Emily Tarsell, LCPC, LCPAT

2314 Benson Mill Road
Sparks, Maryland 21152

Opposed to HB 87 / SB 135

February 2020

I am Emily Tarsell, mother and therapist, and I oppose this bill. Uptake of mandated teen vaccines in MD are already greater than 90% except for the **optional** HPV vaccine, Gardasil. So increasing uptake of Gardasil is likely the motive for this bill. But there are strong medical and moral reasons why Gardasil uptake is low and why **it was withdrawn in other countries.**

We already have safe and effective ways to prevent cervical cancer with Pap screening which you must have even with vaccination. Fears of HPVs are overblown. They clear naturally 95% of the time and HPV related cancer is very rare. Plus, the vaccine has never been demonstrated to prevent any cancers.

No 16 year old is going to know if they are HPV positive, but if they are, getting vaccinated increases their risk of getting cervical cancer. They won't know that they risk sterility or a multitude of other serious outcomes if vaccinated.

No health care provider is going to tell you this. I know from personal experience. Twelve years ago my 20 y/o daughter Christina and I were misled by a provider and told that the HPV vaccine was" safe, effective and would prevent cervical cancer." Chris agreed to vaccination, took the series and died 18 days after the last shot. You cannot imagine the anguish of seeing your beautiful child suddenly lifeless.

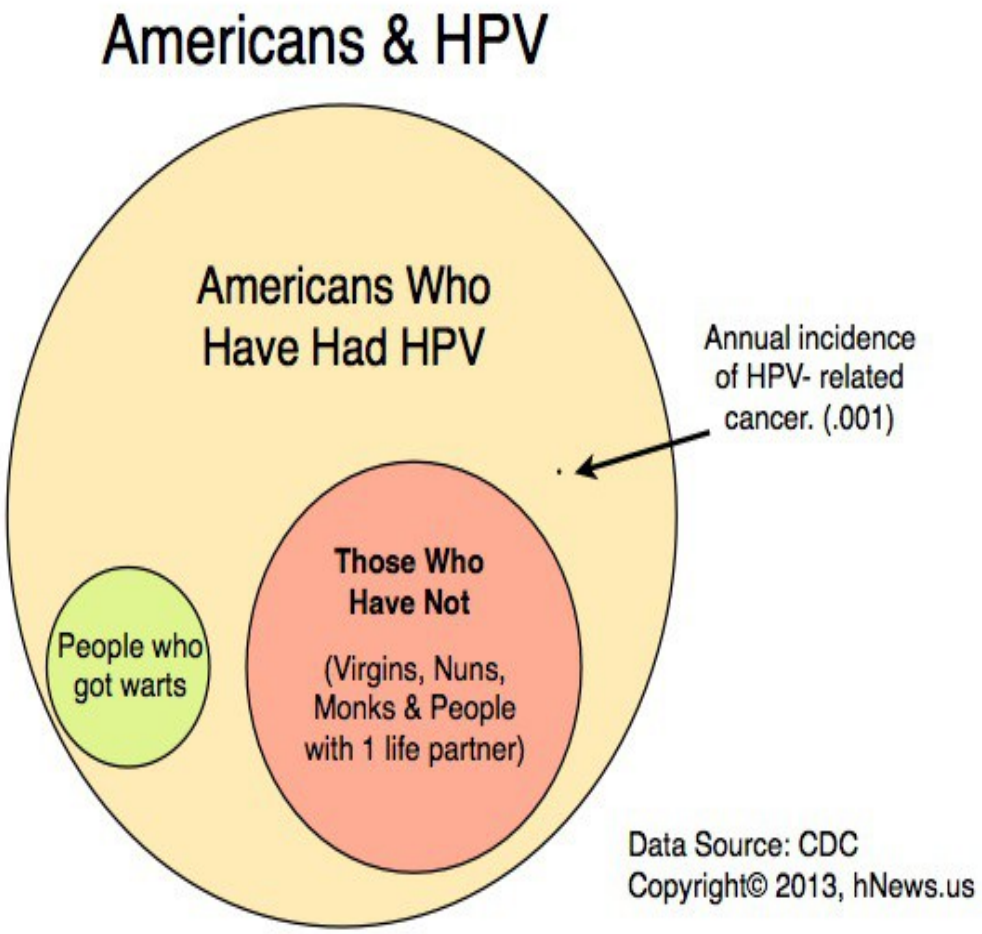
Experts determined that she died from the vaccine and after 8 years of litigation in the vaccine court, the government conceded that Gardasil caused her death. The drug maker, Merck paid no compensation because they have complete liability protection. In fact they profited from my daughter's death and the deaths of more than 534 others.

Why were we misled? Well if one knows the truth, one will likely decline the vaccine. It's all about the money: $750 a head x thousands = millions in profits.

In March 2018 I attended a meeting sponsored by MDDOH and paid for by Merck titled"*HPV Vaccination Symposium, Providers are the Key."* The message presented there was NOT about safety or effectiveness, but about increasing uptake of Gardasil (see pages 29-32). They advised providers to **avoid** discussion, give multiple vaccinations concurrently and forcefully **"DO**" . Bribe, cajole, bully, scare, mislead - but **"DO"** increase uptake and there will be a big bonus.

Do not sacrifice our children for a fistful of dollars. Vote with your conscience and your heart and veto HB 87 / SB135. Christina and I thank you.

Emily Tarsell tarsell@comcast.net www.gardasil-and-unexplained-deaths.com


Americans & HPV
Americans Who Have Had HPV
Annual incidence of HPV- related cancer. (.001)
Those Who Have Not
(Virgins, Nuns, Monks & People with 1 life partner)
People who got warts
Data Source: CDC
Copyright© 2013, hNews.us

HPV-associated Cancers: Incidence

Cancer	Incidence Count	Incidence Rate
Cervical	228	6.7
Anal	140	2.0
Penile	13	**
Vaginal	31	0.8
Vulvar	95	2.6
Oropharyngeal***	185	2.4

Rates are per 100,000 and are age-adjusted to the 2000 U.S. Standard Population
*** Incidence Rates based on case counts of 1-15 are suppressed per MDH/MCR Data Use Policy*
Incidence Source: SEERstat static data as of 01032018
***Oropharyngeal cancer data reflect the incidence rates *for Tonsil and Oropharynx cancer.*
Note: Cancers have varying levels of association with HPV. Inclusion in this presentation does not imply that each case was associated with HPV infection.

HPV-associated Cancers: Mortality

Cancer	Mortality Count	Mortality Rate
Cervical	69	1.9
Anal	24	0.3
Penile	<10	**
Vaginal	<10	**
Vulvar	18	**
Oropharyngeal***	33	**

Rates are per 100,000 and are age-adjusted to the 2000 U.S. Standard Population
<10= Death counts of 0-9 are suppressed per MDH/CCPC Mortality Data Suppression Policy
*** Mortality Rates based on death counts of 0-19 are suppressed per MDH/CCPC Mortality Data Suppression Policy*
Mortality Source: CDC Wonder, 2015, as of 02/21/2018
***Oropharyngeal cancer data reflect the mortality rates *for Tonsil and Oropharynx cancer.*
Note: Cancers have varying levels of association with HPV. Inclusion in this presentation does not imply that each case was associated with HPV infection.

HOPKINSMEDICINE

Winter 2017

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.

House Staff, Pediatrics, 1959–62 | Emeritus Professor of Pediatrics

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

INFECTIOUS AGENTS AND CANCER

LETTER TO THE EDITOR Open Access

HPV vaccines and cancer prevention, science versus activism

Lucija Tomljenovic[1*], Judy Wilyman[2], Eva Vanamee[3], Toni Bark[4] and Christopher A Shaw[1]

Abstract

The rationale behind current worldwide human papilloma virus (HPV) vaccination programs starts from two basic premises, 1) that HPV vaccines will prevent cervical cancers and save lives and, 2) have no risk of serious side effects. Therefore, efforts should be made to get as many pre-adolescent girls vaccinated in order to decrease the burden of cervical cancer. Careful analysis of HPV vaccine pre- and post-licensure data shows however that both of these premises are at odds with factual evidence and are largely derived from significant misinterpretation of available data.

Letter

The recent Editorial by Silvia de Sanjosé* [1] is problematic from a variety of perspectives. Mainly, it attempts to portray a complex issue as a simple dichotomy between supposedly unjustified "anti-HPV vaccine activism" and alleged absolute science which has presumably provided indisputable evidence on HPV vaccine safety and efficacy.

In spite of much unwarranted and premature optimism, the fact is however that HPV vaccines have not thus far prevented a single case of cervical cancer (let alone cervical cancer death). Instead, what the clinical trials have shown is that HPV vaccines can prevent some of the pre-cancerous CIN 2/3 lesions associated with HPV-16 and HPV-18 infection, a large fraction of which would spontaneously resolve *regardless* of the vaccination status [2-4]. For example, in adolescent women aged 13 to 24 years, 38% of CIN 2 resolve after one year, 63% after two and 68% after three years [5]. Moreover, the validity of CIN 2 being a cancer precursor is questionable due to high misclassification rates and poor intra- and inter-observer reproducibility in diagnosis, as well as high regression rates [6-9]. According to Castle *et al.* [7] CIN 2 is the least reproducible of all histopathologic diagnoses and may in part reflect sampling error. While CIN 3 is a more reliable marker for cancer progression than CIN 2, the use of this marker is not without caveats [2,10].

Indeed, the optimistic assumption that HPV vaccination (even *if* proven effective against cervical cancer as claimed), will result in 70% reduction of cervical cancers appears to be largely based on premature, exaggerated and invalid surrogate marker-based extrapolations [2,11]. Crucially, these assumptions failed to take into account several important real-world factors such as:

(1) reliability of surrogate-markers (i.e., whether they can accurately measure what they are purport to measure);
(2) efficacy against oncogenic HPV strains not covered by the vaccine;
(3) possibility of increased frequency of infections with these types;
(4) efficacy in women acquiring multiple HPV types;
(5) effects in women with pre-existing HPV infections

It is also noteworthy that Merck's HPV vaccine Gardasil received priority *Fast* Track approval by the U.S. Food and Drug Administration (FDA) after a 6-month review process, despite the fact that it failed (and still 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 the loop electrosurgical excision procedure (LEEP) in preventing cervical cancers, nor can it improve the diagnosis of serious cervical cancer outcomes [12]. In this regard, Gerhardus and Razum have recently noted

* Correspondence: lucijat77@gmail.com
[1]Neural Dynamics Research Group, Vancouver General Hospital Research Pavilion, University of British Columbia, 828 W. 10th Ave, Vancouver, BC V5Z 1L8, Canada
Full list of author information is available at the end of the article

that the "*. . .unwarranted confidence in the new* [*HPV*] *vaccines led to the impression that there was no need to actually evaluate their effectiveness*" [11].

Similarly, the notion that HPV vaccines have an impressive safety profile can only be supported by highly flawed design of safety trials [2,13] and is contrary to accumulating evidence from vaccine safety surveillance databases and case reports which continue to link HPV vaccination to serious adverse outcomes (including death and permanent disabilities) [2,4,14]. For example, compared to all other vaccines in the U.S. vaccination schedule, Gardasil alone is associated with 61% of all serious adverse reactions (including 63.8% of all deaths and 81.2% cases of permanent disability) in females younger than 30 years of age [12].

Although a report to a vaccine safety surveillance system does not by itself prove that the vaccine caused an adverse reaction, the unusually high frequency of adverse reactions related to HPV vaccines reported worldwide, as well as their consistent pattern (i.e. nervous system-related disorders rank the highest in frequency), points to a potentially causal relationship [2]. Furthermore, matching the data from vaccine surveillance databases is an increasing number of case reports documenting similar serious adverse reactions associated with HPV vaccine administration, with nervous system and autoimmune disorders being the most frequently reported in the medical literature [15-24].

In summary, the optimistic claims that HPV vaccines will prevent cervical cancers and save lives, and that they are extremely safe, rest on assumptions which are misinterpreted and presented to the public as factual evidence. We thus conclude that further reduction of cervical cancers might be best achieved by optimizing cervical screening (which carries no serious health risks) and targeting other factors of the disease rather than by the reliance on vaccines with questionable efficacy and safety profiles [2,25].

To those who wish to promote HPV vaccination as a means for reducing cervical cancer burden, perhaps the following should be asked:

1. HPV vaccines have not been demonstrated to prevent any cervical cancers so why are they being promoted as cervical cancer vaccines?
2. If the majority of HPV infections and a great proportion of pre-cancerous lesions clear spontaneously and without medical treatment and are thus not a reliable indication of cancer later in life, then how can these end-points be used as a reliable indicator of the number of cervical cancer cases that will be prevented by HPV vaccines?
3. How can the clinical trials make an accurate estimate of the risk associated with HPV-vaccines if they are methodologically biased to produce type-2 errors (false negatives [2,4,13])?
4. Can a passive monitoring system such as that used by most vaccine surveillance systems world-wide allow the medical regulatory agencies to make accurate estimates on the real frequency of HPV-vaccine related adverse reactions?
5. Can an accurate estimate of the real frequency of HPV-vaccine related adverse reactions be made if appropriate follow-up and thorough investigation of suspected vaccine related ADRs is not conducted but instead, these cases are a-priori dismissed as being unrelated to the vaccine?
6. Why are women not informed of the fact that in some circumstances (i.e., prior exposure to vaccine-targeted and non-targeted HPV types), HPV vaccination may accelerate the progression of cervical abnormalities [4,26-28]?
7. How can women make a fully informed decision about whether or not to consent to vaccination if crucial information regarding HPV vaccine efficacy and safety is not being disclosed to them?
8. Should the medical health regulators and authorities rely solely on data provided by the vaccine manufacturers to make vaccine-policy decisions and recommendations [12,29]?

Competing interests

The authors declare that they have no conflict of interests.

Authors' contributions

LT was involved in choosing the topic and drafting the initial manuscript. CAS, JW, EV and TB were involved in critically revising the manuscript and additional content. The authors have read and approved the manuscript.

This work was supported by the Dwoskin and Katlyn Fox Family Foundations.

Author details

[1]Neural Dynamics Research Group, Vancouver General Hospital Research Pavilion, University of British Columbia, 828 W. 10th Ave, Vancouver, BC V5Z 1L8, Canada. [2]School of Social Sciences, Media and Communication, University of Wollongong, Wollongong 2522, Australia. [3]Department of Structural and Chemical Biology, Mount Sinai School of Medicine, 1425 Madison Ave., Rm 1623, New York, NY 10029, USA. [4]School of Public Health-Healthcare Emergency Management, Boston University, Boston, MA 02118, USA.

Received: 9 January 2013 Accepted: 21 January 2013
Published: 1 February 2013

References

1. de Sanjose S: **HPV prevention series.** *Infect Agent Cancer* 2012, **7**(1):37.
2. Tomljenovic L, Shaw CA, Spinosa JP: **Human Papillomavirus (HPV) Vaccines as an option for preventing cervical malignancies: (How) effective and safe?** *Curr Pharm Des* 2012, :CPD-EPUB-20120924-13. Epub ahead of print.
3. Tomljenovic L, Shaw CA: **Who profits from uncritical acceptance of biased estimates of vaccine efficacy and safety?** *Am J Public Health* 2012, **102**(9): e13–e14.
4. Tomljenovic L, Shaw CA: **Human papillomavirus (HPV) vaccine policy and evidence-based medicine: are they at odds?** *Ann Med* 2011, doi:10.3109/07853890.2011.645353.
5. Moscicki AB, Ma Y, Wibbelsman C, Darragh TM, Powers A, Farhat S, Shiboski S: **Rate of and risks for regression of cervical intraepithelial neoplasia 2 in adolescents and young women.** *Obstet Gynecol* 2010, **116**(6):1373–1380.

6. Castle PE, Schiffman M, Wheeler CM, Solomon D: **Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2.** *Obstet Gynecol* 2009, **113**(1):18–25.
7. Castle PE, Stoler MH, Solomon D, Schiffman M: **The relationship of community biopsy-diagnosed cervical intraepithelial neoplasia grade 2 to the quality control pathology-reviewed diagnoses: an ALTS report.** *Am J Clin Pathol* 2007, **127**(5):805–815.
8. Castle PE, Schiffman M, Wheeler CM, Wentzensen N, Gravitt PE: **Impact of improved classification on the association of human papillomavirus with cervical precancer.** *Am J Epidemiol* 2009, **171**(2):155–163.
9. Carreon JD, Sherman ME, Guillén D, Solomon D, Herrero R, Jerónimo J, Wacholder S, Rodríguez AC, Morales J, Hutchinson M, *et al*: **CIN2 is a much less reproducible and less valid diagnosis than CIN3: results from a histological review of populationbased cervical samples.** *Int J Gynecol Pathol* 2007, **26**(4):441–446.
10. Schiffman M, Rodriguez AC: **Heterogeneity in CIN3 diagnosis.** *Lancet Oncol* 2008, **9**(5):404–406.
11. Gerhardus A, Razum O: **A long story made too short: surrogate variables and the communication of HPV vaccine trial results.** *J Epidemiol Community Health* 2010, **64**(5):377–378.
12. Tomljenovic L, Shaw CA: **Too fast or not too fast: the FDA's approval of Merck's HPV vaccine gardasil.** *J Law Med Ethics* 2012, **40**(3):673–681.
13. Tomljenovic L, Shaw CA: **No autoimmune safety signal after vaccination with quadrivalent HPV vaccine Gardasil?** *J Intern Med* 2012, **272**(5):514–515.
14. Souayah N, Michas-Martin PA, Nasar A, Krivitskaya N, Yacoub HA, Khan H, Qureshi AI: **Guillain-Barre syndrome after Gardasil vaccination: data from vaccine adverse event reporting system 2006–2009.** *Vaccine* 2011, **29**(5):886–889.
15. Mendoza Plasencia Z, Gonzalez Lopez M, Fernandez Sanfiel ML, Muniz Montes JR: **Acute disseminated encephalomyelitis with tumefactive lesions after vaccination against human papillomavirus.** *Neurologia* 2010, **25**(1):58–59.
16. Wildemann B, Jarius S, Hartmann M, Regula JU, Hametner C: **Acute disseminated encephalomyelitis following vaccination against human papilloma virus.** *Neurology* 2009, **72**(24):2132–2133.
17. DiMario FJ Jr, Hajjar M, Ciesielski T: **A 16-year-old girl with bilateral visual loss and left hemiparesis following an immunization against human papilloma virus.** *J Child Neurol* 2010, **25**(3):321–327.
18. Pugnet G, Ysebaert L, Bagheri H, Montastruc JL, Laurent G: **Immune thrombocytopenic purpura following human papillomavirus vaccination.** *Vaccine* 2009, **27**(28):3690.
19. Melo Gomes S, Glover M, Malone M, Brogan P: **Vasculitis following HPV immunization.** *Rheumatology (Oxford)* 2012:2012. doi:10.1093/rheumatology/kes168.
20. Chang J, Campagnolo D, Vollmer TL, Bomprezzi R: **Demyelinating disease and polyvalent human papilloma virus vaccination.** *J Neurol Neurosurg Psychiatry* 2011, **82**(11):1296–1298.
21. McCarthy JE, Filiano J: **Opsoclonus Myoclonus after human papilloma virus vaccine in a pediatric patient.** *Parkinsonism Relat Disord* 2009, **15**(10):792–794.
22. Della Corte C, Carlucci A, Francalanci P, Alisi A, Nobili V: **Autoimmune hepatitis type 2 following anti-papillomavirus vaccination in a 11-year-old girl.** *Vaccine* 2011, **29**(29–30):4654–4656.
23. Sutton I, Lahoria R, Tan IL, Clouston P, Barnett MH: **CNS demyelination and quadrivalent HPV vaccination.** *Mult Scler* 2009, **15**(1):116–119.
24. Tomljenovic L, Shaw AC: **Death after quadrivalent human papillomavirus (HPV) vaccination: causal or coincidental?** *Pharm Reg Affairs* 2012, **S12**:001. doi:104172/2167-7689S12-001.
25. Tomljenovic L, Shaw CA: **Mandatory HPV vaccination.** *JAMA* 2012, **307**(3):254. author reply 254–255.
26. Spinosa JP, Riva C, Biollaz J: **Letter to the editor response to the article of Luisa Lina Villa HPV prophylactic vaccination: the first years and what to expect from now, in press.** *Cancer Lett* 2011, **304**(1):70.
27. U.S. Food and Drug Administration Vaccines and Related Biological Products Advisory Committee (VRBPAC): *VRBPAC Background Document: Gardasil™ HPV Quadrivalent Vaccine. May 18, 2006 VRBPAC Meeting: [http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.pdf].*
28. Beller U, Abu-Rustum NR: **Cervical cancers after human papillomavirus vaccination.** *Obstet Gynecol* 2009, **113**(2 Pt 2):550–552.
29. Mello MM, Abiola S, Colgrove J: **Pharmaceutical companies' role in state vaccination policymaking: the case of human papillomavirus vaccination.** *Am J Public Health* 2012, **102**(5):893–898.

doi:10.1186/1750-9378-8-6
Cite this article as: Tomljenovic *et al.*: HPV vaccines and cancer prevention, science versus activism. *Infectious Agents and Cancer* 2013 **8**:6.

VRBPAC Background Document
Gardasil™ HPV Quadrivalent Vaccine
May 18, 2006 VRBPAC Meeting

1. Evaluation of the potential of Gardasil™ to enhance cervical disease in subjects who had evidence of persistent infection with vaccine-relevant HPV types prior to vaccination.

The results of exploratory subgroup analyses for study 013 suggested a concern that subjects who were seropositive and PCR-positive for the vaccine-relevant HPV types had a greater number of CIN 2/3 or worse cases as demonstrated in the following table:

Table 17. Study 013: Applicant's analysis of efficacy against vaccine-relevant HPV types CIN 2/3 or worse among subjects who were PCR positive and seropositive for relevant HPV types at day 1. [From original BLA, study 013 CSR, Table 11-88, p. 636] **Gardasil™ N=2717**					**Placebo N=2725**					
Endpoint	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	N (subgroup)	Number of cases	PY at risk	Incidence Rate per 100 person years at risk	Observed Efficacy	95% CI
HPV 6/11/16/18 CIN 2/3 or worse	156	**31**	278.9	11.1	137	**19**	247.1	7.7	-44.6%	<0.0, 8.5%

In Summary: Females who were positive for HPV 16 or 18 had a significant 44.6 % increased risk of developing cervical disease and cervical cancer **if they got HPV vaccine inoculations.** Consumers are not told of this risk and there is no recommendation for pretesting to see if one has had previous exposure to these HPVs before inoculation.

VRBPAC Meeting. *VRBPAC Background Document. Gardasil HPV Quadrivalent Vaccine.* May 18, 2006; 13-14. http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222B3.pdf. Accessed February 20, 2012.

COMMENT

Increased incidence of cervical cancer in Sweden: Possible link with HPV vaccination

LARS ANDERSSON

Abstract

The Centre for Cervical Cancer Prevention in Sweden has noted in its annual report a substantial increase in the incidence of invasive cervical cancer, especially during the two years 2014 and 2015. I have sub-grouped the data according to age, using the same statistical database of the National Board of Health and Welfare as used by the authors of the above-mentioned report. The increase in the incidence of cervical cancer was shown to be most prominent among women 20–49 years of age while no apparent increase was observed among women above 50. The FDA has noted in the clinical trials referred to it for marketing approval that women exposed to the human papilloma virus (HPV) prior to vaccination had an increase in premalignant cell changes compared with placebo controls. I discuss the possibility that HPV vaccination could play a role in the increase in the incidence of cervical cancer by causing instead of preventing cervical cancer disease in women previously exposed to HPV. A time relationship exists between the start of vaccination and the increase in the incidence of cervical cancer. The HPV vaccines were approved in 2006 and 2007, respectively and most young girls started to be vaccinated during 2012–2013.

Introduction

The Centre for Cervical Cancer Prevention (NKCx) in Sweden has noted in its annual report of 2017(1), which includes data upto 2016, a substantial increase in the incidence of invasive cervical cancer, especially during the years 2014 and 2015. An English translation of the increase in the incidence of cervical cancer is given in Table 1 (1:p 45).

The report states (translation):

> *"The age-standardised incidence of invasive cervical cancer in Sweden has increased substantially in the last two years (20%) and there is a statistically significant increase for the entire period 2005–2015. The incidence in Sweden for 2014–2015 is 11.5 per 100,000 women. The increase in the last two years can be seen in all counties except Södermanland, Skåne, Jämtland and Västerbotten. Substantial and statistically significant increases are seen for Östergötland, Jönköping, Blekinge, Halland, Värmland, Örebro and Dalarna, with an average yearly increase of 7%–8%. Tendencies of substantial increases are also seen for Uppsala, Gotland, Västmanland and Västerbotten with yearly average increases of 4% or more."*

Table 1

Age-standardised (according to the standard Swedish population in 2000) incidence of invasive cervical cancer (per 100,000 women)

County	2006 –2009	2010 –2013	2014 –2015	Average change 2005 – 2015 expressed as percentage	p value for trend
Sweden, total	9.71	9.56	11.49	1.7	0.03
Stockholm	11.59	9.87	10.59	-0.8	0.51
Uppsala	11.16	14.17	16.02	3.8	0.20
Södermanland	8.45	12.43	10.57	2.3	0.40
Östergötland	8.87	14.47	15.04	7.3	<0.05
Jönköping	5.33	8.38	11.17	6.4	0.04
Kronoberg	8.99	6.14	13.15	1.1	0.78
Kalmar	12.78	7.39	11.83	-2.4	0.50
Gotland	8.00	6.47	14.18	6.5	0.32
Blekinge	13.47	14.16	17.00	8.2	<0.05
Skåne	9.50	9.21	9.48	-1.6	0.22
Halland	8.84	10.78	11.47	7.4	0.04
Västra Götaland	8.96	7.98	11.04	1.4	0.55
Värmland	6.81	9.23	13.61	8.1	<0.01
Örebro	8.22	9.51	12.29	8.3	<0.05
Västmanland	9.19	10.60	11.31	4.1	0.07
Dalarna	8.08	8.70	13.93	7.8	0.01
Gävleborg	11.68	11.04	14.28	1.9	0.24
Västernorrland	7.61	5.57	11.59	-1.9	0.66
Jämtland	9.74	9.80	9.85	0.0	0.99
Västerbotten	7.39	9.36	8.94	4.0	0.06
Norrbotten	13.60	8.34	14.24	-0.6	0.86

The above information was gathered from the statistical database managed by the National Board of Health and Welfare in Sweden. The author of the report suggested that it is important to track the causes of the increase in the incidence of cervical cancer. However, no explanations were given for the increase in the incidence of cervical cancer by the NKCx in its annual report (1).

For analysis, I have sub-grouped the data according to age,

Author: **Lars Andersson** (lars.andersson2@outlook.com), Department of Physiology and Pharmacology, Karolinska Institutet, SE-171 77 Solna, SWEDEN

To cite: Andersson L. Increased incidence of cervical cancer in Sweden: Possible link with HPV vaccination. *Indian J Med Ethics*. Published online on April 30, 2018 DOI:10.20529/IJME.2018.037.

Manuscript Editor: Sandhya Srinivasan

using the statistical database of the National Board of Health and Welfare (the same database used in reference [1]). In addition, the relevant literature was surveyed to put the current data in perspective.

Results

The increase in the incidence of cervical cancer was shown to be most prominent among women 20–49 years of age while no apparent increase was observed among women above 50 (Figure 1). The number of cases in the 20–49-year group increased from 202 cases in 2006 to 317 cases in 2015 (an increase of 50%). In 2015, there were 1.9 million women in Sweden between 20–49 years of age according to Statistics Sweden (2). The incidence of cervical cancer is therefore 0.17% for women in the 20–49-year group (317 cases per 1.9 million women). Figure 2 shows the relative change between 2006 and 2015 for each 10-year age group cohort, which illustrates the more pronounced increase in the incidence of cancer among the younger age groups.

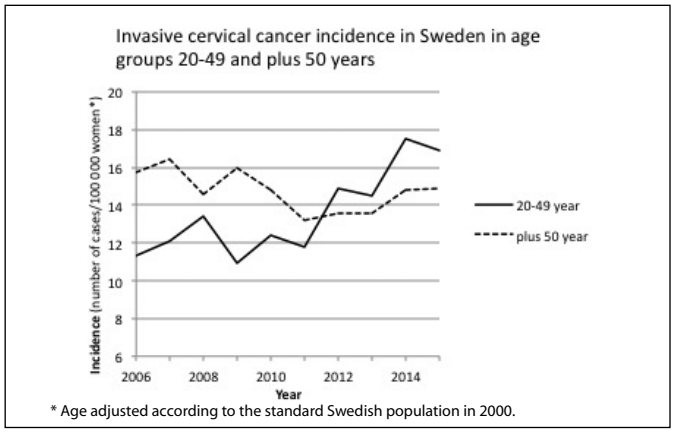


Fig. 1: Increase in incidence of cervical cancer among younger women (<50 years) as compared with women ≥50 years. The data shows the number of cases/100,000 women from 2006 to 2015.

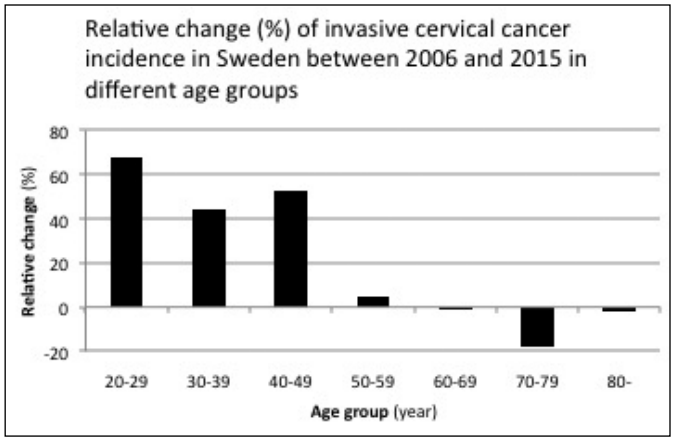


Fig. 2: The relative change in percentage of invasive cervical cancer incidence in Sweden between 2006 and 2015 in different age groups. The figure is based on data from the statistical database of the National Board of Health and Welfare in Sweden. The incidence of cancer is age-adjusted according to the standard Swedish population in 2000.

Discussion

I discuss below some possible explanations for the increase in the incidence of cervical cancer among young women in Sweden.

A change in the routine or other technical or methodological changes during the study period may affect the reported incidence of cervical cancer due to changes in the sensitivity of the diagnostic tools. The reported change in the incidence among younger women and the fact that the increase was noted in most counties in Sweden argue against this explanation. Neither was such an explanation given by the NKCx in Sweden in its annual report of 2017, with data up to 2016 (1). Recently, when the Swedish media discussed the increase in the incidence of cervical cancer, health authorities were unable to explain the increase.

Another possibility is that HPV vaccination could play a role in the increase in the incidence of cervical cancer. About 25% of cervical cancers have a rapid onset of about 3 years including progression from normal cells to cancer (3,4). Therefore, an increase may be seen within a short period of time. Gardasil was approved in Sweden in 2006. In 2010, the vaccination of a substantial number of girls started. In 2010, about 80% of the 12-year-old girls were vaccinated. Combined with 59% of the 13–18-year-old girls vaccinated through the catch-up programme in the same period, one can say that most girls were vaccinated. Thus, the oldest girls in the programme were 23 years old in 2015; and this is well within the younger age group shown in Fig. 1. For the older age group represented in Fig. 1, data on exposure to vaccinations is not available. In 2012–2013, most young girls were vaccinated.

The vaccine does not need to initiate the cancer process. There is a possibility of the vaccine acting as a facilitator in an ongoing cancer process. I discuss below some possible mechanisms of how the vaccine might influence the incidence of cervical cancer.

The efficacy of HPV-vaccines has been evaluated by studying premalignant cell changes in the cervix called CIN2/3 and cervical adenocarcinoma in situ or worse (5). The efficacy was calculated for individuals who have not been exposed to HPV 16 and 18. These individuals are called naïve. The vaccine is efficacious only in individuals not previously exposed to HPV 16 and 18 (naïve individuals). If an individual has already been exposed to HPV 16 and 18, no new antibodies are made. Therefore, the vaccine will not work for non-naïve individuals. HPV 16 and 18 are responsible for about 70% of all cervical cancers (5). It is therefore crucial to give the vaccine to naïve individuals. During their review of Gardasil by the FDA, the efficacy of the vaccine was also evaluated on individuals who were exposed to the oncogenic HPV strains before vaccination since individuals who are non-naïve will also receive the vaccination. A concern was raised for disease enhancement (increase in CIN 2/3, cervical adenocarcinoma *in situ* or worse) in this subgroup (5). In these individuals, the efficacy was -25.8% (95% CI: -76.4, 10.1%) (5). Thus, vaccination with Gardasil

of non-naïve individuals who had HPV 16/18 oncogenes before vaccination showed a higher level of premalignant cell changes than did placebo. The FDA statisticians could not draw any firm conclusions. In their analysis, the FDA included only cases with HPV 16/18. If cases with oncogenes other than HPV 16/18 had been included in the analysis, the efficacy of data could have been even more unfavourable.

The increase in premalignant cell changes in non-naïve individuals, as suggested by the FDA, is consistent with the knowledge that vaccination can cause reactivation of both target and non-target viruses (6–12). For Gardasil, the HPV types 16 and 18 are called target HPVs since the vaccine contains antigens for these two HPV types. Other HPV types for which the vaccine does not contain any antigens are called non-target HPVs. For individuals exposed to Gardasil, evidence of a selective and significant reactivation of the oncogenic non-target HPV types 52 and 56 was reported in the genital tract for all women (13). This article studied women 13–22 and 23–40 years of age from 2008 to 2013. The target HPVs 16 and 18 decreased only in the younger age group but oncogenic non-target HPVs increased in both the groups, 20%–40% and 8%–30%, respectively. The increase in the total burden of non-target oncogenic HPVs for vaccinated individuals may be consistent with the findings in the FDA report where the efficacy of the HPV vaccine was less favourable for non-naïve women compared with those on placebo. A possible mechanism to explain the increased incidence of cervical cancer may therefore be virus reactivation as described above.

In the evaluation of Gardasil by the FDA, it was found that about 25% of all individuals were non-naïve in the pivotal trial (5). There are more than 200 types of HPVs, of which 12 are currently classified as high-risk cancer types (14). HPV may be found in non-sexually active girls (15). It may be transmitted through non-sexual means, either by way of mother to child, from contact with infected items, from self-inoculation or hospital-acquired infection (16), or via blood (17,18). The virus can lie latent in any tissue and escape detection by standard techniques (19). It can also be redistributed systemically during the lytic cycle into previous virus-free tissues (auto-inoculation), for example infecting an earlier virus-free cervix. Recently, it was shown that previously HPV-positive women with normal cytology remained at increased risk of pre-neoplasia (CIN3) despite two follow-up HPV-negative tests (20). "Proving that HPV is absolutely gone is, of course, impossible," state Brown and Weaver in an editorial in 2013 (21). Therefore, non-naïve-individuals can be seen among females at all ages. Sometimes these individuals have measurable HPV and sometimes not. When taking these results into account, the proportion of non-naïve individuals may be underestimated in the studies.

Since the vaccine is recommended for up to 45 years in the European Economic Area, it is possible that the vaccination has facilitated the development of new or existing cervical cancer among women who were non-naïve at the time of vaccination. Vaccination against HPV has started in Sweden during the study period. Gardasil, the vaccine mostly used in Sweden, was approved in September 2006. There are no statistics for the overall use of Gardasil in Sweden. For young girls (12–13 years of age) there are special programmes for vaccination. About 75%–80% of all girls are vaccinated in this age group (22). For older girls there are catch-up programmes. For older girls/women who will be vaccinated on-demand, data on frequency of vaccination are missing. The increase in the incidence of cervical cancer between 2006 and 2015 was 50% (corresponding to 115 absolute cases). Therefore, the vaccination coverage of the Swedish population does not need to be very high to explain a role for the vaccine. The findings could be consistent with on-demand vaccination of women above 18. In Sweden there were 702,946 cervical cell screenings performed on women aged 23–60 years in 2016 (1).

Could the HPV vaccination cause an increase in invasive cervical cancer instead of preventing it among already infected females and thereby explain the increase in the incidence of cancer reported by the NKCx in Sweden? The increased incidence among young females, the possibility of virus reactivation after vaccination, the increase in premalignant cell changes shown by the FDA for women who were already exposed to oncogenic HPV types and the time relationship between the start of vaccination and the increase in cervical cancer in Sweden could support this view. The answer to this question is vital for correctly estimating the benefit-risk of this vaccine. More studies focused on already HPV-infected individuals are needed to solve this question.

***Conf ict of interest**: None declared.*

References

1. Nationellt Kvalitetsregister för Cervixcancerprevention (NKCx), Center för Cervixcancerprevention [cited 2018 Mar 22]. Available from: http://nkcx.se/templates/_rsrapport_2017.pdf [Swedish]
2. Statistics Sweden [cited 2018 Mar 22]. Available from: http://www.statistikdatabasen.scb.se/pxweb/sv/ssd/START__BE__BE0101__BE0101A/BefolkningR1860/?rxid=f45f90b6-7345-4877-ba25-9b43e6c6e299
3. Bain RW, Crocker DW. Rapid onset of cervical cancer in an upper socioeconomic group. *Am J Obstet Gynecol*. 1983;146(4):366–71.
4. Hildesheim A, Hadjimichael O, Schwartz PE, Wheeler CM, Barnes W, Lowell DM, Willett J, Schiffman M. Risk factors for rapid-onset cervical cancer. *Am J Obstet Gynecol*. 1999;180(3 Pt 1):571–7.
5. FDA Gardasil Clinical Review 2006[cited 2018 Mar 22]. Available from; http://www.impfkritik.de/download/gardasil_fda_464_pages.pdf (pp. 359-360)
6. Walter R, Hartmann K, Fleisch F, Reinhart WH, Kuhn M. Reactivation of herpesvirus infections after vaccinations *Lancet*. 1999;353(9155):810.
7. Bayas JM, González-Álvarez R, Guinovart C. Herpes zoster after yellow fever vaccination. *J Travel Med*. 2007;14(1):65–6.
8. Rothova A, de Groot JD, Mudrikova T. Reactivation of acute retinal necrosis after flu H1N1 vaccination. *Br J Ophthalmol*. 2011;95(2):291. doi: 10.1136/bjo.2010.185983. Epub 2010 Aug 23.
9. Hwang CW Jr, Steigleman WA, Saucedo-Sanchez E, Tuli SS. Reactivation of herpes zoster keratitis in an adult after varicella zoster vaccination. *Cornea*. 2013 Apr;32(4):508–9. doi: 10.1097/ICO.0b013e318277acae.
10. Hassman LM, DiLoreto Jr DA. Immunologic factors may play a role in herpes simplex virus 1 reactivation in the brain and retina after influenza vaccination. *IDCases*. 2016 Sep 22;6:47–51. eCollection 2016.
11. Jastrzebski A, Brownstein S, Ziai S, Saleh S, Lam K, Jackson WB. Reactivation of herpes zoster keratitis with corneal perforation after zoster vaccination. *Cornea*. 2017 Jun;36(6):740–2. doi: 10.1097/

ICO.0000000000001203.
12. Lieberman A, Curtis L. HSV2 reactivation and myelitis following influenza vaccination. *Hum Vaccin Immunother*. 2017 Mar 4;13(3):572–3. doi: 10.1080/21645515.2016.1235105.
13. Söderlund-Strand A, Uhnoo I, Dillner J. Change in population prevalences of human papillomavirus after initiation of vaccination: The high-throughput HPV monitoring study. *Cancer Epidemiol Biomarkers Prev*. 2014 Dec;23(12):2757–64. doi: 10.1158/1055-9965.EPI-14-0687. Epub 2014 Nov 7.
14. Human papillomavirus vaccines. WHO position paper, May 2017 [cited 2018 Mar 22]. Available from: http://www.who.int/wer
15. Hamsikova E, Smahelova J, Ludvikova V, Salakova M, Rychla J, Skrenkova J, Rob L, Tachezy R. The prevalence of HPV infections in HPV-vaccinated women from the general population. *APMIS*. 2017 Jun;125(6):585–95. doi: 10.1111/apm.12677. Epub 2017 Mar 15.
16. Ryndock EJ, Meyers C. A risk for non-sexual transmission of human papillomavirus? *Expert Rev Anti Infect Ther*. 2014 Oct;12(10):1165–70. doi: 10.1586/14787210.2014.959497.
17. Bodaghi S, Wood LV, Roby G, Ryder C, Steinberg SM, Zheng ZM. Could human papillomaviruses be spread through blood? *J Clin Microbiol*. 2005;43(11):5428–34.
18. Chen AC, Keleher A, Kedda MA, Spurdle AB, McMillan NA, Antonsson A. Human papillomavirus DNA detected in peripheral blood samples from healthy Australian male blood donors. *J Med Viro*l. 2009 Oct;81(10):1792–6. doi: 10.1002/jmv.21592.
19. Freitas AC, Mariz FC, Silva MA, Jesus AL. Human papillomavirus vertical transmission: review of current data. *Clin Infect Dis*. 2013 May;56(10):1451–6. doi: 10.1093/cid/cit066. Epub 2013 Feb 7.
20. Polman NJ, Veldhuijzen NJ, Heideman DAM, Snijders PJF, Meijer CJLM, Berkhof J. HPV-positive women with normal cytology remain at increased risk of CIN3 after a negative repeat HPV test. *Br J Cancer.* 2017 Nov 7;117(10):1557–61. doi: 10.1038/bjc.2017.309. Epub 2017 Sep 7.
21. Brown DR, Weaver B. Human papillomavirus in older women: new infection or reactivation? *J Infect Dis.* 2013 Jan 15;207(2):211–12. doi: 10.1093/infdis/jis662. Epub 2012 Dec 12.
22. The Public Health Agency of Sweden [cited 2018 Mar 22]. Available from: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistikdatabaser-och-visualisering/vaccinationsstatistik/statistik-for-hpv-vaccinationer/

Sin Hang Lee, MD
Milford Hospital

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.

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.

Primary author: Scott S. Field, MD
January 2016

References:

1. Colafrancesco S, Perricone C, Tomljenovic L, Shoenfeld Y. Human papilloma virus vaccine and primary ovarian failure: another facet of the autoimmune/inflammatory syndrome induced by adjuvants. *Am J Reprod Immunol*. 2013; 70:309-316.
2. Little DT, and Ward HR. Adolescent premature ovarian insufficiency following human papillomavirus vaccination: a case series seen in general practice. *J Inv Med High Imp Case Rep.* 2014; doi: 10.1177/2324709614556129, pp 1-12.
3. Wise LD, Wolf JJ, Kaplanski CV, Pauley CJ, Ledwith BJ. Lack of effects on fertility and developemental toxicity of a quadrivalent HPV vaccine in Sprague-Dawley rats. *Birth Defects Res B Dev*. 2008; 83(6):561-572.
4. Segal L, Wilby OK, Willoughby CR, Veenstra S, Deschamps M. Evaluation of the intramuscular administration of *Cervarix*™ vaccine on fertility, pre- and post-natal development in rats. *Reprod Toxicol*. 2011; 31:111-120.

5. Information available through http://wonder.cdc.gov/vaers.html
6. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/excipient-table-2.pdf
7. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111287.pdf , p. 373.
8. Vichnin M, Bonanni P, Klein NP, Garland SM, Block SL, Kjaer SK, et. al. An overview of quadrivalent human papillomavirus vaccine safety – 2006 to 2015. *Pediatr Inf Dis J*. 2015; doi: 10.1097/INF.0000000000000793, pp 1-48.
9. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111287.pdf, p. 394, 396.

Other key features of the ADRs reported with HPV vaccines are the diversity of the symptoms and their development in a multi-layered manner over an extended period of time. The ADRs include c consciousness; systemic pain, including headache, myalgia, arthralgia, back pain and other pain; motor dysfunction, such as paralysis, muscular weakness, exhaustion and involuntary movements including dizziness, hypotension, tachycardia, nausea, vomiting and diarrhoea; respiratory dysfunction, including dyspnoea and asthma; endocrine disorders, such as menstrual disorder ar n symptoms, such as anxiety, frustration, hallucinations and overeating; higher brain dysfunction and cognitive impairments, including memory impairment, disorientation and loss of concentr n In some cases, these symptoms impair learning and result in extreme fatigue and decreased motivation, having a negative impact on everyday life (**8**, **9**, **10**, **11**). The situation in Japan is similar to t serious and complex symptoms that develop across multiple body systems over an extended period of time (**12**, **13**).

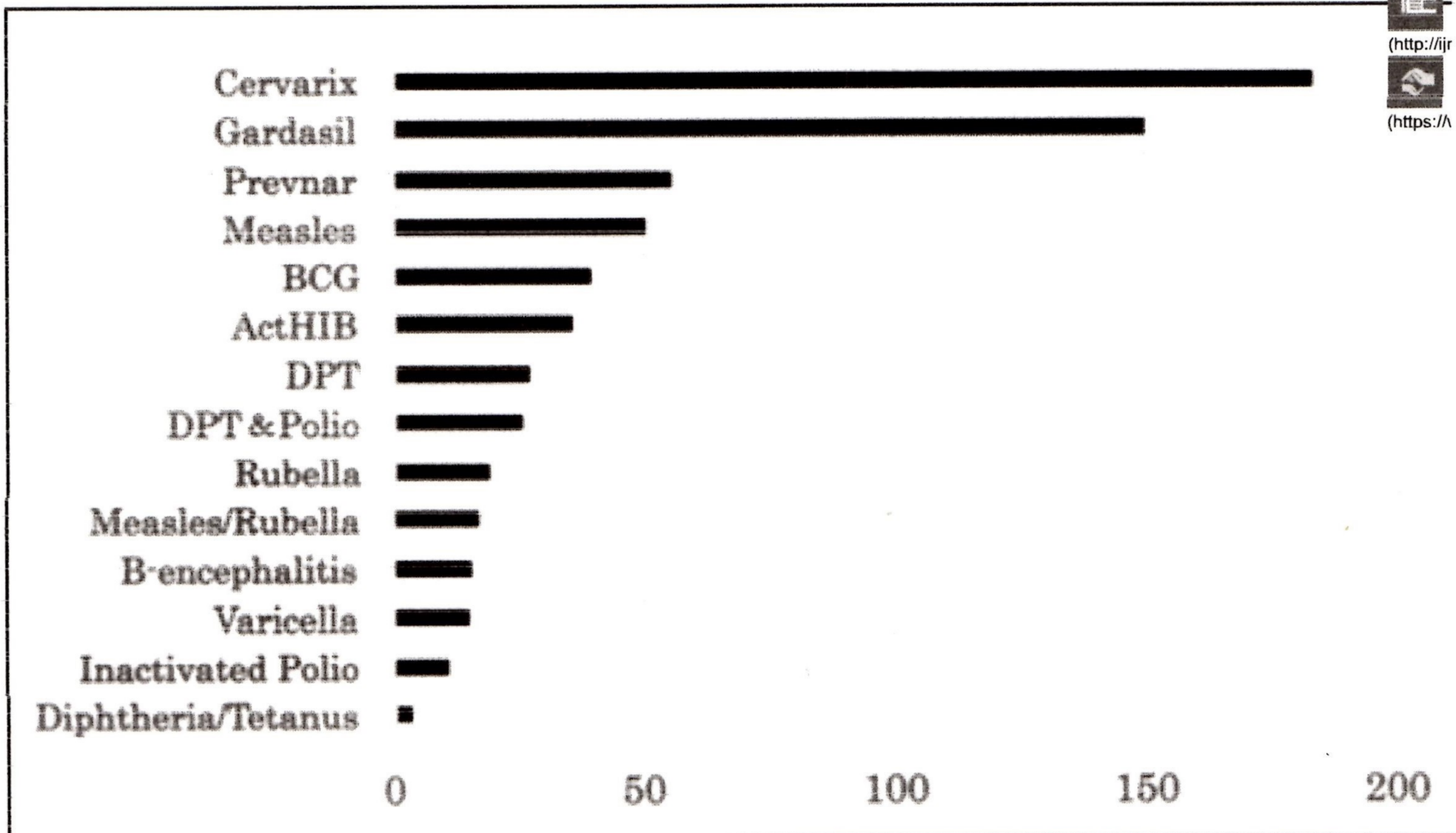


Fig. 1: Severe ADRs from HPV vaccines and other vaccines in Japan. Data sourced from the national adverse events following immunisation (AEFI) registry in 2013–2016. (ADRs/106inoculations, Bacillus Calmette–Guerin; DPT: diphtheria–pertussis–tetanus

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.

PUBLISHED RULING ON REMAND FINDING ENTITLEMENT[1]

Clinical Research and Trials

Case Report ISSN: 2059-0377

Cardiac arrest following HPV Vaccination

Shani Dahan[1-3], Yahel Segal[1,2], Amir Dagan[3], Yehuda Shoenfeld[1,2,4*], Michael Eldar[5] and Darja Kanduc[6]

[1]Zabludowicz Center for Autoimmune Diseases Sheba Medical Center, Tel-Hashomer, Israel

[2]Sackler Faculty of Medicine, Tel Aviv University, Israel

[3]Department of medicine 'B', Assuta Ashdod Medical Center, Ashdod, Israel, affiliated with Ben-Gurion University of the Negev

[4]Incumbent of the Laura Schwarz-Kipp chair for research of autoimmune diseases, Sackler Faculty of Medicine, Tel Aviv University, Israel

[5]The Neufeld Cardiac Research Institute, The Heart Institute, Chaim Sheba Medical Center, Ramat Gan, Israel.

[6]Department of Biosciences, Biotechnologies and Biopharmaceutics, University of Bari, Bari, Italy

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.

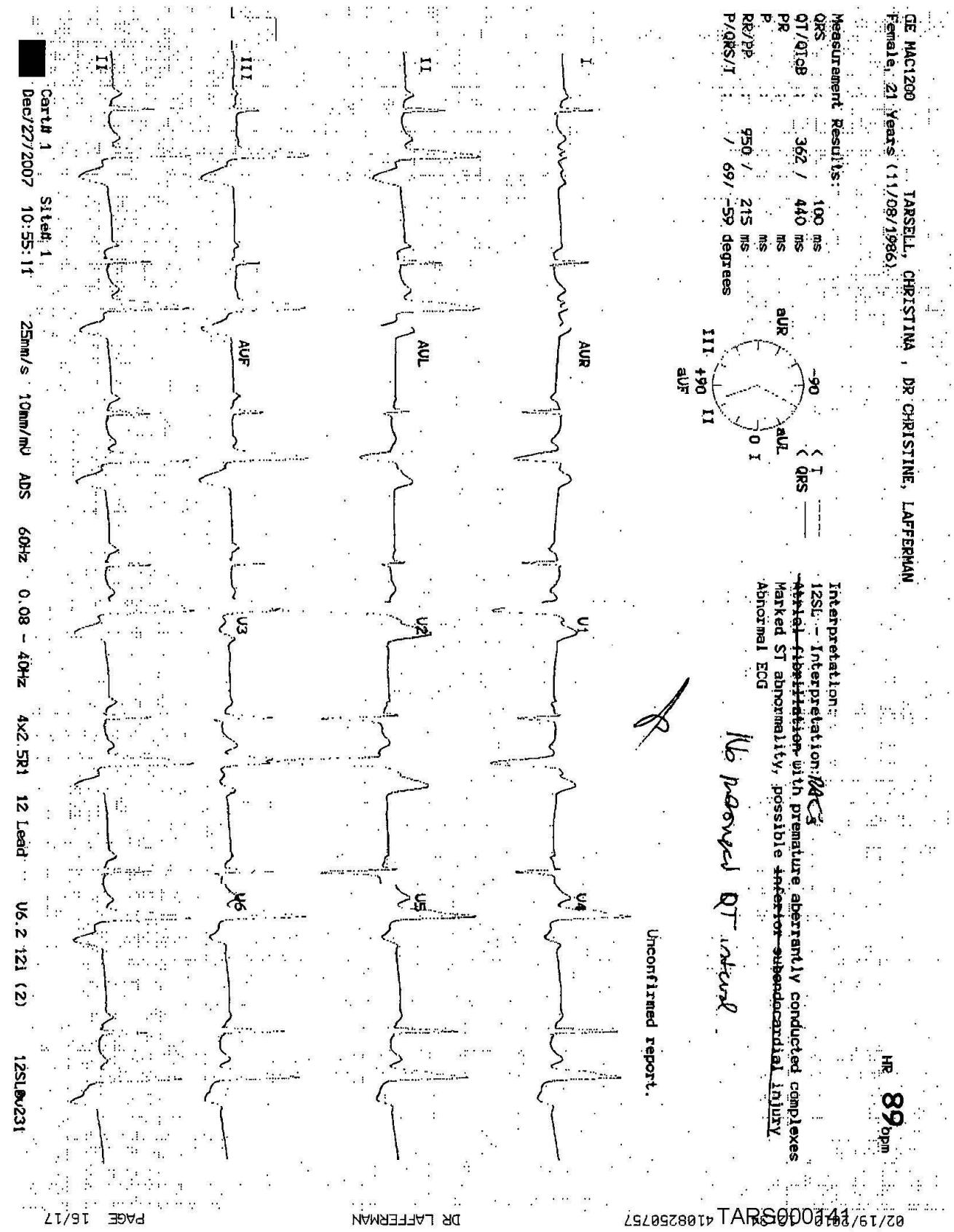
The median time from the last HPV vaccination to death was 14.5 days, a time-frame consistent with our case, in which the death occurred less than three weeks after HPV vaccine administration. We have conducted a search in the VAERS database in order to evaluate the current number of death cases related 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

Correspondence to: Yehuda Shoenfeld MD, FRCP, MaACR, The Zabludowicz Center for Autoimmune Diseases, Chaim Sheba Medical Center, Tel-Hashomer 52621, Israel, Tel: 972-3-5308070; Fax: 972-3-5352855; E-mail: shoenfel@post.tau.ac.il

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

Received: September 23, 2019; **Accepted:** October 03, 2019; **Published:** October 07, 2019


GE MAC1200
TARSELL, CHRISTINA , DR CHRISTINE, LAFFERMAN
Female, 21 Years (11/08/1986)
HR 89 bpm
Measurement Results:
QRS 100 ms
QT/QTcB 362 / 440 ms
PR ms
P ms
RR/PP 950 / 215 ms
P/QRS/T / 69 / -59 degrees
Interpretation:
12SL - Interpretation: MAC3
Marked ST abnormality, possible inferior subendocardial injury
Abnormal ECG
No prolonged QT interval.
Unconfirmed report.
02/19/2010 10:54
41082507S7
TARS000141
DR LAFFERMAN
PAGE 16/17
Cart# 1
Site# 1
Dec/27/2007 10:55:11
25mm/s 10mm/mV ADS 60Hz 0.08 - 40Hz 4x2.5R1 12 Lead V6.2 121 (2) 12SLNv231

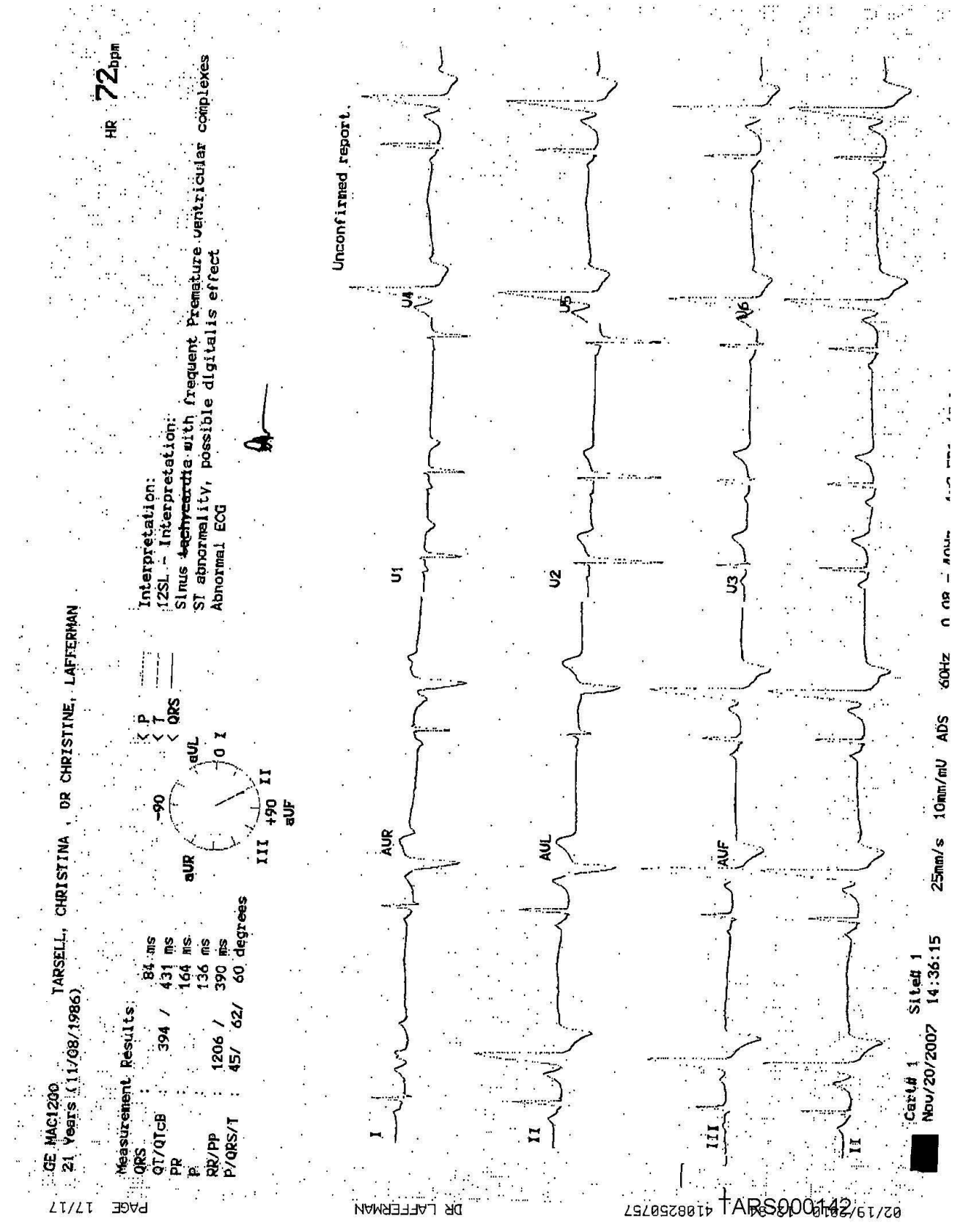


Figure 1. ECG showing frequent premature ventricular complexes and ST abnormalities

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.

References

1. Agmon-Levin N, Paz Z, Israeli E, Shoenfeld Y (2009) Vaccines and autoimmunity. *Nature Reviews Rheumatology* 11: 648.
2. Segal Y, Calabrò M, Kanduc D, Shoenfeld Y (2017) Human papilloma virus and lupus: the virus, the vaccine and the disease. *Curr Opin Rheumatol* 29: 331-342.
3. Guimaraes LE, Baker B, Perricone C, Shoenfeld Y (2015) Vaccines, adjuvants and autoimmunity. *Pharmacol Res* 100: 190-209.
4. Tommasino M (2014) The human papillomavirus family and its role in carcinogenesis. Seminars in cancer biology, Elsevier.
5. Iversen OE, Miranda MJ, Ulied A, Soerdal T, Lazarus E, et al. (2016) Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women. *JAMA* 316: 2411-2421. [Crossref]
6. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, et al. (2007) Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *New England Journal of Medicine* 356: 1928-1943.
7. Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, et al. (2009) Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 302: 750-757. [Crossref]
8. http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_ppi.pdf
9. Dahan S, Tomljenovic L, Shoenfeld Y (2016) Postural Orthostatic Tachycardia Syndrome (POTS)--A novel member of the autoimmune family. *Lupus* 25: 339-342.
10. Tomljenovic L, Shaw CA (2013) Human papillomavirus (HPV) vaccine policy and evidence-based medicine: Are they at odds? *Ann Med* 45: 182-193.
11. Lee SH (2012) Detection of human papillomavirus L1 gene DNA fragments in postmortem blood and spleen after Gardasil® vaccination-A case report. *Advances Biosc Biotech* 3: 1214-1224.
12. Lee SH (2012) Detection of human papillomavirus (HPV) L1 gene DNA possibly bound to particulate aluminum adjuvant in the HPV vaccine Gardasil. *J Inorg Biochem* 112: 85-92.
13. Lee SH (2013) Topological conformational changes of human papillomavirus (HPV) DNA bound to an insoluble aluminum salt-A study by low temperature PCR. *Advances Biol Chem* 3: 76-85.
14. http://www.who.int/vaccines/en/olddocs/humanpapill.html
15. Merck Research LaboratoriesGARDASIL® (2010) Human Papillomavirus [Types 6, 11, 16, 18] Recombinant Vaccine). Vaccines and Related Biological Products Advisory Committee (VRBPAC) Briefing Document. Presented to VRBPAC on 17th November 2010.
16. https://www.ema.europa.eu/en/documents/product-information/gardasil-epar-product-information_en.pdf
17. Caulfield MJ, Shi L, Wang S, Wang B, Tobery TW, et al. (2007) Effect of alternative aluminum adjuvants on the absorption and immunogenicity of HPV16 L1 VLPs in mice. *Hum Vaccin* 3: 139-145. [Crossref]
18. Sparwasser T, Miethke T, Lipford G, Erdmann A, Hacker H, et al. (1997) Macrophages sense pathogens via DNA motifs: induction of tumor necrosis factor-alpha-mediated shock. *Eur J Immunol* 27: 1671-1679.
19. Kumar A, Paladugu B, Mensing J, Parrillo JE (2007) Nitric oxide-dependent and -independent mechanisms are involved in TNF-alpha -induced depression of cardiac myocyte contractility. *Am J Physiol Regul Integr Comp Physiol* 292: R1900-R1906.
20. Pomara C, Neri M, Bello S, Pennella A, Turillazzi E, et al. (2010) TNF-alpha and interleukin myocardial expression in a case of fatal sudden cardiac failure during clinic reactivation of systemic lupus erythematosus. *Lupus* 19: 1246-1249.
21. Quinaglia ESJC, Coelho-Filho OR, Andrade JM, Quinaglia T, Modolo RG, et al. (2013) Peri-Infarct Zone Characterized by Cardiac Magnetic Resonance Imaging is Directly Associated with the Inflammatory Activity During Acute Phase Myocardial Infarction. *Inflammation*.
22. Emura I, Usuda H (2011) Biochemical, cytological and histopathological examination of sudden unexpected death in infancy. *Pathol Int* 61: 469-474.
23. Kanduc D (2011) Potential cross-reactivity between HPV16 L1 protein and sudden death-associated antigens. *J Exp Ther Oncol* 9: 159-165.

24. Gerull B, Heuser A, Wichter T, Paul M, Basson CT, et al. (2004) Mutations in the desmosomal protein plakophilin-2 are common in arrhythmogenic right ventricular cardiomyopathy. *Nat Genet* 36: 1162-1164.

25. Syrris P, Ward D, Evans A, Asimaki A, Gandjbakhch E, et al. (2006) Arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in the desmosomal gene desmocollin-2. *Am J Hum Genet* 79: 978-984.

26. Corrado D, Basso C, Buja G, Nava A, Rossi L, et al. (2001) Right bundle branch block, right precordial st-segment elevation, and sudden death in young people. *Circulation* 103: 710-717. [Crossref]

27. Cho Y, Park T, Yang DH, Park HS, Chae J, et al. (2003) Arrhythmogenic right ventricular cardiomyopathy and sudden cardiac death in young Koreans. *Circ J* 67: 925-928. [Crossref]

28. Nucifora G, Benettoni A, Allocca G, Bussani R, Silvestri F (2008) Arrhythmogenic right ventricular dysplasia/cardiomyopathy as a cause of sudden infant death. J Cardiovasc Med (Hagerstown) 9: 430-431.

29. Matsuo K, Kurita T, Inagaki M, Kakishita M, Aihara N, et al. (1999) The circadian pattern of the development of ventricular fibrillation in patients with Brugada syndrome. *Eur Heart J* 20: 465-470.

30. Paul M, Meyborg M, Boknik P, Gergs U, Schmitz W, et al. (2011) Autonomic dysfunction in patients with Brugada syndrome: further biochemical evidence of altered signaling pathways. *Pacing Clin Electrophysiol* 34: 1147-1153.

31. Kanduc D (2012) Peptide cross-reactivity: the original sin of vaccines. *Front Biosci* 4: 1393-1401.

32. Kanduc D (2009) Quantifying the possible cross-reactivity risk of an HPV16 vaccine. *J Exp Ther Oncol* 8: 65-76. [Crossref]

33. Trost B, Lucchese G, Stufano A, Bickis M, Kusalik A, et al. (2010) No human protein is exempt from bacterial motifs, not even one. *Self Nonself* 1: 328-334. [Crossref]

34. Trost B, Kusalik A, Lucchese G, Kanduc D (2010) Bacterial peptides are intensively present throughout the human proteome. *Self Nonself* 1: 71-74.

35. Gatto M, Agmon-Levin N, Soriano A, Manna R, Maoz-Segal R, et al. (2013) Human papillomavirus vaccine and systemic lupus erythematosus. *Clin Rheumatol* 32: 1301-1307.

36. Zafrir Y, Agmon-Levin N, Paz Z, Shilton T, Shoenfeld Y (2012) Autoimmunity following Hepatitis B vaccine as part of the spectrum of 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants' (ASIA): analysis of 93 cases. *Lupus* 21: 146-152.

HPV Vaccination Symposium: Providers Are The Key

Saturday, March 3, 2018

The Gathering Place
6120 Day Long Lane, Clarksville, MD 21029

9:30 – 10:00	**Registration**
10:00 – 10:15	**Welcome and Opening Remarks** TBD (Howard Haft, MD, MMM, CPE, FACPE, Maryland Department of Health)
10:15 – 11:15	**Overview of HPV and Related Cancers** Kevin Cullen, MD, University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center
11:15 – 12:00	**Increasing HPV Vaccination Rates: Introduction to Quality Improvement** Alix Casler, MD, FAAP, Chief of Pediatrics, Orlando Health Physicians Associates
12:00 – 12:45	**Lunch**
12:45 – 1:30	**Increasing HPV Vaccination Rates: Quality Improvement in Practice** Diana Fertsch, MD, FAAP, President, Maryland Chapter of the American Academy of Pediatrics
1:30 – 2:30	**Increasing HPV Vaccination Rates: A Panel of Perspectives** Susan Chaitovitz, MD, FAAP, Pediatrician, The Pediatric Center of Frederick Niharika Khanna, MD, MBBS, DGO, Associate Professor, Family and Community Medicine, University of Maryland School of Medicine Margo Watson, MD, Vice-chair, Department of Obstetrics/Gynecology, Howard County General Hospital Moderator: Anna McCrerey, MPH, Bureau Director, Cancer and Chronic Disease, Prevention and Health Promotion Administration, Maryland Department of Health
2:30 – 2:45	**Closing Remarks** TBD

MDAAP HPV Initiatives (2016-2017)

- SHIFT from education/CME to QUALITY IMPROVEMENT (QI)
- SHIFT from KNOWING to DOING
- Applied for district-wide QI Project (District 3 – NJ, MD, PA, DE, WDC, WVa)
- Awarded funding for MDAAP to enroll Maryland practices into a QI Project to Improve HPV Vaccination Rates

Announce

Really?
Don't Educate…
DO Manipulate?

Note **child's age.**

Announce the child is due for **3 vaccines** recommended for children this age, placing HPV vaccine in **middle of list.**

Say you will vaccinate **today.**

Move on with the visit.

Physician Incentives

- Competition
- Wine
- Quality Bonus Structure

ORLANDO HEALTH