Oppose HB 87 / SB 135
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District 46

HB 87/SB135 is not about public health. Uptake of mandated teen vaccines in Maryland is already at **rates above 90%**. There is no public health crisis. Of the two optional vaccines, Flu and the HPV Vaccine, Gardasil, **Gardasil is the one specifically for the teen population. That is the real target of this bill**. But uptake of Gardasil is low for good reasons:

1. The CDC says that " half of all new HPV infections are in boys and girls aged 15-24." But they don't tell you that 95% of the time they clear on their own with no problem. They also don't tell you that those who are HPV positive at the time of inoculation with Gardasil actually **increase their risk of getting cervical cancer by more than 44%.** Clearly teens should **not be vaccinated** since if they have exposure already it will clear on its own 95% of the time and if they do not know they are HPV positive they are put at more risk of getting cervical cancer.

2. Published studies show that in ALL countries where uptake of HPV vaccines like Gardasil was high, **cervical cancer in the vaccinated population has sharply increased.**

3. There are reports of premature ovarian failure in girls who have been vaccinated. That means these girls can no longer have children. Thus, for some, vaccination is a form of sterilization.

4. The CDC acknowledges that seizures following Gardasil vaccination happen sometimes minutes, hours, days, or weeks later. Imagine the risk to a 16 year old that is unaccompanied by a parent or guardian when they could experience seizures or have a seizure while driving home after vaccination? And if the teen has seizures and the parent is unaware that their child was vaccinated, they would not know how to treat the problem or to report it.

5. A minor would not know that there are no studies regarding the safety of getting multiple vaccinations concurrently. Yet providers are being taught to give multiple vaccines along

with Gardasil. A minor is vulnerable to coercion or bullying by the provider to comply with this unethical practice.

6. If the minor had post vaccination adverse events including those from multiple inoculations, the parents would not know to file a claim in the Court of Federal Claims. Even if they did, the case would be thrown out if confounded by having received multiple vaccines concurrently.

It is clear this bill is not about public health or giving a minor a voice for self protection. It does just the opposite and puts the teen at greater risk for getting the very disease the vaccine is supposed to prevent. The bill would increase vaccine uptake, but not in the child's interest. It would be in the interest of those profiting from vaccine sales. Please look at the data I have provided and vote “No” on HB87/SB135.

Supporting Documents that Coincide with Points:

Document 1:

Holland, M. (2018). *The HPV Vaccine on Trial.* New York: Skyhorse Publishing.

Negative efficacy chart shows that if a female is HPV positive and gets Gardisil, it greatly increases her risk of getting precancerous lesions or cervical cancer.

Document 2:

Chart shows that in countries with high HPV Vaccine uptake, cervical cancer in the vaccinated population has increased sharply. This is only one chart from the UK but the same outcome has been found by Dr. Delepine in ALL countries with high uptake.

Documents 3 and 4:

Just two of several studies showing loss of fertility in some girls due to premature ovarian failure after HPV Vaccination.

Document 5:

This shows a concern about HPV Vaccines from the American Academy of Physicians.

The clinical trial results show this risk, which should have prompted Merck and GSK to strongly consider screening before vaccination, or prescreening. Instead, by recommending the vaccine for children who are sexually naive, this appeared to avoid the problem of so-called "negative efficacy."

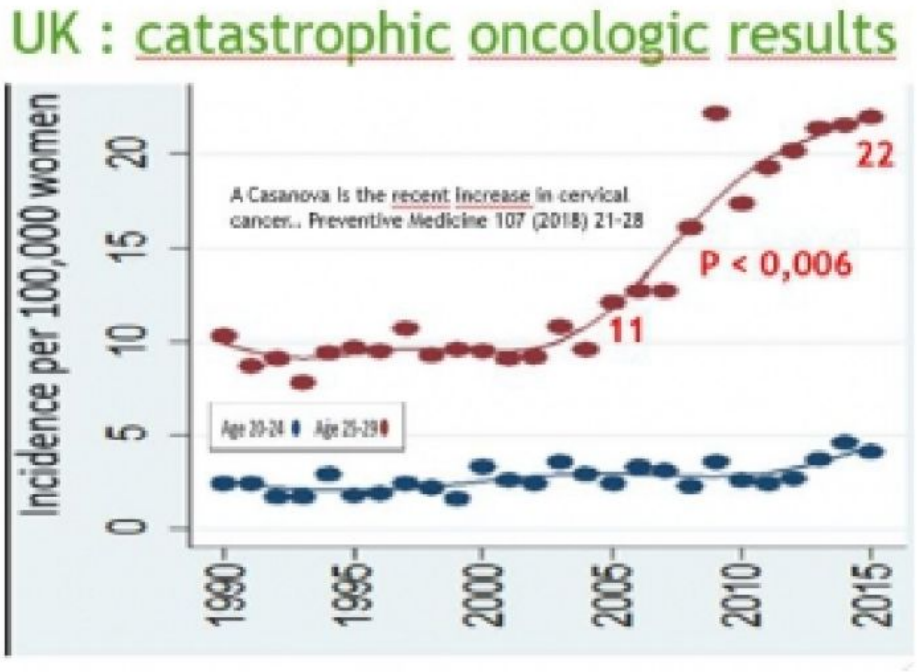
In the trials, Merck reported that women who had a current HPV 16 or 18 infection *and* evidence of prior exposure to those types on day 1 were *44.6 percent* more likely to develop CIN2 or CIN3 lesions or worse compared to the fauxcebo group, even within a few years of receiving the vaccine:[1]

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%

Negative Efficacy: Gardasil
Source May 2006 VRBPAC Background Document, at 13 (Table 17) (emphasis added).[2]

(nb: PCR positive means a positive HPV DNA test result, suggesting current infection; seropositive means testing positive for HPV antibodies in the blood, suggesting a prior exposure.)



SAME PARADOXICAL PHENOMENON OF GARDASIL IN SWEDEN : THE RATE OF CANCER INCREASES IN THE VACCINATED AGE GROUPS . *ALERT!*

PARADOXICAL EFFECT OF ANTI-HPV VACCINE GARDASIL ON CERVICAL CANCER RATE

State of published results in registers, on January 2019

Dr G Delépine, oncologist, surgeon

BMJ Case
Report

PDF Findings that shed new light on the possible pathogenesis of a disease or an adverse effect *Premature ovarian failure 3 years after menarche in a 16-year-old girl following human papillomavirus vaccination*

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Summary

Premature ovarian failure in a well adolescent is a rare event. Its occurrence raises important questions about causation, which may signal other systemic concerns. This patient presented with amenorrhoea after identifying a change from her regular cycle to irregular and scant periods following vaccinations against human papillomavirus. She declined the oral contraceptives initially prescribed for amenorrhoea. The diagnostic tasks were to determine the reason for her secondary amenorrhoea and then to investigate for possible causes of the premature ovarian failure identified. Although the cause is unknown in 90% of cases, the remaining chief identifiable causes of this condition were excluded. Premature ovarian failure was then notified as a possible adverse event following this vaccination. The young woman was counselled regarding preservation of bone density, reproductive implications and relevant follow-up. This event could hold potential implications for population health and prompts further inquiry.

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9

Human Papilloma Virus Vaccine and Primary Ovarian Failure: Another Facet of the Autoimmune/Inflammatory Syndrome Induced by Adjuvants

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Keywords Autoantibodies, autoimmune/inflammatory syndrome induced by adjuvants, autoimmunity, human papilloma virus, primary ovarian failure

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Post-vaccination autoimmune phenomena are a major facet of the auto- immune/inflammatory syndrome induced by adjuvants (ASIA) and vaccines, including HPV, have been identified as possible causes.

of study The medical history of three young women who presented with second- ary amenorrhea following HPV vaccination was collected. rd- ing type of vaccine, number of vaccination, personal, clinical and serological features, as well as response to treatments were analyzed.

All three patients developed secondary amenorrhea following HPV vacci- nations, which did not resolve upon treatment with hormone replace- apies. In all three cases sexual development was normal and genetic screen revealed no pertinent abnormalities (i.e., Turner's syn- drome, test were all negative). Serological evaluations showed low levels of estradiol and increased FSH and LH and in two cases, specific odies were detected (antiovarian and anti thyroid), suggesting that the HPV vaccine triggered an autoimmune response. Pelvic ultra- sound did any abnormalities in any of the three cases. All three patients experienced a range of common non-specific post-vaccine symp- toms including eadache, sleep disturbances, arthralgia and a range of cognitive and psychiatric disturbances. According to these clinical features, a diagnosis

y ovarian failure (POF) was determined which also fulfilled the required criteria for the ASIA syndrome.

Conclusion We documented here the evidence of the potential of the HPV vaccine to trigger a life-disal number of similar reports of post HPV vaccine-linked autoimmunity and the uncertainty of long-term cli of public health that warrants further rigorous inquiry.

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immediately

started to complain of burning and heavy sensation in the injected arm, followed by skin rash and fever. Nausea and stomach aches lasted for 2 days after the injection, while in the subsequent 2weeks, she further complained of cramping and headache. At the time of the second vaccine administration, she reported similar injection site related symptoms, accompanied by sleep disturbances, such as insomnia and night sweats. At the time of the third injection, the patient continued to experience the same symptoms: burning, pain and heavy sensation in the injected arm, headache and cramping. Insomnia associated with night sweats persisted and she started complaining of arthralgia, anxiety and depression. The patient reported that her last period occurred shortly after the last injection of the HPV vaccine. The hormonal screening showed the presence of increased follicle-stimulating hormone (FSH) and luteinizing hormone (LH) associated with very low levels of estradiol. Beta human chorionic gonadotropin (HCG) tested negative excluding pregnancy. The karyotype study was 46, XX, while molecular studies ruled out Fragile X syndrome and mutated follicle-stimulating hormone receptor (FSHR) gene. A pelvic ultrasound did not show any abnormality. According to these clinical and serological findings, POF diagnosis was determined. Even though the patient started therapy with medroxyprogesterone to stimulate bleeding, no improvement occurred and she continued to experience the same symptoms.

Introduction

Vaccines against human papilloma virus (HPV) are skin rash and fever. Nausea and stomach aches thought to represent a useful approach in the fight lasted for 2 days after the injection, while in the against cervical cancer. Although vaccines have pro- subsequent 2weeks, she further complained of ven to be a successful and cost-effective asset for pre- cramping and headache. At the time of the second ventive medicine, local or systemic adverse events, vaccine administration, she reported similar injection following vaccination, have been described. Specifi- site related symptoms, accompanied by sleep distur- cally, there are increasing reports that autoimmune bances, such as insomnia and night sweats. At the disorders can develop after vaccination.[1–4] At the time of the third injection, the patient continued to same extent, the association between infectious experience the same symptoms: burning, pain and agents exposure and the development of autoim- heavy sensation in the injected arm, headache and mune diseases is well established.[5,6] Recently, a new cramping. Insomnia associated with night sweats syndrome, namely the autoimmune/inflammatory persisted and she started complaining of arthralgia, syndrome induced by adjuvants (ASIA) or Shoen- anxiety and depression. The patient reported that feld's syndrome,[7–12] has been defined, alluding to the her last period occurred shortly after the last injec- key role of adjuvants in inducing autoimmunity. The tion of the HPV vaccine. The hormonal screening syndromes included in ASIA entail immune-medi- showed the presence of increased follicle-stimulating ated conditions that appear following a chronic stim- hormone (FSH) and luteinizing hormone (LH) asso- ulation of the immune system by agents with ciated with very low levels of estradiol. Beta human adjuvant characteristics.[7,10] Post-vaccination autoim- chorionic gonadotropin (HCG) tested negative mune phenomena represent a major issue of ASIA excluding pregnancy. The karyotype study was 46 and different vaccines, including the HPV vaccine, XX, while molecular studies ruled out Fragile X have been found as possible causes.[3,9,13] Primary syndrome and mutated follicle-stimulating hormone ovarian failure (POF) is a clinical condition with com- receptor (FSHR) gene. A pelvic ultrasound did not plex aetiology in which autoimmune mechanisms show any abnormality. According to these clinical represent 20–30% of the cases.[14] This assertion is and serological findings, POF diagnosis was supported by different evidences: the presence of determined. Even though the patient started therapy lymphocytic oophoritis, the detection of ovarian au- with medroxyprogesterone to stimulate bleeding, no toantibodies and the frequent association with other improvement occurred and she continued to experi- autoimmune diseases.[14] Herein, we describe three

ence abnormal vaginal bleeding, night sweats, hot clinical cases, including two sisters, who developed
flashes and sleep disturbances. POF following administration of the HPV vaccine. Genetic, metabolic and external
environmental fac- tors were excluded as POF causes, while the common

Case 2

denominator was the previous vaccination with HPV
This patient (the younger sister of the above- leading to the development of immune-mediated am-
mentioned case) received three administrations of enorrhoea.
the quadrivalent HPV vaccine at the age of 13 under the same protocol as her sister. At that time, she had

Case 1

normal growth and sexual development. The patient complained, 10 days after the first injection, of gen- A young
previously healthy girl received three
eral symptoms such as depression and sleep distur- administrations of the quadrivalent HPV vaccine (T0,
bances. She also experienced episodes of T1 after 4 months, T2 after 9 months) when she was
lightheadedness and tremulousness, anxiety, panic 14 years old. Six months before the first injection,
attacks and difficulties in focusing/concentrating in the patient had menarche. Her psycho-physical and
her school work. She had menarche at the age of sexual development were normal except that at the
15 years, followed by another period 1 month later time she received the first HPV vaccine dose, she
and none thereafter. Laboratory analysis showed was complaining of irregular periods (every
high serum levels of FSH and LH with undetectable 2 months). After the first vaccination, the patient
estradiol. The genetic test for Turner's syndrome,

vaccine Fragile X syndrome and FSHR gene was performed
manufacturer, the authors emphasized the and resulted negative. Interestingly, the patient
fact that the post-marketing reporting of vaccine tested positive for antiovarian antibodies. She under-
adverse events is voluntary and consequently, it is went a pelvic ultrasound without an evidence of
not always possible to reliably estimate the fre- abnormalities. In the light of these findings, a diag-
quency of such reactions, let alone to establish a nosis of POF was determined and the patient was
causal relationship to the vaccine. Further according treated with several different hormonal replacement
to the authors, there may potentially be a group for therapies with a poor therapeutic response.
whom the HPV vaccine is contraindicated and because the occurrence of POF carries major health

Case 3

implications, a long-term follow-up of ovarian func- tion in a cohort of HPV vaccinated woman should The patient
received the quadrivalent HPV vaccine
be undertaken.[15] in three administrations (T0, T1 after 2 months, T2
POF is a syndrome consisting of primary or sec- after 4 months) at the age of 21 years. Menarche
ondary amenorrhoea, hypergonadotropinemia and occurred when she was 13 years old with normal
hypoestrogenemia. POF affects 1% of women under monthly periods and a flow of 5−7 days, with mild
40 years of age, 0.1% under 30 and 0.01% of cramps. A normal sexual development was reported.
women under 20 years and it is an important cause Few months after the last injection of HPV vaccine,
of infertility and psychological stress.[14] POF in young she started complaining of irregular menses (off by

women can indeed have significant consequences 1–2 weeks) without an increase in bleeding or pain. for future health and prospects of motherhood. The The irregular periods worsened and the patient aetiology includes specific genetic mutations reported on menstruations every 3months with (referred to oocyte, enzymes or hormones receptors), bleeding only for 2 days. For this reason, she started autoimmune or environmental causes (such as viral drospirenone/ethinyl estradiol. Nonetheless, no infections, chemotherapy, radiotherapy and pelvic improvement occurred and after discontinuation of surgery) or metabolic disturbances.[14] The possible therapy, at the age of 23 years, she complained of autoimmune origin for POF has been speculated for amenorrhoea. The laboratory tests showed the pres- a long time,[16] and one of the evidence which sup- ence of very low levels of estradiol and increased ports this origin is its frequent association with other FSH and LH. Testosterone, cortisol and prolactin autoimmune diseases (i.e. thyroiditis, Addison's dis- serum level were found normal. Although the ease, autoimmune polyglandular syndrome, systemic thyroid hormones were also in the normal range, lupus erythematosus, Sjogren's syndrome, haemolyt- the patients had positive antithyroid peroxidise (TPO) ic anaemia and idiopathic thrombocytopenic pur- antibodies (134 IU/mL, n.v. 0–34). The karyotype pura).[17] The presence of autoantibodies reactive to evaluation and the search for Fragile X syndrome dis- different parts of the ovary has been detected in played no aberrations. A transvaginal and pelvic many POF cases and the most commonly recognized ultrasound did not reveal any abnormality. According autoantigens are on the ooplasm, theca, granulose, to these findings and clinical features, a diagnosis of corpus luteum or zona pellucida.[18–20] More specific POF was determined. Thus, a therapy with medroxy- antigenic targets of autoantibodies have been identi- progesterone and estradiol was attempted, however, fied in steroid cell enzymes including 3b-hydroxys- it did not improve her clinical condition. teroid dehydrogenase (3b-HSD), cytochrome P450 side-chain cleavage enzyme (P450SCC) and 17○-

Discussion

hydroxylase/17,20 lyase enzyme (CYP17A1).[14] Nonetheless, the detection of such antibodies has Herein, we have described three cases of POF follow- yielded conflicting results because of the different ing HPV vaccination. To the best of our knowledge, stages of disease in which the tests were conducted, an additional case of POF in a 16-year-old young methodological differences and the multiplicity of woman who was vaccinated with the quadrivalent potential immune targets. In our cases, only one of HPV recombinant vaccine has already been reported the three patients had positive antiovarian antibod- by Little and Ward.[15] In this case, as in our three ies. Given the difficulties in detecting these antibod- cases, no other possible causes of POF were identi- ies, an autoimmune origin of POF may be fied other than the HPV vaccine. Quoting the HPV speculated for the other two cases. Indeed, the pres-

Table I The Suggested Criteria of Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA)[7] in the Current Three Cases of Post-Human Papilloma Virus Vaccine Manifested Primary Ovarian Failure (POF). Note That for Positive Diagnosis of ASIA, Fulfilment of Either Two Major or One Major and Two Minor Criteria is Required

	Case 1	Case 2	Case 3
Major criteria			
1. Exposure to an external stimuli (infection, vaccine and/or immune adjuvants) prior to clinical manifestations	+	+	+
2. The appearance of 'typical' clinical manifestations;			
Myalgia, muscle weakness	À	À	Not reported
Arthralgia and/joint pain	+	À	À
Chronic fatigue, un-refreshing sleep or sleep disturbances	+	+	Not reported
Neurological manifestations	+	+	Not reported
Cognitive disturbances	À	+	Not reported
Pyrexia	À	À	À
3. Removal of inciting agent induces improvement	NA	NA	NA
4. Typical biopsy of involved organs	Not assessed	Not assessed	Not assessed
Minor criteria			
1. The appearance of autoantibodies (antiovarian, anti-TPO)	À	+	+
2. Other clinical manifestations (e.g. amenorrhoea)	+	+	+
3. Specific HLA (e.g. HLA DRB1, HLA DQB1)	Not assessed	Not assessed	Not assessed
4. Evolvement of an autoimmune disease (POF)	+	+	+

ence of antiovarian antibodies in the second case, in addition to the finding of the anti-TPO antibodies in the third case, lends support to the idea that autoim- mune responses underlying POF can develop follow- ing HPV vaccination. Moreover, as POF developed in two sisters, a genetic susceptibility predisposing to post-vaccination POF is probable. The very unusual early age of disease onset may reinforce this sugges- tion as it was already observed in other immune- mediated diseases.[21,22] Furthermore, the patients experienced not only POF but also a constellation of other symptoms, including arthralgia, sleep distur- bances and cognitive dysfunction, consistent with the diagnosis of the ASIA syndrome (Table I).[7,9]

POF as a Part of the ASIA Syndrome

The three cases of POF described herein clearly ful- filled the criteria for the ASIA syndrome (Table I). ASIA comprises a group of diseases including post- vaccination phenomena,[9,11,13] silicone implant− induced autoimmunity,[23] Gulf War syndrome,[24] macrophagic myofasciitis with chronic fatigue syndrome[25,26] and the sick-building syndrome[27] which share a common set of signs and symptoms. Shoenfeld and Agmon-Levin[7] proposed four major and four minor criteria for ASIA (Table I), and to diagnose ASIA, fulfilment of either two major or one major and two minor criteria is required. The criteria for ASIA enable the inclusion of patients with well-defined autoimmune diseases (i.e. multi- ple sclerosis, lupus) as well as those with ill-defined and non-specific yet clinically relevant conditions (i.e. myalgia, chronic fatigue and cognitive distur- bances) under the spectrum of vaccine adjuvant- associated conditions.[9] The inclusion of the latter category of manifestations under ASIA is of special importance as these non-specific manifestations are all too easily ignored or disregarded as irrelevant and non-vaccine related not only by patients and physi- cians, but also by scientists involved in design of vaccine trials.[28,29] Nonetheless, many ill-defined medical conditions that fall under the ASIA spec- trum are frequently disabling and thus of significant clinical relevance.[9,25]

Apart from a shared set of clinical manifestations, the other main common feature in ASIA is the pres- ence of an immune adjuvant. An adjuvant is defined as 'any substance that acts to accelerate, prolong or enhance antigen-specific immune response'.[24] The adjuvant is able to stimulate the immune system and to increase the response to a vaccine, without having any specific antigenic effect in itself.[24] Vaccines, which contain infectious antigens either attenuated or recombinant, may induce

autoimmunity by means of similar ‘infectious’ mechanisms such as molecular

vaccines mimicry, epitope spreading, bystander activation and
appear to be autoimmune neurological dis- polyclonal activation.[30,31] When this occurs, it can be
eases.[49,50] For instance, Sutton et al.[42] reported five subacute or sometimes a long time after the vaccina-
cases of female patients who developed a multifocal tion (i.e. months to years),[32–37] which leads to diffi-
or atypical demyelinating syndrome within 21 days culties in identifying a definite causality between
of immunization with the quadrivalent HPV vaccine. vaccination and autoimmune phenomena. The latter
As hypothesized by the authors, the temporal associ- will most commonly occur in genetically predisposed
ation with demyelinating events in these cases may individuals. Indeed, personal or familial susceptibility
be explained by the potent immune-stimulatory to autoimmunity and adverse response to a prior
properties of HPV virus-like particles which comprise dose of the vaccine both appear to be associated with
the vaccine. Similarly, Chang et al.[51] reported two a higher risk of post-vaccination autoimmunity.[3,9]
cases who developed CNS demyelination closely fol- lowing the administration of the HPV vaccine. Acute

HPV Vaccines and Autoimmunity

disseminated encephalomyelitis in young women (15 and 17 years old) within 3–8 weeks after HPV In the current
literature, there are numerous cases
vaccination has also been described.[52,53] Altogether, substantiating the link between adverse immune
these observations led to the hypothesis that the reactions and HPV vaccines, including fatal reactions.
HPV vaccine may have been released too quickly For example, Lee[38] recently reported a case of a
into the market, in the absence of rigorous safety teenage girl who underwent sudden unexpected
evaluations.[49,54,55] Indeed, Gardasil appears to have death approximately 6 months after her third Garda-
failed to meet a single one of the four criteria sil HPV vaccine booster. The patient experienced
required by the FDA for Fast Track approval.[54] adverse manifestations shortly after the first dose of Gardasil injection (i.e.
dizziness spells, paraesthesia and memory lapses) which were further exacerbated after the 2nd vaccine booster after
which she also

Adjuvants in HPV Vaccines and Assessment of HPV Vaccine Safety in Clinical Trials

developed excessive tiredness (indicative of chronic
One of the most commonly used adjuvant in vaccines fatigue), night sweats, loss of ability to use common
is aluminium[24] which is also present in HPV vaccines. objects, intermittent chest pain and sudden
There are two different brands of the HPV vaccine: the unexpected ‘racing heart’. Although the autopsy
quadrivalent Gardasil (MSD) and the bivalent Cer- examination failed to identify any toxicological,
varix (GSK). Both are composed of HPV L1 proteins microbiological or anatomical cause of death, further
that self-assemble to form virus-like particles but dif- investigations carried by Dr. Lee[39] showed that the
fer in the use of adjuvants.[56] While the first contains post-mortem blood and splenic tissues tested positive
only aluminium hydroxyphosphate sulphate, the sec- for HPV-16 L1 gene DNA fragments corresponding to
ond contains a combination of an oil-based adjuvant those previously found in 16 separate Gardasil vials

monophosphoryl lipid A (MPL) and aluminium hydroxide (a proprietary brand of the vaccine manufacturer otherwise known as ASO4), thus leading to diverse boosts in immune responses between the two HPV vaccines.[57] Another difference is the medium in which the vaccines are produced, *Trichoplusiani* cells for the Cervarix and *Saccharomyces cerevisiae* for the Gardasil. This distinction is even more intriguing because we know the potential of yeast to trigger autoimmune responses.[58] Nonetheless, a recent large observational study on the safety of the quadrivalent HPV vaccine allegedly identified no safety concerns.[59] However, several important biases might have contributed to the negative findings of the study. Firstly, the study included all women who received at least one dose of the vaccine, thus making most prevalent adverse events associated with this particular population less sensitive for the detection of serious adverse reactions (given that such events occur with much lesser frequency when fewer doses of the vaccine are administered). Secondly, the study was entirely funded by the quadrivalent HPV vaccine manufacturer Merck and all authors received previous founding from Merck and/or were consultants for the HPV vaccine manufacturer.[59]

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Additionally, thus far HPV vaccination has been linked to several autoimmune diseases, including Guillain-Barr´e syndrome,[41] other demyelinating neuropathies,[42–44] systemic lupus erythematosus,[3] pancreatitis,[45] vasculitis,[46] thrombocytopenic purpura[47] and autoimmune hepatitis.[48] Of note, the HPV vaccine allegedly identified no autoimmune safety concerns.[59] However, several important biases might have contributed to the negative findings of the study. Firstly, the study included all women who received at least one dose of the vaccine, thus making most prevalent adverse events associated with this particular population less sensitive for the detection of serious adverse reactions (given that such events occur with much lesser frequency when fewer doses of the vaccine are administered). Secondly, the Injury Compensation Program. LT, SC and CP research team failed to recruit appropriate expertise for diagnosis of autoimmune disorders. Namely, no immunologist/autoimmunologist, neurologist and ophthalmologist were present during the initial screening of the study participants which is particularly surprising in view of the fact that autoimmune conditions of interest that were examined included rheumatological, autoimmune disorders and neurological/ophthalmic conditions.[29,59] Finally, the Safety Review Committee failed to take into account the fact that autoimmune manifestations may be non-specific and not fitting a well-defined autoimmune condition[9,25,28] yet severely disabling.[26,35,60] Of note, the study was entirely funded by the quadrivalent HPV vaccine manufacturer Merck and all authors received previous founding from Merck and/or were consultants for the HPV vaccine manufacturer.[59]

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Finally, a further major bias in evaluating HPV vaccine safety comes from the fact that in all clinical trials for both Gardasil and Cervarix, safety outcomes were compared between vaccine recipients and those who received an aluminium adjuvant containing 'placebo'.[49,50] This practice is common in vaccine trials,[61] despite much evidence showing that alumin- ium in vaccine relevant exposures can be toxic to humans,[34,35,60] and therefore, its use as a 'placebo control' in vaccine trials can no longer be justified.[61]

Conclusions

We documented here the evidence indicating the potential of the HPV vaccine to trigger a life-disabling autoimmune-mediated condition such as POF. Given that persistently infected women with HPV seem not to develop cancer if they are regularly screened and that the long-term clinical benefits of HPV vaccination are still a matter of speculation, a more rigorous assessment of vaccine risks and bene- fits is recommend.[49,50,62] Thus, physicians should remain within the rigorous rules of evidence-based medicine, to adequately assess the risks versus the benefits of HPV vaccination.[63,64]

Disclosure

An informed consent has been received from the patients present their cases. Y Shoenfeld has served

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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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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,

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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.

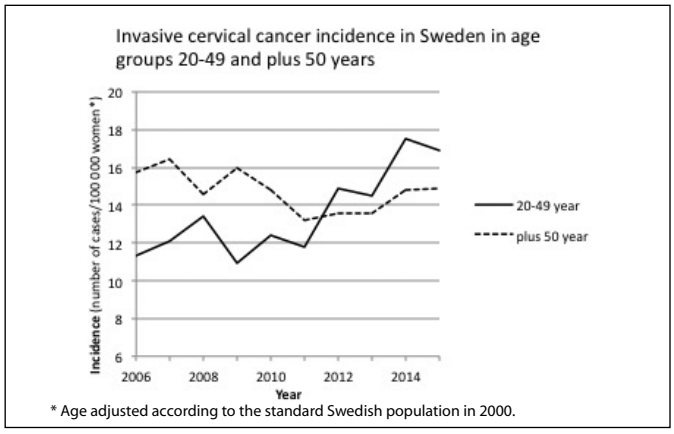

Fig. 1: Increase in incidence of cervical cancer among younger women (<50 years) as compared with women ≥50 years. The data shows the number of cases/100,000 women from 2006 to 2015.

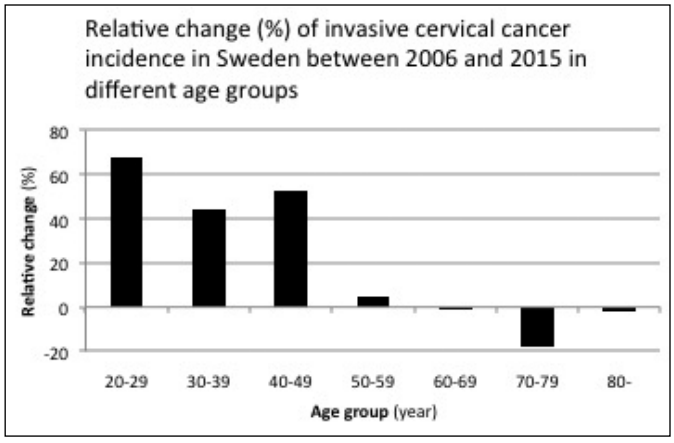

Fig. 2: The relative change in percentage of invasive cervical cancer incidence in Sweden between 2006 and 2015 in different age groups. The figure is based on data from the statistical database of the National Board of Health and Welfare in Sweden. The incidence of cancer is age-adjusted according to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

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