non-binary individuals have increased visibility in the vaccine campaigns.

With the HPV vaccine campaign being an international effort, significant changes ought to be made globally to ensure that non-female populations receive adequate vaccine coverage in countries outside of the United States. Through expansions in research and policy, more individuals can be protected against HPV-associated cancers. A first step can be to change the language on the World Health Organization website to state all genders, instead of “young adolescent girls.” With these small but progressive steps forward, gendered innovations have the potential to make HPV-associated cancers a disease of the past.

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