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# *Receipt of HPV Vaccine Associated with Increased Prevalence of High-Risk HPV Infections*

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## ABSTRACT

Identifying possible negative side effects of vaccines helps to determine whether benefits outweigh the costs of a medical intervention that claims to prevent a disease. Such a cost-benefit analysis is essential both for vaccine policy as well as informed consent. This study seeks to determine whether the use of the human papillomavirus (HPV) vaccine is related to an increase in high-risk (HR), possibly cancer related, HPV infections. Data from the U.S. National Health and Examination Nutrition Survey reveal a statistically significantly higher percentage of women who received an HPV vaccine carried an HR-HPV than women who did not receive an HPV shot (Rao-Scott Chi-square contrast p-value of 0.002). Vaccine recipients tested positive less frequently for HPVs targeted by the vaccines, but had a higher prevalence of other HR (cancer related) HPVs. The results suggest that a thorough investigation of the effects of HPV vaccines on HR-HPV viruses (and other pathogens) not targeted by them is warranted.

**Keywords:** *aluminum adjuvant, HPV vaccine, type-replacement, vaccine safety*

## Introduction

According to statistics reported by the World Health Organization, cervical cancer kills nearly 300,000 women each year (World Health Organization, 2021). Muñoz et al. (2004) reported finding HPV DNA in 96% of cervical cancer specimens worldwide . Some HPVs are designated as particularly high-risk (HR) due to their prior association with cancer — at least 20 HR-HPV strains are in that HR list, with types 16 and 18 being the most commonly found in cases of cervical cancer (Halec et al., 2014; Muñoz et al., 2004).

Since 2006, three vaccines to address HPVs have been licensed in several countries. Gardasil™ and Cervarix™ target the HR-HPV types 16 and 18. Gardasil 9™ additionally targets HR-HPV types 31,

33, 45, 52, and 58. Despite the promise of these immunizations, some researchers question whether vaccination against HPVs can prevent cervical cancer (Rees et al., 2020).

## Study Design

One early indication of the potential for cervical cancer is an HR-HPV infection. To determine the presence of HR-HPV infections in U.S. women, data from the National Health and Nutrition Examination Survey (NHANES) were used (Centers for Disease Control and Prevention, 2019) .The Survey is a nonrandom sampling of the noninstitutionalized civilian U.S. population. The National Center for Health Statistic at the Centers for Disease Control and Prevention (CDC) administers the Survey and chooses participants based on socioeconomic and demographic criteria. The surveyors assign each respondent a weight so that the result is an estimate of the findings had the entire noninstitutionalized civilian U.S. population been surveyed (Chen et al., 2020). Analysis in this paper uses weighted frequencies reported in NHANES.

Data gathered during the Survey were used to compare the prevalence of HPV types of women who had received an HPV vaccine with those who had not. Starting in 2007, the Survey asks participants to provide information concerning their HPV vaccine status: "IMQ040: Has the survey participant ever received one or more doses of the HPV vaccine?" Responses could be (1) yes, (2) no, (7) refused, (9) don't know, or (.) missing. Additionally, selected female participants provide self-administered vaginal swabs that NHANES investigators can use to test for the presence of an HPV infection.

The method of collection could lead to uneven participation. Only certain segments of the U.S. population might be willing or able to participate in the sample collection. Although NHANES strives to reflect the general American civilian population, the use of mobile examination centers (MECs) could exclude women at the socioeconomic extremes. Wealthy gated communities may not accept MECs, while MECs may be reluctant or unable to enter poorer neighborhoods if they are dangerous. While the results of this study may be applicable only to the segments of the U.S. population that participate in the sample collection, there is no *a priori* reason to believe women in different socioeconomic segments are different biologically.

The method of collection could also lead to uneven specimen quality. Self-collected specimens may vary in precision. Such uneven collection reliability increases the noise in the samples and increases the probability of finding no results. The fact that statistically significant results are found means the observations are so strong that they overcome this potential hurdle.

NHANES includes information on positive tests for the presence of individual HPV types. Since 2003, NHANES reports results of the Roche Linear Array Assay (Linear Array) tests, which are known to detect the presence, not only of the 20 HR HPVs, but also 17 additional HPVs, 37 in all at the time of this writing, and can differentiate the specific type of HPV detected in any given swab.

Controversy surrounds the use of the Linear Array as a means to determine HPV genotyping. The U.S. Food and Drug Administration has not approved the Linear Array, but the Canada has licensed the test (Canadian Agency for Drugs and Technologies in Health, 2013). Additionally, the World Health Organization (WHO) found in 2010 that the Linear Array was "not proficient" in six out of 17 (35%) labs (Eklund et al., 2012). The following year, however, WHO found improvement in the

Linear Array with four out of 18 (22%) labs being "not proficient" (Eklund et al., 2014). Despite the disagreements, the Linear Array is one of the most widely used tests for genotyping HPV (Flores-Miramontes et al., 2015).

The current analysis was restricted to women aged 20 to 29. The HPV Centre reports that the prevalence of HPV is highest among women younger than 25 years old (HPV Centre, 2015). During the years of this study – 2007 to 2016 – the CDC recommended the HPV vaccine for women aged 9 to 26, so women most likely to have been given the opportunity to receive the shot were included. An additional consideration in determining the age range to study is the observation that 90% of HPV infections clear within two years without medical intervention (World Health Organization, n.d.). Of course, older women might have had an HPV when they were younger, but their immune systems may have cleared it, or it may no longer be detectable by the testing applied.

In this study, the crucial data consisted of instances of detected presence of HR-HPV infections in vaccinated versus unvaccinated women. Research by Muñoz et al. (2004) and Halec et al. (2014) was relied on to identify the 20 cancer related HR-HPVs focused on here. The percentage of women aged 20 to 29 who tested positive for any HR-HPV type was calculated as well as the percentage of women who tested positive for any HR-HPV in the following subgroups: the original vaccine types targeted by all the vaccines (16/18), additional HR types not targeted in the original vaccines (26/31/33/35/39/45/51/52/53/56/58/59/66/67/68/70/73/82), HR types that were added as targets in the second-generation Gardasil9™ vaccine (16/18/31/33/45/52/58), as well as the known additional HR types not targeted in Gardasil9™ (26/35/39/51/53/56/59/66/67/68/70/73/82).

## Statistical Analysis

The SURVEYFREQ in SAS 9.4 was used to create tables that report the presence of an HR-HPV virus according to HPV vaccine status. Subgroup indicator variables were formed by creating an indicator variable for each HR-HPV type (= 1 if the swab was positive for a particular HR-HPV or 0 if the swab was negative). If any of the indicator variables was 1, the subgroup indicator was 1; if all of the indicator variables were 0, the subgroup indicator was 0.

Table 1 reports the results of comparing the presence of HR-HPV infections in women who received the HPV vaccine with those who did not.

Results for the presence of any HR-HPV infection reveal that more vaccinated women had at least one HR-HPV infection compared with women who did not receive the shot. The Rao-Scott Chi-square contrast of 9.54 was statistically significant with a p-value of 0.002.

Results regarding the vaccine-type infections show that the first-generation Gardasil™ and Cervarix™ vaccines seem to reduce infections by the targeted HR-HPVs, but not other HR-HPVs. Fewer women who received an HPV vaccine had an HPV type 16 or 18 infection at the time of testing than women who did not receive the shot (Rao-Scott Chi-square p-value of 0.0002). However, a greater percentage of vaccinated women had a nonvaccine HR-HPV infection than women who did not receive the shot (Rao-Scott Chi-square p-value of <0.0001).

Selection bias might exist among females who choose to get an HPV shot because they have multiple sex partners and may recognize their increased risk of developing HPV infections. Such individuals, we may expect, would be more likely to take a shot of HPV vaccine than females who limit themselves to fewer partners. To determine whether selection bias is driving the results, the subset of females who report having three or more partners in a lifetime is examined and reported in Table 2.

Results from Tables 1 and 2 show, as expected, that females with three or more sexual partners are indeed more likely to have an HPV in a tested swab regardless of whether or not they got an HPV shot. Among women who received the shot, 58.2% with three or more partners tested positive for at least one HR-HPV versus the overall average of 46.7%. The corresponding numbers for women who did not receive the vaccine, were 48.4% and 38.0%.

Comparing the percentage of women who received the shot in the total sample against the more sexually active subset reveals the extent of any potential selection bias. Recall from the 'Study design' section that each respondent is weighted according to her representation of the noninstitutionalized civilian U.S. population. Table 1 reports that the weighted frequency of women who received the shot was 5.1 million or 28.4% of the entire sample. Table 2 reports that 30.0% of the subset of the sexually more active group received the shot. The perception of increased risk (if it exists in the sexually more active group; which accounted for 63.0% of the total sample) cannot account for the magnitude of the contrast between all of the 2.4 million HPV vaccine recipients who tested positive for any HPV (46.7%), against 38.0% of the 4.9 million persons who tested positive for at least one HPV but did not receive any HPV vaccine at all. If there is a slight selection bias causing women with more than three lifetime sex partners to be more likely to get an HPV shot, it has far too small an impact to explain the Rao-Scott Chi-square contrast at 9.5401, significant at $p < .002$, showing that women who got an HPV shot were more likely to test positive for at least one HPV than women who did not take the shot.

Results from both Table 1, which reports statistics for the entire sample, and Table 2, which reports statistics for the more sexually active subgroup, show that vaccinated women are less likely to develop the HR-HPVs that all the vaccines target (HPV16 and HPV18), but they are more likely to develop the HR-HPVs not targeted by the vaccines.

The promise of Gardasil9™ was to aim at more HR-HPVs. It was licensed in the United States in December 2014. Given that the youngest women in this study were 20 years old in 2016 and, also that most women receive the HPV shot in their teens, not many in the data set at issue here could have received Gardasil9™. Examining how the new vaccine might influence the prevalence of HR-HPVs could nonetheless be instructive to determine whether the new shot could prevent the HR-HPVs that are most common.

**Table 1. Prevalence ratios of vaccine and non-vaccine HR-HPV types, women aged 20-29, by HPV vaccine status, 2007-2016**

| | All HR-HPV Types[1] | | Vaccine HPV Types[2] | | Non-vaccine HR-HPV Types[3] | |
|---|---|---|---|---|---|---|
| **Test result →** | **Positive** | **Negative** | **Positive** | **Negative** | **Positive** | **Negative** |
| Received HPV shot | | | | | | |
| Frequency | 256 | 284 | 28 | 512 | 248 | 292 |
| Weighted frequency | 2,390,506 | 2,725,593 | 226,451 | 4,889,647 | 2,345,108 | 2,770,991 |
| Percentage | 46.73% | 53.27% | 4.43% | 95.57% | 45.84% | 54.16% |
| Did not receive shot | | | | | | |
| Frequency | 593 | 913 | 149 | 1357 | 540 | 966 |
| Weighted frequency | 4,908,542 | 8,007,100 | 1,364,955 | 11,550,688 | 4,477,926 | 8,437,716 |
| Percentage | 38.00% | 62.00% | 10.57% | 89.43% | 34.67% | 65.33% |
| Rao-Scott Chi-square | **9.5401** | | **13.4895** | | **17.1953** | |
| p > Chi-square | 0.002 | | 0.0002 | | <0.0001 | |
| Prevalence rate | | | | | | |
| Received HPV shot | 0.4673 | | 0.0443 | | 0.4584 | |
| Did not receive HPV shot | 0.38 | | 0.1057 | | 0.3467 | |
| Relative prevalence rate | 1.2295 | | 0.4188 | | 1.3221 | |
| Attributable prevalence rate | 0.0872 | | -0.0614 | | 0.1117 | |

Statistically significant results in **bold.**

[1] Any high-risk (HR) HPV vaccine type = 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 70, 73, 82.

[2]Vaccine (Gardasil™ or Cervarix™) HR-HPV types = 16, 18.

[3]Nonvaccine (Gardasil™ or Cervarix™) HR-HPV types = 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 70, 73, 82.

**Table 2. Prevalence ratios of vaccine and non-vaccine HR-HPV types, women aged 20-29 who report having 3 or more sexual partners, by HPV vaccine status, 2007-2016**

| | All HR-HPV Types | | Vaccine HPV Types[1] | | Non-vaccine HR-HPV Types[2] | |
|---|---|---|---|---|---|---|
| **Test result →** | **Positive** | **Negative** | **Positive** | **Negative** | **Positive** | **Negative** |
| Received HPV shot | | | | | | |
| Frequency | 207 | 142 | 21 | 329 | 202 | 148 |
| Weighted frequency | 1,981,513 | 1,423,998 | 168,586 | 3,236,926 | 1,952,787 | 1,452,725 |
| Percentage | 58.19% | 41.81% | 4.95% | 95.05% | 57.34% | 42.66% |
| Did not receive shot | | | | | | |
| Frequency | 443 | 446 | 117 | 772 | 403 | 486 |
| Weighted frequency | 3,844,646 | 4,105,148 | 1,127,111 | 6,822,684 | 3,488,508 | 4,461,287 |
| Percentage | 48.36% | 51.64% | 14.18% | 85.82% | 43.88% | 56.12% |
| Rao-Scott Chi-square | **9.763** | | **14.1659** | | **20.5366** | |
| p > Chi-square | 0.0018 | | 0.0002 | | <0.0001 | |
| Prevalence rate | | | | | | |
| Received HPV shot | 0.5819 | | 0.0495 | | 0.5734 | |
| Did not receive HPV shot | 0.4836 | | 0.1418 | | 0.4388 | |
| Relative prevalence rate | 1.2031 | | 0.3492 | | 1.3067 | |
| Attributable prevalence rate | 0.0982 | | -0.0923 | | 0.1346 | |

Statistically significant results in **bold.**

[1]Vaccine (Gardasil™ or Cervarix™) HR-HPV types = 16, 18.

[2]Nonvaccine (Gardasil™ or Cervarix™) HR-HPV types = 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 70, 73, 82.

**Table 3: Prevalence ratios of Gardasil9™ vaccine and non-vaccine HR-HPV types, women aged 20-29, by vaccine status & number of lifetime sexual partners, 2007-2016**

| | Any Gardasil9™ HR-HPV type: Full Sample[1] | | Non-vaccine HR-HPV Types: Full Sample[2] | | Any Gardasil9™ HR-HPV type: >=3 sexual partners[1] | | Non-vaccine HR-HPV Types: >=3 sexual partners[2] | |
|---|---|---|---|---|---|---|---|---|
| **Test result →** | **Positive** | **Negative** | **Positive** | **Negative** | **Positive** | **Negative** | **Positive** | **Negative** |
| Received HPV shot | | | | | | | | |
| Frequency | 105 | 435 | 217 | 323 | 87 | 263 | 176 | 174 |
| Weighted frequency | 920,126 | 4,195,972 | 2,050,474 | 3,065,624 | 776,256 | 2,629,256 | 1,716,021 | 1,689,490 |
| Percentage | 17.98% | 82.02% | 40.08% | 59.92% | 22.79% | 77.21% | 50.39% | 49.61% |
| Did not receive shot | | | | | | | | |
| Frequency | 300 | 1206 | 451 | 1055 | 233 | 656 | 334 | 555 |
| Weighted frequency | 2,523,769 | 10,391,874 | 3,772,636 | 9,143,006 | 2,067,745 | 5,882,049 | 2,946,663 | 5,003,132 |
| Percentage | 19.54% | 80.46% | 29.21% | 70.79% | 26.01% | 73.99% | 37.07% | 62.93% |
| Total | | | | | | | | |
| Frequency | 405 | 1641 | 668 | 1378 | 320 | 919 | 510 | 729 |
| Weighted frequency | 3,443,895 | 14,587,846 | 5,823,110 | 12,208,630 | 2,844,001 | 8,511,305 | 4,662,684 | 6,692,622 |
| Percentage | 19.10% | 80.90% | 32.29% | 67.71% | 25.05% | 74.05% | 41.06% | 58.94% |
| | | | | | | | | |
| Rao-Scott Chi-square | 0.4419 | | **18.8236** | | 1.0422 | | **19.6306** | |
| p > Chi-square | 0.5062 | | <0.0001 | | 0.3073 | | <0.0001 | |
| Prevalence rate | | | | | | | | |
| Received HPV shot | 0.1798 | | 0.4008 | | 0.2279 | | 0.5039 | |
| Did not receive HPV shot | 0.1954 | | 0.2921 | | 0.2601 | | 0.3707 | |
| Relative prevalence rate | 0.9204 | | 1.3721 | | 0.8764 | | 1.3595 | |
| Attributable prevalence rate | -0.0156 | | 0.1087 | | -0.0322 | | 0.1332 | |

Statistically significant results in **bold.**

[1]Gardasil9™ HR-HPV types = 16, 18, 31, 33, 45, 52, 58.

[2]Nonvaccine Gardasil9™ HR-HPV types = 26, 35, 39, 51, 53, 56, 59, 66, 67, 68, 70, 73, 82.

Table 3 shows that a greater percentage of women who received an HPV vaccine developed an HR-HPV infection that Gardasil9™ does not target than women who did not receive a shot with a Rao-Scott Chi-square p-value of <0.0001. No statistically significant difference exists between vaccine recipients versus non-recipients experiencing one or more of the seven HR-HPVs that Gardasil9™ addresses. Had vaccine recipients received the new vaccine, they may have been less likely to develop a vaccine-targeted HR-HPV. However, the vaccine does not address the remaining 13 known HR-HPV infections that women can experience and vaccine recipients tended to develop more of those than non-recipients. These results also hold for women with three or more sexual partners in a lifetime.

The results suggest that women who received the HPV vaccine were, in this data sample, more prone to a nonvaccine HR-HPV infection than unvaccinated women. These results are consistent with the findings of Guo et al. (2015) Those researchers did not explore the possible causes of their findings, but did recommend the development of vaccines targeting a greater number of HPVs.

## Discussion of findings

A possible explanation for increased overall prevalence of HR-HPVs in vaccine recipients can be inferred from Gravitt (2011) who explained how women who are DNA negative for an HPV, but had a prior HPV infection, could experience a reactivation. Trial data show women who were already infected at the time of vaccination had a ***higher*** incidence of dysplasia than infected women who did not receive the shot (VRBPAC, 2006), an undesirable effect euphemized as "negative efficacy" (Holland et al., 2018).

At least two studies find that immunocompromised women tend to have more HR-HPV reactivations than women with stronger immune systems. Strickler et al. (2005) find the reactivation of HR-HPVs in sexually inactive HIV-positive women increases as the number of CD4+ T-cells decreases. Theiler et al. (2010) find higher HPV reactivation among HIV-positive women, not only because of increased sexual risk factors, but also because of their decreased ability to clear infections due to immunosuppression.

Conversely, adjuvants such as aluminum that purport to enhance the immune response to vaccine components could also be associated with reactivation. A healthy person possesses CD4+ cells that help mount an appropriate immune response when challenged by a pathogen such as a virus. These cells differentiate into Th1 cells that attack intracellular pathogens and Th2 cells that attack extracellular pathogens (Romagnani, 1996). A well-regulated immune system creates a balance between Th1 cells and Th2 cells. By design, aluminum skews the immune response away from Th1 toward Th2 response, either by promoting Th2 or inhibiting Th1 or both (Marrack et al., 2009; McKee et al., 2007). If a person's immune system is already compromised, the skewing could be even more pronounced potentially increasing the undesired "negative efficacy" (Li et al., 2015; Oleszycka et al., 2018).

All licensed HPV vaccines contain some form of aluminum as an adjuvant to assist in evoking an immune response. By reducing the relative activity of the Th1 response, aluminum adjuvants could be interfering with a female's ability to control an intracellular latent HPV virus. Moreover, the

aluminum adjuvant used in HPV vaccines could create greater toxicity at the injection site, thereby eliciting a greater Th2 response and skewing the immune response further in the direction of a negative effect (Shardlow et al., 2018).

Another issue with the increase of nonvaccine HPVs is the heterologous or non-specific effects of vaccines. Vaccines not only target a specific pathogen, but can also cross-react with other pathogens. Since each individual has a unique set of pathogens, the cross-reaction can create uncertain results (Benn et al., 2013). In some cases, the cross-reaction is positive and prevents a non-targeted pathogen from causing disease. However, the cross-reaction can be detrimental and the immune response could increase vulnerability to disease (Sharma & Thomas, 2014). While the HPV vaccines usually reduce the number of infections by targeted HPVs, the effects on nontargeted HPVs – latent or active – is not well studied.

## Conclusion

Women who received an HPV vaccine appear to have more HR-HPV infections than women who did not receive the shot. Studies report that immunocompromised women are more susceptible to the negative effects of the HPV vaccine, specifically susceptibility to the reactivation of latent viruses and other non-specific effects of vaccines. Policymakers who are deciding whether to promote an HPV vaccine should weigh the benefit of lowering the prevalence of certain types of HR-HPVs against the possibility of increasing vulnerability to other types of HR-HPVs and possibly other pathogens. Potential vaccine recipients should also consider the possible side effects, negative efficacy, of any HPV vaccine on non-targeted but HR-HPVs.

## Competing interests

The author filed a claim under the Vaccine Injury Compensation Program on behalf of her daughter. The Special Master dismissed the claim due to untimely filing. The claim did not include the HPV vaccine. The author served on the Board of Directors of Sensible Action for Ending Mercury-Induced Neurological Disorders (SAFEMINDS) from 2007 to 2011..

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