ABC Response to HPV Vaccine adverse events:

1. The adverse events reported in Slade's article are quite significant. In developed countries, with Pap screening programs, the overall, average death rate of cervical cancer is 3 women per 100,000 women in the population. There are health disparity issues that create pockets of the US with up to 7.2 deaths of cervical cancer/100,000 per year, with higher death rates due to more advanced disease upon detection which is less likely to be curable.

The success rate of early detection of Pap screening over the past 60 years has been phenomenal with a decline to 75% of previous levels. Half of the women currently who develop cervical cancer are those who have never had a single Pap test; 10% of the women who develop cervical cancer had their last Pap test more than 5 years ago; 10% are given incorrect follow up advice from their physicians and the remaining women were failed by the Pap technology. Again, the average number of women dying from cervical cancer is 3 per 100,000 women, regardless if they were screened.

The risks of being treated for CIN with an excisional procedure are reported to increase the woman's chance of a low birth weight infant, of premature delivery and operative delivery. These risks occur at a 70-300% increase over women who have not had excisional therapy. Approximately 1% of screened women receive excisional therapies per year (500,0000 women per year).

Primary prevention of cervical cancer with Gardasil is limited to HPV 16, 18 and 31 related CIN 2/3+ disease. At the level of secondary screening, Gardasil is estimated to prevent about 55% of the abnormal Pap tests if 100% of the sexually active population is vaccinated. The other vaccinated women (~45%) who go on to develop cervical disease are still at risk for reproductive disabilities from excisional treatments as mentioned above.

The benefit to vaccination for the individual is an increased chance that her continued Pap tests will be normal. The benefit to public health is nothing unless the protection lasts for at least 15 years, and over 70% of all sexually active females of all ages are vaccinated. The incidence of cervical cancer is estimated to remain at the current 3/100,000 women until vaccination provides public health benefit, estimated in decades.

The risks of serious adverse events including death reported in Slade's article were 3.4/100,000 doses distributed (772/23 million doses distributed). The rate of serious adverse events is greater than the death rate of cervical cancer. Gardasil has been associated with at least as many serious adverse events as there are new deaths from cervical cancer developing each year. Indeed, the risks of vaccination are underreported in Slade's article, as they are based on a denominator of doses distributed from Merck's warehouse. Up to a third of those doses may be in refrigerators waiting to be dispensed as the autumn onslaught of vaccine messages is sent home to parents the first day of school. Should the denominator in Slade's work be adjusted to account for this, and then divided by three for the number of women who would receive all three doses, the incidence rate of serious adverse events increases up to five fold. How does a parent value that information?

Unlike Menactra which prevents an immediate death from meningitis, also made by Merck and with a known disclosure of increased incidence of Guillain Barre syndrome, a serious adverse event, Gardasil

will only prevent cervical cancers decades from now in women who continue to participate in Pap screening. The tolerance for serious adverse events in a vaccine that prevents a disease that can kill within 24 hours after contracting the bacteria is different than the tolerance for serious adverse events in a vaccine that prevents disease from a virus that is mostly cleared by the body within 2 years of infection and does not progress to advanced stages of cancer unless there has been no screening for decades.

It is time to develop shared decision making tools that include the values of women or their surrogate decision makers about the benefits and risks of Gardasil for the prevention of cervical cancer.

Of course, in developing countries where there is no safety Pap screening for women repeatedly over their lifetimes, the risks of serious adverse events may be acceptable as the incidence rate of cervical cancer is five to 12 times higher than in the US, dwarfing the risk of death reported after Gardasil.

2. Our institutional policy is up for revision, so that women must be informed of the 3.4/100,000 rate of serious adverse events that have been reported with Gardasil and that the only known benefit to receiving three doses of Gardasil will be a greater chance that their Pap screens over the next 5 years will be normal. [We only have data showing Gardasil is protective for 5 years.] We will place greater emphasis presenting both the risks and benefits Gardasil may have for older teenagers and those in their twenties who are able to form their own value judgments and make their own decisions.

Our institution is not ready to accept the level of evidence of protection Gardasil has reported in males for male vaccination against cancers.

3. Parents and women must know that deaths occur. Not all deaths that have been reported were represented in Slade's work, leaving the parents of the deceased teenagers in despair that the CDC is ignoring the very rare but real occurrences that need not have happened if parents were given information stating that there are real, but small risks of death surrounding the administration of Gardasil. Because numbers are small, but real, instead of statistical significance geared toward removing a valuable vaccine from the market, the emphasis should indeed be on the biological plausibility of the SAE's occurrence with acknowledgement that a Pap screening option is available that is 100% effective in removing and treating early precancerous and cancerous disease should the woman/family have no tolerance for a serious adverse event.

4. The marketing of Gardasil was much too aggressive. The 'one less' campaign was deceptive. I have patients now with LSIL coming to colposcopy who say, "This is caused by HPV??? But isn't HPV what is in that Gardasil vaccine?? But, I am not supposed to get HPV because I got all three doses of Gardasil??? Is someone not telling me the truth???" These women are very angry. [Please see the New York Times article in which I am interviewed in August 20, 2008 (exactly a year ago!!)for more of my thoughts on the aggressiveness of the advertising campaigns]. Rothman and Rothman have done a good job in exposing the vulnerabilities of small medical societies to the seduction not only of a new funding stream

to support their primary missions, but also the seduction of power in creating a single minded message given to elite chosen 'speakers' who will faithfully carry only the society's message to tens of thousands of outlets. Rothman and Rothman left out the role of the pediatric societies. Rothman and Rothman also left out the role of the CDC in crafting the ACIP recommendations. Adolescent preventive visits have always been very low. There are important adolescent counseling topics that can be offered at the 11-14, 15-17 and 18-21 year old groups. Of these three age groups, the pediatrician has the highest chances of seeing the 11-14 year old group as parents still have to drive them to the office. The CDC has made a concerted effort to create an adolescent platform at the 11-14 age group so that these preventive measures can be addressed:

Physical Growth and Development
Physical and Oral Health, Body Image, Eating Habits [nutritional counseling], Physical Activity
Social and Academic Competence
Connectedness with family, peers and community, Interpersonal relationships, School/job performance
Emotional Well-being
Coping, Mood regulation, Mental health, Sexuality
Risk Reduction
Tobacco, alcohol or other drugs, Pregnancy, STIs, Immunizations
Violence and Injury Prevention
Safety belt and helmet use, Substance abuse and riding in a vehicle, Guns, Interpersonal violence [fights, dating violence, stalking], bullying

In co-opting the HPV vaccine to spearhead this movement for adolescent preventive visits, the ACIP recommendations moved tangentially away from the age group of women who had been studied for efficacy, immunogenicity and safety, and for whom real disease reduction was demonstrated within the 5 years Gardasil was studied.

The future expectations women hold because they have received free doses of Gardasil purchased by philanthropic foundations, by public health agencies or covered by insurance is the true threat to cervical cancer in the future. Should women stop Pap screening after vaccination, the cervical cancer rate will actually increase per year. Should women believe this is preventive for all cancers - something never stated, but easily inferred by many in the population-- a reduction in all health care will compound

our current health crisis. Should Gardasil not be effective for more than 15 years, the most costly public health experiment in cancer control will have failed miserably.

5. Another JAMA article (Oct 22/29, 2008) that explicitly did not review vaccines as they are under the purview of the ACIP pointed out facts that are applicable to a new drug brought to market. The mean time to elicit a safety-related regulatory action was 3.7 years after approval. 71% of the safety-related regulatory actions were issued within 5 years after regulatory approval. 29% chance of a first safety-related regulatory action within 10 years of approval. The time to safety related regulatory action will probably be different for vaccines. Only time will tell if the rate of serious adverse events will increase. The only mitigating redemption of more serious adverse events is knowing that with full disclosure of possible benefits and risks of vaccination and screening these girls/women have made an informed and shared decision.

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Conflict of interest: The institutions at which I have undertaken HPV vaccine trials have received funding from Merck and GlaxoSmithKline to support clinical trials on the vaccines discussed in this comment. I have also received honoraria from Merck and GlaxoSmithKline for speaking and for participation on advisory boards.

The following is a response that I sought from a parent whose daughter has died after receiving Gardasil.

Response to JAMA articles on Gardasil

August 16, 2009

Emily Tarsell

A report can only be as good as the information that makes up the report. The information in this post licensure safety of Gardasil report, even by the reporter's own admission, is greatly compromised by the inadequacies of the reporting system. Yet the reporter goes on to draw conclusions about the vaccine's safety based on this inadequate data, and this is both misleading and dangerous.

Some of the problems with the data are as follows:

1. By the reporters own admission, 68%of the responses came from Merck. Of these, 89% "do not include sufficient information to allow medical review of the cases." That is a hugh block of missing information. There are no checks and balances about the reporting and no follow up with families to gather histories or data clarification.
2. Because it is a passive reporting system, people do not know to report, especially for events that happen days or weeks after the office visit. This skews the reported events toward those made shortly after the shot, and makes it appear that if something is going to happen, it is fairly immediate. This is contradicted by the evidence I have from dozens of families.
3. There is no way in the current system to capture a worsening of conditions over time and with each additional shot.
4. Because the public is told the vaccine is safe and are not informed of possible side effects, people do not report events. People (including doctors) assume post-vaccine events are unrelated to the vaccine. For example, I never reported that my daughter had a chronic cough, sinus congestion, a rash, hair loss, dizziness, and fatigue because I assumed these didn't have anything to do with the vaccine. It is only after her death and an autopsy that we realize these symptoms were all related to the pulmonary edema and intraaveolar hemorrhages. These findings are consistent with forms of vasculitis that are mediated by the immune system and could well have been a consequence of the vaccine. However none of this data is captured in this report where her death is listed as one of those "undetermined".
5. I doubt and question the number of reported deaths, particularly the number of "undetermined" deaths reported which is quoted to be four. I personally have copies of six autopsies for Gardasil related deaths prior to 2009, four of which are "unexplained." I know there are other VAERS reports of "unexplained" deaths for which I do not have reports, so the total number of cases has got to be more than four.
6. The report is inconsistent in what is being reported and measured. Sometimes it reports symptoms like syncope, dizziness, headaches and nausea. Sometimes it reports diagnostic categories like Guillain-Barre Syndrome, Motor Neuron Disorder or Autoimmune Disorders, etc.

Other times, it reports conditions like Pregnancy or Death. Since there is no common denominator of what is being measured, it fragments and obscures the picture. A better picture might be obtained by recording only symptoms, by case, in relation to each shot. This would require follow up but you would then be able to compare apples with apples. (I have been gathering data from families in this regard).

7. It is also puzzling to me why symptoms like seizures, numbness, muscle weakness or respiratory problems are not among the symptoms discussed. This is especially so since apparently they appeared in great enough numbers to recently prompt Merck to petition the CDC to add "respiratory, thoracic and mediastinal disorders," "pulmonary embolus" and "syncope, sometimes associated with tonic-clonic movements and other seizure-like activity" to their list of warnings and precautions on package inserts for Gardasil.
8. The diagnostic categories make it seem that the adverse effects are diverse, unrelated and in such small numbers as to be statistically insignificant. If these cases were compared symptomatically, one might see that they have a lot in common. For example, are not Guillain-Barre, transverse myelitis and autoimmune disorder all immune system related responses involving inflammation, including possible inflammation of the blood vessels resulting in insufficient blood flow? Could they not all (including pancreatitis) have a common immune related vaccine trigger that is manifesting somewhat differently depending on the systems affected? Might many of them be forms of vasculitis or autoimmune responses? Many doctors have not been able to diagnose what is happening or have changed diagnosis more than once. This suggests uncertainty about diagnostic labels. It is also amazing that vasculitis is not among the diagnostic categories mentioned.
9. If seen as immune or autoimmune related responses that cut across categories, the number of adverse incidences begins to be significant. If in addition, those discounted "undetermined" deaths were researched in more detail might they also add to the numbers of immune related adverse responses? The data I have from several families suggest they would.

I cannot speak to the safety data of the pre licensure trials because I am unfamiliar with that. However, if the post licensure data collection process is modeled after the pre licensure model, then I guess the latter would have the same flaws.

With regard to the marketing of the vaccine, it is amazing how successful Merck was at pushing the right buttons to get normally rational and intelligent people to fall for their propaganda. In my case, I am normally suspect of any new drug and know to wait a few years to see how it plays out. In this case, I suppressed that instinct because they pushed the "cancer" button. Having had a sister die of ovarian (not cervical) cancer, I became anxious thinking of my daughter and the possibility that she might have a gene for such. Even though cervical cancer is different from ovarian cancer and without further research, and because her doctor was recommending it and telling us it was safe, I encouraged my perfectly healthy daughter to have the shots. She died 18 days after the third shot and I know it was the Gardasil. This was a totally unnecessary risk and we would have declined the shots in a heartbeat if we had been given any of the risk/benefit facts.

Regarding cost-effectiveness of the vaccine, it seems premature to determine this. It is unknown how long the vaccine is effective, and whether or not a booster would be required. There are, in the mean time, millions of dollars being spent on treatments for girls having adverse reactions, not to mention their pain and suffering; and the priceless loss of life for those who died.

Thank you for the opportunity to respond to these papers.

Emily Tarsell