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Oppose HB 530 / SB 355

I am Emily Tarsell, mother and therapist and I oppose this bill which would lower the age from 11 to 9 years for a child to receive Gardasil, an HPV vaccine, from a pharmacist. Gardasil is for antibodies against sexually transmitted viruses, something that a 9 year old will likely not be exposed to for another 8 to 12 years. The effectiveness of the vaccine has not been demonstrated to be long lasting, especially for this age group. According to the package insert, "The duration of immunity following …. vaccination with GARDASIL 9 has not been established" and the "Effectiveness of GARDASIL 9 against persistent infection… in 9- through 14-year-old girls and boys ...was *inferred*." Also, the number of boys and girls in clinical trials between 9 and 14 was very small, only 300 of each. The benefit of the vaccine to a 9 year old is thus highly speculative and unsupported by data.

HPVs are transmitted sexually, not in school settings or public places and not among pre-teens. Those marketing the vaccine like to say that pre-teens have a more "robust" response to Gardasil 9 as though that were a good thing. Robust can be a euphemism for strongly reactive to the injection of a neurotoxic, inflammatory, aluminum adjuvant which is associated with neurological disorders and brain inflammation. The sample size of preteens in clinical trials is too small to assess safety and the so-called "control" group in clinical trials did not get a true placebo.

The CDC itself has said that the adverse event reports for Gardasil are 3x greater than that for all other vaccines combined. These include seizures, debilitating headaches, paralysis, joint and muscle pain, autoimmune disorders, extreme fatigue, arrhythmia, hair loss, ovarian failure, gut and sleep disorders, and even cervical cancer and death. I know of an 11 year old, Jenny, who died after Gardasil inoculation. My own daughter, Christina, died 12 years ago from Gardasil. And yes, our experts proved it and the government conceded in the vaccine court that Gardasil caused her death.

Why on Earth would one offer a 9 yo a vaccine which poses significant risk of harm with no proven benefit? Please veto this bill. While it might be good for industry and provider profits, it is bad for children's health.

Christina and I thank you.
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Table 19: Summary of Month 7 Anti-HPV cLIA Geometric Mean Titers in the PPI* Population of Boys and Men

Population	N†	n‡	% Seropositive (95% CI)	GMT (95% CI) mMU§/mL
Anti-HPV 6				
9- through 15-year-old boys	1072	884	99.9 (99.4, 100.0)	1037.5 (963.5, 1117.3)
16- through 26-year-old boys and men	2026	1093	98.9 (98.1, 99.4)	447.8 (418.9, 478.6)
Anti-HPV 11				
9- through 15-year-old boys	1072	885	99.9 (99.4, 100.0)	1386.8 (1298.5, 1481.0)
16- through 26-year-old boys and men	2026	1093	99.2 (98.4, 99.6)	624.3 (588.4, 662.3)
Anti-HPV 16				
9- through 15-year-old boys	1072	882	99.8 (99.2, 100.0)	6056.5 (5601.3, 6548.7)
16- through 26-year-old boys and men	2026	1136	98.8 (97.9, 99.3)	2403.3 (2243.4, 2574.6)
Anti-HPV 18				
9- through 15-year-old boys	1072	887	99.8 (99.2, 100)	1357.4 (1249.4, 1474.7)
16- through 26-year-old boys and men	2026	1175	97.4 (96.3, 98.2)	402.6 (374.6, 432.7)

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).
†Number of individuals randomized to the respective vaccination group who received at least 1 injection.
‡Number of individuals contributing to the analysis.
cLIA = Competitive Luminex Immunoassay
CI = Confidence Interval
GMT = Geometric Mean Titers
§mMU = milli-Merck Units

Table 20: Persistence of Anti-HPV cLIA Geometric Mean Titers in 9- Through 45-Year-Old Girls and Women

Assay (cLIA)/ Time Point	9- to 15-Year-Old Girls (N* = 1122)		16- to 26-Year-Old Girls and Women (N* = 9859)		27- to 34-Year-Old Women (N* = 667)		35- to 45-Year-Old Women (N* = 957)	
	n[†]	GMT (95% CI) mMU[‡]/mL	n[†]	GMT (95% CI) mMU[‡]/mL	n[†]	GMT (95% CI) mMU[‡]/mL	n[†]	GMT (95% CI) mMU[‡]/mL
Anti-HPV 6								
Month 07	917	929.2 (874.6, 987.3)	3329	545.0 (530.1, 560.4)	439	435.6 (393.4, 482.4)	644	397.3 (365.2, 432.2)
Month 24	214	156.1 (135.6, 179.6)	2788	109.1 (105.2, 113.1)	421	70.7 (63.8, 78.5)	628	69.3 (63.7, 75.4)
Month 36[§]	356	129.4 (115.6, 144.8)	-	-	399	79.5 (72.0, 87.7)	618	81.1 (75.0, 87.8)
Month 48[¶]	-	-	2514	73.8 (70.9, 76.8)	391	58.8 (52.9, 65.3)	616	62.0 (57.0, 67.5)
Anti-HPV 11								
Month 07	917	1304.6 (1224.7, 1389.7)	3353	748.9 (726.0, 772.6)	439	577.9 (523.8, 637.5)	644	512.8 (472.9, 556.1)
Month 24	214	218.0 (188.3, 252.4)	2817	137.1 (132.1, 142.3)	421	79.3 (71.5, 87.8)	628	73.4 (67.4, 79.8)
Month 36[§]	356	148.0 (131.1, 167.1)	-	-	399	81.8 (74.3, 90.1)	618	77.4 (71.6, 83.6)
Month 48[¶]	-	-	2538	89.4 (85.9, 93.1)	391	67.4 (60.9, 74.7)	616	62.7 (57.8, 68.0)
Anti-HPV 16								
Month 07	915	4918.5 (4556.6, 5309.1)	3249	2409.2 (2309.0, 2513.8)	435	2342.5 (2119.1, 2589.6)	657	2129.5 (1962.7, 2310.5)
Month 24	211	944.2 (804.4, 1108.3)	2721	442.6 (425.0, 460.9)	416	285.9 (254.4, 321.2)	642	271.4 (247.1, 298.1)
Month 36[§]	353	642.2 (562.8, 732.8)	-	-	399	291.5 (262.5, 323.8)	631	276.7 (254.5, 300.8)
Month 48[¶]	-	-	2474	326.2 (311.8, 341.3)	394	211.8 (189.5, 236.8)	628	192.8 (176.5, 210.6)
Anti-HPV 18								
Month 07	922	1042.6 (967.6, 1123.3)	3566	475.2 (458.8, 492.1)	501	385.8 (347.6, 428.1)	722	324.6 (297.6, 354.0)
Month 24	214	137.7 (114.8, 165.1)	3002	50.8 (48.2, 53.5)	478	31.8 (28.1, 36.0)	705	26.0 (23.5, 28.8)
Month 36[§]	357	87.0 (74.8, 101.2)	-	-	453	32.1 (28.5, 36.3)	689	27.0 (24.5, 29.8)
Month 48[¶]	-	-	2710	33.2 (31.5, 35.0)	444	25.2 (22.3, 28.5)	688	21.2 (19.2, 23.4)

*N = Number of individuals randomized in the respective group who received at least 1 injection.
[†]n = Number of individuals in the indicated immunogenicity population.
[‡]mMU = milli-Merck Units
[§]Month 37 for 9- to 15-year-old girls. No serology samples were collected at this time point for 16- to 26-year-old girls and women.
[¶]Month 48/End-of-study visits for 16- to 26-year-old girls and women were generally scheduled earlier than Month 48. Mean visit timing was Month 44. The studies in 9- to 15-year-old girls were planned to end prior to 48 months and therefore no serology samples were collected.
cLIA = Competitive Luminex Immunoassay
CI = Confidence Interval
GMT = Geometric Mean Titers

Table 21: Persistence of Anti-HPV cLIA Geometric Mean Titers in 9- Through 26-Year-Old Boys and Men

Assay (cLIA)/ Time Point	9- to 15-Year-Old Boys (N* = 1072)		16- to 26-Year-Old Boys and Men (N* = 2026)	
	n[†]	GMT (95% CI) mMU[‡]/mL	n[†]	GMT (95% CI) mMU[‡]/mL
Anti-HPV 6				
Month 07	884	1037.5 (963.5, 1117.3)	1094	447.2 (418.4, 477.9)
Month 24	323	134.1 (119.5, 150.5)	907	80.3 (74.9, 86.0)
Month 36[§]	342	126.6 (111.9, 143.2)	654	72.4 (68.0, 77.2)
Month 48[¶]	-	-	-	-
Anti-HPV 11				
Month 07	885	1386.8 (1298.5, 1481.0)	1094	624.5 (588.6, 662.5)
Month 24	324	188.5 (168.4, 211.1)	907	94.6 (88.4, 101.2)
Month 36[§]	342	148.8 (131.1, 169.0)	654	80.3 (75.7, 85.2)
Month 48[¶]	-	-	-	-
Anti-HPV 16				
Month 07	882	6056.5 (5601.4, 6548.6)	1137	2401.5 (2241.8, 2572.6)
Month 24	322	938.2 (825.0, 1067.0)	938	347.7 (322.5, 374.9)
Month 36[§]	341	708.8 (613.9, 818.3)	672	306.7 (287.5, 327.1)
Month 48[¶]	-	-	-	-
Anti-HPV 18				
Month 07	887	1357.4 (1249.4, 1474.7)	1176	402.6 (374.6, 432.6)
Month 24	324	131.9 (112.1, 155.3)	967	38.7 (35.2, 42.5)
Month 36[§]	343	113.0 (94.7, 135.0)	690	33.4 (30.9, 36.1)
Month 48[¶]	-	-	-	-

*N = Number of individuals randomized in the respective group who received at least 1 injection.
[†]n = Number of individuals in the indicated immunogenicity population.
[‡]mMU = milli-Merck Units
[§]Month 36 time point for 16- to 26-year-old boys and men; Month 37 for 9- to 15-year-old boys.
[¶]The studies in 9- to 15-year-old boys and girls and 16- to 26-year-old boys and men were planned to end prior to 48 months and therefore no serology samples were collected.
cLIA = Competitive Luminex Immunoassay
CI = Confidence Interval
GMT = Geometric Mean Titers

Tables 18 and 19 display the Month 7 immunogenicity data for girls and women and boys and men. Anti-HPV responses 1 month postdose 3 among 9- through 15-year-old adolescent girls were non-inferior to anti-HPV responses in 16- through 26-year-old girls and women in the combined database of immunogenicity studies for GARDASIL. Anti-HPV responses 1 month postdose 3 among 9- through 15-year-old adolescent boys were non-inferior to anti-HPV responses in 16- through 26-year-old boys and men in Study 5.

On the basis of this immunogenicity bridging, the efficacy of GARDASIL in 9- through 15-year-old adolescent girls and boys is inferred.

GMT Response to Variation in Dosing Regimen in 18- Through 26-Year-Old Women

Girls and women evaluated in the PPE population of clinical studies received all 3 vaccinations within 1 year of enrollment. An analysis of immune response data suggests that flexibility of ±1 month for Dose 2 (i.e., Month 1 to Month 3 in the vaccination regimen) and flexibility of ±2 months for Dose 3 (i.e., Month 4 to Month 8 in the vaccination regimen) do not impact the immune responses to GARDASIL.

Duration of the Immune Response to GARDASIL

The duration of immunity following a complete schedule of immunization with GARDASIL has not been established. The peak anti-HPV GMTs for HPV types 6, 11, 16, and 18 occurred at Month 7. Anti-HPV GMTs for HPV types 6, 11, 16, and 18 were similar between measurements at Month 24 and Month 60 in Study 2.

14.9 Long-Term Follow-Up Studies

The protection of GARDASIL against HPV-related disease continues to be studied over time in populations including adolescents (boys and girls) and women who were enrolled in the Phase 3 studies.

Persistence of Effectiveness

An extension of Study 4 used national healthcare registries in Denmark, Iceland, Norway, and Sweden to monitor endpoint cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer among 2,650 girls and women 16 through 23 years of age at enrollment who were randomized to vaccination with GARDASIL and consented to be followed in the extension study. An interim analysis of the per-protocol effectiveness population included 1,902 subjects who completed the GARDASIL vaccination series within one year, were naïve to the relevant HPV type through 1 month postdose 3, had no protocol violations, and had follow-up data available. The median follow-up from initial vaccination was 6.7 years with a range of 2.8 to 8.4 years. No cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, cervical cancer, vulvar cancer, or vaginal cancer were observed over a total of 5,765 person-years at risk.

An extension of a Phase 3 study (Study 7) in which 614 girls and 565 boys 9 through 15 years of age at enrollment were randomized to vaccination with GARDASIL actively followed subjects for endpoint cases of HPV 6-, 11-, 16-, or 18-related persistent infection, CIN (any grade), AIS, VIN, VaIN, cervical cancer, vulvar cancer, vaginal cancer, and genital lesions from the initiation of sexual activity or age 16 onwards. An interim analysis of the per-protocol effectiveness population included 246 girls and 168 boys who completed the GARDASIL vaccination series within one year, were seronegative to the relevant HPV type at initiation of the vaccination series, and had not initiated sexual activity prior to receiving the third dose of GARDASIL. The median follow-up, from the first dose of vaccine, was 7.2 years with a range of 0.5 to 8.5 years. No cases of persistent infection of at least 12 months' duration and no cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade), AIS, VIN, VaIN, cervical cancer, vulvar cancer, vaginal cancer, or genital lesions were observed over a total 1,105 person-years at risk. There were 4 cases of HPV 6-, 11-, 16-, or 18-related persistent infection of at least 6 months' duration, including 3 cases related to HPV 16 and 1 case related to HPV 6, none of which persisted to 12 months' duration.

Persistence of the Immune Response

The interim reports of the two extension studies described above included analyses of type-specific anti-HPV antibody titers at 9 years postdose 1 for girls and women 16 through 23 years of age at enrollment (range of 1,178 to 1,331 subjects with evaluable data across HPV types) and at 8 years postdose 1 for boys and girls 9 through 15 years of age at enrollment (range of 436 to 440 subjects with evaluable data across HPV types). Anti-HPV 6, 11, 16, and 18 GMTs as measured by cLIA were decreased compared with corresponding values at earlier time points, but the proportions of seropositive subjects ranged from 88.4% to 94.4% for anti-HPV 6, from 89.1% to 95.5% for anti-HPV 11, from 96.8% to 99.1% for anti-HPV 16, and from 60.0% to 64.1% for anti-HPV 18.

14.10 Studies with RECOMBIVAX HB [hepatitis B vaccine (recombinant)]

The safety and immunogenicity of co-administration of GARDASIL with RECOMBIVAX HB [hepatitis B vaccine (recombinant)] (same visit, injections at separate sites) were evaluated in a randomized, double-blind, study of 1871 women aged 16 through 24 years at enrollment. The race distribution of the girls and women in the clinical trial was as follows: 61.6% White; 1.6% Hispanic (Black and White); 23.8% Other; 11.9% Black; 0.8% Asian; and 0.3% American Indian.

Subjects either received GARDASIL and RECOMBIVAX HB (n = 466), GARDASIL and RECOMBIVAX HB-matched placebo (n = 468), RECOMBIVAX HB and GARDASIL-matched placebo (n = 467) or RECOMBIVAX-matched placebo and GARDASIL-matched placebo (n = 470) at Day 1, Month 2 and Month 6. Immunogenicity was assessed for all vaccines 1 month post completion of the vaccination series.

Persistence of Immune Response to GARDASIL 9

The duration of immunity following a 3-dose schedule of vaccination with GARDASIL 9 has not been established. The peak anti-HPV GMTs for each vaccine HPV type occurred at Month 7. Proportions of individuals who remained seropositive to each vaccine HPV type at Month 24 were similar to the corresponding seropositive proportions at Month 7.

Administration of GARDASIL 9 to Individuals Previously Vaccinated with GARDASIL

Study 4 evaluated the immunogenicity of GARDASIL 9 in 921 girls and women (12 through 26 years of age) who had previously been vaccinated with GARDASIL. Prior to enrollment in the study, over 99% of subjects had received three injections of GARDASIL within a one year period. The time interval between the last injection of GARDASIL and the first injection of GARDASIL 9 ranged from approximately 12 to 36 months.

Seropositivity to HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58 in the per protocol population ranged from 98.3 to 100% by Month 7 in individuals who received GARDASIL 9. The anti-HPV 31, 33, 45, 52 and 58 GMTs for the population previously vaccinated with GARDASIL were 25-63% of the GMTs in the combined populations from Studies 1, 2, 3, and 5, who had not previously received GARDASIL, although the clinical relevance of these differences is unknown. Efficacy of GARDASIL 9 in preventing infection and disease related to HPV Types 31, 33, 45, 52, and 58 in individuals previously vaccinated with GARDASIL has not been assessed.

Concomitant Use of Hormonal Contraceptives

Among 7,269 female recipients of GARDASIL 9 (16 through 26 years of age), 60.2% used hormonal contraceptives during the vaccination period of clinical studies 1 and 2. Use of hormonal contraceptives did not appear to affect the type specific immune responses to GARDASIL 9.

14.5 Immune Responses to GARDASIL 9 Using a 2-Dose Regimen in Individuals 9 through 14 Years of Age

Effectiveness of GARDASIL 9 against persistent infection and disease related to vaccine HPV types in 9- through 14-year-old girls and boys who received a 2-dose regimen was inferred from non-inferiority comparison conducted in the PPI population in Study 8 of GMTs following vaccination with GARDASIL 9 among 9- through 14-year-old girls and boys who received a 2-dose regimen (at 0, 6 months or 0, 12 months) with those among 16- through 26-year-old girls and women who received a 3-dose regimen (at 0, 2, 6 months). Anti-HPV GMTs at one month after the last dose among 9- through 14-year-old girls and boys who received 2 doses of GARDASIL 9 were non-inferior to anti-HPV GMTs among 16- through 26-year-old girls and women who received 3 doses of GARDASIL 9 (Table 11).

One month following the last dose of the assigned regimen, between 97.9% and 100% of subjects across all groups became seropositive for antibodies against the 9 vaccine HPV types (Table 11).

In the same study, in girls and boys 9 through 14 years old, GMTs at one month after the last vaccine dose were numerically lower for some vaccine types after a 2-dose schedule than in girls 9 through 14 years old after a 3-dose schedule (HPV types 18, 31, 45, and 52 after 0, 6 months and HPV type 45 after 0, 12 months; Table 11). The clinical relevance of these findings is unknown.

Duration of immunity of a 2-dose schedule of GARDASIL 9 has not been established.

Table 11: Summary of Anti-HPV cLIA Geometric Mean Titers in the PPI* Population at One Month After the Last Vaccine Dose Among Subjects Who Received 2 Doses† or 3 Doses† of GARDASIL 9 (Study 8)

Population (Regimen)	N	n	GMT mMU‡/mL	GMT Ratio relative to 3-dose regimen in 16- through 26-year-old girls and women (95% CI)
Anti-HPV 6				
9- to 14-year-old girls (0, 6)†	301	258	1657.9	2.15 (1.83, 2.53)§
9- to 14-year-old boys (0, 6)†	301	263	1557.4	2.02 (1.73, 2.36)§
9- to 14-year-old girls and boys (0, 12)†	300	257	2678.8	3.47 (2.93, 4.11)§
9- to 14-year-old girls (0, 2, 6)†	300	254	1496.1	1.94 (1.65, 2.29)¶
16- to 26-year-old women (0, 2, 6)†	314	238	770.9	1
Anti-HPV 11				
9- to 14-year-old girls (0, 6)†	301	258	1388.9	2.39 (2.03, 2.82)§
9- to 14-year-old boys (0, 6)†	301	264	1423.9	2.45 (2.09, 2.88)§
9- to 14-year-old girls and boys (0, 12)†	300	257	2941.8	5.07 (4.32, 5.94)§
9- to 14-year-old girls (0, 2, 6)†	300	254	1306.3	2.25 (1.90, 2.66)¶
16- to 26-year-old women (0, 2, 6)†	314	238	580.5	1
Anti-HPV 16				
9- to 14-year-old girls (0, 6)†	301	272	8004.9	2.54 (2.14, 3.00)§
9- to 14-year-old boys (0, 6)†	301	273	8474.8	2.69 (2.29, 3.15)§
9- to 14-year-old girls and boys (0, 12)†	300	264	14329.3	4.54 (3.84, 5.37)§
9- to 14-year-old girls (0, 2, 6)†	300	269	6996.0	2.22 (1.89, 2.61)¶
16- to 26-year-old women (0, 2, 6)†	314	249	3154.0	1
Anti-HPV 18				
9- to 14-year-old girls (0, 6)†	301	272	1872.8	2.46 (2.05, 2.96)§
9- to 14-year-old boys (0, 6)†	301	272	1860.9	2.44 (2.04, 2.92)§
9- to 14-year-old girls and boys (0, 12)†	300	266	2810.4	3.69 (3.06, 4.45)§
9- to 14-year-old girls (0, 2, 6)†	300	270	2049.3	2.69 (2.24, 3.24)¶
16- to 26-year-old women (0, 2, 6)†	314	267	761.5	1
Anti-HPV 31				
9- to 14-year-old girls (0, 6)†	301	272	1436.3	2.51 (2.10, 3.00)§
9- to 14-year-old boys (0, 6)†	301	271	1498.2	2.62 (2.20, 3.12)§
9- to 14-year-old girls and boys (0, 12)†	300	268	2117.5	3.70 (3.08, 4.45)§
9- to 14-year-old girls (0, 2, 6)†	300	271	1748.3	3.06 (2.54, 3.67)¶
16- to 26-year-old women (0, 2, 6)†	314	264	572.1	1
Anti-HPV 33				
9- to 14-year-old girls (0, 6)†	301	273	1030.0	2.96 (2.50, 3.50)§
9- to 14-year-old boys (0, 6)†	301	271	1040.0	2.99 (2.55, 3.50)§
9- to 14-year-old girls and boys (0, 12)†	300	269	2197.5	6.31 (5.36, 7.43)§
9- to 14-year-old girls (0, 2, 6)†	300	275	796.4	2.29 (1.95, 2.68)¶
16- to 26-year-old women (0, 2, 6)†	314	279	348.1	1
Anti-HPV 45				
9- to 14-year-old girls (0, 6)†	301	274	357.6	1.67 (1.38, 2.03)§
9- to 14-year-old boys (0, 6)†	301	273	352.3	1.65 (1.37, 1.99)§
9- to 14-year-old girls and boys (0, 12)†	300	268	417.7	1.96 (1.61, 2.37)§
9- to 14-year-old girls (0, 2, 6)†	300	275	661.7	3.10 (2.54, 3.77)¶
16- to 26-year-old women (0, 2, 6)†	314	280	213.6	1
Anti-HPV 52				
9- to 14-year-old girls (0, 6)†	301	272	581.1	1.60 (1.36, 1.87)§
9- to 14-year-old boys (0, 6)†	301	273	640.4	1.76 (1.51, 2.05)§
9- to 14-year-old girls and boys (0, 12)†	300	268	1123.4	3.08 (2.64, 3.61)§
9- to 14-year-old girls (0, 2, 6)†	300	275	909.9	2.50 (2.12, 2.95)¶
16- to 26-year-old women (0, 2, 6)†	314	271	364.2	1
Anti-HPV 58				
9- to 14-year-old girls (0, 6)†	301	270	1251.2	2.55 (2.15, 3.01)§
9- to 14-year-old boys (0, 6)†	301	270	1325.7	2.70 (2.30, 3.16)§
9- to 14-year-old girls and boys (0, 12)†	300	265	2444.6	4.98 (4.23, 5.86)§
9- to 14-year-old girls (0, 2, 6)†	300	273	1229.3	2.50 (2.11, 2.97)¶

16- to 26-year-old women (0, 2, 6)[†]	314	261	491.1	1

*The PPI population consisted of individuals who received all assigned vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the last vaccination dose and blood collection for immunogenicity assessment, and were seronegative to the relevant HPV type(s) (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) prior to dose 1.

[†]2-dose regimen (0, 6): vaccination at Day 1 and Month 6; 2-dose regimen (0, 12): vaccination at Day 1 and Month 12; 3-dose regimen (0, 2, 6): vaccination at Day 1, Month 2, and Month 6. The data are from Study 8 (NCT01984697).

[‡]mMU=milli-Merck Units

[§]Demonstration of non-inferiority required that the lower bound of the 95% CI of the GMT ratio be greater than 0.67

[¶]Exploratory analysis; criterion for non-inferiority was not pre-specified

N = Number of individuals randomized to the respective vaccination group who received at least 1 injection

n = Number of individuals contributing to the analysis.

CI=Confidence Interval

cLIA=competitive Luminex Immunoassay

GMT=Geometric Mean Titer

14.6 Studies with Menactra and Adacel

In Study 5, the safety and immunogenicity of co-administration of GARDASIL 9 with Menactra [Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine] and Adacel [Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap)] (same visit, injections at separate sites) were evaluated in 1,237 boys and girls 11 through 15 years of age at enrollment.

One group received GARDASIL 9 in one limb and both Menactra and Adacel, as separate injections, in the opposite limb concomitantly on Day 1 (n = 619). The second group received the first dose of GARDASIL 9 on Day 1 in one limb then Menactra and Adacel, as separate injections, at Month 1 in the opposite limb (n = 618). Subjects in both vaccination groups received the second dose of GARDASIL 9 at Month 2 and the third dose at Month 6. Immunogenicity was assessed for all vaccines one month post vaccination (one dose for Menactra and Adacel and three doses for GARDASIL 9).

Assessments of post-vaccination immune responses included type-specific antibody GMTs for each of the vaccine HPV types at four weeks following the last dose of GARDASIL 9; GMTs for anti-filamentous hemagglutinin, anti-pertactin, and anti-fimbrial antibodies at four weeks following Adacel; percentage of subjects with anti-tetanus toxin and anti-diphtheria toxin antibody concentrations ≥0.1 IU/mL at four weeks following Adacel; and percentage of subjects with ≥4-fold rise from pre-vaccination baseline in antibody titers against *N. meningitidis* serogroups A, C, Y, and W-135 at four weeks following Menactra. Based on these measures, concomitant administration of GARDASIL 9 with Menactra and Adacel did not interfere with the antibody responses to any of the vaccines when compared with non-concomitant administration of GARDASIL 9 with Menactra and Adacel.

15 REFERENCES

1. Study 1 NCT00543543
2. Study 2 NCT00943722
3. Study 3 NCT01304498
4. Study 4 NCT01047345
5. Study 5 NCT00988884
6. Study 6 NCT01073293
7. Study 7 NCT01651949
8. Study 8 NCT01984697

16 HOW SUPPLIED/STORAGE AND HANDLING

GARDASIL 9 is supplied in vials and syringes.

Carton of ten 0.5-mL single-dose vials. NDC 0006-4119-03

Carton of ten 0.5-mL single-dose prefilled Luer Lock syringes with tip caps. NDC 0006-4121-02

Store refrigerated at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light.

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ENVIRONMENT AND AUTOIMMUNITY

Behavioral abnormalities in female mice following administration of aluminum adjuvants and the human papillomavirus (HPV) vaccine Gardasil

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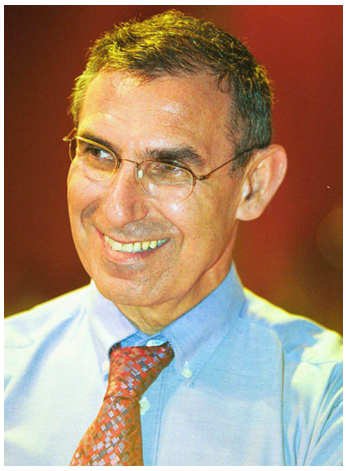

Yehuda Shoenfeld

Abstract Vaccine adjuvants and vaccines may induce autoimmune and inflammatory manifestations in susceptible individuals. To date most human vaccine trials utilize aluminum (Al) adjuvants as placebos despite much evidence showing that Al in vaccine-relevant exposures can be toxic to humans and animals. We sought to evaluate the effects of Al adjuvant and the HPV vaccine Gardasil versus the true placebo on behavioral and inflammatory parameters in female mice. Six-week-old C57BL/6 female mice were injected with either, Gardasil, Gardasil + pertussis toxin (Pt), Al hydroxide, or, vehicle control in amounts equivalent to human exposure. At 7.5 months of age, Gardasil and Al-injected mice spent significantly more time floating in the forced swimming test (FST) in comparison with vehicle-injected mice (Al, $p = 0.009$; Gardasil, $p = 0.025$; Gardasil + Pt, $p = 0.005$). The increase in floating time was already highly significant at 4.5 months of age for the Gardasil and Gardasil + Pt group ($p \leq 0.0001$). No significant differences were observed in the number of stairs climbed in the staircase test which measures locomotor activity. These results indicate that differences observed in the FST were unlikely due to locomotor dysfunction, but rather due to depression. Moreover, anti-HPV antibodies from the sera of Gardasil and Gardasil + Pt-injected mice showed cross-reactivity with the mouse brain protein extract. Immunohistochemistry analysis revealed microglial activation in the CA1 area of the hippocampus of Gardasil-injected mice. It appears that Gardasil via its Al adjuvant and HPV antigens has the ability to trigger neuroinflammation and autoimmune reactions, further leading to behavioral changes.

Keywords Gardasil · Aluminum · ASIA syndrome · Autoantibodies · Autoimmunity · Neuroinflammation

Abbreviations

Al	Aluminum
ASIA	Autoimmune/autoinflammatory syndrome induced by adjuvants
β2-GPI	β2-Glycoprotein I
FST	Forced swimming test
HPV	Human papilloma virus
Pt	Pertussis toxin
U. S FDA	United States Food and Drug Administration

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Caution on Mass HPV Vaccination

One reason for the relatively low uptake of the HPV vaccine, as Dr. Krishna Upadhya suggests, may be that parents and pediatricians want to avoid the subject of sex (Second Opinion, Fall 2016). There are, however, cogent reasons why HPV vaccination is not in the best interests of children.

Fourteen million people may be infected with HPV in the United States annually, as Dr. Upadhya says, but vaccination is being promoted not to prevent HPV infection itself but to prevent cervical cancer, with which some strains of HPV are associated. From 2008 to 2012, the average annual number of cervical cancers diagnosed in the United States was 11,771 (or 7.4 of every 100,000 females). That may seem high—actually, it's about the same as the number of infants with phenylketonuria detected by newborn screening in the U.S. annually—but in 1975, 30 years before HPV vaccination began, the incidence was twice as high, at 14.8 of every 100,000 females.

This drop is attributable primarily to Pap screening of women, beginning in their 20s. Unfortunately, HPV vaccination cannot replace Pap screening because the vaccines do not protect against all cervical cancer-related strains of HPV. Since vaccinated women should continue to have Pap smears, those cases prevented by vaccination would have been detected anyway. There is, unfortunately, evidence that HPV vaccination has lowered the rate of Pap screening.

Nor is HPV vaccination without harm. Associations with primary ovarian failure and other autoimmune disorders have been reported. Until more data are collected, caution is needed in promoting mass vaccination.

Neil A. Holtzman, M.D., M.P.H.

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http://www.hopkinsmedicine.org/news/publications/hopkins_medicine_magazine/letters/winter-2017

Too Fast or Not Too Fast: The FDA's Approval of Merck's HPV Vaccine Gardasil

Lucija Tomljenovic and Christopher A. Shaw

Introduction

There are not many public health issues where views are as extremely polarized as those concerning vaccination policies. Ever since its *Fast Track* approval by the U.S. Food and Drug Administration (FDA) in 2006, Merck's human papilloma virus (HPV) vaccine Gardasil has been sparking controversy. Initially, the criticism has been focused at Merck, due to their overly aggressive marketing strategies and lobbying campaigns. According to a 2007 editorial in *Nature Biotechnology*,[1] "Surrounded by a chorus of disapproval, Merck cracked. As *Nature Biotechnology* went to press, the company announced a cessation of all efforts to lobby for US state laws requiring compulsory vaccination." Subsequently, questions have been raised whether it was appropriate for vaccine manufacturers to partake in public health policies when their conflicts of interests were so obvious. Some of their advertising campaign slogans, such as "cervical cancer kills x women per year" and "your daughter could become one less life affected by cervical cancer,"[2] seemed more designed to promote fear rather than evidence-based decision making about the potential benefits of the vaccine versus any risks. Although, conflicts of interests do not necessarily mean that the product itself is faulty, marketing claims should be carefully examined against factual science data. Currently, Gardasil vaccination is strongly recommended by the U.S. and other health authorities while public concerns about safety and efficacy of the vaccine appear to be increasing. This discrepancy leads to some important questions that need to be resolved. The current review examines key issues of this debate in light of currently available research evidence.

The HPV Vaccine Debate

In June 2006 the U.S. Food and Drug Administration (FDA) approved Gardasil, the first vaccine against the human papilloma virus (HPV).[3] The quadrivalent vaccine targeting four common HPV strains (6, 11, 16 and 18) was the first pharmaceutical product specifically developed to protect against cervical cancer.[4] Five years later, Gardasil became a key topic in the U.S. 2011 Republican presidential debate when Congresswoman Michelle Bachmann criticized Texas Governor Rick Perry over his prior executive order to make the vaccine mandatory.[5] Bachmann later expressed serious concerns about the safety of the vaccine which added even more heat to the already controversial subject.

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The American Academy of Pediatrics (AAP) responded promptly to Bachmann stating that there was "absolutely no scientific validity" behind her allegations. According to the AAP, "Since the vaccine has been introduced, more than 35 million doses have been administered, and it has an excellent safety record." The AAP further stated that "this is a life-saving vaccine that can protect girls from cervical cancer."[6] Yet, not every organization fully agreed. The Association of American Physicians and Surgeons (AAPS) opined, "…this HPV vaccine costs hundreds of dollars for something that most of the recipients do not even need protection against." "There was no public health justification for requiring this [vaccine] to attend school," stated the AAPS, elaborating that, "without adequate testing but with well-placed political funding and lobbyists, Merck pushed for requiring that the HPV vaccine, Gardasil, be given to young schoolgirls as a condition for entering sixth grade. But the disease it supposedly protects against is not even contagious in the school environment."[7] What are the reasons behind such polarized views, and why does the AAP statement fail to settle the debate on Gardasil? In view of future vaccination policies, these issues need to be carefully examined.

Promoting Gardasil: Too Much Too Soon?

According to the latest report by the U.S. Centers for Disease Control and Prevention (CDC), only 32% of girls aged 13 to 17 completed the full three-dose series for Gardasil in 2010. The CDC concluded that "stronger provider recommendations for HPV vaccination, implementing reminder-recall systems, eliminating missed opportunities, and educating parents of adolescents regarding the risk for HPV infection and the benefits of vaccination, are needed to effectively protect adolescent girls against cervical cancer."[8] In reference to the CDC report and the low HPV vaccine uptake rate, a recent article in *JAMA* stated that "if voluntary vaccination proves unsuccessful, states should seriously consider compulsory vaccination laws without generous exemptions."[9]

Certainly, the medical profession has a responsibility to promote vaccinations with those vaccines whose safety and efficacy have been thoroughly demonstrated. Nonetheless, the fact that Merck waged an aggressive lobbying campaign with state governments to make Gardasil mandatory and funded educational programs for the U.S. professional medical associations (PMAs) as a marketing strategy to promote vaccine use, raised the question whether Gardasil vaccination was promoted by the medical community from an evidence-based medicine perspective.[10] Indeed, according to a 2007 editorial in *Nature Biotechnology*, "In its rush to market its human papillomavirus vaccine, Merck forgot to make a strong and compelling case for compulsory immunization."[11] Furthermore, a 2009 *Special Communication* in *JAMA*[12] revealed that much of the educational material delivered by the PMAs failed to address the full complexity of the issues surrounding the vaccine and did not provide balanced recommendations on potential risks and hoped-for benefits. Notably, Merck-sponsored educational programs delivered by the PMAs strongly promoting HPV vaccination began in 2006, more than a year before the clinical trials containing important safety and efficacy data were published.[13] What followed were Merck's aggressive advertising campaigns telling young women worldwide that they would be "one less" life affected by cervical cancer.[14] Merck's "one less" campaign was so successful that in 2006, Gardasil was named the pharmaceutical "brand of the year" for building "a market out of thin air."[15] The wider scientific community, however, was not so impressed by Merck's "one less" business success. In a telling 2007 editorial in the *American Journal of Bioethics,* Glenn McGee and Summer Johnson noted, "Just as pizza bearing cheerleader drug reps are a poor substitute for medical education, pharmaceutical company lobbying is a poor substitute for well-reasoned public health policymaking."[16]

Indeed, how could Merck and the FDA which approved Gardasil be so certain about the effects of the vaccine a year before final safety and efficacy data became available? The current public skepticism surrounding the HPV vaccine appears to indicate that this question has not yet been adequately answered. In order to do so, we examined the basis on which the FDA approved Gardasil.

Gardasil and the FDA: The Basis for Fast Track Approval

Gardasil received a *Fast Track* approval by the FDA following a six-month priority review process.[17] According to the FDA, to be fast-tracked the drug must target a serious disease and fill an *unmet medical need.*[18] The latter is defined as providing a therapy where none exists or, providing a therapy which may be potentially superior to an existing therapy. In order to gain approval, a *Fast Track* drug must demonstrate the following:[19]

1. Show superior effectiveness to existing treatments (if such are available)

2. Avoid serious side effects of an available treatment
3. Improving the diagnosis of a serious disease where early diagnosis results in an improved outcome
4. Decrease a clinically significant toxicity of an accepted treatment

Cervical cancer is a serious disease, affecting almost half a million women world-wide on an annual basis.[20] Nonetheless, almost 90% of cervical cancer deaths occur in developing countries where regular Papanicolaou (Pap) screening procedures are either non-existent or of very limited availability.[21] In contrast, in developed countries cervical cancer mortality rates are very low (1.4-1.7/100,000 women).[22] That Pap testing alone has decreased mortality from cervical cancer in the developed world by 70% in the last few decades is well established.[23] On the contrary, to date, clinical trial evidence has not demonstrated that Gardasil can actually prevent cervical cancer (let alone cervical cancer deaths because the follow-up period was too short (5 years,[24] while cervical cancer takes 20-40 years to develop from the time of acquisition of HPV infection).[25] What Gardasil has been demonstrated to prevent are infections with two out of 15 oncogenic HPV strains (HPV-16 and HPV-18) and pre-cancerous cervical intraepithelial neoplasia (CIN) 1-3 lesions,[26] both of which were used as surrogate endpoints to cervical cancer.

According to the FDA, a drug that receives *Fast Track* designation is eligible for *Accelerated Approval*, which is, "approval on an effect on a surrogate, or substitute endpoint reasonably likely to predict clinical benefit."[27] The *Accelerated Approval*, which is temporary, is expressly designed to get drugs on the market *before* they demonstrate any real benefit. Indeed the very reason why the FDA instituted the *Accelerated Approval* process is to expedite access to potentially important therapies while being mindful of the fact that obtaining data on clinical outcomes can take a long time.[28] Nonetheless, the *Accelerated Approval* based on a surrogate endpoint (i.e., CIN 1-3), is given on the condition that post-marketing clinical trials (otherwise known as phase 4 trials) verify the anticipated clinical benefit. If, however, the confirmatory phase 4 trials do not show that the drug provides real clinical benefit, then the "FDA has regulatory procedures in place that could lead to removing the drug from the market."[29]

During the longest reported follow-up of Gardasil trial participants (5 years), the vaccine was found to be highly efficacious against persistent HPV infections and CIN 1-3 lesions.[30] However, the reported combined efficacy pertaining to the reduction of HPV-16/18 related CIN 1-3 is of little value in determining the true long-term prophylactic potential of the vaccine. The reason for this is that in the natural course of cervical cancer, only a small fraction of CIN 1 lesions will progress to CIN 2 lesions and likewise, only a small fraction of CIN 3 lesions will eventually progress to cervical cancer. Specifically, long-term research data show that as much as 60% of CIN 1 lesions spontaneously regress, 30% persist, 10% progress to CIN 3, and only 1% eventually progress to invasive cancer.[31] Therefore, in any female population, there will be many more CIN 1 lesions than all CIN 2s, CIN 3s and cervical cancers put together. CIN 1, however, is neither an adequate marker of cervical cancer progression nor an adequate surrogate endpoint for assessing long-term clinical benefits in HPV vaccine trials (due to their benign nature and high frequency of regression).[32] Thus, the reported pooled efficacy against CIN 1-3 in Gardasil post-licensure trial[33] gave a highly misleading impression about the true clinical value of the vaccine, given that the vast majority of the lesions within the trial population would have comprised of CIN 1 lesions.

Although the results from the 3-year follow-up pre-licensure trials inspired much confidence in Gardasil's prophylactic potential as they showed >97% vaccine effectiveness against HPV-16/18 related CIN 2/3+ lesions, the corresponding figures against CIN 2/3+ caused by all HPV types were well below 40%.[34] This information is frequently overlooked even though it is crucial for assessing the long-term protective efficacy of the vaccine. Indeed, because of the possibility of infections with HPV types not covered by the vaccine and/or multiple infections including these types, any meaningful assessment of a true prophylactic value from Gardasil vaccination, which would likely result in a real clinical benefit (i.e., a global reduction of the cervical cancer burden), must take into consideration analysis of vaccine efficacy against CIN 2/3+ caused by *all* relevant (high risk) HPV types.[35] When taken together, the results from pre-clinical trials that the true HPV vaccine efficacy lies anywhere between 16.9% and 70%.[36] Given the demonstrable success of Pap screening programs in achieving a 70% reduction in cervical cancer mortality in developed countries, it is unlikely that vaccination with Gardasil would have a notable impact in reducing further the global cervical cancer burden beyond that accomplished by Pap screening.

Thus, with regard to efficacy, although Gardasil partially satisfies the FDA's criteria for *Accelerated Approval* (as prevention of high-risk HPV infection and precancerous lesions perfectly fits the FDA's defi-

nition of a surrogate endpoint),[37] ultimately it does not satisfy the criteria for *Fast Track* approval as the vaccine fails to show superior efficacy to Pap screening. In spite of this, the vaccine manufacturer as well as the U.S. medical authorities continue to promote Gardasil as if indeed it already had post-phase 4 confirmatory trial approval (i.e., demonstrated efficacy against cervical cancer). For example, Merck states that "Gardasil does more than help prevent cervical cancer"[38] while the AAP describes Gardasil as a "life-saving vaccine."[39] Similarly, the FDA and the CDC maintain that Gardasil is "an important cervical cancer prevention tool that will potentially benefit the health of millions of women"[40] and that thus, stronger provider recommendations for HPV vaccination "are needed to effectively protect adolescent girls against cervical cancer."[41] However, in light of Merck's limited 5-year follow-up data, these claims are demonstrably inaccurate. In other words, in the absence of adequate phase 4 confirmatory trials, the notion that Gardasil prevents cervical cancer remains speculative. In this context, it is worth noting that the existing clinical trials show that antibodies against HPV-18 from Gardasil fall rapidly, with 35% of women having no measurable antibody titers at 5 years.[42] This outcome suggests that rather than preventing future cases of cervical cancer cases, Gardasil may only be effective in postponing them.

Also of note is that Gardasil is a prophylactic vaccine and will not treat pre-existing HPV infections and pre-existing pre-cancerous lesions, nor cervical cancer.[43] Notably, the opposite is true, at least according to Merck's pre-licensure trial data, which show that in such cases the vaccine may exacerbate the very disease it is designed to prevent.[44]

Adverse Reactions from Gardasil

As of September 2012, a total of 21,265 adverse reactions (ADRs) have been reported from Gardasil in the U.S. alone, including 78 deaths, 363 life-threatening ADRs, and 609 events which resulted in permanent disability (Table 1). Compared with all other vaccines, Gardasil alone was associated with >60% of all serious ADRs (including 61.9% of all deaths, 64.9% of all life-threatening reactions and 81.8% cases of permanent disability) in females younger than 30 years (Table 2).

Table 1

Summary of Adverse Reactions (ADRs) Following Vaccination with Gardasil in the U.S. Reported to VAERS in the Post-Licensure Period (June 2006-September 2012).

VAERS Internet Database[66] was searched using the following criteria: 1) Vaccine Products: HPV4 (Human Papilloma Virus Types 6, 11, 16, 18); 2) Gender (all genders); 3) Age (all ages); 4) Territory (the United States); 5) Date Vaccinated (2006-2012; Gardasil post-licensure period).

Total	21,265
Deaths	78
Life-threatening	363
Permanently disabled Serious	609 1669
Prolonged hospitalization	212
Emergency room visit	9565

Table 2

Age-Adjusted Rate of Adverse Reactions (ADRs) Related to Gardasil Compared with All Other Vaccines in the U.S. Reported to the Vaccine Adverse Event Reporting System (VAERS) as of September 11, 2012.

VAERS Internet Database[67] was searched using the following criteria: 1) Vaccine Products: HPV4 (Human Papilloma Virus Types 6, 11, 16, 18) and All Vaccine Products; 2) Gender (female); 3) Age (6 to 29 years; target age group for HPV vaccines); 4) Territory (the United States); 5) Date Vaccinated (2006-2012; Gardasil post-licensure period).

Events	Gardasil	All vaccines	% ADRs from Gardasil
All Serious	14,991 1313	79,657 2157	18.8 60.9
Deaths	39	63	61.9
Life-threatening	296	456	64.9
Permanently disabled	482	589	81.8
Prolonged hospitalization	175	236	74.2
Emergency room visit	7015	13,295	52.8

A report to a passive vaccine surveillance system such as U.S. VAERS does not by itself prove that the vaccine caused an ADR. However, the unusually high frequency of ADRs related to HPV vaccines reported worldwide, as well as their consistent pattern (i.e. nervous system-related disorders rank the highest in frequency),[45] point to a potentially causal relationship. Furthermore, matching the data vaccine surveillance databases, is an increasing number of case reports documenting similar serious ADRs associated with Gardasil administration, with nervous system disorders being the most frequently reported ADRs.[46] Cumulatively, these data suggest that the risks of HPV vaccination may not have been fully evaluated in pre-licensure clinical trials. A careful review of pre-licensure safety data on Gardasil confirms this concern.

For example, like many other vaccine trials, Gardasil trials used an aluminum-containing placebo.[47] Although historically aluminum adjuvants have been portrayed as inherently safe, studies in animal models and humans have demonstrated their ability to inflict immuno-inflammatory conditions by themselves.[48] Cumulatively this research has led to the identification of an "autoimmune/inflammatory syndrome induced by adjuvants" (coined "ASIA"), that encompasses several adjuvant-triggered medical conditions which are characterized by a misregulated immune response.[49] For this reason, Exley notes, "it is necessary to make a very strong scientific case for using a placebo which is itself known to result in side effects and I have not found any scientific vindication for such in the recent human vaccination literature."[50]

According to Merck, the number of girls aged 9-26 years who reported a serious ADR from Gardasil indicative of an autoimmune disorder during pre-licensure clinical trials was 245, compared to the 218 in the aluminum "placebo" group.[51] Thus at best, Gardasil was shown to be as safe as its potentially neuro-immunotoxic constituent aluminum.

In contrast to Gardasil vaccination, a procedure which uses a speculum to take cells from the cervix does not carry a risk of death, or neurological or autoimmune complications. Neither is the loop electrosurgical excision procedure (LEEP), which is used to remove high-grade CIN 2/3 lesions in women who test positive on a Pap screen, a risk for such serious ADRs.

The poor design of existing vaccine safety and efficacy trials may be reflective of the fact that in the past two decades the pharmaceutical industry has gained unprecedented control over the evaluation of its own products. As noted by the former Editor-in-Chief of the *New England Journal of Medicine* Dr. Marcia Angell, "Drug companies now finance most clinical research on prescription drugs, and there is mounting evidence that they often skew the research they sponsor to make their drugs look better and safer."[52] With regard to Gardasil, we noted that often in trials sponsored by the vaccine manufacturer, the assessment of the frequency of ADRs was limited to those trial cohorts which comprised of participants who did not receive the full three doses of the HPV vaccine.[53] The result of such population sample bias is a lesser sensitivity for detecting serious ADRs, as such events may be expected to occur less frequently if fewer doses of the vaccine are administered.

In a lengthy report of potential conflicts of interests of the Gardasil pre-licensure FUTURE II trial study, the majority of authors declared "receiving lecture fees from Merck, Sanofi Pasteur, and Merck Sharp & Dohme." In addition, it was declared that "Indiana University and Merck have a confidential agreement that pays the university on the basis of certain landmarks regarding the HPV vaccine."[54] Commenting on conflicts of interests in HPV vaccine trials in the 2009 *JAMA* editorial, Haug noted that, "When weighing evidence about risks and benefits, it is also appropriate to ask who takes the risk, and who gets the benefit. Patients and the public logically expect that only medical and scientific evidence is put on the balance. If other matters weigh in, such as profit for a company or financial

Merck's HPV vaccine Gardasil failed (and continues to fail) to meet a single one of the four criteria required by the FDA for *Fast Track* approval. Gardasil is demonstrably neither safer nor more effective than Pap screening combined with LEEP, nor can it improve the diagnosis of serious cervical cancer outcomes. In spite of this, Gardasil continues to be promoted as if it already had post-phase 4 confirmatory trial approval and proven efficacy against cervical cancer.

or professional gains for physicians or groups of physicians, the balance is easily skewed. The balance will also tilt if the adverse events are not calculated correctly."[55]

Clear evaluation of risks is important for vaccines, which, contrary to other drugs, are administered predominantly to healthy individuals and often to prevent a disease to which an individual may never be exposed. Because of this, according to the FDA, "there is low tolerance for significant adverse events associated with vaccines-that is, caused by vaccines."[56] Thus, it may be worth re-considering whether it is prudent to put preadolescent girls at risk of death or a life-long neurodegenerative/autoimmune condition for a vaccine that has not thus far prevented a single case of cervical cancer, when the same can be prevented with regular Pap screening and LEEP, neither of which carry such risks.

FDA and Merck: What Have We Learned from Vioxx?

The U.S. FDA is not infallible. The Agency's approval of rofecoxib (Vioxx) in 1999 resulted in the "single greatest drug safety catastrophe in the history of this country or the history of the world."[57] This charge was laid by Dr. David Graham, the FDA associate director in the Office of Drug Safety, at the U.S. senate hearings on the FDA, Vioxx and its manufacturer, Merck. Senator Grassley added that the FDA "has lost its way when it comes to making sure drugs are safe" and that its relationship with drug companies was "too cosy." Dr. Graham concurred, stating that the FDA "as currently configured is incapable of protecting America against another Vioxx."[58] It took an estimated 88,000 to 139,000 Americans to suffer heart attacks and strokes as a result of taking Vioxx[59] before the drug was withdrawn from the market in 2004.[60]

In 2006 when Gardasil gained FDA approval, the acting FDA Commissioner Andrew von Eschenbach requested that the Science Board, which is the Advisory Board to the Commissioner, form a Subcommittee to assess whether science and technology at the FDA can support current and future regulatory needs. The findings of the Subcommittee as outlined in the Science and Mission at Risk Report were as follows.[61]

- The Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities
- The FDA's inability to keep up with scientific advances means that American lives are at risk
- The world looks to the FDA as a leader in medicine and science. Not only can the agency not lead, it can't even keep up with the advances in science

The Subcommittee concluded that "in contrast to previous reports that have issued many of the same warnings, there are now sufficient data proving that failure to act in the past has jeopardized the public's health." In light of these and other admissions by the Subcommittee (Table 3), as well as what appear to be legitimate concerns regarding both vaccine safety and effectiveness,[62] perhaps it is warranted for the FDA to re-evaluate its *Fast Track* approval of Gardasil.

Currently, however, "Based on the review of available information by FDA and CDC, Gardasil continues to be safe and effective, and its benefits continue to outweigh its risks."[63] In regard to what constitutes

Table 3

Major Findings from the FDA Science and Mission at Risk Report[68]

Mission Statement and Overview
• The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs
• The benefits of a robust, progressive Agency are enormous; the risks of a debilitated, under-performing organization are incalculable
Major Findings
• The FDA cannot fulfill its mission because its scientific base has eroded and its scientific organizational structure is weak
• The development of medical products based on "new science" cannot be adequately regulated by the FDA
• There is insufficient capacity in modeling, risk assessment and analysis
• The FDA science agenda lacks a coherent structure and vision, as well as effective coordination and prioritization
• Due to constrained resources and lack of adequate staff, the FDA cannot adequately monitor development of food and medical products because it is unable to keep up with scientific advances
• The FDA cannot fulfill its mission because its IT infrastructure is obsolete, unstable, and lacks sufficient controls to ensure continuity of operations or to provide effective disaster recovery services
• Reports of product dangers are not rapidly compared and analyzed, as inspectors' reports are still handwritten and slow to work their way through the system.
• There are inadequate emergency backup systems in place, which has resulted in the loss of FDA data in the past
• Recommendations of excellent FDA reviews are seldom followed*

*The Subcommittee's final conclusions and recommendations: "There is a long history of excellent reviews of the FDA that have been followed by little to no action taken to achieve the recommendations. Our final recommendation is based in our belief that effective resolution of the issues outlined in this report is urgent. In contrast to previous reports that have issued many of the same warnings, there are now sufficient data proving that failure to act in the past has jeopardized the public's health."

as "available information" according to the U.S. FDA, "FDA routinely reviews manufacturing information and has not identified any issues affecting the safety, purity, and potency of Gardasil."[64]

Any federal agency responsible for assuring drug safety should not exclusively rely on data provided by the drug manufacturer, as unreliable research (i.e., use of an reactive and potentially toxic placebo) cannot be used to reliably evaluate the safety of any drug.

Conclusion

Merck's HPV vaccine Gardasil failed (and continues to fail) to meet a single one of the four criteria required by the FDA for *Fast Track* approval. Gardasil is demonstrably neither safer nor more effective than Pap screening combined with LEEP, nor can it improve the diagnosis of serious cervical cancer outcomes. In spite of this, Gardasil continues to be promoted as if it already had post-phase 4 confirmatory trial approval and proven efficacy against cervical cancer. Given the demonstrable success of regular Pap smear screens in reducing the incidence of mortality from cervical cancer in the developed world, which is currently very low (i.e., 1.4-2.3/100,000 women), it is further unlikely that HPV vaccination (even if proven effective against cervical cancer) would reduce mortality rates beyond those already accomplished with routine Pap screening.[65] Thus, further reduction of cervical cancer burden may be best achieved by targeting other risk factors of the disease (i.e., smoking, use of oral contraceptives, multiple sexual partners, or suboptimal hygiene and nutritional status, etc.) in conjunction with regular Pap screens.

Coercive measures such as vaccine mandates supported solely by vaccine manufacturer's data do little to instill public confidence in vaccination programs. Physicians and other medical authorities need to adopt a more rigorous evidence-based medicine approach in order to give a balanced and objective evaluation of vaccine risks and benefits to their patients. The public equally needs life-saving drugs as it needs protection from potentially hazardous ones.

Note

LT and CAS conducted a histological analyses of autopsy brain samples from two Gardasil-suspected death cases. CAS is a founder and shareholder of Neurodyn Corporation, Inc. The company investigates early state neurological disease mechanisms and biomarkers. This work and any views expressed within this manuscript are solely those of the authors and not of any affiliated bodies or organizations.

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Does neurotransmission impairment accompany aluminium neurotoxicity?

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Abstract

Neurobehavioral disorders, except their most overt form, tend to lie beyond the reach of clinicians. Presently, the use of molecular data in the decision-making processes is limited. However, as details of the mechanisms of neurotoxic action of aluminium become clearer, a more complete picture of possible molecular targets of aluminium can be anticipated, which promises better prediction of the neurotoxicological potential of aluminium exposure. In practical terms, a critical analysis of current data on the effects of aluminium on neurotransmission can be of great benefit due to the rapidly expanding knowledge of the neurotoxicological potential of aluminium. This review concludes that impairment of neurotransmission is a strong predictor of outcome in neurobehavioral disorders. Key questions and challenges for future research into aluminium neurotoxicity are also identified.

Keywords: Aluminium; Neurotoxicity; Neurotransmission

1. Backward-looking to neurotoxicity

Alum has been used as an astringent and as a mordant in dyeing since the ancient Egyptian, Greek and Roman times. The isolation of pure aluminium, the 13th element of the periodic table, in 1827 is generally attributed to Wohler. The potential neurotoxic action of parenterally administered aluminium salts was, however, noted earlier by Orfila (1814) and Siem (1885) [1,2]. The blood clotting properties of alum led to the discovery of its neurotoxic effects on man in 1886 [3]. Soon after, in 1897, Döllken [1] found that the injection of aluminium tartrate into the brain of a rabbit produced degeneration. Since the beginning of the XX century, the neurotoxicity of aluminium has been questioned. The first clinical report on human poisoning by aluminium appeared in the *Lancet* in 1921, which mentioned overt neurological symptoms [4]. The works of Seibert and Wells, Kopeloff and Klatzo are among the pioneering studies of the deleterious effects of aluminium compounds on the Central Nervous System, namely structural changes in response to systemic administration [5], epileptogenic action of alumina cream [6] and neurofibrillary degeneration in rabbit brain [7].

Nowadays, aluminium is extensively used and its alloys and compounds are crucial in many industrial fields. Among them, aluminium oxide and sulfate are the compounds of greatest importance in technological terms. Curiously, aluminium phosphide (used as a rodenticide, insecticide and cereal grain fumigant [8]), aluminium fumes and dust, fibrous forms of aluminium oxide and aluminium sulfate are substances that appear on lists of toxic chemicals published by agencies devoted to define the relative toxicity risk of materials. There are only a few existing regulations and international guidelines for aluminium, including the "Drinking water quality guidelines for aluminium, WHO 2004" and the "Carcinogenicity classification for aluminium production, IARC 1987". The Environmental Health Criteria 194, produced within the framework of the Inter-Organization Programme for the

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In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

EMILY TARSELL, as the Executrix of the Estate of CHRISTINA TARSELL, Petitioner,	*	No. 10-251V
	*	Special Master Christian J. Moran
	*	Filed: September 25, 2017
v.	*	
SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	*	Entitlement; human papillomavirus ("HPV") vaccine; sudden death; plausible medical theory; onset of arrhythmia; challenge-rechallenge

Mark T. Sadaka, Mark T. Sadaka, LLC, Englewood, NJ, for petitioner;
Ann D. Martin, United States Dep't of Justice, Washington, D.C., for respondent.

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Cardiac arrest following HPV Vaccination

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Case report

A 20-years-old healthy female developed new-onset cardiac abnormalities discovered on a routine primary care visit, when she received her 2nd dose of the HPV vaccine. The patient had no significant past medical history apart from hypothyroidism, a single episode of febrile seizure at the age of 2 and receiving the first dose of HPV vaccine 3 weeks prior. In previous routine medical visits by various healthcare providers there was no indication of an irregular heartbeat or an arrhythmia. There was no family history of heart disorders or sudden cardiac death. During this visit to her new adult primary care doctor, a baseline physical examination revealed irregular heart rhythm. An ECG was performed showing frequent premature ventricular complexes and ST abnormalities (Figure 1). The patient had another abnormal ECG a week later during a follow up visit, which similarly demonstrated premature aberrantly conducted complexes and a marked ST abnormality. An echocardiogram was negative for any structural heart anomalies. Finally, a week following her third vaccination with the HPV vaccine, the patient started to experience dizziness, joint pain and unusual fatigue. Less than 3 weeks later, she was found dead from a cardiac arrest during her night sleep. A full autopsy analysis revealed no anatomical, histological, toxicological, genetic or microbiological findings that might be linked to a potential cause of death.

Introduction

The first vaccine was created back in 1798, when Edwards Jenner inoculated individuals with fluid from the blisters of smallpox disease [1]. Thereafter, the use of vaccination spread globally, leading to eradication of lethal infectious. However, over the years, worries have been raised regarding the safety of certain vaccines.

Vaccine-associated adverse events are mainly acute and transient; other reactions, such as autoimmune phenomena, are uncommon [2]. Post-vaccination autoimmunity, although uncommon, is well described and include conditions such as Guillain–Barre syndrome, immune thrombocytopenic purpura, Postural Orthostatic Tachycardia Syndrome (POTS) and other autoimmune manifestations [3].

The human papilloma virus (HPV) vaccine

HPV is a group of viruses belonging to a family of double-stranded circular DNA viruses, capable of infecting epithelial cells of the skin, oral and genital mucosa. HPV-16 & HPV-18 are responsible for about 70% of cervical cancers worldwide, HPV-6 and HPV-11 are the most common causes of genital warts [4].

There are three types of HPV vaccines available as of date: the bivalent Cervarix (aimed against serotypes 16 and 18), the quadrivalent Gardasil (aimed against serotypes 6, 11, 16 and 18) and the 9-valent vaccine (aimed against serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58) [5]. Vaccination with HPV vaccines was found to be effective, providing a long-lasting protection against HPV infection and premalignant lesions [6].

Herein, we intend to review current data regarding the relationship between HPV vaccination and susceptibility to sudden cardiac death.

Evidence of increased risk of sudden death and cardiac related deaths in association with the HPV vaccine

The first larger post-licensure analysis of side effets using the Vaccine Adverse Event Reporting System (VAERS) database [7] identified 32 deaths among 12,424 HPV Vaccine-related reports received during the period from June 1, 2006 to December 31, 2008. Out of these 32 deaths, at least 6 were cardiac-related deaths, confirmed by autopsy reports and medical records. The rate of these cardiac deaths did not produce a significant safety signal.

The median time from the last HPV vaccination to death was 14.5 days, a time-frame consistent with our case, in which the death occurred less than three weeks after HPV vaccine administration. We have conducted a search in the VAERS database in order to evaluate the current number of death cases related to HPV vaccination. We were surprised to find out a total number of 292 cases (Table 1), out of them there were 2 cases of cardiac death and 11 more cases of sudden death.

However, it is obvious that VAERS has limitations, since the postmarket reporting of side effects is discretionary and the reports are collected from a population of unknown size. Consequently, it is not possible to estimate the frequency of adverse events or to establish a

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Key words: *HPV Vaccine, sudden death, cardiac arrest, ASIA syndrome, molecular mimicry, Nocturnal cardiac arrhythmia*

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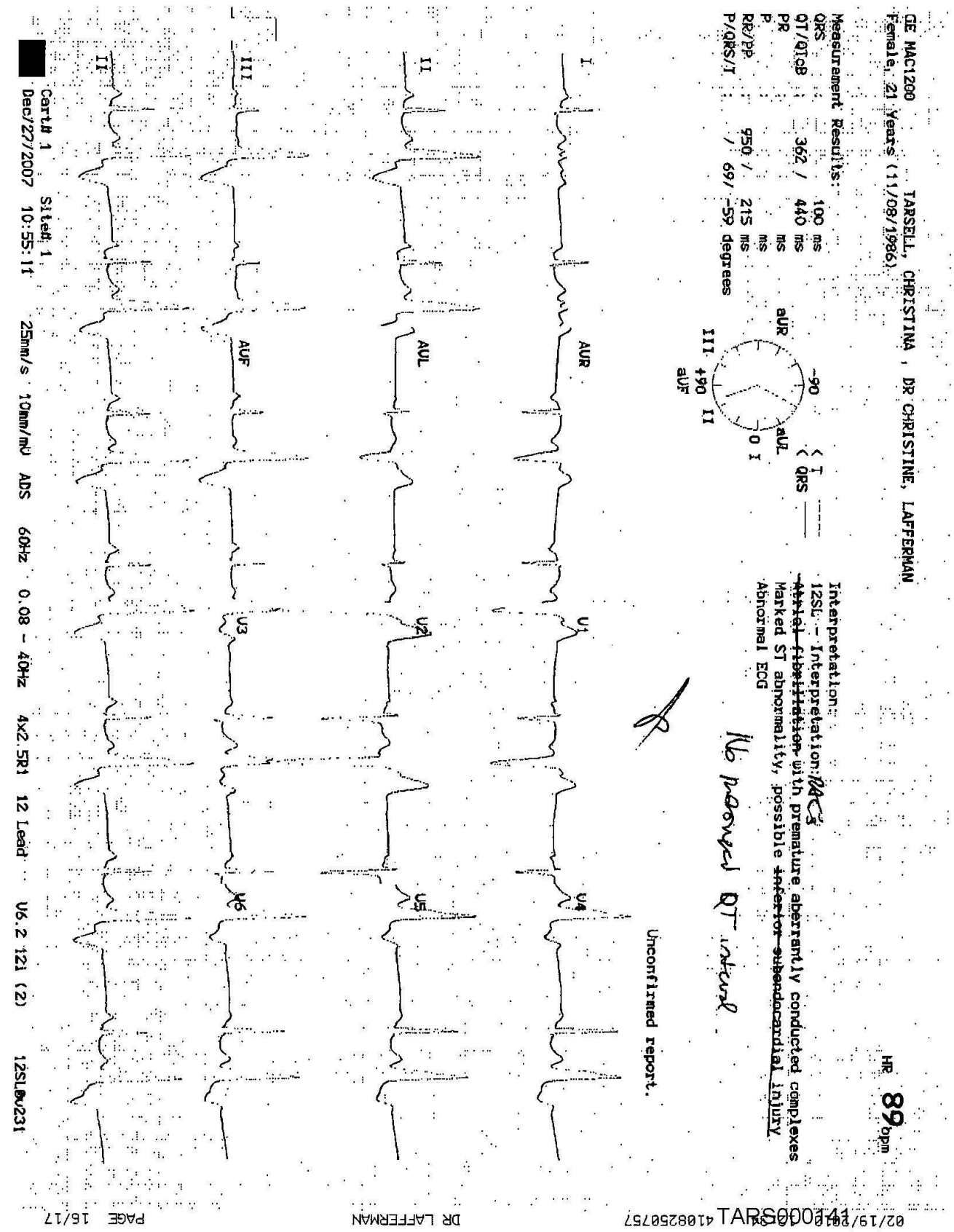
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Female, 21 Years (11/08/1986)
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PR ms
P ms
RR/PP 950 / 215 ms
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Interpretation:
12SL - Interpretation: MAC3
Marked ST abnormality, possible inferior subendocardial injury
Abnormal ECG
No prolonged QT interval.
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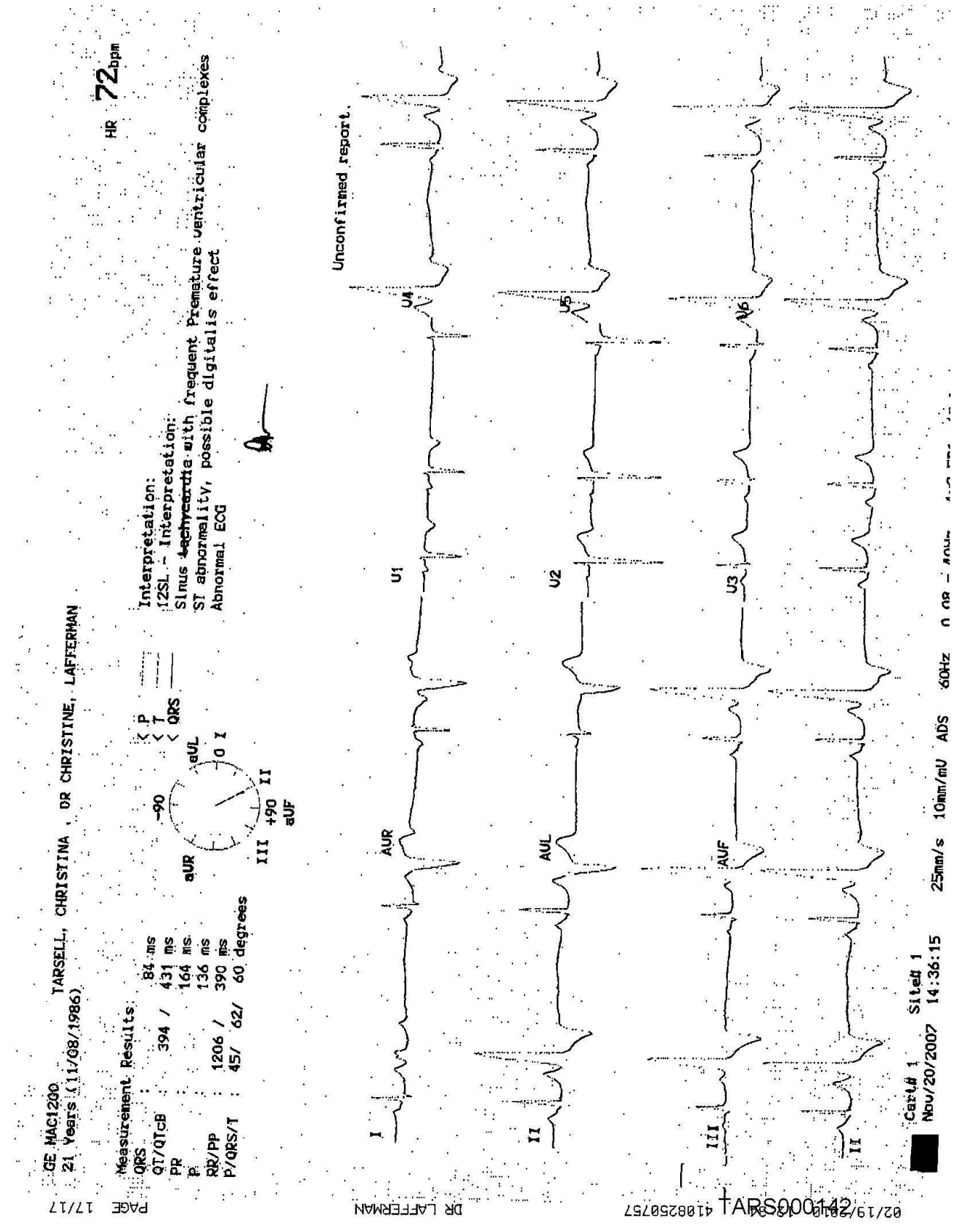

Figure 1. ECG showing frequent premature ventricular complexes and ST abnormalities

Table 1. A search in the VAERS database in order to evaluate the current number of death cases related to HPV vaccination, updated on 2.5.2017

Symptoms	Vaccine	Events reported	Percent
Brain death	HPV (Gardasil)	2	0.68%
Brain death	HPV (Gardasil 9)	1	0.34%
Death	HPV (Gardasil)	228	78.08%
Death	HPV (Gardasil 9)	4	1.37%
Death	HPV (No brand name)	36	12.33%
Death	HPV (Cervarix)	12	4.11%
Sudden cardiac death	HPV (Gardasil)	2	0.68%
Sudden death	HPV (Gardasil)	11	3.77%

cause and effect relationship *via* VAERS and similar passive-reporting systems. Moreover, cardiac arrhythmias are not currently listed ore fully recognized as a possible adverse reaction to vaccines [8]. In many cases cardiac-related manifestations are vague and non-specific and hence readily misdiagnosed or underappreciated [9].

Another major limitation of the VAERS analysis by Slade, *et al.* [7] should be mentioned. Namely, the authors used the distributed and not the administered doses as the denominator when calculating the rate of adverse events. Based on adverse event data from countries that track the administered doses, the rate of adverse events are likely underestimated by five to tenfold [10]. Thus, the actual number of adverse events including cardiac-related fatalities in association with HPV vaccine could be much higher than currently reported.

Possible mechanism for HPV-vaccine induced cardiac arrhythmias

HPV-16 DNA - stimulated secretion of tumor necrosis factor

In addition to VAERS data, there is at least one relevant case reported in the medical literature [11] which relates to a previously healthy 18 year old girl who suffered a sudden death during her night sleep, six months after her 3rd HPV vaccine injection [11]. Although her death occurred many months after the last dose of HPV vaccine, her symptoms began shortly after the 1st dose and included a range of non-specific complaints, including headaches, dizziness spells, memory lapses and difficulty thinking. After receiving her 2nd injection, she also developed intermittent arm weakness, fatigue, signs of peripheral neuropathy, and palpitations. These symptoms persisted until her untimely death. Full autopsy analysis revealed no findings that might be linked to a potential cause of death. However, HPV-16 L1 gene DNA fragments were detected in the post-mortem blood and spleen tissue analysis. These were identical in sequence the fragments previously found in16 separate HPV vaccine vials. These 16 vials were from different vaccine lots and originated from different countries, including the U.S., Russia, Bulgaria and India, which indicates a widespread contamination process during HPV vaccine manufacture [12]. Moreover, these fragments detected in the HPV vaccine were bound to the aluminum adjuvant used in the vaccine formulation, which likely provided protection against endogenous nucleases [13]. This may be the explanation for their persistence in the blood over 6 months following injection. Interestingly, although the World Health Organization webpage specifically state that HPV vaccine is a highly purified vaccine and contain no DNA fragments [14-16], the findings of such DNA residuals in HPV vaccine vials [12], and in the tissues of the deceased vaccinated girl, show that the methods of purifications are not very efficient.

The HPV-16 L1 gene DNA fragments detected in the postmortem blood and splenic tissue in this case are presumably present in the nucleated cells, probably macrophages. It has been shown that the injection of free HPV-16 L1 plasmid DNA Intramuscularly in mice can activate the immune system by inducing a strong CD8 T cell response [17]. Furthermore, the presence of DNA fragments in macrophages may cause release of various cytokines, including tumor necrosis factor (TNF)- α [18], a recognized myocardial depressant [19] and marker for sudden cardiac death [20-22]. Interestingly, in a study of 8 cases of sudden infant deaths, all of occurred during sleep, Emura, *et al.* [22] found elevated levels of TNF- α and other pro-inflammatory cytokines in peripheral blood smear preparations that were significantly above normal thresholds. Because of this, Emura, *et al.* concluded that cytokine abnormality may be one of the underlying mechanisms in sudden infant death syndrome [22].

Molecular mimicry

In addition, there are other factors that might contribute to determine adverse cardiovascular events including sudden death following HPV vaccination. Kanduc [23] found a shared pattern between 34 pentamers from the HPV viral capsid protein and human protein. These proteins, when altered, have been shown to play a major role in arrhythmias, cardiovascular diseases and sudden death. For example, 9 out of the 34 viral pentamers belong to the human protein, Titin, a key component in the assembly and functioning of striated muscles. Defects in Titin may cause ventricular cardiomyopathy characterized by a high risk of cardiac failure and sudden cardiac death. Other significant matches include components of intercellular desmosome junctions such as plakophilin-2, desmoplakins, and desmocollin-2. Defects in these desmosomal proteins have been reported in arrhythmogenic right ventricular cardiomyopathy [24,25] which as mentioned above, has previously been linked to sudden cardiac death during sleep [26-28]. The voltage-dependent L-type calcium channel subunit alpha-1C has also been shown to match with the HPV-16 L1 sequence. This protein in known to be a altered in the Brugada syndrome, an important arrhythmogenic disorder associated with high-risk nocturnal arrhythmias [29,30].

Extending the peptide matching analyses to L1 proteins from the four strains (HPV 6, 11, 16, and 18) (Table 2), it emerges an even more impressive immunocrossreactive potential that specifically threatens the cardiac functions. Space precludes a detailed peptide-by-peptide discussion. Suffice to say that the peptide overlap between HPV L1 antigens and human Titin escalates to 41 pentapeptides (excluding multiple occurrences).

The cited investigation by Kanduc [23] and data from Table 2 confirm and extend previous reports describing a high level of homology between microbial antigens and the human proteome [31-34]. Furthermore, they suggest that possible immune cross-reactions deriving from utilization of HPV L1 proteins in current HPV vaccines might be a risk for cardiovascular events. A better understanding of potential antigen cross-reactivity, which at present is abysmally lacking, is necessary to minimise post-vaccination events [23].

Summary

The development of vaccines has proven to be a successful and cost-effective for global human health, and they present an essential part of preventive modern medicine.

It is obvious that vaccines are administered to millions of people worldwide, and that not everyone develops serious adverse manifestations. Hence, clearly there are some prior susceptibilities that make some people more at risk of experiencing an adverse reaction

Table 2. Peptide sharing between HPV L1 and human proteins that, when altered, are associated to sudden death

Peptide sequence	HPV strain	Human protein associated to sudden death
AGAVG	16	ACADM. Medium-chain specific acyl-CoA dehydrogenase, mitochondrial. ACADM defects associate with fasting hypoglycemia, hepatic dysfunction and encephalopathy, often resulting in death [39]
LGVGI GSSRL	16 18	ACADV. Very long-chain specific acyl-CoA dehydrogenase, mitochondrial. One major phenotype is a childhood form, with high mortality and high incidence of cardiomyopathy [40]
PGSCV	18	AKAP9. A-kinase anchor protein 9. AKAP9 defects may cause long QT syndrome, a heart disorder characterized by a prolonged QT interval and ventricular arrhythmias. They cause syncope and sudden death in response to exercise or emotional stress, and can present with a sentinel event of sudden cardiac death in infancy [41]
LCSIT	6,11	ANK2. Ankyrin-2. Involved in long QT syndrome, A heart disorder characterized by a prolonged QT interval on the ECG and polymorphic ventricular arrhythmias. They cause syncope and sudden death in response to exercise or emotional stress, and can present with a sentinel event of sudden cardiac death [42]
GTVCK LQAGL QAGLR	11 16 18	CAC1C. Voltage-dependent L-type calcium channel subunit alpha-1C. Defects in CAC1C are the cause of 1) Timothy syndrome, a disorder characterized by multiorgan dysfunction including lethal arrhythmia; 2) Brugada syndrome 3, characterized by the association of Brugada syndrome with shortened QT intervals. Ventricles beat so fast that the blood is prevented from circulating efficiently in the body. When this situation occurs, the individual will faint and may die in a few minutes if the heart is not reset [43, 44]
RPSDS	6, 11	CACB2. Voltage-dependent L-type calcium channel subunit beta-2. Involved in a heart disease characterized by the association of Brugada syndrome with shortened QT intervals. Ventricles beat so fast that the blood is prevented from circulating efficiently in the body and the individual will faint and may die in a few minutes [44, 45]
AGAVG NKFGL	16 18	CMC2. Calcium-binding mitochondrial carrier protein Aralar2. A form of citrullinemia characterized primarily by elevated serum and urine citrulline levels; characterized by neuropsychiatric symptoms including abnormal behaviors, loss of memory, seizures and coma. Death can result from brain edema [46]
SVTTS	6	CSRP3. Cysteine and glycine-rich protein 3. Associated with dilated and hypertrophic phenotypes of cardiomyopathy ventricular dilation and impaired systolic function, resulting in congestive heart failure and arrhythmia. Patients are at risk of premature death. The symptoms include dyspnea, syncope, collapse, palpitations, and chest pain. They can be readily provoked by exercise [47, 48]
SDVPI TKTKK STSET	6 11 16	ECHB. Trifunctional enzyme subunit beta, mitochondrial. Altered ECHB can lead to hypoglycemia, cardiomyopathy, sensorimotor axonopathy. Sudden infant death may occur. Most patients die from heart failure [49]
LQPPP; QPPPG	16	FEV. Protein FEV. Functions in the maintenance of the central serotonergic neurons. FEV defects associate with susceptibility to sudden infant death. Pathogenic mechanisms precipitating an infant sudden death remain elusive [50]
RVNVG; VNVGM VHTPS; HTPSG GVEVG LILHY	6,11 11 16 18	FLNC. Filamin-C. Hypertrophic ventricular cardiomyopathy. Symptoms include dyspnea, syncope, collapse, palpitations, and chest pain, that can be readily provoked by exercise. High risk of cardiac failure and sudden cardiac death [51]
PSTAP	11	GATA5. Transcription factor GATA-5. Involved in atrial fibrillation, characterized by disorganized atrial electrical activity and ineffective atrial contraction promoting blood stasis in the atria and reduces ventricular filling. It can result in palpitations, syncope, thromboembolic stroke, and congestive heart failure, arrhythmia. Patients are at risk of premature death [52]
RTSVG; TSVGS	6	JPH2. Junctophilin-2. JPH2 is necessary for proper intracellular Ca2+ signaling in cardiac myocytes via its involvement in ryanodine receptor-mediated calcium ion release. Involved in hypertrophic ventricular cardiomyopathy. Symptoms include dyspnea, syncope, collapse, palpitations, and chest pain, that can be readily provoked by exercise. High risk of cardiac failure and sudden cardiac death [53]
RVFRI RVFRV; PASPG	16 18	KCND3. Potassium voltage-gated channel subfamily D member 3.Involved in Brugada syndrome, a tachyarrhythmia that can cause the ventricles to beat so fast that the blood is prevented from circulating efficiently in the body. The individual will faint and may die in a few minutes if the heart is not reset [54]
GTLED KKRKL	6, 11, 16 16	MYH6. Myosin-6. Involved in hypertrophic ventricular cardiomyopathy; symptoms include dyspnea, syncope, collapse, palpitations, and chest pain. They can be readily provoked by exercise. High risk of cardiac failure and sudden cardiac death [55]
GTLED KKRKL	6, 11,16 16	MYH7. Myosin-7. Associated with hypertrophic ventricular cardiomyopath. The symptoms include dyspnea, syncope, collapse, palpitations, and chest pain; high risk of cardiac failure and sudden cardiac death [56]
GTLED EKEKQ	6, 11,16 11	MYH7B. Myosin-7B. Associated with left ventricular noncompaction.
VGEPV	6, 11	MYPC3. Myosin-binding protein C, cardiac-type. Involved in ventricular cardiomyopathy.Symptoms are: dyspnea, syncope, collapse, palpitations, and chest pain. They can be provoked by exercise. Risk of cardiac failure and sudden cardiac death [57]
VTTSS KVSGL PPTTS; RSAPS; TTSSK	6 16 18	MYPN. Myopalladin. Component of the sarcomere that tethers together nebulin (skeletal muscle) and nebulette (cardiac muscle) to alpha-actinin, at the Z lines [58]
LPPPS	18	NU155. Nuclear pore complex protein Nup155. Involved in atrial fibrillation, a common sustained cardiac rhythm disturbance. Atrial fibrillation is characterized by disorganized atrial electrical activity and ineffective atrial contraction promoting blood stasis in the atria and reduces ventricular filling. It can result in palpitations, syncope, thromboembolic stroke, and congestive heart failure [59]
MFARH	6, 11	RN207. RING finger protein 207. Plays a role in cardiac repolarization possibly by stabilizing membrane expression of the potassium channel KCNH2/HERG [60]
KVVLP	6 11	RYR2. Ryanodine receptor 2. Calcium channel that mediates the release of Ca2+ and thereby plays a key role in triggering cardiac muscle contraction. Involved in arrhythmogenic right ventricular dysplasia; and in ventricular tachycardia, that may degenerate into cardiac arrest and cause sudden death [61, 62]
GLQPP	16	RYR1. Ryanodine receptor 1. Plays a key role in triggering muscle contraction following depolarization of T-tubules. Associated with malignant hyperthermia, accelerated muscle metabolism, contractures, metabolic acidosis, tachycardia and death [63]
PEKEK; EKEKQ KLDDT	6, 11 11 16, 18	SCN8A. Sodium channel protein type 8 subunit alpha. SCN8A alterations may associate with early-onset seizures, features of autism, intellectual disability, ataxia, and sudden unexplained death in epilepsy [64].

GRSSI; KRANK; RANKT; RSSIR;SDVPI; VGSSI; VSKAS GEPVP; KSDVP; KTVVP; PSDST; SITLS; TVVPK; VENSG; VGEPV;VVDTT; VVPKV; YQYRV KVNKT; NRSSV; SKSAT; SVSKS; VSKPS DTTRS HVEEY AGLKA; KKYTF; KVSGL PPAPK SEVPL; STANL STILE; TSRLL; VGENV VVDTT GLPDT; LELKN; NKFGL; PPPTT;YQYRV; VPPPP	6 6,11 11 6,11,16 6,18 16 16,18 18	TITIN. Titin. Key component in the assembly and functioning of vertebrate striated muscles. Defects in Titin may cause ventricular cardiomyopathy characterized by a high risk of cardiac failure and sudden cardiac death [65]
EKEKP	6	TRDN. Triadin. Involved in excitation-contraction coupling in the heart and in regulating the rate of heart beats. Involved in ventricular tachycardia that may degenerate into cardiac arrest and cause sudden death. Patients present with recurrent syncope, or sudden death after physical activity or emotional stress [66]
TLEDT PGGTL	6,11,16 16	TRPM4. Transient receptor potential cation channel subfamily M member 4. Involved in atrio-ventricular block causing syncope and sudden death [67]
NPYFR	18	TSYL1. Testis-specific Y-encoded-like protein 1. Involved in sudden infant death with dysgenesis of the testes syndrome. Features included bradycardia, hypothermia, severe gastroesophageal reflux, laryngospasm, bronchospasm, and abnormal cardiorespiratory patterns during sleep [68]

to vaccination than others. Among these are genetic factors, personal and familial history of relevant symptoms, hypersensitivity and a prior adverse response to vaccination [35,36]. These factors should be routinely addressed, in order to identify the patients who might be prone to vaccine associated adverse events and give them the best possible care.

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Review

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Will HPV vaccination prevent cervical cancer?

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Summary

We conducted a critical appraisal of published Phase 2 and 3 efficacy trials in relation to the prevention of cervical cancer in women. Our analysis shows the trials themselves generated significant uncertainties undermining claims of efficacy in these data. There were 12 randomised control trials (RCTs) of Cervarix and Gardasil. The trial populations did not reflect vaccination target groups due to differences in age and restrictive trial inclusion criteria. The use of composite and distant surrogate outcomes makes it impossible to determine effects on clinically significant outcomes. It is still uncertain whether human papillomavirus (HPV) vaccination prevents cervical cancer as trials were not designed to detect this outcome, which takes decades to develop. Although there is evidence that vaccination prevents cervical intraepithelial neoplasia grade 1 (CIN1) this is not a clinically important outcome (no treatment is given). Trials used composite surrogate outcomes which included CIN1. High efficacy against CIN1+ (CIN1, 2, 3 and adenocarcinoma in situ (AIS)) does not necessarily mean high efficacy against CIN3+ (CIN3 and AIS), which occurs much less frequently. There are too few data to clearly conclude that HPV vaccine prevents CIN3+. CIN in general is likely to have been overdiagnosed in the trials because cervical cytology was conducted at intervals of 6–12 months rather than at the normal screening interval of 36 months. This means that the trials may have overestimated the efficacy of the vaccine as some of the lesions would have regressed spontaneously. Many trials diagnosed persistent infection on the basis of frequent testing at short intervals, i.e. less than six months. There is uncertainty as to whether detected infections would clear or persist and lead to cervical changes.

Keywords

Vaccination programmes, cervical cancer

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The human papillomavirus (HPV) vaccination programme aims to prevent cervical cancer. Globally around 13.1/100,000 women are diagnosed with cervical cancer each year.[2] Typically, vaccination is offered to girls aged 9–13 years before sexual debut and naïve to HPV infection. Box 1 gives an overview of licensing and indications in Europe and the US.

Public health agencies promote the position that the vaccine has been shown to prevent cervical cancer (see Supplement 1). Not all routinely emphasise the limitations of the evidence or the uncertainties which we will discuss.

Background

A key issue for the design of trials and studies of efficacy is the complexity of the epidemiology of the HPV subtypes and the lesions used as surrogate endpoints for cervical cancer, each with their own different natural histories, prevalence and incidence and strength of association with cancer. These measures, especially if combined as composite surrogate endpoints in trials, generate new uncertainties.

i) HPV infection

There are 100+ types of the HPV: 12 of which are carcinogenic to humans, according to the International Association of Cancer Research (IARC).[4] Types vary in prevalence, as does their association with cervical cancer. HPV vaccines are licensed for use against oncogenic HPV types 16 and 18 and now 31, 33, 45, 52, 58 in Gardasil-9. Gardasil and Gardasil-9 are also licensed against non-oncogenic types 6 and 11 linked to genital warts.

The lifetime risk of an incident of HPV infection is 79%;[5] the majority of HPV infections are transient and 67% clear within one year.[6] Around 10% of women without CIN have HPV infection at any one time.[7] The mechanism of progression from HPV infection to cervical cancer and its precursors is not well understood.[4,8–11]

ii) Cervical cancer and pre-cancerous lesions as surrogate endpoints

New Concerns about the Human Papillomavirus Vaccine

American College of Pediatricians – January 2016

The American College of Pediatricians (The College) is committed to the health and well-being of children, including prevention of disease by vaccines. It has recently come to the attention of the College that one of the recommended vaccines could possibly be associated with the very rare but serious condition of premature ovarian failure (POF), also known as premature menopause. There have been two case report series (3 cases each) published since 2013 in which post-menarcheal adolescent girls developed laboratory documented POF within weeks to several years of receiving Gardasil, a four-strain human papillomavirus vaccine (HPV4).[1,2] Adverse events that occur after vaccines are frequently not caused by the vaccine and there has not been a noticeable rise in POF cases in the last 9 years since HPV4 vaccine has been widely used.

Nevertheless there are legitimate concerns that should be addressed: (1) long-term ovarian function was not assessed in either the original rat safety studies[3,4] or in the human vaccine trials, (2) most primary care physicians are probably unaware of a possible association between HPV4 and POF and may not consider reporting POF cases or prolonged amenorrhea (missing menstrual periods) to the Vaccine Adverse Event Reporting System (VAERS), (3) potential mechanisms of action have been postulated based on autoimmune associations with the aluminum adjuvant used[1] and previously documented ovarian toxicity in rats from another component, polysorbate 80,[2] and (4) since licensure of Gardasil® in 2006, there have been about 213 VAERS reports (per the publicly available CDC WONDER VAERS database) involving amenorrhea, POF or premature menopause, 88% of which have been associated with Gardasil.[5] The two-strain HPV2, Cervarix™, was licensed late in 2009 and accounts for 4.7 % of VAERS amenorrhea reports since 2006, and 8.5% of those reports from February 2010 through May 2015. This compares to the pre-HPV vaccine period from 1990 to 2006 during which no cases of POF or premature menopause and 32 cases of amenorrhea were reported to VAERS.

Many adolescent females are vaccinated with influenza, meningococcal, and tetanus vaccines without getting Gardasil®, and yet only 5.6% of reports related to ovarian dysfunction since 2006 are associated with such vaccines in the absence of simultaneous Gardasil administration. The overwhelming majority (76%) of VAERS reports since 2006 with ovarian failure, premature menopause, and/or amenorrhea are associated *solely* with Gardasil®. When VAERS reports since 2006 are restricted to cases in which amenorrhea occurred for at least 4 months and is not associated with other known causes like polycystic ovary syndrome or pregnancy, 86/89 cases are associated with Gardasil, 3/89 with Cervarix™, and 0/89 with other vaccines administered independently of an HPV vaccine.[5] Using the same criteria, there are only 7 reports of amenorrhea from 1990 through 2005 and no more than 2 of those associated with any one vaccine type.

Few other vaccines besides Gardasil® that are administered in adolescence contain polysorbate 80.[6] Pre-licensure safety trials for Gardasil used placebo that contained polysorbate 80 as well as aluminum adjuvant.[2,7] Therefore, if such ingredients could cause ovarian dysfunction, an increase in amenorrhea probably would not have been detected in the placebo controlled trials. Furthermore, a large number of girls in the original trials were taking hormonal contraceptives which can mask ovarian dysfunction

including amenorrhea and ovarian failure.[2] Thus a causal relationship between human papillomavirus vaccines (if not Gardasil® specifically) and ovarian dysfunction cannot be ruled out at this time.

Numerous Gardasil safety studies, including one released recently,[8] have looked at demyelinating and autoimmune diseases and have not found any significant problems. Unfortunately, none of them except clinical safety pre-licensure studies totaling 11,778 vaccinees[9] specifically addressed post-vaccination ovarian dysfunction. While data from those studies do not indicate an increased rate of amenorrhea after vaccination, the essential lack of saline placebos and the majority of participants taking hormonal contraceptives in those studies preclude meaningful data to rule out an effect on ovarian function.

A Vaccine Safety Datalink POF study is planned to address an association between these vaccines and POF, but it may be years before results will be determined. Plus, POF within a few years of vaccination could be the tip of the iceberg since ovarian dysfunction manifested by months of amenorrhea may later progress to POF. Meanwhile, the author of this statement has contacted the maker of Gardasil®, the Advisory Committee on Immunization Practices (ACIP), and the Food and Drug Administration (FDA) to make known the above concerns and request that (1) more rat studies be done to look at long-term ovarian function after HPV4 injections, (2) the 89 VAERS reports identified with at least 4 months amenorrhea be reviewed by the CDC for further clarification since the publicly available WONDER VAERS database only contains initial reports, and (3) primary care providers be notified of a possible association between HPV and amenorrhea. A U.S. Government Representative responded that they "will continue to conduct studies and monitor the safety of HPV vaccines. Should the weight of the evidence from VAERS or VSD and other sources indicate a likely causal association between POF and HPV vaccines, appropriate action will be taken in terms of communication and public health response."

The College is posting this statement so that individuals considering the use of human papillomavirus vaccines could be made aware of these concerns pending further action by the regulatory agencies and manufacturers. While there is no strong evidence of a causal relationship between HPV4 and ovarian dysfunction, this information should be public knowledge for physicians and patients considering these vaccines.

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The Truth About HPV

The vaccine that so many people now are talking about may not be necessary to prevent cervical cancer.

Each year in the US, 55 million women receive a Pap test to check for abnormal cells that might be an early sign of cervical cancer. Of these, 3.5 million tests show abnormalities that require medical follow-up, and about 12,000 women are diagnosed as having cervical cancer.

Recent development: Since 2006, when the pharmaceutical company Merck began TV and print advertisements for Gardasil, a vaccine against the mainly sexually transmitted *human papillomavirus* (HPV), which is present in up to 99% of cervical cancer cases, many women have been increasingly confused about their real risks for the disease and what role a vaccine may play in preventing it.

Gardasil is also FDA-approved for preventing certain vulvar and vaginal cancers in females and for preventing genital warts in males and females. It was recently approved to prevent anal cancer in males and females. Cervarix, another HPV vaccine, was approved by the FDA in 2009.

For the facts that every woman should know about HPV and cervical cancer, *Bottom Line/Health* spoke with renowned HPV expert Sin Hang Lee, MD, a pathologist who has studied cervical cancer for more than 50 years and trained in the laboratory of Dr. Georgios Papanicolaou, the scientist who developed the "Pap" test (formerly called the "Pap smear") to detect cervical cancer. *His most important insights…*

FACT 1: There is no cervical cancer crisis. Thanks to regular use of the Pap test, the incidence of cervical cancer has been dramatically reduced. Of the Pap tests performed annually in the US, only about 0.02% result in a diagnosis of cervical cancer when a biopsy is performed.

If all women got annual Pap tests—and the tests were analyzed properly (not all HPV tests distinguish between benign HPV strains, or genotypes, and those that may cause cancer)—death from cervical cancer would be extremely rare. The disease is highly preventable if lesions are detected in a precancerous stage. *Note:* The American College of Obstetricians and Gynecologists (ACOG) revised its recommendations for Pap tests in 2009. For women ages 21 to 30 without symptoms or risk factors, the ACOG recommends the test every two years…and every three years for women age 30 and older and who had three consecutive normal tests. Discuss the frequency of your Pap tests with your doctor.

FACT 2: The concern over HPV infection is overblown. While HPV can cause cervical cancer, the story

Bottom Line/Health interviewed Sin Hang Lee, MD, a pathologist at Milford Hospital and director of Milford Medical Laboratory (a subsidiary of the hospital that provides comprehensive testing), both in Milford, Connecticut. Dr. Lee is an internationally recognized expert in the area of human papilloma virus and has developed a DNA sequencing test to identify specific HPV genotypes.

is more nuanced than people are led to believe from public service announcements and vaccine ads.

There are about 200 known genotypes of HPV, but only 13 are considered "high risk" for causing cervical cancer—HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68. Of these, HPV-16 and HPV-18 are believed to cause 70% of all cervical cancers. That means that you can have any of the 187 other genotypes without having an increased risk of developing cervical cancer. The prevalence of high-risk genotypes varies world-wide and depends in part on a woman's level of sexual activity. *Important:* Nearly all cases of genital warts are caused by two low-risk genotypes, HPV-6 and HPV-11. This means that warts you can see and feel are annoying but usually not dangerous.

Even better news: Even though there is no treatment for HPV infection, women's immune systems are typically effective at fighting HPV. More than 90% of HPV infections disappear on their own and do not progress to precancerous stages or cancer. In fact, the average HPV infection lasts only about six months. This means that a woman who receives testing when the infection is active may be HPV-negative within a matter of months.

The women who should be most concerned about cervical cancer are those infected with a high-risk genotype and in which the infection is *persistent* (lasting more than six months). Women typically undergo repeat testing every six months until the infection clears, and a biopsy may be recommended if an infection of the same genotype persists while the Pap test is still abnormal or questionable.

FACT 3: HPV vaccines don't guarantee cancer prevention. Gardasil prevents infection with four genotypes—the high-risk HPV-16 and HPV-18 and the low-risk-for-cancer, genital wart–causing HPV-6 and HPV-11. (Cervarix prevents only HPV-16 and HPV-18.)

Some women consider it useful to be protected against two of the 13

cancer-causing genotypes. However, most women are unaware that there is no evidence showing how long the vaccine will remain effective.

Important: I recommend that women who want to get the HPV vaccine ask their gynecologists to make sure that they are not already infected with HPV 16 or HPV 18. There is some evidence that women who get the vaccine when they are infected with HPV—especially HPV-16 and HPV-18—have an *increased* risk of developing cervical cancer.

Reported side effects of the Gardasil and Cervarix vaccines include temporary pain and swelling at the injection site and headache. As of September 2010, the CDC reported 30 confirmed deaths of females who received Gardasil, though it is not proven that the vaccine caused these deaths. The agency did not publish data on reported deaths from Cervarix.

FACT 4: Not all HPV testing is adequate. Historically, HPV tests have not distinguished between benign and specific cancer-causing genotypes. Newer HPV tests, including Cervista HPV HR, are designed to detect when any of the 13 cancer-causing genotypes or the intermediate-risk genotype HPV-66 is present, but it does not identify the specific genotype. To identify the specific HPV genotype—with virtually no risk for false-positive results or misidentification—physicians can request a *DNA sequencing test*. This test is available from the nonprofit organization SaneVax, Inc., *www.SaneVax.org*. The cost is $50.