Thursday, March 8, 2018

To Whom It May Concern:

**Correcting Errors About the Risk of HPV and the HPV Vaccine:**

HPV vaccines were initially licensed in 2006, aimed at preventing high-risk strains of HPV, strains that can cause cancer or genital warts. For a variety of reasons, uptake of HPV vaccines remains low in the United States <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4716467/> . Several states have undertaken efforts to improve uptake, using a variety of policy mechanisms, to improve uptake.

In response, several persons or group, many of which (though not all) can be fairly described as anti-vaccine, have made a series of claims about HPV vaccines, claiming the efforts were unjustified on policy grounds and the vaccines unsafe and/or unnecessary.

This post addresses those claims with referenced, science-based information, explaining why the policy efforts to improve HPV uptake are well-founded, and the arguments against them either inaccurate or unconvincing.

Importance and Effectiveness:

HPV infections are very common, and cause substantial harms and deaths. Increasing vaccine uptake can reduce those harms, and is a legitimate, well-justified public health goal.

* HPV infections cause tens of thousands of cancers and thousands of deaths each year. HPV vaccines can prevent the vast majority of that cancer. The lifetime risk for women for one of these cancers – cervical cancer alone – is 1:161. <https://www.cancer.org/cancer/cancer-basics/lifetime-probability-of-developing-or-dying-from-cancer.html> Low uptake, therefore, which leaves a risk of many cancers and deaths, can fairly be described as a public health crisis. [https://www.cdc.gov/cancer/HPV/statistics/index.htm](https://www.cdc.gov/cancer/hpv/statistics/index.htm)
* Most HPV cases clear on their own, but those that do not can lead to cancer or death. [https://www.cdc.gov/std/HPV/stdfact-HPV.htm](https://www.cdc.gov/std/hpv/stdfact-hpv.htm)
* There is increasing evidence that the vaccine reduces HPV infections with cancer-causing strains. The evidence comes from studies in the United States, http://pediatrics.aappublications.org/content/early/2016/02/19/peds.2015-1968 and <https://www.ncbi.nlm.nih.gov/pubmed/26123561>, in Australia, <https://www.ncbi.nlm.nih.gov/pubmed/23087430>, and in Scotland https://wwwnc.cdc.gov/eid/article/22/1/15-0736\_article. While it is too early to see the effect on cancer rates just yet, the reduction in infection, and dramatic reductions in precancerous lesions, are strong evidence that the vaccine is working as expected [http://www.kegel.com/HPV/faq/#effectiveness-pap](http://www.kegel.com/hpv/faq/#effectiveness-pap). In other words, if a person isn’t infected, they cannot develop precancerous lesions; preventing precancerous lesions means the vaccinated person doesn’t go on to develop cancer.
* The vaccine has been shown to be safe even for people who are infected with the HPV vaccine at the time of vaccination. However, some people who are opposed to the HPV vaccine claim such people have a higher risk of developing cancer, citing the outcomes for one subgroup in one clinical trial. This fear was addressed at the May 2006 meeting of the FDA body that oversees the safety of vaccines, the Vaccines and Related Biological Products Advisory Committee. To paraphrase the report prepared for the meeting <http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.pdf> the subgroup that showed a higher risk in the pre-2006 trials had other enhanced risk factor developing cancers, compared to the subjects who received placebo. Other subgroups in the study did not have larger numbers of subgroups that developed cervical disease. A later, larger study of over 17,000 women showed that women receiving the HPV vaccine after being infected with HPV did not have a higher risk of developing cancer. <http://www.ncbi.nlm.nih.gov/pubmed/20139221>
* The vaccine does not increase the risk for later cervical disease. Some anti-vaccine activists claim that “girls who received the four strain HPV shot, when assessed 10 years later, were actually more likely to be infected with high risk, low risk, and all strains of HPV. The four vaccine strains were reduced-- but other, possibly more pathogenic, HPV viruses moved in to fill the void.”. This is the “replacement risk” argument. This claim cites a 2015 poster presentation, which was later published in Human Vaccines & Immunotherapeutics. <http://www.tandfonline.com/doi/abs/10.1080/21645515.2015.1066948?journalCode=khvi20#.V3PX5bgrKUk> The published article actually says the difference between vaccinated and non-vaccinated women was much reduced after adjusting for sexual behavior variables, and that women who were vaccinated early with the four-serotype vaccine may benefit from the newer, nine-serotype vaccine. Further, later studies did not find the “replacement risk” phenomenon <http://www.jahonline.org/article/S1054-139X(16)30452-9/abstract>, <http://www.kegel.com/HPV/faq/#replacement>. In short, the “replacement risk” phenomenon alleged is not borne out by current research.

Safety:

The data showing HPV vaccines safe is abundant. A recent review found that with studies in over 2 million people, and data from 70 countries, no real safety concerns were found related to HPV vaccines. <https://link.springer.com/article/10.1007/s40264-017-0625-z> If readers would like a complete list of HPV vaccine safety studies, this site summarizes the safety data on HPV vaccines with links to the studies [http://www.kegel.com/HPV/safety/](http://www.kegel.com/hpv/safety/).

**Addressing Common Themes Repeated by Opponents of the HPV Vaccine to Challenge this Data:**

Complaints About “No True Placebo Testing” and the Types Of Placebo Used in Trial

* Several anti-vaccine activists are troubled by the fact that the control used in the trials for Gardasil was a solution containing the other vaccine ingredients, including AAHS, an aluminum salt adjuvant used for decades in infant vaccines like hepatitis B and others. These issues were specifically addressed by a vaccinologist in a recent article, which is quoted here at some length: <https://sciblogs.co.nz/diplomaticimmunity/2018/02/21/the-brouhaha-around-placebo-choice-in-vaccine-trials/>

“The placebo effect

The key objective of a placebo is to allow the participant to believe they have received the medicine being tested. In the case of an injectable vaccine the most common reaction is injection site pain, sometimes with minor redness and swelling. Often, the added adjuvant (immune enhancer) can be the main cause of the reaction and it is just doing its job. From a vaccinology perspective a mild to moderate injection site reaction is generally a good thing.

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**The role of the antigen**

Another factor in placebo selection is the importance of understanding the role of the active ingredient (antigen or antibody generator). What difference to the reactogenicity and safety profile does the addition of the active ingredient play?

Many vaccine developers prefer to balance the safety profile (identified in the trial) by ensuring the products in the vaccine carrier are present in both the active and placebo products. This means both the active and placebo study arm should both have the same local reaction to the impurities and other ingredients such as buffers and adjuvants. Any additional reaction rates will be related to the active ingredient.

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Anyway, the choice of vaccine formulation minus the active ingredient as a placebo provides important data about the role of the active ingredient, which is the new kid on the block. Its behaviour when administered alone (without adjuvant in earlier phase studies) and in the full formulation is important.

Using the vaccine formulation mix minus the active ingredient is a normal practice in vaccine trials for the reasons outline above. For example, of three trials from different manufacturers for the same type of vaccine I am aware of, one used an adjuvant in the active formulation, and the adjuvant was not included in the placebo. Two of the three used the vaccine formulation mix in the placebo; the other trial used just saline as the placebo.”

* The use of AAHS (an aluminum salt adjuvant) in placebo trials is an industry standard in vaccine trials where adjuvants are used, including previous HPV vaccine trials. The use of AAHS in the control arm of the Gardasil trials was clearly stated. Nonetheless, in one instance, an anti-vaccine activist suggested that the use of an AAHS solution in Gardasil trials was “fraud”, because the control wing of the trial was not “completely inert”. This claim is baseless. The researchers did not conceal or mislead; the difference between the active wing and the placebo wing of the trials were clear. The charged language is troubling, and should be considered as reflective of the frame of mind of those making the allegation.

Deaths Of Subjects During the Study Period

* The sad fact is that children and adults do die, from accidents or diseases. In large-scale studies of any medication, even for healthy children and adults, there are always deaths in the study populations which are unrelated to the medication being studied. With respect to the HPV vaccine trials, anti-vaccine activists make much of the fact some subjects died during the study period, as described in the product insert. What they ignore or hide is that (1) the deaths were roughly equivalent in the vaccine group and the control groups, and (2) the deaths were for causes completely unrelated to vaccines. [[1]](#footnote-1) <https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf> Obviously, gunshot wounds, tuberculosis, and the other causes of death cited in the insert as cannot be attributed to the vaccine or to an injection containing tiny amounts of aluminum salts.
* While one anti-vaccine source claimed the death rates were higher than the average in the population, they provided no direct source for that claim, which can therefore not be verified and cannot be assumed correct.
* Among the deaths reported in the produce insert – deaths occurring during the trial – were deaths from suicide and drug overdose. Both are tragic, but these are different categories. The Gardasil insert, however, did not separate deaths by suicide from deaths from drug overdoses. One anti-vaccine source claimed the rate of suicide in the trial was too high compared to rates in the population. This rests on reports of 8 deaths: 2 received the vaccine, and 6 received an AAHS control. This claim is problematic in several ways:
  + Since the category in question is drug overdose/suicide a calculation comparing the members of the category to only suicide rates in the general rates of the population is simply wrong: it ignores drug overdoses.
  + No specific source was provided for the calculations of the rate of suicide in the population. They cannot, therefore, be verified – or relied upon.
  + Out of the 8 cases in these categories only two received the vaccine, and 6 received an AAHS control. First, this undermines the focus on the vaccine. Second, it is unconvincing to claim that a shot in the arm that contains tiny amounts of an aluminum adjuvants in amounts no greater than that given to infants would cause a health teen to commit suicide. The anti-vaccine sources offer no mechanisms by which that could happen, and it is implausible on its face.

Reliance on Adverse Effects Reporting Systems

* There are several systems to report adverse effects of medications. One in the US is the Vaccine Adverse Effects Reporting System (VAERS). Anti-vaccine activists refer to reports made to adverse events reporting systems as evidence that the vaccine is dangerous. To use VAERS as evidence of vaccine dangers is a misuse of the system. VAERS accepts any report submitted to it, and without verification, those reports do not show causation. Further, in 2014 the CDC analyzed VAERS reports related to HPV vaccines and found no serious problems reflected in them. <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6305a1.htm>
* Another reporting system is Vigibase, the international reporting system for case reports on all kinds of medication. Like VAERS, Vigibase warns against using the system to infer causation. These kinds of reports cannot establish causation.

<http://www.vigiaccess.org>

* There are studies with a small number of cases reporting that conditions such as Chronic Fatuige Syndrome (CFS), Postural Orthostatic Tachycardia Syndrome (POTS), and various autoimmune conditions occur after vaccination. Anti-vaccine activists use these studies to “prove” the dangers of vaccines, especially HPV. These small case studies, however, run against the largescale studies that looked at whether the vaccines caused these problems – and found they did not. See: <http://www.kegel.com/hpv/safety/> for summaries of and links to the studies.
* In 2013, the Japanese government decided to withdraw the recommendation that Japanese girls receive the HPV vaccine. This decision came after a dubious study was made much of in the Japanese media, and after numerous startling media accounts of girls suffering a range of symptoms that the media linked to the HPV vaccine. The Vaccine Adverse Reactions Review Committee, a task force established by the Japanese Ministry of Health, Labor, and Welfare’s Health Science Council, has repeatedly concluded that no causal link exists between HPV vaccines and symptoms described in the media. The vaccine is still available in Japan to families that want to pay out of pocket for it. A study of 70,960 vaccinated and nonvaccinated adolescent girls from Nagoya also found no significant association between 24 alleged vaccine-induced symptoms and the HPV vaccines <https://www.wsj.com/articles/stopping-the-spread-of-japans-antivaccine-panic-1480006636>

There are several Japanese physicians who are still campaigning for re-approval of the vaccine https://www.nature.com/press\_releases/john-maddox-2017.html. Nonetheless, anti-vaccine activists also point to Japan’s withdrawal of support for the HPV vaccine as proof of the vaccine’s dangers. Japan’s problematic decision is certainly not a reason for the United States to lessen its protection of its citizens.

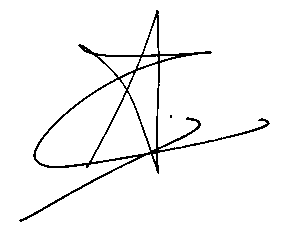
* In 2017, the Nordic Cochrane organization made a complaint to the European Ombudsman, claiming problems with HPV vaccines. Anti-vaccine activists exploit this complaint to prove the dangers of the HPV vaccine. However, the activists fail to mention that the complaint was rejected by the Ombudsman, which concluded: "There was no maladministration by the European Medicines Agency in the handling of the referral procedure on the HPV vaccines." <http://nordic.cochrane.org/sites/nordic.cochrane.org/files/public/uploads/european_ombudsmans_decision_16_oct_2017.pdf>

While the organization, allegedly, has complained about the Ombudsman’s decision, at this point, their complaint stands rejected, found baseless by the Ombudsman.

In short, extensive data shows HPV vaccines are safe. The counters raised by anti-vaccine activists are very, very weak.

Please do not hesitate to contact me with further questions at [reissd@uchastings.edu](mailto:reissd@uchastings.edu) or 510-666-0173.

Best Wishes,



Dorit Reiss

1. The most common cause of death was motor vehicle accident (5 individuals who received GARDASIL and 4 individuals who received AAHS control), followed by drug overdose/suicide (2 individuals who received GARDASIL and 6 individuals who received AAHS control), gunshot wound (1 individual who received GARDASIL and 3 individuals who received AAHS control), and pulmonary embolus/deep vein thrombosis (1 individual who received GARDASIL and 1 individual who received AAHS control). In addition, there were 2 cases of sepsis, 1 case of pancreatic cancer, 1 case of arrhythmia, 1 case of pulmonary tuberculosis, 1 case of hyperthyroidism, 1 case of post-operative pulmonary embolism and acute renal failure, 1 case of traumatic brain injury/cardiac arrest, 1 case of systemic lupus erythematosus, 1 case of cerebrovascular accident, 1 case of breast cancer, and 1 case of nasopharyngeal cancer in the group that received GARDASIL; 1 case of asphyxia, 1 case of acute lymphocytic leukemia, 1 case of chemical poisoning, and 1 case of myocardial ischemia in the AAHS control group; and 1 case of medulloblastoma in the saline placebo group.” <https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf> [↑](#footnote-ref-1)