Response to the Opinion Paper Authored by Dr Diane Harper "Current prophylactic HPV vaccines and gynecologic premalignancies" Published in *Curr Opin Obstet Gynecol 2009;21:457-464*.

Richard M Haupt MD and Carlos Sattler MD

Merck, West Point, PA

The opinion paper authored by Dr. Harper contains inaccuracies and assumptions not supported by the currently available data.

The review compares the efficacy estimates observed after vaccination with a quadrivalent (Gardasil) and bivalent (Cervarix) vaccine. Efficacy estimates alone cannot be compared across studies and populations in order to infer differences in vaccine impact. This position is supported by the World Health Organization (WHO), as stated in its recently published HPV vaccines position paper *"Differences among the efficacy trials of the quadrivalent and bivalent vaccines in terms of choice of placebo recipients or control subjects, immunological assays and populations analysed preclude direct comparison of results for the 2 vaccines"*.[1]

In order to properly compare the efficacy estimates (i.e., relative risk reductions), it is essential to understand and consider the impact that certain factors have on relative risk reductions. Interpretation of the results of the HPV vaccine efficacy trials must consider the differences in study population characteristics, study design, and endpoint ascertainment between the bivalent and quadrivalent vaccine trials. There are substantial differences that can fully explain variations in the percent efficacy estimates, without a true difference in the impact conferred by the vaccines.

For example, the baseline prevalence of vaccine oncogenic HPV types is nearly twice as high in the Gardasil study population (HPV 16 DNA positive: 9%; HPV 18 DNA positive: 4%)[2,3] compared to the Cervarix study population (HPV 16 DNA positive: 5%; HPV 18 DNA positive: 2%).[4] Furthermore, time to event curves included in the publications of these vaccines suggest that the incidence of HPV-related disease among the placebo arm is also substantially higher in the Gardasil study population compared to the Cervarix study population.[5,6] The illustration below demonstrates the impact of prevalence and incidence on the percent efficacy estimates in a hypothetical intention-to-treat population analysis.

As the illustration shows, differences in prevalence and incidence of infection and disease can have a profound impact on efficacy estimates (67% vs 50%). These differences in efficacy estimates are apparent ***despite the lack of a differential impact on the amount of disease prevented*** (30 cases

prevented in both study populations). Additionally, there are other factors that can impact the observed efficacy estimates. These include differences in endpoint ascertainment, as reflected by differences in endpoint adjudication panels and HPV detection assays. These could further account for differences in efficacy estimates observed.

Illustration: Impact of Differences in HPV Prevalence and Incidence on Percent Efficacy Estimates

	Population with Lower Prevalence and Incidence			**Population with Higher Prevalence and Incidence**		
	Placebo	Vaccine	Cases Prevented	Placebo	Vaccine	Cases Prevented
Baseline prevalence	5	5		10	10	
Cases accrued during follow-up	40	10	**30**	50	20	**30**
Total number of cases	45	15		60	30	
Estimated Efficacy	**67%**				**50%**	

Same number of disease cases prevented but different efficacy estimates

Another simple way to explain the differences in percent efficacy estimates between the Gardasil and Cervarix clinical trials is shown below, using actual data from the Gardasil trials. As shown in the below table, vaccination of a population that is more HPV naive (i.e., low prevalence, low incidence) results in 43% efficacy for pre-cancerous cervical lesions (CIN3 and AIS) with an estimated 170 cases prevented annually per 100,000 vaccinated women. Vaccination of a population with high prevalence and high incidence (intention-to-treat population) resulted in an observed efficacy of 18%; however, the number of cases prevented per 100,000 vaccinated women was 180. It would not be proper to compare the 43% efficacy with the 18% efficacy in order to made statements such as *"the vaccine given to the generally HPV naive population is superior to the vaccine that was given to the intention-to-treat population"*. As we have illustrated here, and as the WHO has stated in its recent opinion, direct comparisons of vaccine efficacy cannot be made. Such a comparison could only be made if the Gardasil and Cervarix trials enrolled women with identical baseline HPV prevalence and incidence, and this was not the case.

Efficacy estimates for two populations in the Gardasil clinical trials.

	Vaccine group		Placebo group			
	No. of women	Rate†	No. of women	Rate†	Efficacy (95% CI)	Number of disease cases prevented annually per 100,000 vaccinated women (95% CI)
Generally HPV naive population (low prevalence, low incidence)						
Any CIN 3 or AIS	4616	0.22	4680	0.39	43 (13, 63)	170 (50 to 280)
Intention-to-treat population (high prevalence, high incidence)						
Any CIN 3 or AIS	8562	0.81	8598	0.98	18 (2.4, 31)	180 (30 to 330)

†Cases per 100 person years at risk

In addition to making inappropriate comparisons of vaccine efficacy, questions regarding the safety of Gardasil were also raised. The opinions expressed are counter to statements made by national and international regulatory and recommending authorities, such as the United States Food and Drug Administration (FDA), the Centers for Disease and Control and Prevention (CDC), The European Medicines Agency, the Australian Therapeutic Goods Administration, and the World Heath Organization, all of which continue to recommend and support vaccination with the quadrivalent HPV vaccine.[7,8] A CDC-FDA report analyzing adverse events following quadrivalent HPV vaccine administration from June 2006 through December 2008 found that "*The findings were generally not that different from what is seen in the safety reviews of other vaccines recommended for a similar age group, 9 to 26 years old (meningitis and Tdap). Based on the review of available information by FDA and CDC, the HPV vaccine continues to be safe and effective, and its benefits continue to outweigh its risks*".[8] Merck has also published extensive safety data for the quadrivalent vaccine, including pregnancy outcomes.[9-11] Comments and opinions regarding Gardasil should consider all of the available data in an effort to provide a broad and balanced perspective on the overall safety profile

The opinion piece also made definitive statements regarding the long term duration of efficacy for the two vaccines. Given that no minimum level of antibody level that affords protection is known (immune correlate), comparing antibody titers alone to provide a marker for vaccine efficacy or duration of protection as suggested in the opinion paper is flawed. Furthermore, the opinions did not consider all of the available data in an effort to provide a broad and balanced perspective. Although the long term duration of protection of Gardasil is currently unknown, there is good evidence of protection through at least 5 years. This was defined through data in one of the phase II studies of Gardasil where 100%

efficacy against clinical disease was seen 5 years after vaccination onset.[12] In this same study, immune memory was also demonstrated; a 4th dose of Gardasil given at year 5 following vaccination onset resulted in a vigorous recall antibody response.[13] Immune memory is usually a hallmark of long-term immunological response, and vaccines that induce immune memory typically have long-term protection. In addition, data from a monovalent type 16 vaccine have demonstrated durable protection through 8.5 years.[14]

We also disagree that there are no documented harms with detecting and treating vulvar and vaginal pre-cancers. These lesions, which are often multifocal, require excisional therapy, which may be extensive and disfiguring. In addition, given that recurrences are not infrequent, long-term follow up is required. The annual progression rate of untreated vulvar carcinoma in situ to invasive cancer is at least 10%. In contrast, cervical intraepithelial neoplasia grade 3 progresses at a rate of about 2%.[15,16] Finally, a recent study has shown that VIN has an adverse impact on quality of life and sexual functioning.[17] While Gardasil has demonstrated high efficacy against VIN 2/3 and VaIN 2/3, precursors of vulvar and vaginal cancer,[18] similar prevention of vulvar and vaginal dysplasia has not been demonstrated by vaccination with Cervarix. Until adequately designed and powered clinical studies demonstrate such efficacy, assumptions that Cervarix is theoretically expected to show similar vulvar and vaginal protection are scientifically invalid.

In addition, although missing from the opinion paper, the efficacy of the quadrivalent vaccine for the prevention of disease in women over aged 26 was recently published in the Lancet.[19] Vaccine efficacy for the prevention of vaccine-type-related disease in the per-protocol efficacy population (cervical intraepithelial neoplasia and external genital lesions) was 92.4% (95% confidence interval of 49.6 to 99.8).

Finally, the review makes no mention of the benefit of protection against HPV 6- and 11-related disease, which is not insignificant. It is possible that the scope of this opinion piece only included pre-malignant lesions. However, since the target audience specifically includes obstetricians and gynecologists, the impact of HPV 6 and 11 diseases, and the potential for their prevention through vaccination with Gardasil, is an important consideration.

In conclusion, this opinion paper has the potential of confusing, rather than guiding, practitioners regarding the potential impact of primary prevention of HPV-related disease, and in particular, the potential impact of the quadrivalent HPV vaccine. We encourage those reading the article to also read the two recent articles which compare and contrast the bivalent and quadrivalent vaccine.[20,21]

Acknowledgements – The authors are employees of Merck, the company that manufactures the quadrivalent vaccine. The authors thank Heather L Sings (Merck).

Reference List

1. World Health Organization. Weekly epidemiological record Relevé épidémiologique hebdomadaire. http://www.who.int/entity/wer/2009/wer8415.pdf accessed December 7, 2009.
2. Garland SM, Hernandez-Avila M, Wheeler CM et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007; 356:1928-1943.
3. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007; 356:1915-1927.
4. Paavonen J, Jenkins D, Bosch FX et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. Lancet 2007; 369:2161-2170.
5. The FUTURE II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3 and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007; 369:1861-1868.
6. Paavonen J, Naud P, Salmeron J et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009; 374:301-314.
7. Australian Government Department of Heath and Ageing Therapeutic Goods Administration. Human papillomavirus vaccine (GARDASIL). Available at http://www.tga.gov.au/alerts/medicines/gardasil.htm. Accessed December 7, 2009.
8. Centers for Disease Control and Prevention. Summary of HPV Adverse Event Reports Published in JAMA. Available at http://www.cdc.gov/vaccinesafety/vaers/HPV_ JAMA.htm Accessed Dec 7, 2009.
9. Block SL, Brown DR, Chatterjee A et al. Clinical Trial and Post-Licensure Safety Profile of a Prophylactic Human Papillomavirus (Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine. Pediatr Infect Dis J 2009.
10. Garland SM, Ault KA, Gall SA et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. Obstet Gynecol 2009; 114:1179-1188.
11. Dana A, Buchanan KM, Goss MA et al. Pregnancy outcomes from the pregnancy registry of a human papillomavirus type 6/11/16/18 vaccine. Obstet Gynecol 2009; 114:1170-1178.
12. Villa LL, Costa RLR, Petta CA et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer 2006; 95:1459-1466.

13. Olsson S-E, Villa LL, Costa R et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like-particle vaccine. Vaccine 2007; 25:4931-4939.
14. Rowhani-Rahbar A, Mao C, Hughes JP et al. Long-term efficacy of a prophylactic human papillomavirus type 16 vaccine. Vaccine 2009; 27:5612-5619.
15. Jones RW. Vulval intraepithelial neoplasia: current perspectives. Eur J Gynaecol Oncol 2001; 22:393-402.
16. Jones RW, Rowan DM, Stewart AW. Vulvar intraepithelial neoplasia: aspects of the natural history and outcome in 405 women. Obstet Gynecol 2005; 106:1319-1326.
17. McFadden KM, Sharp L, Cruickshank ME. The prospective management of women with newly diagnosed vulval intraepithelial neoplasia: clinical outcome and quality of life. J Obstet Gynaecol 2009; 29:749-753.
18. Joura EA, Leodolter S, Hernandez-Avila M et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16 and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three clinical trials. Lancet 2007; 369:1693-1702.
19. Munoz N, Manalastas R, Pitisuttihum P et al. Safety, immunogenicity, and efficacy of quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine in adult women between 24 and 45 years of age: a randomized, double-blind trial. Lancet 2009; 373:1921-1922.
20. Agorastos T, Chatzigeorgiou K, Brotherton JM, Garland SM. Safety of human papillomavirus (HPV) vaccines: a review of the international experience so far. Vaccine 2009; 27:7270-7281.
21. Stanley M. Prospects for new human papillomavirus vaccines. Curr Opin Infect Dis 2009.