Medicines Adverse Reactions Committee

Meeting date	**10 September 2015**	Agenda item	3.2.3
Title	**Gardasil and autoimmune diseases**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice/ For information
Active constituent	**Medicines**		**Sponsors**
Human papillomavirus type 6 L1 protein, type 11 L1 protein, type 16 L1 protein and type 18 L1 protein	**Gardasil**		**Bio CSL for MSD**
Funding	Fully funded for girls aged under 18 years or patients aged under 25 years old with confirmed HIV infection or in transplant patients.		
Previous MARC meetings	Gardasil has only been discussed previously in relation to CARM case reports.		
International action	The EMA have announced an investigation into HPV vaccine and complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). This review will complete at the end of the year.		
Prescriber Update	None		
Schedule	Prescription medicine		
Usage data	Over 200,000 girls and women have received at least one dose in NZ Worldwide cumulative exposure post-marketing, to the end of May 2015 was 63.6 million. Cumulative exposure in clinical trials was 29,932		
Advice sought	**The Committee is asked to advise whether:** – There is a safety concern relating to development of autoimmune conditions after HPV vaccination		

Table of Contents

1.0 PURPOSE

Gardasil is a recombinant vaccine against human papilloma virus (HPV) types, 6,11,16 and 18. It is prepared from highly purified virus-like particles (VLPs) of the major capsid protein of the four stains 6, 11, 16 and 18. The vaccine is produced in recombinant yeast: *Saccharomyces cerevisiae* and the VLPs self-assemble and are adsorbed onto amorphous aluminium hydroxyphosphate sulphate.

Gardasil is indicated in females 9 to 45 years for the prevention of cervical, vulvar, vaginal and anal cancer, precancerous or dysplastic lesions, genital warts and infection caused by human papillomavirus types 6, 11, 16 and 18. In males 9-26 years of age it is indicated for the prevention of anal cancer, precancerous or dysplastic lesions, external genital lesions and infection caused by HPV types 6, 11, 16 and 18.

Cervarix is a similar vaccine against HPV types 16 and 18.

Both HPV vaccines are approved in New Zealand but only Gardasil is funded. The immunisation schedule is 0,2 and 6 months (ie second dose is given 2 months after the first dose and the third dose is given 6 months after the first dose).

Some HPV infections are sexually transmitted (including 6, 11, 16, and 18), consequently HPV vaccines have attracted concern from people who are anti-vaccine and those who consider that this vaccine promotes promiscuity.

Medsafe periodically receives media questions, Official Information Act (OIA) requests, Ministerial letters and consumer correspondence regarding the safety of HPV vaccine.

The purpose of this paper is to provide information on the possible association between HPV vaccine and autoimmune conditions. The possible association between HPV vaccine and CRPS and POTS will be discussed in a future paper.

2.0 BACKGROUND

2.1 Gardasil efficacy

Of the approximately 100 types of HPV that can infect human epithelium, more than 40 can cause ano-genital infections and 15 have been associated with cervical cancer occurrence. HPV 16 and 18 are the most frequent and aggressive strains(approximately 70% of cervical cancer). Although the evolution from cervical intraepithelial neoplasia (CIN) to invasive cancer proceeds slowly and PAP testing (Smear test) can identify CIN, cervical cancer remains the fourth commonest cause of cancer-related death worldwide.

The efficacy of Gardasil in the pre-approval clinical studies is outlined in the data sheet. In female subjects, CIN 2/3 and AIS are the immediate precursors of invasive squamous cell carcinoma and invasive adenocarcinoma of the cervix, respectively. Their detection and removal has been shown to prevent invasive cancer (secondary prevention); thus, these were the primary efficacy outcomes of the registrations studies.

The efficacy of Gardasil or the HPV component of Gardasil was assessed in 6 placebo-controlled, double-blind, randomized Phase II and III clinical studies.

- One Phase II study evaluated all four components (i.e., HPV 6, 11, 16, and 18) (Protocol 007, N = 551 females).
- An additional phase II study evaluated the HPV 16 component of Gardasil (Protocol 005, N=2,391 females).
- Three Phase III studies, termed FUTURE (Females United To Unilaterally Reduce Endo/Ectocervical Disease), evaluated GardasilL in 5,442 (FUTURE I),12,157 (FUTURE II), and 3,817 (FUTURE III) females.

- A fourth Phase III study, Protocol 020, evaluated Gardasil in 4055 males, including a subset of 598 men (Gardasil = 299; placebo = 299) who self-identified as having sex with men (MSM population).

Together, these studies evaluated 24,358 females 16 through 45 years of age and 4055 males 16 through 26 years of age at enrolment, the majority of whom had been sexually active.

In the clinical studies, HPV status was not assessed before subjects were enrolled. Thus, subjects who had been exposed to a vaccine HPV type prior to enrolment were included in the studies for evaluation. Overall, 73% of 16 through 26 year old females and 67% of 24 through 45 year old females were naïve to all 4 vaccine HPV types at enrolment. Overall, 83% of 16- through 26-year-old males were naïve to all 4 vaccine HPV types at enrollment.

Table 1 Analysis of efficacy of Gardasil in the Per protocol evaluation population by HPV type in the combined protocols

Population	GARDASIL		Placebo		% Efficacy (95% CI)
	n	Number of cases	n	Number of cases	
HPV 16- or 18-related CIN 2/3 or AIS*	8,493	2**	8,464	112	98.2 (93.5, 99.8)
HPV 16-related	7402	2**	7205	93	97.9 (92.3, 99.8)
HPV 18-related	7382	0	7316	29	100.0 (86.6, 100.0)
HPV 6-, 11-,16-, or 18-related CIN (CIN 1, CIN 2/3) or AIS***	7,864	9†	7,865	225	96.0 (92.3, 98.2)
HPV 6-related	6902	0	6828	47	100.0 (92.0, 100.0)
HPV 11-related	6902	0	6828	12	100.0 (64.5, 100.0)
HPV 16-related	6647	8†	6455	137	94.3 (88.5, 97.6)
HPV 18-related	7382	1†	7316	61	98.4 (90.6, 100.0)
HPV 6- or 11-related Genital Warts***	6,932	2	6,856	189	99.0 (96.2, 99.9)
HPV 6-related	6,932	2	6,856	166	98.8 (95.7, 99.9)
HPV 11-related	6,932	0	6,856	32	100.0 (88.0, 100.0)

*Protocols 005, 007, 013 (FUTURE I), and 015 (FUTURE II) combined. Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria. Subjects in Protocol 005 do not contribute to the endpoints related to Type 18.
**There were two cases of CIN 3 that occurred in the group that received GARDASIL (FUTURE II).In the first case HPV 16 and HPV 52 were detected. This subject was chronically infected with HPV 52 (infection at Day 1, and Months 32.5 and 33.6) in 8 of 11 specimens, including tissue that was excised during LEEP (Loop Electro-Excision Procedure). HPV 16 was found in 1 of 11 specimens at Month 32.5. HPV 16 was not detected in tissue that was excised during LEEP. In the second case HPV 16, HPV 51, and HPV 56 were detected. This subject was infected with HPV 51 (infection detected by PCR at Day 1) in 2 of 9 specimens. HPV 56 was detected (in tissue excised during LEEP) in 3 of 9 specimens at Month 52. HPV 16 was detected in 1 of 9 specimens at a month 51 biopsy. Given that these cases occurred in the context of mixed infection, with the dominant type being the non-vaccine HPV type, it is likely that the relevant vaccine HPV type was not the causal HPV type. Based on this assessment, it can be inferred that vaccine efficacy against HPV 16/18-related CIN 2/3 or AIS was 100%.
***Protocols 007, 013 (FUTURE I), and 015 (FUTURE II) combined. Analyses of the combined trials were prospectively planned and included the use of similar study entry criteria.
†Among 9 cases of HPV 6-, 11-, 16-, or 18-related CIN (any grade) or AIS detected in the PPE population, 6 cases are likely to be due to a non-vaccine HPV type and not to a vaccine HPV type.
n= Number of subjects with at least one follow-up visit after Month 7
CI = Confidence Interval
Note: Point estimates and confidence intervals are adjusted for person-time of follow-up.

The immunogenicity of Gardasil was assessed in 23,951, 9- through 45- year old females (Gardasil N = 12,634; placebo N = 11,317) and 5,417 males aged 9 through 26 years (Gardasil N=3,109; placebo N=2,308).

Because of the very high efficacy of Gardasil in clinical trials, it has not been possible to establish minimum anti-HPV 6, anti-HPV 11, anti-HPV 16, and anti-HPV 18 antibody levels that protect against clinical HPV disease.

Comment

It is considered likely that the protective antibody level is below the level of detection of current assays.

Table 2 Summary of percent seroconversion and anti-HPV cLIA GMTs at month 7 in the PPI population of 9-45 year old women

Population	N**	n***	% Seropositive (95% CI)	GMT (95% CI) mMU/mL†
Anti-HPV 6				
9- through 15-year-old girls	1,122	917	99.9 (99.4, 100.0)	929.2 (874.6, 987.3)
16- through 26-year-old girls and women	9,859	3,329	99.8 (99.6, 99.9)	545.0 (530.1, 560.4)
27- through 34-year-old women	667	439	98.4 (96.7, 99.4)	435.6 (393.4, 482.4)
35- through 45-year-old women	957	644	98.1 (96.8, 99.0)	397.3 (365.2, 432.2)
Anti-HPV 11				
9- through 15-year-old girls	1,122	917	99.9 (99.4, 100.0)	1,304.6 (1,224.7, 1,389.7)
16- through 26-year-old girls and women	9,859	3,353	99.8 (99.5, 99.9)	748.9 (726.0, 772.6)
27- through 34-year-old women	667	439	98.2 (96.4, 99.2)	577.9 (523.8, 637.5)
35- through 45-year-old women	957	644	97.7 (96.2, 98.7)	512.8 (472.9, 556.1)
Anti-HPV 16				
9- through 15-year-old girls	1,122	915	99.9 (99.4, 100.0)	4,918.5 (4,556.6, 5,309.1)
16- through 26-year-old girls and women	9,859	3,249	99.8 (99.6, 100.0)	2,409.2 (2,309.0, 2,513.8)
27- through 34-year-old women	667	435	99.3 (98.0, 99.9)	2,342.5 (2,119.1, 2,589.6)
35- through 45-year-old women	957	657	98.2 (96.8, 99.1)	2,129.5 (1,962.7, 2,310.5)
Anti-HPV 18				
9- through 15-year-old girls	1,122	922	99.8 (99.2, 100.0)	1,042.6 (967.6, 1,123.3)
16- through 26-year-old girls and women	9,859	3,566	99.4 (99.1, 99.7)	475.2 (458.8, 492.1)
27- through 34-year-old women	667	501	98.0 (96.4, 99.0)	385.8 (347.6, 428.1)
35- through 45-year-old women	957	722	96.4 (94.8, 97.6)	324.6 (297.6, 354.0)

*The PPI population consisted of individuals who received all 3 vaccinations within pre-defined day ranges, did not have major deviations from the study protocol, met predefined criteria for the interval between the Month 6 and Month 7 visit, and were naïve (PCR negative and seronegative) to the relevant HPV type(s) (types 6, 11, 16, and 18) prior to dose 1 and through 1 month Postdose 3 (Month 7).

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

***Number of individuals contributing to the analysis

†mMU = milli-Merck units

CI = Confidence Interval

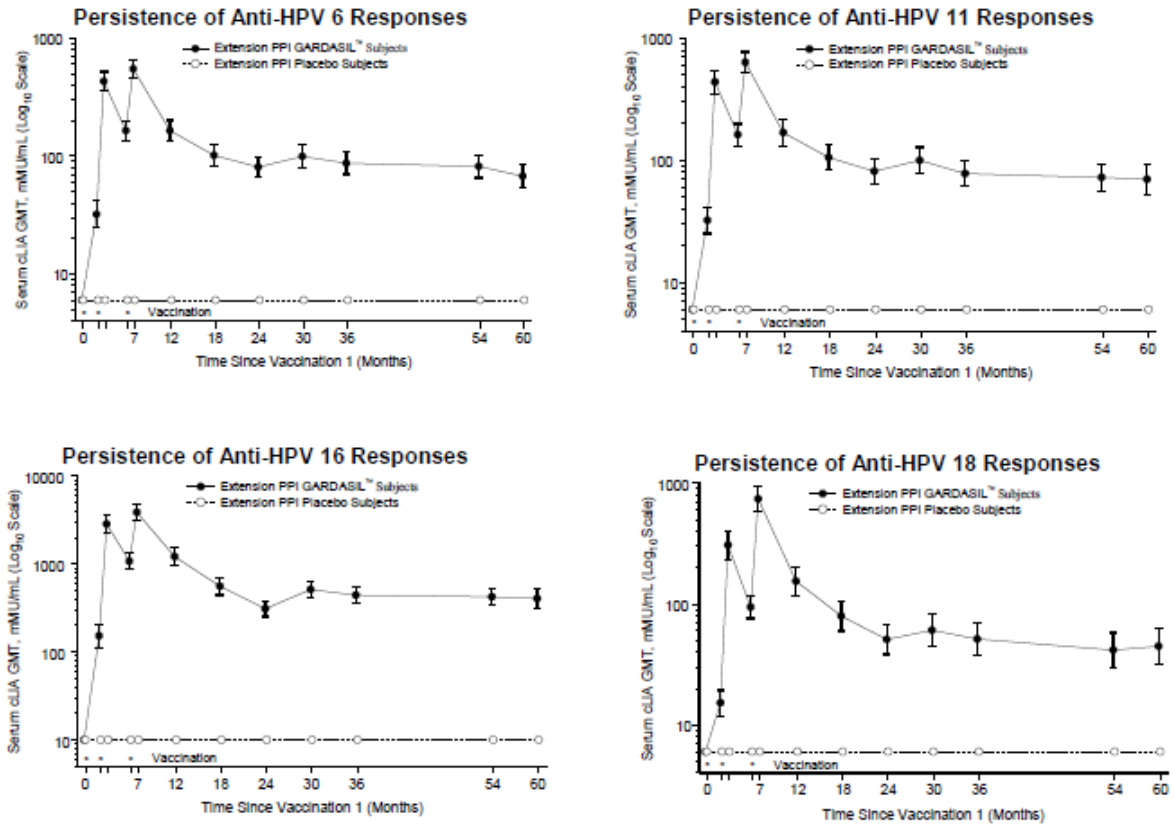


Figure 1 Persistence of anti-HPV responses following three dose regimen

Medsafe comments:

Efficacy in terms of the primary outcome of reducing precancerous or dysplastic lesions was shown in the older aged women. The efficacy was bridged to younger ages (9-16) through measurement of antibodies, since these girls were not yet at risk of HPV infection and CIN.

Post-market data from Australia indicate that the incidence of cervical abnormalities being detected through smear testing has already dropped: HR 0.72 (0.58-0.91) comparing vaccinated with non-vaccinated subjects[1]

2.2 Autoimmune disorders

An autoimmune disorder occurs when the body's immune system attacks and destroys healthy body tissue by mistake. The exact cause of autoimmune disorders is unknown. Many autoimmune disease have similar symptoms, they usually fluctuate between periods of remission and flare ups. Autoimmune disease often run in families and 75% of those affected are women.

Autoimmune disorders include: Addison's disease, celiac disease, dermatomyositis, Graves disease, Hashimoto's thyroiditis, Multiple Sclerosis (MS), Myasthenia gravis, pernicious anaemia, reactive arthritis, Rheumatoid arthritis (RA), Sjogren syndrome, Systemic lupus erythematosus (SLE), type I diabetes, Guillian Barre Syndrome (GBS) and Acute disseminated encephalomyelitis (ADEM).

It is claimed that vaccinations could induce a small increased risk of multiple sclerosis and other demyelinating conditions. There has been a hypothesis that vaccination with recombinant hepatitis B vaccine can cause MS, due to a potential for molecular mimicry between this vaccine and myelin basic protein. Similar concerns have also focussed on HPV vaccines.

The Institute of medicine (IOM) (USA) has produced a review of the adverse effects of medicines which includes helpful information.[2]

In evaluating the vaccines for a causal relation with demyelinating disease, several facts need to be considered:

- natural infections with measles and mumps viruses have been associated with ADEM.
- ADEM and GBS in humans, generally occur after an interval of 5 days to 6 weeks following infection (not clinical disease) or injection of antigen.
- ADEM and GBS can occur after the administration of either live attenuated or killed vaccines (in the case of vaccinia virus and the swine influenza vaccines, respectively).

Thus, it is biologically plausible that injection of an inactivated virus, bacterium, or live attenuated virus might induce in the susceptible host an autoimmune response by deregulation of the immune response, by nonspecific activation of the T cells directed against myelin proteins, or by autoimmunity triggered by sequence similarities of proteins in the vaccine to host proteins such as those of myelin. The latter mechanism might evoke a response to a self antigen, so-called molecular mimicry

2.2.1 Immune response and autoimmunity

T cells are the subset of lymphocytes that develop in the thymus. Two T cell subsets, CD8+ and CD4+ T cells, are activated via recognition of peptides derived from antigen. For activation of T cells to

[1] Gertig DM, Brotherton JM, Budd AC et al 2013 'Impact of a population based HPV vaccination program on cervical abnormalities: a data linkage study' BMC Med 11:227

[2] Stratton K, Ford A, Rusch et al 2012 'Adverse effects of vaccines evidence and causality' The National Academies Press Washington DC.

occur, the peptides are bound to major histocompatibility complexes (MHCs) expressed on the surface of specialized white blood cells called antigen-presenting cells.

T cells have various functions in the immune response. CD8+ T cells express a T cell receptor (TCR) that binds peptide-class I MHC complexes. CD8+ T cells that express different TCRs allow for recognition of many different antigens. CD8+ T cells which then respond against cytosolic infections such as viruses, intracytoplasmic bacteria, and protozoa. Activated CD8+ T cells induce death of infected cells through mechanisms that include (1) release of granules containing the pore-forming molecular perforin or (2) engagement of Fas receptors on target cells. Both mechanisms induce apoptosis, or programmed cell death, in the target cell. In addition, activated CD8+ T cells secrete cytokines, molecules critical to intercellular communication, that recruit and activate macrophages and neutrophils.

CD4+ T cells are predominantly activated in response to extracellular antigens that are endocytosed or phagocytosed, broken down into peptides, and bound to class II MHC molecules on the surface of professional antigen-presenting cells. Activated CD4+ T cells direct aspects of the immune response via the secretion of immunoregulatory cytokines and other soluble mediators. These inflammatory mediators can induce B cells to undergo immunoglobulin (Ig) class switching (e.g., IgM to IgE); to support the activity of CD8+ T cells; to recruit and activate eosinophils, basophils, neutrophils, mast cells, and macrophages; and to down-regulate immune responses.

Antibodies are antigen-binding proteins produced by terminally differentiated effector B cells called plasma cells. Antibodies that bind antigens derived from the host organism (i.e., self-antigens) are referred to as autoantibodies. Autoantibodies are considered one of the hallmarks of certain autoimmune diseases; however, the presence of autoantibodies does not correlate perfectly with disease. Autoantibodies have been detected in healthy individuals as well as those with autoimmune diseases. The mechanisms whereby autoantibodies exert their effects in the disease process are the same used by antibodies against foreign antigens (i.e., non-self-antigens). These include, but are not limited to, opsonization, neutralization, complement activation, augmentation, and engagement of constant region (Fc) receptors.

Antibody-antigen interactions can lead to complement activation. Antibodies against bacteria lead to complement activation resulting in elimination of the bacteria.

Autoantibodies use multiple mechanisms during a disease process. Antigen-bound autoantibodies can both (1) engage Fc receptors and (2) induce activation of the complement system. These processes lead to the activation of inflammatory cells such as neutrophils and macrophages, and to generation of proinflammatory mediators that play pathogenic roles in autoimmune diseases.

Molecular mimicry is sequence and/or conformational homology between an exogenous agent (foreign antigen) and self-antigen leading to the development of tissue damage and clinical disease from antibodies and T cells directed initially against the exogenous agent that also react against self-antigen. Molecular mimicry as a mechanism that can cause pathologic damage and disease has been demonstrated in several animal models, most notably experimental allergic encephalomyelitis (EAE) in mice and rabbits

2.2.2 Evidence Needed to Conclude That Molecular Mimicry Is Operative in a Clinical Case or an Animal Model of Disease

Essential to concluding molecular mimicry contributes to a clinical case or animal model of disease are the following: (1) a susceptible host whose genetic background and adaptive immune responses allows emergence of self-reactive immunity, (2) exposure to an exogenous agent which expresses antigens that are immunologically similar to self-antigen(s), and (3) a host immune response to the exogenous agent that cross-reacts with biologically relevant host tissue structures and causes tissue damage and clinical disease.

Proving that a particular human autoimmune disease is due to molecular mimicry is problematic. A realistic and consistent temporal relationship between exposure to exogenous antigen and development of disease must be documented. This can be difficult in the case of a natural exposure to pathogen where infection may have been subclinical, making it impossible to define an exact temporal relationship.

Linear amino acid sequence homology or even similar conformational structure between an exogenous agent and a self-antigen alone are not sufficient to prove that molecular mimicry is the pathogenic mechanism for a disease. Many such homologies exist, and the vast majority of these are not associated with biologically relevant autoimmune phenomena or actual human disease.

Finding a tissue-specific antibody response following exposure to an exogenous agent is also, by itself, not proof of molecular mimicry as the pathologic mechanism of disease. Both naturally occurring and post-infectious cross-reactive antibodies and T cells are relatively common and most frequently not pathogenic. Cross-reacting antibodies can also be secondary to nonspecific tissue injury (and to consequent expression of otherwise occult self-antigens) rather than primary to tissue injury itself. Moreover, in some circumstances, infection with viruses that express antigens having immunologic cross-reactivity with self-proteins can actually protect against autoimmune disease in certain animal models.

Neither the *in vitro* demonstration of cross-reacting antibodies nor T cell activation by antigen-MHC complexes proves pathogenic mimicry. An *in vivo* pathogenic autoimmune attack would also require the demonstration of local binding of antibody with activation of the complement cascade, activation of the appropriate co-stimulatory T cell signals and cytokines, and/or involvement of other pathogenic effector mechanisms in a biologically relevant tissue site.

2.2.3 Molecular mimicry

Examples of a natural infection, vaccine, or drug exposure thought to cause a clinical condition or disease that is due to molecular mimicry. While molecular mimicry is a well-established mechanism in selected animal models, its relevance to human autoimmune disease remains in most cases to be convincingly proven. Nevertheless, there is some experimental evidence that suggests or implicates this mechanism in certain human autoimmune diseases including (among others).

- Rheumatic fever associated with group A streptococcal infection.
- HLA B27-associated spondyloarthropathies and several antigens from Shigella, Yersinia, and Klebsiella bacteria.
- Multiple sclerosis and exposure to several different viruses.
- Insulin-dependent diabetes mellitus and Coxsackievirus B4.
- Demyelinating diseases and hepatitis B:

Amino acid homology between myelin basic protein (MBP) and hepatitis B virus polymerase (HBVP) has been reported. In addition, injection of a HBVP immunologic epitope shared with MBP into rabbits resulted in demyelinating disease, antibodies against MBP, and T cell reactivity. However, infection with hepatitis B is not associated with the development of demyelinating diseases. Furthermore, the recombinant vaccines contain hepatitis B surface antigen not hepatitis B virus polymerase.

2.2.4 Autoreactivity/Bystander Activation/Hyperresponsiveness

Autoreactivity can result from expression and immune recognition of self-antigens that have been modified by some extrinsic factor (e.g., binding of a reactive chemical or viral element) so that they appear foreign to the immune system. The response to such neo-antigens would cease when the

transforming agent is removed. Examples include drug modifications of normal proteins, hapten-carrier complexes, and oxidative modification of normal cellular constituents.

In bystander activation, there is a robust or exaggerated immune response to an exogenous agent that induces local tissue inflammation and stimulation of otherwise normal unaffected cells. This inflammation can result in the release of normally sequestered self-antigens. The inflammation can result in nonspecific activation of previously dormant autoreactive CD4+ cells that then react against the newly released self-antigens.

2.2.5 Natural history of selected autoimmune conditions

ADEM is characterised by acute depression of consciousness and mutifocal neurologic findings that usually occur a few days or weeks following vaccine administration or virus like disease. It is characterised pathologically by diffuse foci of perivenular inflammation and demyelination that are most prominent in the white matter of the brain and spinal cord.

GBS comprises a group of peripheral nerve disorders characterised by weakness or paralysis believed to be of autoimmune aetiology. The median estimated incidence is 1.1 per 100,000 person years in Western countries. The putative risk factors include age, sex and viral or bacterial infections. The symptoms of GBS usually appear over the course of a single day and progress for 3 days to 4 weeks. The major symptom is weakness, generally symmetrical usually ascending and usually affecting the legs more than the arms. About 30% of patients require respiratory support at some stage. Fever and constitutional symptoms are not usually present. The mortality rate is 5% or less. Recovery takes a few weeks to well over a year. Some 15-20% of survivors manifest some residual findings and around 5% have serious residual disabilities.

Factors affecting prognosis include age, and severity of the neuropathy and early treatment.

Over half of all patients with GBS have a history of preceding acute infectious illness, either respiratory or gastrointestinal in the 1 to 4 weeks prior to the onset of neuropathic symptoms. Infectious agents linked to GBS include *campylobacter jejuni*, *mycoplasma pneumonia*, cytomegalovirus, Epstein Barr virus, vaccina virus and HIV.

The demyelinating lesions of MS occur in multiple locations within the nervous system but must occur at different times. A prospective study of patients with MS showed that exacerbations appeared to be more frequent after non-specific viral illnesses. Therefore it would be feasible that vaccines might precipitate an exacerbation either in a pre-disposed patient or in one with already established disease. However there is no clear-cut causal relation between any virus or vaccine and MS.

There are approximately 4000 people in NZ with MS. The prevalence in the South Island is approximately twice that in the upper half of the North Island. Most people are diagnosed between the ages of 20 and 40. Similarly in the US the prevalence above the 37th parallel is 110-140 cases / 100,000 people below the 37th parallel the prevalence is 57-78 cases/100,000.

MS is more common in women than men , the ratio is 2:1.

SLE is an autoimmune connective tissue disease. Prevalence varies from 20 to 70 per 100,000. It occurs 9 times more often in women than men especially aged 15-35 years. The cause is believed to be an environmental trigger which results in a defective immune response is people who are genetically susceptible. SLE does run in families but no single causal gene has been identified.

SLE symptoms vary widely and come and go unpredictably. Diagnosis can be difficult and may take years. Females tend to have more relapses, a low white blood cell count Raynauds phenomenon and psychiatric symptoms. Women with SLE are at higher risk of HPV infection resulting in cancer.

2.3 Assessing causality in case reports

The Institute of medicine has issued advice on assessing causality with vaccines.[3] A vaccine safety committee was formed under US law to consider adverse events to vaccines in childhood (IOM-VSC). The Committee considered that there were 3 types of causal questions.

1. Can it? Can the vaccine cause the adverse event at least in certain people under certain circumstances?

2. Did it? Given an individual who has received the vaccine and developed the adverse event, was the event caused by the vaccine?

3. Will it? Will the next person who receives the vaccine experience the adverse event because of the vaccine or how frequently will vaccine recipients experience the adverse event?

2.3.1 Can it?

The Committee considered the following criteria to be relevant.

- Strength of association
- Analytic bias
- Dose-response effect
- Statistical significance
- Consistency
- Biologic plausibility and coherence

Although can it? Causality is usually addressed from epidemiologic studies an affirmative answer can occasionally be obtained from individual case reports. Thus if one or more cases can be clearly shown to be caused by a vaccine then can it is also answered. The Committee considered that lack of case reports could not be used to demonstrate an absence of causality.

2.3.2 Did it?

The information that is useful in assessing causality in individual reports was considered under the following criteria.

- Previous general experience with the vaccine – how long was it on the market, what is the exposure, what is the background rate, does a similar event occur in animals exposed to the vaccine?
- Alternative aetiological candidates – can a pre-existing or new illness explain the adverse event, does the event occur spontaneously, were other drugs or procedures administered at the same time?
- Susceptibility of the recipient – have they received the vaccine before, do they have a susceptible genetic profile?
- Timing of events – Is the timing of the onset as expected if the vaccine is the cause, how does the timing differ from other candidates, how does the timing depend on the suspected causal mechanism?
- Characteristics of the adverse event – are there any laboratory tests that support or undermine the hypothesis of vaccine causation, was there a local reaction at the vaccination site?
- Dechallenge – did the event diminish as would be expected for a vaccine caused event, did treatment of the adverse event cloud interpretation of the evolution of the event?
- Rechallenge – was the vaccine re-administered did the adverse event recur?

[3] Stratton KR, Howe CJ and Johnston RB 1994 'Adverse events associated with childhood vaccines: evidence bearing on causality' National Academy Press Washington DC.

2.4 Anticipated reporting of immune-related adverse events

Callreus et al [4] used a nationwide hospitalisation registry to estimate the incidence rate of immune mediated disorders before HPV vaccine introduction in Denmark (Table 3).

Table 3 Autoimmune disorders among Danish born females 12-15 years old in the period 1995-2005

	All hospital contacts		First hospital contacts			Type of contact								Calendar year			Sex	
	IR[a]	95% CI	IR	95% CI		Emergency department			Inpatients			Outpatients		Trend			Incidence rate ratio	
						IR	95% CI		IR	95% CI		IR	95% CI	Increase in IR per year	95% CI		Ratio of IR in females and IR in males (95% CI)	
Any autoimmune disorder	413.7	401.0	426.9	109.0	102.5	115.9	2.3	1.5	3.5	61.5	56.6	66.7	45.3	41.1	49.8	5.3	3.1	7.6	1.14	1.04	1.25
Type 1 diabetes	135.8	128.5	143.4	24.5	21.5	27.9	0.5	0.2	1.3	22.8	19.9	26.0	1.2	0.6	2.1	3.4	−1.1	8.1	0.71	0.60	0.84
Juvenile arthritis	101.2	95.0	107.9	18.5	16.0	21.5	0.5	0.2	1.3	5.0	3.8	6.7	13.0	10.9	15.5	9.2	3.6	15.0	1.37	1.09	1.71
Crohns's disease	42.1	38.1	46.4	9.4	7.6	11.5	–	–	–	6.4	5.0	8.2	3.0	2.1	4.3	−0.5	−7.4	6.9	0.88	0.66	1.16
Ulcerative colitis	20.2	17.5	23.3	8.2	6.5	10.2	–	–	–	4.8	3.6	6.4	3.4	2.4	4.8	3.4	−4.2	11.7	1.33	0.95	1.86
Basedow's disease	15.1	12.8	17.8	6.9	5.4	8.8	0.1	0.0	0.8	4.5	3.3	6.0	2.3	1.5	3.5	6.5	−2.1	15.9	5.18	2.86	9.40
Henoch-Schönlein's purpura	14.8	12.5	17.4	8.4	6.7	10.5	0.3	0.1	1.0	6.5	5.1	8.3	1.6	1.0	2.6	6.0	−1.8	14.5	0.96	0.71	1.31
Psoriasis	14.1	11.9	16.7	8.2	6.5	10.2	0.3	0.1	1.0	1.7	1.0	2.8	6.2	4.8	8.0	4.4	−3.3	12.8	1.70	1.18	2.44
Systemic lupus erythematosus	10.2	8.3	12.5	1.6	1.0	2.6	–	–	–	1.3	0.7	2.2	0.3	0.1	1.0	−5.3	−20.5	12.7	3.11	1.13	8.55
Hashimoto's thyroiditid	9.5	7.7	11.6	6.2	4.8	8.0	–	–	–	2.4	1.6	3.7	3.7	2.7	5.2	9.3	−0.1	19.6	7.51	3.59	15.74
Gluten sensitive enteropathy	6.6	5.1	8.4	3.2	2.2	4.6	–	–	–	1.6	1.0	2.6	1.6	1.0	2.6	24.9	8.7	43.6	2.07	1.12	3.85
Polymyositis/dermatomyositis	6.2	4.8	8.0	0.3	0.1	1.0	–	–	–	0.2	0.1	0.8	0.1	0.0	0.8	53.5	−13.7	173.0	0.62	0.15	2.60
Rheumatoid arthritis	5.7	4.4	7.5	4.5	3.3	6.0	0.5	0.2	1.3	0.6	0.3	1.4	3.3	2.3	4.7	1.6	−8.4	12.7	2.72	1.53	4.84
Idiopathic thrombocytopenic purpura	5.7	4.4	7.5	2.4	1.6	3.7	–	–	–	1.9	1.2	3.0	0.5	0.2	1.3	5.7	−8.2	21.8	0.85	0.49	1.48
Addisons's disease	4.5	3.3	6.0	1.0	0.5	1.8	–	–	–	0.6	0.3	1.4	0.3	0.1	1.0	39.0	4.1	85.6	2.33	0.72	7.57
Raynaud's disease	3.5	2.5	4.9	2.8	1.9	4.1	0.1	0.0	0.8	0.2	0.1	0.8	2.4	1.6	3.7	7.7	−5.8	23.1	2.99	1.40	6.39
Guillain-Barré syndrome	3.1	2.1	4.4	1.4	0.8	2.4	–	–	–	1.3	0.7	2.2	0.1	0.0	0.8	7.7	−10.9	30.1	1.12	0.51	2.46
Erythema nodosa	2.9	2.0	4.2	2.4	1.6	3.7	–	–	–	1.7	1.0	2.8	0.7	0.4	1.6	2.5	−10.9	17.9	0.74	0.44	1.27
Systemic sclerosis (scleroderma)	2.8	1.9	4.1	1.0	0.5	1.8	–	–	–	0.2	0.1	0.8	0.7	0.4	1.6	−11.0	−29.4	12.1	2.33	0.72	7.57
Myasthenia gravis	2.7	1.8	3.9	0.5	0.2	1.3	–	–	–	0.1	0.0	0.8	0.4	0.2	1.1	−1.5	−27.1	33.0	5.18	0.61	44.35
Vitiligo	2.0	1.3	3.2	1.4	0.8	2.4	–	–	–	–	–	–	1.4	0.8	2.4	−8.7	−24.5	10.4	1.35	0.59	3.07
Localized lypus erythematosus	1.8	1.1	2.9	1.0	0.5	1.8	–	–	–	0.4	0.2	1.1	0.5	0.2	1.3	−4.8	−24.0	19.2	–	–	–
Wegener's granulomatosis	1.8	1.1	2.9	0.1	0.0	0.8	–	–	–	0.1	0.0	0.8	–	–	–	−30.0	−71.3	70.3	0.52	0.05	5.71
Localized scleroderma	1.7	1.0	2.8	1.1	0.6	2.0	–	–	–	–	–	–	1.1	0.6	2.0	3.2	−16.6	27.7	2.59	0.81	8.26
Multiple sclerosis	1.7	1.0	2.8	0.6	0.3	1.4	–	–	–	0.4	0.2	1.1	0.2	0.1	0.8	−0.4	−24.3	31.1	2.07	0.52	8.29
Sarcoidosis	1.1	0.6	2.0	0.7	0.4	1.6	–	–	–	0.3	0.1	1.0	0.4	0.2	1.1	−7.7	−28.7	19.5	0.91	0.33	2.50
Acute rheumatic fever	1.1	0.6	2.0	0.5	0.2	1.3	–	–	–	0.3	0.1	1.0	0.2	0.1	0.8	27.5	−10.1	80.9	0.58	0.19	1.72
Behcet's syndrome	1.0	0.5	1.8	0.5	0.2	1.3	0.1	0.0	0.8	0.2	0.1	0.8	0.2	0.1	0.8	23.7	−11.8	73.4	5.18	0.61	44.35

[a] Incidence rates per 100,000 person-years with 95% confidence intervals.

[4] Callreus T, Svanstroem H, Nielsen et al 2009 'Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events' Vaccine 27: 2954-2958

The investigation cohort included 418,289 girls aged 12-15 years. The authors calculated incidence rates of hospital contacts with immune mediated disorders in girls aged 12-15 years in the 1995-2005 period.. Rates were calculated according to type of immune-mediated disorder, type of hospital contact and calender year. Crude incidence rate ratios were calculated comparing rates in girls with boys.

The authors estimated the expected number of cases of immune mediated disorders occurring in temporal relationship to HPV vaccination purely by chance under the following conditions.

- HPV vaccination does not increase the risk
- The schedule was 0-2-6 months.

The first hospital contact rate (in 100,000 person-years) was converted to rates in units relevant to the temporal relationship under evaluation. These rates were then multiplied by 3 (3 doses of vaccine) and then further multiplied by 100,000 to get the number of cases per 100,000 fully vaccinated girls in the specific time period.

In Table 3 the autoimmune disorder incidence rates are presented. Very rare conditions are not included (ankylosing spondylitis, autoimmune haemolytic anaemia, Kawasaki's disease, phemphigoid, pemphigus foliaceus, pemphigus vulgaris, pernicious anaemia, polyarteritis nodosa, primary biliary cirrhosis, Reiter's syndrome and Sjoegren's syndrome). During the study period the overall first hospital contact rates increased by 5.3 contacts per 100,000 person-years per year.

In Table 4 the number of cases of immune mediated disorders occurring within different time periods from vaccination by chance is presented.

Table 4 Expected number of cases (per 100,000 fully vaccinated girls aged 12-15 years) in temporal relation to HPV vaccination purely by chance

Condition	Within 1 day	Within 1 week	Within 6 weeks
Allergic disorders			
Asthma	1.5	10.2	61.3
Allergic rhinitis	0.5	3.4	20.7
Urticaria	0.2	1.7	10.1
Atopic dermatitis	0.2	1.7	9.9
Allergic conjunctivitis	0.1	0.6	3.8
Autoimmune disorders			
Type 1 diabetes	0.2	1.4	8.4
Juvenile arthritis	0.2	1.1	6.4
Crohn's disease	0.1	0.5	3.2
Henoch-Schönlein's purpura	0.1	0.5	2.9
Ulcerative colitis	0.1	0.5	2.8

Siegrist et al[5] performed a similar study. The Northern California Kaiser Permanente (NCKP) database was used to compute the rates of emergency consultations, hospitalizations and outpatient consultations for relevant conditions prior to the introduction of HPV vaccination.
The authors assumed a 0-1-6 months vaccine schedule and defined several time windows after each putative vaccine dose during which a previous HPV immunization would likely be considered as a triggering or precipitating event. The proportion of subjects with expected temporal associations between a medical event and trigger administered at 0-1-6 months intervals was calculated by dividing the yearly rate of event by the number of corresponding at-risks periods taking into consideration overlapping periods. It was corrected for vaccine coverage likely to be reached in the adolescent (80%) and the young adult (40%) population.

[5] Siegrist C-A, Lewis EM, Eskola J et al 2007 'Human papilloma virus immunization in adolescent and youg adults. A cohort study to illustrate what events might be mistaken for adverse reactions' Pediatric Infectious Dis J 26: 979-984

Table 5 NCKP Emergency room utilisation by female adolescent and young women

ICD-9 Codes	Diagnoses	Adolescents		Adults Rates per 100,000
		Frequency Counts	Rates per 100,000	
49390	Asthma without status asthmaticus	366	170	183
49392	Asthma—acute exacerbation	319	148	176
49391	Asthma—status asthmaticus	14	6.50	7.20
9953	Allergic reaction, unspecified	182	84.7	167
7080–89	Allergic urticaria	128	59.5	97.5
4779	Allergic rhinitis	40	18.6	19.0
37205	Allergic conjunctivitis	25	11.6	9.00
6918	Allergic atopic dermatitis	10	4.70	1.40
9950	Anaphylactic shock	8	3.70	7.70
7291	Myalgia and myositis	39	18.1	40.2
25011	Diabetes—ketoacidosis, juvenile	38	17.7	12.6
25000	Diabetes adult	27	12.6	39.3
25010	Diabetes—ketoacidosis, adult	24	11.2	14.9
25001	Diabetes juvenile	21	9.80	1.13
3510	Bell's palsy	15	7.00	20.3
3643	Iridocyclitis	8	3.70	5.00
7100	Systemic lupus erythematosus	4	1.90	15.4
24290	Thyrotoxicosis	4	1.90	6.80
3709	Keratitis	3	1.40	6.30
5559	Regional enteritis	2	0.9	7.70

Table 6 2005 NCKP hospital admissions and outpatient consultations for autoimmune conditions in adolescent girls and young women

ICD-9 Codes	Diagnoses	Adolescents		Adults Rates per 100,000
		Frequency Counts	Rates per 100,000	
Hospitalizations				
(. . .)	Thyroid disorders	35	16.3	286.77
556.X	Ulcerative colitis	22	10.2	14.90
7100	Systemic lupus erythematosus	18	8.4	31.16
555.X	Regional enteritis	16	7.4	20.32
71430	Juvenile rheumatoid arthritis	9	4.2	19.87
2794	Autoimmune disorders (NS)	6	2.8	2.26
37730	Optic neuritis	6	2.8	1.81
340	Multiple sclerosis	2	0.9	9.94
3570	Acute polyneuritis	1	0.45	1.81
Outpatient care				
Several	Thyroid disorders	859	396	1412.05
556.X	Ulcerative colitis	76	35.4	117.52
555.X	Regional enteritis	68	31.6	97.18
7100	Systemic lupus erythematosus	63	52.9	120.23
7140	Rheumatoid arthritis	29	13.5	119.33
37730	Optic neuritis	10	4.7	13.56
340	Multiple sclerosis	9	4.2	64.18
71659	Polyarthritis	7	3.3	30.74

NS indicates not significant.

Table 7 Coincident temporal associations with putative placebo injections administered at 0-1-6 months to all adolescent and young women

Age Group	Condition	Rate per 100,000 by Temporal Association Windows		
		1 d	1 wk	6 wk
Adolescent	ER consultation/asthma	2.7	18.8	81.3
	ER consultation/allergy	1.5	10.6	45.8
	ER consultation/diabetes	0.4	2.9	12.8
	Hospitalization/inflammatory bowel disease	0.2	1.0	4.5
	Hospitalization/thyroid disease	0.1	0.9	4.0
	Hospitalization/SLE	0.1	0.5	2.0
	Hospitalization/MS or optic neuritis	0.0	0.2	1.0
Adults	ER consultation/asthma	3.0	21.2	91.5
	ER consultation/allergy	2.5	17.4	75.3
	ER consultation/diabetes	0.6	3.9	17.0
	Hospitalization/thyroid disease	2.4	16.6	71.8
	Hospitalization/inflammatory bowel disease	0.3	2.0	8.8
	Hospitalization/SLE	0.3	1.8	7.8
	Hospitalization/MS or optic neuritis	0.1	0.7	3.0

MS indicates multiple sclerosis; SLE, systemic lupus erythematosus.

3.0 SCIENTIFIC INFORMATION

Recent published information including case reports and observational studies is outlined in this section.

3.1 Case reports

3.1.1 Della Corte et al[6]

An 11-year-old girl was admitted to the author's hospital because of a 14-day period of jaundice and elevated serum levels of aminotransferases. At admission she had hepatosplenomegaly and jaundice. The results of blood tests showed elevated aspartate aminotransferase (416 IU/l), alanine aminotransferase (735 IU/l) and total bilirubin (4.9 mg/dl) with normal value of gamma-glutamyltranspeptidase (23 IU/l). Albumin and International Normalized Ratio (INR) were normal. Anti-LKM (anti liver kidney microsomal) antibodies tested by indirect immunofluorescence were positive at high titer (1:10,240). Antibodies anti-SMA and ANA were negative. Moreover a hypergammaglobulinemia (22.8%) and increased serum IgG levels (1.852 mg/dl) were detected. Serologic tests for hepatitis A, B, and C viruses, Epstein Barr virus, cytomegalovirus and parvovirus B19 were negative. Metabolic and genetic disorders were ruled out based on the following investigations: alpha-1-antitrypsin serum levels and phenotype, urinary copper excretion, ceruloplasmin serum levels, and sweat test. There was no history of drug intake.

Thirty-six days before the onset of liver disease the patient had a vaccination against human papillomavirus with HPV-16/18 AS04- adjuvanted cervical cancer vaccine (Cervarix batch: AHPVA044DD). The family history was unremarkable for autoimmune diseases. Histology showed active hepatitis with inflammatory infiltrate containing lymphomonocytes in the portal tract, invading the lobule, and producing interface hepatitis with diffuse hepatocyte necrosis and piecemeal necrosis

On the basis of laboratory and histological findings, Autoimmune hepatitis (AIH) type 2 was suspected. According to the criteria of the International Autoimmune Hepatitis Group the diagnosis of AIH was confirmed (score >15). No clinical or laboratory signs of other autoimmune disorders were present. As soon as AIH was diagnosed, prednisone, at a dosage of 2 mg/kg daily, was started. After four weeks the liver function tests and other laboratory parameters were normal (score after therapy 19). Thereafter, prednisone therapy was progressively tapered to a maintenance dosage of 2.5 mg daily, with persistent normality of liver function test results. Considering that AIH can coexist with several autoimmune disorders such as thyroiditis, nephritic syndrome, Behcet disease, ulcerative colitis, insulin-dependent diabetes, celiac disease, hypoparathyroidism and Addison disease, a wide laboratoristic screening to rule out these conditions has been done.

Although the finding of AIH in our patient may be coincidental, the authors suggest that the occurrence of the autoimmune liver disease may be related to the stimulation of immune system by a vaccine that could have triggered the disease in a genetically predisposed individual.

Comments
No other published case reports of autoimmune hepatitis were identified. Therefore, even if vaccination induced AIH in this case it does not appear to be a public health issue

[6] Della Corte C, Carlucci A, Francalanci P et al 2011 ' Autoimmune hepatitis type 2 following anti-papillomavirus vaccination in a 11-year-old girl' vaccine 29:4654-4656

3.1.2 Gatto[7]

The authors report 6 cases of women who presented with SLE or SLE-like disease following HPV vaccination. In one patient SLE flare was reported rather than new onset disease.

Patient 1

A 32-year-old woman was admitted to the hospital 5 days following the third immunization with GardasilTM. On admission, she suffered from general weakness, severe myalgia, polyarthralgia, anorexia, severe skin rash (urticarial-like), malar rash, aphtous stomatitis, pharyngodynia, cervical lymphadenopathy (more than 3.5 cm), and hair loss. In addition, in the 4 weeks prior to her hospitalization she lost 10 kg of body weight.

The patient was diagnosed as having SLE and treatment with high-dose prednisone (PDN) and hydroxychloroquine (HCQ) was commenced with gradual clinical improvement. PDN therapy was tapered slowly up to 5 mg/day, HCQ was continued at 400 mg/day along with supplementation of calcium and vitamin D. Eight months afterwards, the patient was in remission, with normalization of inflammatory laboratory parameters (CRP, ESR), as well as blood counts and complement levels.

Patient 2

A 29-year-old woman was admitted to the hospital 3 weeks following the second dose of Gardasil due to severe weakness, diarrhoea, and elevated markers of inflammation. On admission, her physical examination revealed malar rash, photosensitivity, arthritis, and alopecia. In the next couple of months, she lost 30 % of her body weight and remained hospitalized.

Her medical history included immune thrombocytopenia diagnosed several years before immunization. At that time, she had normal bone marrow biopsies and no detectable serum autoantibodies, including ANA. She was treated with PDN and intravenous immunoglobulins. Two years prior to the administration of HPV vaccine, she underwent splenectomy with normalization of her platelet counts, and abortion of additional therapies. Of note, the patient was immunized with pneumococcal vaccine, as required, before splenectomy with no adverse events. In addition, the patient was diagnosed with early cervical intraepithelial neoplasia related to HPV months before immunization with Gardasil. Her family medical history was unremarkable for autoimmune disorders.

Patient 3

A 16-year-old high school girl was admitted to the Infectious Diseases Department because of high-grade fever (39.5 °C), generalized asthenia, diffuse polyarthralgia, and multiple erythematous annular cutaneous lesions on the face, trunk, and lower limbs which occurred 8 days after the first dose of Gardasil. While she received the vaccine, she developed low-grade fever, which was interpreted as viral flu syndrome. Her medical and family histories were remarkable for Raynaud's phenomenon while her maternal aunt was diagnosed with systemic sclerosis. A diagnosis of "lupus-like" syndrome was determined and the patient was treated with intravenous high-dose methylprednisolone followed by oral PDN.

Patient 4

A 16-year-old high school girl was admitted to the hospital with a preliminary diagnosis of fever of unknown origin, which appeared for the first time 3 weeks after the second dose of Gardasil. Fever was prolonged, mainly present in the morning, and rose up to 39 °C. In addition, pharyngodynia, erythematous skin lesions of elbows and knees, generalized asthenia, anorexia, polyarthralgia, and headaches were present. Autoantibodies profile demonstrated persistent positivity of anti-

[7] Gatto M, Agmon-Levin N, Soriano A et al 2013 'Human papillomavirus vaccine and systemic lupus erythematosus' Clin Rheumatol 32: 1301-1307

cardiolipin IgM and LAC (lupus anticoagulant). Magnetic resonance imaging of the brain excluded the presence of brain abnormalities consistent with antiphospholipid syndrome.

Her medical history was remarkable for recurrent tonsillitis during childhood and a streptococcus group B infection 1 year before admission, treated with penicillin. In addition, the patient suffered from Raynaud's phenomenon grade II, defined by nailfold capillaroscopy. Her family history was also remarkable for Raynaud disease of patient's mother. The patient was diagnosed with fever in a patient with vaccination, compatible with the autoimmune/auto inflammatory syndrome induced by adjuvants (ASIA).

Patient 5

A 19-year-old SLE patient was diagnosed with SLE flare 10 days following the second dose of Gardasil, while in retrospect minor symptoms were already acknowledged following the first immunization.

Patient 6

A 13-year-old African-American female approached her general physician 3 weeks following immunization with the second dose of Gardasil due to swelling of her index finger and a rash. During the following couple of months, she developed erythematous rash on her face, fever, periorbital oedema, weight loss, malaise, fatigue, cervical, axillary and inguinal lymphadenopathy, as well as mild anaemia. At this stage, she was referred to a rheumatologist who noted that she had a petechial rash, alopecia, leucopenia of 2,100 cells/mm3, and mild thrombocytopenia. The patient was diagnosed with SLE. Notably, her personal medical history was remarkable only for common infections and a rash due to pityriasis rosea treated and resolved several months before immunization. Her family history revealed several members of the family with autoimmune diseases including SLE.

The author's believe the above reported cases reveal a temporal association between immunization with Gardasil and the appearance of a spectrum of SLE-like conditions. In this study, all patients had a personal or family history of autoimmune-rheumatic conditions suggesting genetic or epigenetic contributing components. It has been noted that some vaccines may trigger autoimmunity in a predisposed recipient, since they widely stimulate the immune system. Thus, one may suggest that a common denominator to post-vaccination autoimmunity is genetic or epigenetic vulnerability, and that personal or familial medical history of autoimmunity should be considered a risk factor for such adverse events. Another point for consideration was reported in four of the patients described. These patients received boost immunization (second or third vaccination) although mild adverse events were observed following a previous dose of Gardasil.

In summary, based on the current data, the authors believe a causal link between HPV vaccination and onset or relapse of SLE is plausible. Therefore, although for most patients, the benefits of immunization outweigh its risks, clinicians must be aware of the odds for an autoimmune disease onset or exacerbation following HPV vaccination.

Comments

The reported onset times in this case series do not appear to be consistent. Symptoms were reported after the first second or third dose. All the patients had risk factors for development of autoimmune disorders. Since patients with SLE are at higher risk of persistent HPV infection and subsequent CIN small studies investigating the efficacy and safety of vaccination have been conducted. In studies with a placebo group the rate of disease flares after vaccination was comparable to the control group[8]. The authors mention ASIA as a cause of autoimmune disease, this topic will discussed with POTS and CRPS.

[8] Pellegrino P, Radice S, Clementi E 2015 'Immunogenicity and safety of the human papillomavirus vaccine in patients with autoimmune disease: a systematic review' vaccine doi:10.1016/j.vaccine.2015.05.041

3.1.3 Pellegrino 2014[9]

ADEM is an uncommon condition, usually preceded by an acute infection. In about 5% of ADEM cases, however, a precedent immunisation was described as the only risk factor.

The authors report on two girls aged 13 and 12 respectively, who developed ADEM following one primary and two booster administrations of HPV vaccine. In both patients' medical history, blood and cerebrospinal fluid (CSF) analyses ruled out a possible infectious aetiology and autoantibody testing was negative for ANA (antinuclear antibody), ANCA (anti-neutrophil cytoplasmic antibody) and AQP4-Ab (aquaporin-4 antibody- related to neuromeyelitis optica).

The 13-year-old Caucasian girl was hospitalised for a unilateral deficit of the second and third cranial nerves and objective signs of meningo-encephalitis 6 months after receiving the third dose of HPV vaccination (unknown manufacturer).

The 12-year-old girl was hospitalised due to the onset of numbness of the left foot, ambulation difficulty, and speech disorder. Parents reported that she had been vaccinated with the third dose of vaccine against qHPV (Quadrivalent/Gardasil) 15 days before.

The authors also analysed data from the Vaccine Adverse Event Reporting System (VAERS), a passive surveillance system that collects vaccine adverse drug reaction data from the USA and other countries. After causality assessment with World Health Organization criteria 12 ADEM reports that could be classified as related to qHPV vaccination between 1 June 2006 and 30 July 2012 were identified. By considering these reports and the number of qHPV doses distributed within this period (46 million doses), the reporting rate was estimated to be $0.26/10^6$ (CI 95%: $0.16/10^6$–$0.37/10^6$). Despite known limitation of VAERS, the authors considered these data strengthened their hypothesis of correlation between HPV immunisation and ADEM. These cases, taking together with pharmacovigilance data and literature findings, indicate the presence of a relationship between ADEM and HPV vaccination.

Comments
ADEM is a listed adverse event for Gardasil. Interestingly, other publications from this group tended to dismiss an association despite the reporting rate remaining the same (See below).

3.1.4 Pellegrino 2014b[10]

The authors analysed and reviewed all case reports and studies with either the onset of an autoimmune disease in vaccinated subjects or the safety in patients with an autoimmune disease. The authors considered solid evidence of a causal relationship was provided in few cases and the risk versus benefit of vaccination is still to be solved.

ADEM following vaccination is a clinical entity poorly described in terms of epidemiological features. Based on the reports to the VAERS and the European adverse event database, the authors recently showed that HPV vaccine is amongst the ones most commonly related to ADEM reports. The incidence of ADEM following immunisation with the HPV vaccine is unknown, but the reporting rate was estimated to be $0.26/10^6$ (CI 95%: $0.16/10^6$–$0.37/10^6$). It is therefore possible that these cases are simply close in time with the HPV vaccination rather than result from it.

Along with the introduction of the HPV vaccine, the onset or exacerbation of MS has been reported in some patients within few days from the vaccine shot. Despite the coincidence in time between vaccine shot and disease onset, it is unclear whether the vaccination had a role in the onset of the

[9] Pellegrino P, Carnovale C, Perrone V et al 2014 'Can HPV immunisation cause ADEM? Two case reports and literature review' MSJ 20: 762-763

[10] Pellegrino P, Carnovale C, Pozzi M et al 2014 'On the relationship between human papilloma virus vaccine and autoimmune diseases' Autoimmunity Reviews 13: 736-741

disease. The reporting rate of MS following HPV vaccination, estimated as previously described for ADEM, was 0.08/100,000 doses in the United States and 0.14/100,000 doses in Australia. The authors compared this with the incidence of MS in the population exposed to the HPV vaccine, estimated to be one case per 100,000 subject every 6 weeks. The authors considered that such disproportion between the reporting rate and the incidence may indicate an absence of correlation between HPV vaccine and MS.

Table 8 Cases of autoimmune disease following HPV vaccination

Ref	Authors	Vaccine	Condition	Age (years)
[20]	Shaffer et al.	Bivalent	ADEM	15
[21]	Wildeman et al.	Quadrivalent	ADEM	20
[22]	Mendoza et al.	Quadrivalent	ADEM	15
[23]	Pellegrino et al.	Quadrivalent	ADEM	13
[23]		Unknown	ADEM	12
[24]	Dimario et al.	Quadrivalent	ADEM	16
[26]	Menge et al.	Quadrivalent	NMO	17
[26]		Quadrivalent	NMO	14
[26]		Quadrivalent	NMO	13
[26]		Quadrivalent	NMO	18
[31]	Sutton et al.	Quadrivalent	CIS	21
[31]		Quadrivalent	CIS	16
[31]		Quadrivalent	CDMS	25
[31]		Quadrivalent	CDMS	21
[31]		Quadrivalent	CDMS	26
[32]	Change et al.	Quadrivalent	CIS	19
[32]		Quadrivalent	CIS	18
[40]	Gatto et al.	Quadrivalent	SLE	32
[40]		Quadrivalent	SLE	29
[40]		Quadrivalent	SLE-like	16
[40]		Quadrivalent	antiphospholipid antibody syndrome	16
[40]		Quadrivalent	SLE	19
[40]		Quadrivalent	SLE	13
[41]	Soldevilla et al.	Unknown	SLE	17
[41]		Unknown	SLE	45
[41]		Unknown	SLE	58
[53]	Colafrancesco	Quadrivalent	POF	14
[53]	et al.	Quadrivalent	POF	13
[53]		Quadrivalent	POF	31
[54]	Little et al.	Quadrivalent	POF	16
[55]	Cerami et al.	Quadrivalent	Autoimmune neuromyotonia	32
[56]	Della Corte et al.	Bivalent	Autoimmune hepatitis type 2	11
[58]	Melo Gomes et al.	Unknown	HSP	15
[58]		Unknown	Cutaneous vasculitis	13
[59]	Watanabe et al.	Unknown	Kikuchi–Fujimoto disease	14
[60]	Yonee et al.	Bivalent	Acute cerebellar ataxia	12
[61]	Katoulis et al.	Quadrivalent	Erythema multiforme	19
[62]	Pugnet et al.	Quadrivalent	Immune thrombocytopenic purpura	16

ADEM: acute disseminated encephalomyelitis; NMO: neuromyelitis optica; CIS: clinical isolated syndrome; CDMS: clinical defined multiple sclerosis; SLE: systemic lupus erythematosus; POF: primary ovarian failure.

The authors have noted an absence of a significant increase in the number of hospital discharges for SLE in patients largely exposed to HPV vaccine. Together with the expected coincidental cases expected to be reported in association with vaccination, these reports indicate the lack of a significant correlation between HPV vaccination and SLE exacerbation.

These lessons about the effect of misinterpretation of the relationship between autoimmune disease and a vaccine should thus be considered when we discuss on the safety of a newly introduced vaccine. Because the immunisation is recommended for groups of patients (young female) in which the incidence of autoimmune disease is high. A confounding factor that adds to the problem is the lack of information on the established incidence of several diseases in some regions of the world; this aspect makes it difficult to assess the baseline incidence of a disease and its change after the introduction of a new vaccine.

Comments

This review indicates the low number of reports of autoimmune conditions temporally associated with HPV vaccination. These authors also published a separate paper on MS (includes the cases outlined above) and concluded there was no association. [11]

[11] Pellegrino P, Carnovale C, Perrone V et al 2013 'No evidence of a link between multiple sclerosis and the vaccine against the human papillomavirus' Eur J Epidemiol 28: 705-707

3.2 Observational Studies

3.2.1 Gee[12]

The authors performed a safety assessment of qHPV vaccine in 7 large managed care organisations (MCOs), part of the vaccine safety datalink. Subjects were females aged 9-26 years exposed between August 2006 and October 2009.

Sequential analyses were conducted weekly to detect associations between qHPV exposure and pre-specified outcomes: GBS, stroke, VTE, appendicitis, seizures, syncope, allergic reactions and anaphylaxis. For rare outcomes, historical background rates were used as the comparison group. For more common outcomes a concurrent unexposed comparison group was used. A standardised review of medical records was conducted for all cases of GBS, VTE and anaphylaxis.

Table 9 Background incidence rates for outcomes used in the Poisson maximum sequential ratio test analyses, Vaccine safety datalink 2006-2009.

Outcome	Comparison window (days)	Chosen data source	Age group (yrs)	Incidence rate (per 100,000 PY)
Guillain–Barré syndrome	1–42	HCUP[a]	9–10	0.945
			11–14	1.257
			15–17	2.130
			18–26	2.251
Appendicitis	0–42	VSD[b]	9–17	133.440
			18–26	124.427
Stroke	0–42	VSD[b]	9–17	2.656
			18–26	7.454
Venus Thromboembolism	1–42	VSD[b]	9–13	3.221
			14–17	13.428
			18–26	73.642

[a] Heath care utilization project data from 1991 to 2004.
[b] VSD data from 2000 to June 2006.

Table 10 Relative risks of selected outcomes following qHPV vaccination in analyses using historical comparison group, Vaccine Safety Datalink 2006-2009

Outcome	Youth/adult	Upper limit	Last week of analysis[a]	Doses adminis-tered	Observed events	Expected events under H0	RR	Log likelihood ratio (LLR)	Critical value of LLR	Signal
Guillain–Barré syndrome	Youth[b]	1	164	416,942	0	0.80	0.00	–	2.81	No
	Adult[b]	1	164	183,616	1	0.48	2.10	0.22	2.86	No
Appendicitis	Youth	60	79	203,890	50	32.80	1.52	3.88	3.86	Yes
	Adult	25	120	139,746	33	25.03	1.32	1.15	3.68	No
Stroke	Youth[b]	1.5	164	416,942	0	1.35	0.00	–	2.97	No
	Adult	1.5	98	112,619	2	1.50	1.33	0.07	2.97	No
Venus Thromboembolism	Youth	4	110	292,302	8	4.04	1.98	1.51	3.25	No
	Adult	15	156	176,194	11	15.00	0.73	–	3.57	No

[a] The earliest of the following: upper limit reached, signal occurred or end of study.
[b] Upper limit not reached – results from the last available week of analysis.
Week 1 defined as August 20, 2006.

Table 11 Relative risks of selected outcomes following qHPV vaccination in analysis using concurrent comparison group, Vaccine Safety Datalink 2006-2009

Outcome	Youth/adult	Upper limit (100 K HPV doses)	Last week of analysis[a]	Doses administered	# of comparison visit	Exposed cases	Un-exposed cases	RR	Si
Seizure	Youth	350	138	351,706	206,045	47	23	1.02	N
	Adult	150	142	150,603	283,666	22	37	1.13	N
Syncope	Youth	350	138	351,630	146,833	610	202	0.86	N
	Adult	150	142	150,544	54,584	170	95	0.54	N
Allergic reactions	Youth	350	138	351,630	146,833	54	29	0.77	N
	Adult	150	142	150,544	54,584	37	8	1.48	N

[a] The earliest of the following: upper limit reached, signal occurred or end of study.
Week 1 defined as August 20, 2006.

[12] Gee J, Naleway A, Shui I et al 2011 'Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the vaccine safety datalink' Vaccine 29: 8279-8284

The authors concluded that they had conducted the largest postlicensure active surveillance of HPV4 in the United States. Although additional study is warranted for a possible association between HPV4 and VTE, the authors found no statistically significant associations between HPV4 and VTE or any of the other pre-specified outcomes of interest. A possible association with VTE following HPV4 administration, although not statistically significant, deserves additional study.

Comments

This initial observational study showed no association between GBS, syncope or seizures and HPV vaccination. GBS associated with HPV vaccination was also looked at by Ojha[13] using VAERS data. No signal was identied.

3.2.2 Chao[14]

The authors report the results of an observational safety study of HPV4 in women to determine the risk of new diagnoses for 16 pre-specified autoimmune conditions.

Table 12 Exposure to HPV4 doses, diagnostic certainty and timing of disease onset

Condition	A. Case Review Committee confirmed new-onset cases[a] *n*	B. Exposed to 1 dose prior to disease onset *n* (% of confirmed cases from A)	C. Exposed to 2 doses prior to disease onset	D. Exposed to 3 doses prior to disease onset	E. Strong level of diagnostic certainty[b]	F. Days to disease onset since 1st dose of HPV4[c] Median (range[d])	G. Age (yrs) at disease onset Median (range[d])
Rheumatologic/autoimmune	25	19 (76)	5 (20)	1 (4)	19 (76)	55 (1–176)	16 (11–23)
Immune thrombocytopenia	11	6 (55)	4 (36)	1 (9)	8 (73)	36 (1–176)	16 (11–18)
Autoimmune haemolytic anaemia	0	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]
Systemic lupus erythematosus[f]	8	8 (100)	0 (0)	0 (0)	8 (100)	44.5 (3–140)	16.5 (13–23)
Rheumatoid arthritis[f]	3	3 (100)	0 (0)	0 (0)	3 (100)	62 (62–106)	18 (16–18)
Juvenile rheumatoid arthritis[f]	3	2 (67)	1 (33)	0 (0)	0 (0)	55 (15–139)	14 (14–14)
Endocrine	67	37	20	9	48 (72)	56 (1–175)	16 (11–25)
Type 1 diabetes[g]	15	9 (60)	2 (13)	3 (20)	11 (73)	56 (7–175)	14 (11–20)
Hashimoto's disease[f]	39	20 (51)	14 (36)	5 (13	30 (77)	52 (1–162)	16 (11–25)
Graves' disease[f]	13	8 (62	4 (31)	1 (8)	7 (54)	56 (1–162)	17 (15–23)
Neurological/ophthalmic	32	19 (59)	9 (28)	4 (13)	21 (66)	46.5 (1–161)	16 (12–27)
Multiple sclerosis	5[h]	3 (60)	1 (20)	1 (20)	4 (80)	73 (14–92)	17 (15–26)
Acute disseminated encephalomyelitis	3[h]	2 (67)	1 (33)	0 (0)	2 (67)	46 (14–62)	16 (15–16)
Other demyelinating diseases of the central nervous system	3[h]	1 (33)	2 (67)	0 (0)	3 (100)	38 (3–67)	17 (14–26)
Guillain–Barrè syndrome	0	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]
Neuromyelitis optica	0	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]
Optic neuritis	6	3 (50)	1 (17)	2 (33)	6 (100)	65.5 (14–144)	15.5 (14–24)
Uveitis	15	10 (67)	4 (27)	1 (7)	5 (33)	45 (1–161)	17 (12–27)

Left to right – in order of appearance by each row.
[a]New onset within 180 days post-HPV4 vaccination.
[b]At least two Case Review Committee members indicated strong level of diagnostic certainty.
[c]Based on the estimated date of disease onset indicated by the Case Review Committee members.
[d]For each confirmed case, the date of disease onset indicated by each Case Review Committee member was averaged to give the averaged date of disease onset for this case. The median and range for all confirmed cases was then calculated based on the averaged date of disease onset for each case.
[e]Not applicable because no cases were confirmed as new onset after vaccination.
[f]Potential cases of five conditions were randomly sampled for case review: systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, Hashimoto's disease and Graves' disease.
[g]One confirmed type 1 diabetes case had four HPV4 doses prior to disease onset.
[h]Three additional subjects were electronically identified as 'other demyelinating disease of the central nervous system' and after case review, one was acute disseminated encephalomyelitis, one was multiple sclerosis, and the third (not counted in this table) was multiple sclerosis with diagnosis prior to vaccination date.

Data from two managed care organisation in California were utilised (Kaiser Permamente Southern California and Northern California). Conditions of interest were ITP, autoimmune haemolytic anaemia, SLE, RA, JRA, T1DM, Hashimoto's disease, Graves Disease, MS, ADEM, vaccine-associated demyelination, GBS, neuromyelitis optica, optic neuritis and uveitis.

[13] Ojha R, Jackson BE, Tota JE et al 2014 'Guillain-Barre syndrome following quadrivalent human papillomavirus vaccination among vaccine-eligible individuals in the United States' Human vaccines & immunotherapeutics 10: 232-237.

[14] Chao C, Klein NP, Velicer CM et al 2011 'Surveillance of autoimmune conditions following routine se of quadrivalent human papillomavirus vaccine' J Int Med 271: 193-203

189,629 women received ≥1 dose of HPV4 between August 2006 and March 2008. Medical records of those with ≥12 month health plan members prior to vaccination were reviewed by clinicians to confirm the diagnosis and determine the date of disease onset. The incidence of each autoimmune condition was estimated for unvaccinated women at one study site using multiple imputations and compared with that observed in vaccinated women. Timing of vaccine associated events was considered to be from the first HPV4 dose to 180 days after the last dose.

Table 13 Incidence rate ratio and 95% confidence interval of select autoimmune conditions in the vaccinated vs non-vaccinated women

	Main comparison				Sensitivity analysis 1 Direct comparison with electronic case identification only (not incorporating new-onset confirmation rate obtained from case review)				Sensitivity analysis 2 Case identification with original ICD-9 codes only[a] (incorporating new-onset confirmation rate obtained from case review)			
	Vaccinated	Unvaccinated			Vaccinated	Unvaccinated			Vaccinated	Unvaccinated		
Condition	No. of Observed cases[b] (Incidence[c])	No. of Estimated cases (Incidence[c])	IRR	95% CI	No. of Observed cases[b] (Incidence[c])	No. of Estimated cases (Incidence[c])	IRR	*P*-value[d]	No. of Observed cases[b] (Incidence[c])	No. of Estimated cases (Incidence[c])	IRR	95% CI
Rheumatologic/autoimmune												
Immune thrombocytopenia	6 (6.8)	33 (5.9)	1.16	(0.85–1.83)	10 (11.4)	56 (10.0)	1.14	0.70	6 (6.8)	31 (5.5)	1.24	(0.91–2.02)
Autoimmune haemolytic anaemia	–	–	–	–	–	–	–	–	–	–	–	–
Systemic lupus erythematosus	10 (11.4)	58 (10.3)	1.07	(0.69–1.60)	31 (35.3)	157 (28.0)	1.26	0.24	8 (9.1)	46 (8.2)	1.10	(0.71–1.66)
Rheumatoid arthritis	4 (4.6)	39 (7.0)	0.71	(0.39–1.45)	8 (9.1)	95 (16.9)	0.54	0.09	3 (3.4)	31 (5.5)	0.70	(0.41–1.60)
Juvenile rheumatoid arthritis	3 (3.4)	43 (7.7)	0.48	(0.26–0.91)	11 (12.5)	106 (18.9)	0.66	0.20	2 (2.3)	38 (6.8)	0.36	(0.14–0.71)
Endocrine												
Type 1 diabetes	9 (10.3)	101 (18.0)	0.57	(0.47–0.73)	12 (13.7)	139 (24.8)	0.55	0.05	8 (9.1)	95 (16.9)	0.54	(0.45–0.70)
Hashimoto's disease[b]	92 (104.8)	455 (81.1)	1.29	(1.08–1.56)	241 (274.6)	1406 (250.6)	1.10	0.19	27 (30.8)	85 (15.2)	2.02	(1.65–2.60)
Graves' disease[b]	16 (18.2)	145 (25.8)	0.72	(0.50–1.01)	44 (50.1)	348 (62.0)	0.81	0.18	6 (6.8)	51 (9.1)	0.76	(0.42–1.10)
Combined Hashimoto's and Graves' disease[b,e]	108 (123.1)	601 (107.1)	1.15	(0.97–1.36)	285 (324.7)	1754 (312.6)	1.04	0.55	33 (37.6)	137 (24.4)	1.54	(1.27–1.92)
Neurological/ophthalmic												
Multiple sclerosis	3 (3.4)	14 (2.5)	1.37	(0.74–3.20)	7 (8.0)	39 (7.0)	1.15	0.74	3 (3.4)	14 (2.5)	1.37	(0.74–3.20)
Acute disseminated encephalomyelitis	–	–	–	–	–	–	–	–	–	–	–	–
Other demyelinating diseases of central nervous system	1 (1.1)	9 (1.6)	0.71	(0.38–2.13)	2 (2.3)	23 (4.1)	0.56	0.43	1 (1.1)	9 (1.6)	0.71	(0.38–2.13)
Guillain-Barré syndrome[f]	–	–	–	–	–	–	–	–	–	–	–	–
Neuromyelitis optica[f]	–	–	–	–	–	–	–	–	–	–	–	–
Optic neuritis	5 (5.7)	22 (3.9)	1.45	(1.00–2.91)	8 (9.1)	45 (8.0)	1.14	0.74	5 (5.7)	22 (3.9)	1.45	(1.00–2.91)
Uveitis	7 (8.0)	67 (11.9)	0.67	(0.49–1.02)	37 (42.2)	212 (37.8)	1.12	0.54	1 (1.1)	5 (0.9)	1.28	(0.53–6.39)

[a]Case identification using original ICD-9 diagnosis codes only – no expanded ICD-9 diagnosis code (e.g. general ICD-9 code 250 for diabetes without specifying code for type 1 diabetes), laboratory or prescription codes were used for case identification.

[b]Observed number of cases and incidence for vaccinated women at Kaiser Permanente Southern California for all autoimmune conditions, except systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, Hashimoto's disease and Graves' disease, for which estimated number of cases and incidence are presented. As sampling was applied in the case review process for these five conditions, the number of cases and incidence are estimated using the multiple imputation approach for these conditions for the vaccinated women, as for the unvaccinated women. Note that the observed number of cases in this table varied from Table 1 as these are cases from the Kaiser Permanente Southern California vaccinated female population only.

[c]Per 100 000 person-years.

[d]New-onset case confirmation rates obtained from the process of medical record review by the Case Review Committee were not applied. As a result, only p-value was calculated for these comparisons.

[e]The combined Hashimoto's and Graves' disease analysis was conducted per the Safety Review Committee's request after reviewing the individual results for Hashimoto's disease and Graves' disease, because of potential similarities in their pathogenesis.

[f]Autoimmune haemolytic anaemia, Guillain-Barré syndrome and neuromyelitis optica were excluded from the background rates comparison analysis because no confirmed cases were found in the vaccinated female population at both Kaiser Permanente Southern and Northern California. Acute disseminated encephalomyelitis was excluded because no confirmed vaccinated case was found at Kaiser Permanente Southern California.

Overall 1014 potential new-onset cases were identified. 719 were eligible for case review; 31-40% were confirmed as new onset (table 10). No cluster of disease onset in relation to vaccination timing, dose sequence or age was found for any autoimmune condition. None of the estimated incidence rate ratios (IRR) were significantly elevated except for Hasimoto's disease IRR 1.29 (1.08-1.56). Further investigation of temporal relationship and biological plausibility revealed no consistent evidence for a safety signal for autoimmune thyroid conditions (Figure 1).

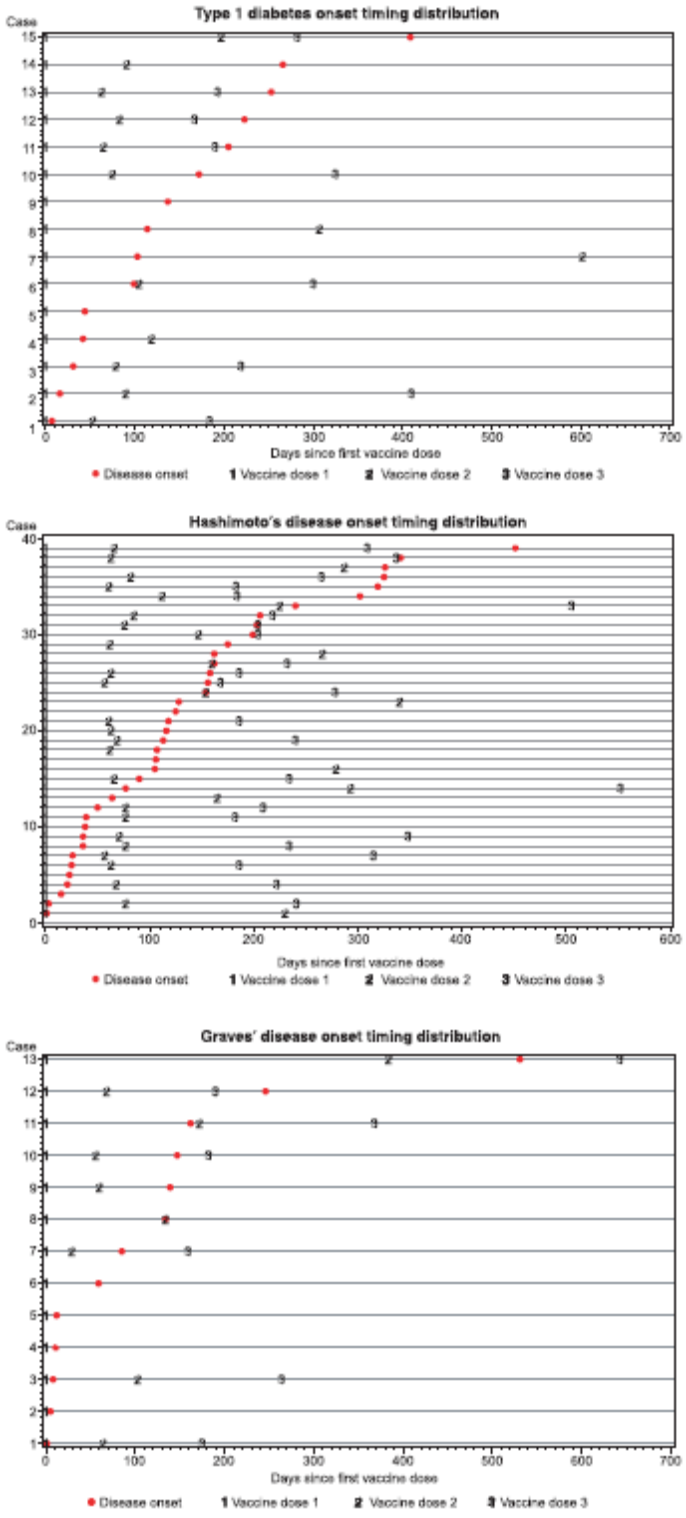


Figure 2 Distribution of date of disease onset for confirmed new onset T1DM, Hashimoto's disease and Graves' Disease cases by doses of HPV4

The authors conclude that there was no clear evidence of a safety signal for autoimmune conditions following vaccination with HPV4. An elevated IRR was seen for Hashimoto's disease a relatively common autoimmune condition in young women. After carefully considering all available safety data the safety review committee and the investigator team interpreted this as unlikely to be a true signal of concern. This conclusion was based on the lack of consistent evidence for a safety signal for

autoimmune thyroid conditions (eg, disease onset was mostly randomly distributed in relation to the vaccination timing).

The initial presentation of autoimmune conditions often involves general symptoms and there is often a lag between initial symptom onset and the correct assignment of diagnosis. To address this issue several strategies were used:

- A 180 day risk period to accommodate lag time for clinical work up.
- Broad highly sensitive case identification criteria.
- Expert panels to confirm diagnosis and date of disease onset
- Only women with ≥12 month membership prior to vaccination were included.

Limitations of the study included.

- Actual timing of initial symptom onset could not always be determined.
- Analyses for many autoimmune conditions were based on a small number of cases which gave the study limited power in examining temporal patterns or estimating the IRR.
- The multiple imputation approach was not a standard methodology for estimating background incidence rates.

Comments

The long onset time is used in observational studies to account for a delay in diagnosis. However, this may mask an association with vaccination since the likely onset time if the vaccine was causal is 5 days to 6 weeks (42 days).

The individual case review appears to have been very important for determining the actual onset of events; further discussion of this was published in the paper outlined below.

For the events that may have a relationship with HPV vaccination and which were subsequently reviewed further the onset times appeared to be randomly distributed. This data would also suggest that HPV vaccination was not inducing events in susceptible patients.

The study is limited by the small number of events.

Overall there was no association between these autoimmune conditions and HPV vaccination.

3.2.3 Jacobsen[15]

This publication provides more information on cases identified in the Chao study. Conducting the above study led the authors to question the adequacy of the exclusion of day 0 events to prevent the erroneous association of prevalent conditions with vaccination.

The authors discuss the 18 confirmed cases of Graves disease diagnosed in day 1-60 following vaccination. Only 6 cases appeared to be truly new onset. Among the the remaining 12 cases, 2 cases had abnormal thyroid stimulating hormone or thyroxine labs drawn prior to or on day 0 but had no documented pre-existing symptoms. The other 10 cases had mention of symptoms of hyperthyroidism referencing a period prior to first qHPV dose.

This unmasking phenomenon, due to health care visits that include vaccination and new workups of preexissting symptoms may not be adequately controlled through the exclusion of day 0 events (since it may take several days for blood results to come through).

Observational studies of vaccine safety often rely on electronically available information on vaccine exposure and subsequent diagnoses. This information often only contains date stamps with no information about the clock time of vaccination or diagnosis. Consequently the temporal

[15] Jacobsen SJ, Sy LS, Ackerson BK et al 2012 'An unmasking phenomenon in an observational post-licensure safety study of adolescent girls and young women' Vaccine 30: 4585-87

relationship between vaccination and a new diagnosis on the day of vaccination can be difficult to ascertain. For example the diagnosis may have been for an incident condition resulting from the vaccination or alternatively the diagnosis may reflect a prevalent condition that led to the healthcare visit during which the vaccine was administered. This paradox has been informally labelled the **day 0 phenomenon**. Because of this most studies do not include the day of vaccination for surveillance of adverse events in the outpatient setting, except for selected fast onset conditions such as anaphylaxis, allergy/wheezing and febrile convulsion.

In the example of Graves' disease, there were several instances in which a TSH or T4 level was measured in response to signs and symptoms observed or reported during the vaccination visit. Had the authors not reviewed the medical records these cases would likely have been attributed to the vaccine rather than the visit per se.

In younger children who are seeing healthcare professionals regularly, the recognition of a new onset chronic condition at vaccination would be relatively rare and approximate the true incidence. In older children and adults care is more intermittent and therefore not providing the opportunity for these diagnosis to be made. In these groups the longer the interval between car episodes the more likely the apparent incidence rate would approach the prevalence of disease because of the lack of opportunity for interim diagnoses.

This phenomenon may be more pronounced in men and likely varies from condition to condition.

Comments
This phenomenon would only be relevant when patients are visiting a healthcare provider for vaccination. In a school based programme it is not clear that the vaccinator would be consulted about prevalent symptoms.

3.2.4 Arnheim-Dahlstroem[16]

The objective of this study was to assess the risk of serious adverse events after vaccination of adolescent girls with qHPV vaccine.

This was a register based cohort study based on individual level data from all 11 to 17 year old adolescent girls in Denmark and Sweden between 1 Oct 2006 and 31 Dec 2010.

The authors measured incident hospital diagnosed autoimmune, neurological and venous thromboembolic events (53 different outcomes) up to 180 days after each qHPV vaccine dose. Only events with at least 5 vaccine exposed cases were considered for further assessment. Outcomes were identified from the national patient registers using ICD10 codes. There was no information on outcomes from primary care.

Adolescent girls were followed from age 10 years to 1 October 2006 until either the occurrence of an adverse event, receipt of qHPV vaccine, death, disappearance from the registers, emigration, 18th birthday or 31 Dec 2010. The authors aggregated the resulting person years of follow up with counts of outcome events according to qHPV vaccine exposure status and analysed these using Poisson regression. This produced incidence rate ratios according to qHPV exposure status. Exposure to qHPV was a time varying variable, thus subjects could contribute person time to the study first as unvaccinated and later as vaccinated, but once vaccinated subjects could not be put into the unvaccinated category again.

[16] Arnheim-Dahlstroem L, Pasternak B, Svanstroem H et al 2013 'Autoimmune, neurological and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study' BMJ 247:f5906

Table 14 Descriptive characteristics of girls aged 10-17 years included in the cohort. Values are numbers (percentages) unless stated otherwise

Characteristics	Overall (n=997 585)	Denmark (n=387 294)	Sweden (n=610 291)
Person years of follow-up	2 797 701	1 090 515	1 707 186
Mean (SD) age at study entry (years)	12.8 (2.7)	12.5 (2.6)	12.9 (2.7)
Year of study entry:			
2006	700 156 (70.2)	260 849 (67.4)	439 307 (72.0)
2007	74 809 (7.5)	32 044 (8.3)	42 765 (7.0)
2008	73 653 (7.4)	31 307 (8.1)	42 346 (6.9)
2009	73 909 (7.4)	31 439 (8.1)	42 470 (7.0)
2010	75 058 (7.5)	31 655 (8.2)	43 403 (7.1)
Exposed to quadrivalent human papillomavirus vaccine			
Mean (SD) age at vaccination (years)	14.6 (1.7)	14.0 (1.6)	15.7 (1.4)
Total vaccine doses, No (% of total No in cohort):	696 420	409 724	286 696
Dose 1	296 826 (29.8)	188 053 (48.6)	108 773 (17.8)
Dose 2	238 608 (23.9)	139 861 (36.1)	98 747 (16.2)
Dose 3	160 986 (16.1)	81 810 (21.1)	79 176 (13.0)
Year of first vaccine dose, No (% of vaccinated):			
2006	426 (0.1)	248 (0.1)	178 (0.2)
2007	22 943 (7.7)	6280 (3.3)	16 663 (15.3)
2008	41 799 (14.1)	12 314 (6.5)	29 485 (27.1)
2009	170 830 (57.6)	133 571 (71.0)	37 259 (34.3)
2010	60 828 (20.5)	35 640 (19.0)	25 188 (23.2)
Data from vaccination registers	572 696 (82.2)	351 804 (85.9)	220 892 (77.0)
Data from prescription registers	123 724 (17.8)	57 920 (14.1)	65 804 (23.0)

Because of rounding, percentages may not total 100.

For all autoimmune and neurological outcomes the period of risk was defined as 180 days after exposure. This period was chosen to allow for the insidious onset of the diseases studies and because diagnostic investigations may take time.

As the recommended qHPV vaccine schedule includes three doses given as 0, 2 and 6 months, any subject could contribute up to three doses in the analysis. The authors counted exposed person time from the date the vaccine was administered and each dose contributed up to 180 (90) days of follow up.

Rate ratios adjusted for age, country, calendar year and parental country of birth, education and socioeconomic status were estimated comparing vaccinated and unvaccinated person time. For outcomes where the rate ratio was significantly increased three criteria were regarded as signal strengthening:

- Analysis based on 20 or more vaccine exposed cases (reliability)
- rate ratio 3.0 or more (strength)
- significantly increased rate ratio in country specific analyses (consistency).

The authors also assessed clustering of events in time and estimated rate ratios for a risk period that started on day 181.

Table 15 Rates of adverse events according to qHPV vaccination status

	Unvaccinated			Within 180 days after qHPV vaccine exposure		
Adverse events	**Person years**	**No of events**	**Incidence rate* (95% CI)**	**Person years**	**No of events**	**Incidence rate* (95% CI)**
Autoimmune						
Thyroid:						
Graves' disease	2 373 554	237	9.99 (8.79 to 11.34)	229 914	27	11.74 (8.05 to 17.12)
Hashimoto's thyroiditis	2 371 866	560	23.61 (21.73 to 25.65)	229 751	50	21.76 (16.49 to 28.71)
Other hyperthyroidism	2 373 629	250	10.53 (9.30 to 11.92)	229 946	23	10.00 (6.65 to 15.05)
Hypothyroidism	2 368 919	1018	42.97 (40.41 to 45.70)	229 563	79	34.41 (27.60 to 42.90)
Gastrointestinal:						
Coeliac disease	2 358 918	1413	59.90 (56.86 to 63.11)	228 820	107	46.76 (38.69 to 56.52)
Crohn's disease	2 372 337	539	22.72 (20.88 to 24.72)	229 825	47	20.45 (15.37 to 27.22)
Ulcerative colitis	2 373 288	350	14.75 (13.28 to 16.38)	229 889	35	15.22 (10.93 to 21.20)
Pancreatitis	2 374 129	103	4.34 (3.58 to 5.26)	230 004	10	4.35 (2.34 to 8.08)
Muscoloskeletal or systemic:						
Ankylosing spondylitis	2 374 065	93	3.92 (3.20 to 4.80)	230 001	8	3.48 (1.74 to 6.96)
Behcet's syndrome	2 374 464	13	0.55 (0.32 to 0.94)	230 025	5	2.17 (0.90 to 5.22)
Henoch-Schönlein's purpura	2 369 280	203	8.57 (7.47 to 9.83)	229 365	17	7.41 (4.61 to 11.92)
Juvenile arthritis	2 366 484	861	36.38 (34.03 to 38.90)	229 202	86	37.52 (30.37 to 46.35)
Myositis	2 373 974	84	3.54 (2.86 to 4.38)	229 988	8	3.48 (1.74 to 6.96)
Rheumatoid arthritis	2 373 763	216	9.10 (7.96 to 10.40)	229 943	27	11.74 (8.05 to 17.12)
Systemic lupus erythematosus	2 374 231	74	3.12 (2.48 to 3.91)	230 005	11	4.78 (2.65 to 8.64)
Vasculitis, unspecified	2 373 826	89	3.75 (3.05 to 4.61)	229 959	14	6.09 (3.61 to 10.28)
Haematological:						
Idiopathic thrombocytopenic purpura	2 373 040	107	4.51 (3.73 to 5.45)	229 896	14	6.09 (3.61 to 10.28)
Dermatological:						
Erythema nodosum	2 373 608	163	6.87 (5.89 to 8.01)	229 935	19	8.26 (5.27 to 12.95)
Localised scleroderma	2 374 016	88	3.71 (3.01 to 4.57)	229 976	6	2.61 (1.17 to 5.81)
Psoriasis	2 368 423	1091	46.06 (43.41 to 48.88)	229 540	80	34.85 (27.99 to 43.39)
Vitiligo	2 372 765	310	13.06 (11.69 to 14.60)	229 886	24	10.44 (7.00 to 15.58)
Miscellaneous						
Raynaud's disease	2 373 798	218	9.18 (8.04 to 10.49)	229 939	37	16.09 (11.66 to 22.21)
Type 1 diabetes	2 363 153	975	41.26 (38.75 to 43.93)	228 965	99	43.24 (35.51 to 52.65)
Neurological						
Bell's palsy	2 370 195	480	20.25 (18.52 to 22.15)	229 675	41	17.85 (13.14 to 24.24)
Epilepsy	2 351 894	1701	72.32 (68.97 to 75.84)	227 897	116	50.90 (42.43 to 61.06)
Narcolepsy	2 374 402	43	1.81 (1.34 to 2.44)	230 018	6	2.61 (1.17 to 5.81)
Optical neuritis	2 374 273	61	2.57 (2.00 to 3.30)	230 013	6	2.61 (1.17 to 5.81)
Paralysis	2 367 206	302	12.76 (11.40 to 14.28)	229 574	20	8.71 (5.62 to 13.50)
Venous thromboembolism†	2 373 786	297	12.51 (11.17 to 14.02)	149 817	21	14.02 (9.14 to 21.50)

Table shows outcomes with five or more vaccine exposed cases.

*Events per 100 000 person years.

†Risk window for venous thromboembolism was within 90 days after vaccine exposure.

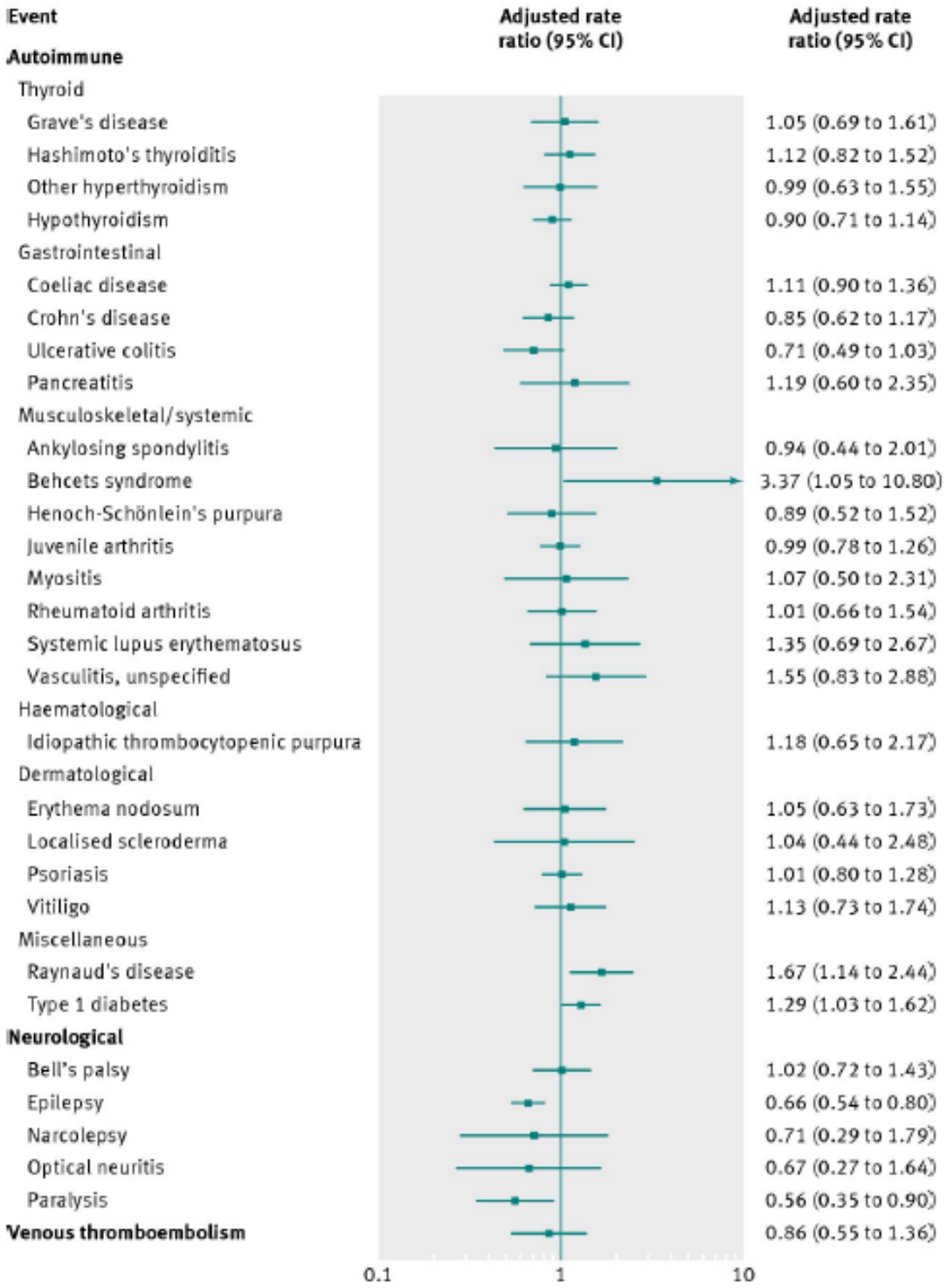


Figure 3 Association between exposure to qHPV vaccine and adverse events in adolescent girls.

997,585 girls aged 10-17 were included. 296,826 received a total of 696,420 qHPV vaccine doses.

Among the 53 outcomes at least 5 vaccine exposed cases occurred in 29 conditions and these were analysed further. Exposure to qHPV was significantly associated with Bechet's syndrome, Raynaud's disease and type 1 diabetes. Each of these outcomes fulfilled only one of the predefined signal strengthening criteria. Furthermore, the pattern of distribution in time after vaccination was random for all 3 and the rate ratios for these outcomes in the period from day 181 after vaccination were similar to the rate ratios in the primary risk period.

The rate ratios for 5 neurological events were not significantly increased and there were inverse associations with epilepsy (RR 0.66 (0.54-0.8)), and paralysis (RR 0.56 (0.35-0.90)) (Figure 3).

There was no association between exposure to qHPV vaccine and VTE (RR 0.86 (0.55-1.36)).

Table 16 Evaluation of signal strengthening criteria among outcomes where rate ratios were significantly increased

Criterion	Behcet's syndrome	Raynaud's disease	Type 1 diabetes
Analysis based on 20 or more vaccine exposed cases	No (n=5)	Yes (n=37)	Yes (n=99)
Rate ratio ≥3.0	Yes (3.37)	No (1.67)	No (1.29)
Significantly increased rate ratios in both countries when analysed separately	No (3.38*, 95% CI 0.83 to 13.84 for Sweden (3 exposed cases); 4.63†, 95% CI 0.64 to 33.66 for Denmark (2 exposed cases))	No (1.86*, 95% CI 1.19 to 2.89 for Sweden (25 exposed cases); 1.46*, 95% CI 0.64 to 3.33 for Denmark (12 exposed cases))	No (1.47*, 95% CI 1.08 to 2.01 for Sweden (47 exposed cases); 1.09*, 95% CI 0.76 to 1.57 for Denmark (52 exposed cases))

*Adjusted for age in two year intervals, calendar year, and parental country of birth, parental education, and paternal socioeconomic status.
†Adjusted for age in two year intervals (model with full adjustment did not converge).

Limitations of the study.

- The case definition was based on hospital diagnoses, but in Denmark and Sweden girls with these severe conditions are under specialised paediatric care.
- Dates of onset of symptoms or disease were not available so date of diagnoses were used. It is possible that a proportion of events attributed to vaccine exposure had symptom onset prior to vaccine exposure. Similarly some events may have been missed that could be attributed to vaccine exposure. The authors therefore used a long risk period of 180 days. However this may have been too short to capture disease with a more insidious onset. Because this may be the case for narcolepsy the authors also conducted a sensitivity analysis starting on day 181 after vaccination. No significant association was observed with narcolepsy.
- An unmasking phenomenon has been described in vaccine safety research. This refers to the fact that the vaccination visit provides an opportunity to evaluate symptoms that may not have been evaluated otherwise and hence that those vaccinated may be more likely to have certain disorders diagnosed. This would bias results towards increased risk attributed to vaccination. This is unlikely for disease with relatively prominent and well recognised symptoms such as T1DM, but is plausible for disease that may present with obscure symptoms or that initially may be interpreted as normal variation such as Raynaud's.

The authors concluded that they found no evidence supporting associations between exposure to qHPV vaccine and autoimmune, neurological and VTE events. Although associations for 3 autoimmune events were initially observed on further assessment these were weak and not temporally related to vaccine exposure. Furthermore the findings need to be interpreted considering the multiple outcome assessed.

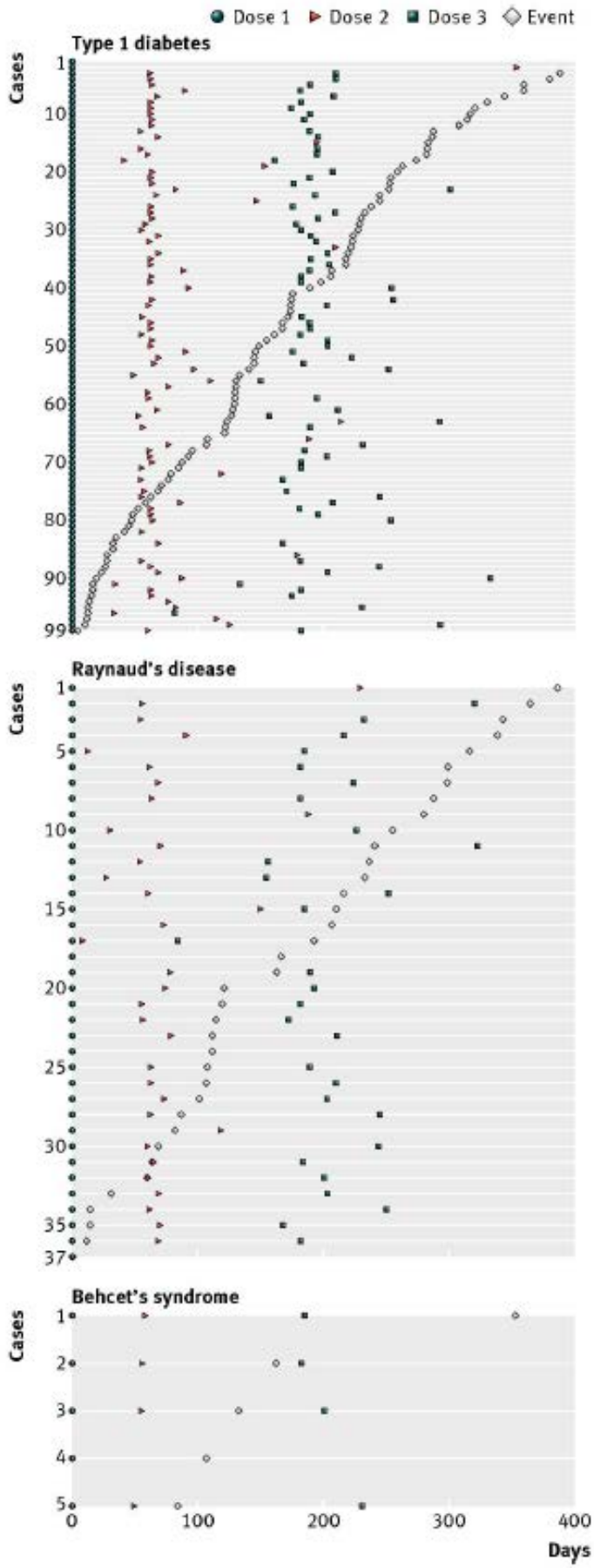


Figure 4 Distribution of cases according to days since first dose of qHPV vaccine.

Comments

The random onset times in relation to vaccination suggests that there is no association. The results appear to be similar to the Chao study adding more weight to the negative association. The study is still somewhat limited by the low number of events.

3.2.5 Grimaldi-Bensouda[17]

The aim of this study was to investigate whether the quadrivalent human papillomavirus vaccine (Gardasil) is associated with a change in the risk of autoimmune disorders (AD) in young female subjects. The authors used a systematic case-control study of incident autoimmune disorders associated with qHPV in young women across France.

The Pharmacoepidemiologic General Research Extension (PGRx) programme is an ongoing research platform recruiting (i) cases of ADs prospectively to clinical registries in France through networks of centres interested in research on Ads [8], and (ii) representative pools of patients from general practice for the selection of controls. Cases and controls drawn from these registries were female, aged 14–26 years, and living in France.

A total of 113 specialised centres recruited (from December 2007 to April 2011) females aged 14–26 years with incident cases of six types of ADs: idiopathic thrombocytopenic purpura (ITP), central demyelination/multiple sclerosis (MS), Guillain– Barre syndrome (GBS), connective tissue disorders (systemic lupus erythematosus (SLE), rheumatoid arthritis/ juvenile arthritis), type 1 diabetes mellitus (T1DM) and autoimmune thyroiditis. Control subjects matched to cases were recruited from general practice.

Recruitment to the registries was exhaustive during the study period (identifying all potentially eligible cases), regardless of any exposure history, including individuals of all ages and both sexes. Amongst the female patients aged 14–26 years included in this study, the first symptoms of AD appeared between 1 December 2006, the date when the quadrivalent HPV vaccine Gardasil was first marketed nationally, and 31 December 2010 (inclusive) for central demyelination or 30 April 2011 (inclusive) for all other ADs.

Human papillomavirus vaccination history was assessed using prescription records received from cases and referents, as well as directly from GPs and during the telephone interviews. Using this method, a high level of agreement (95.9%) between medical records and patients' reports of HPV vaccination was demonstrated in a validation study

Cases and referents underwent a standardised telephone interview including questions concerning socio-demographic, medical and lifestyle factors, as well as all use of medicines (prescription or over the counter) and vaccines within 24 months before the recruitment consultation date. Interviews were conducted within 45 days of recruitment by trained interviewers blind to case/ referent status. An interview guide was provided to patients prior to the interview. The index date was the date of the first clinical sign or symptom suggestive of the AD in the case, reported by the recruiting specialist. The same date was taken as the index date for each matched control. Only factors reported for the period on or before the index date were included in the analysis.

[17] Grimaldi-Bensouda L, Guillemot D, Godeau B et al 2014 'Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects' J Int Med 275: 398-408

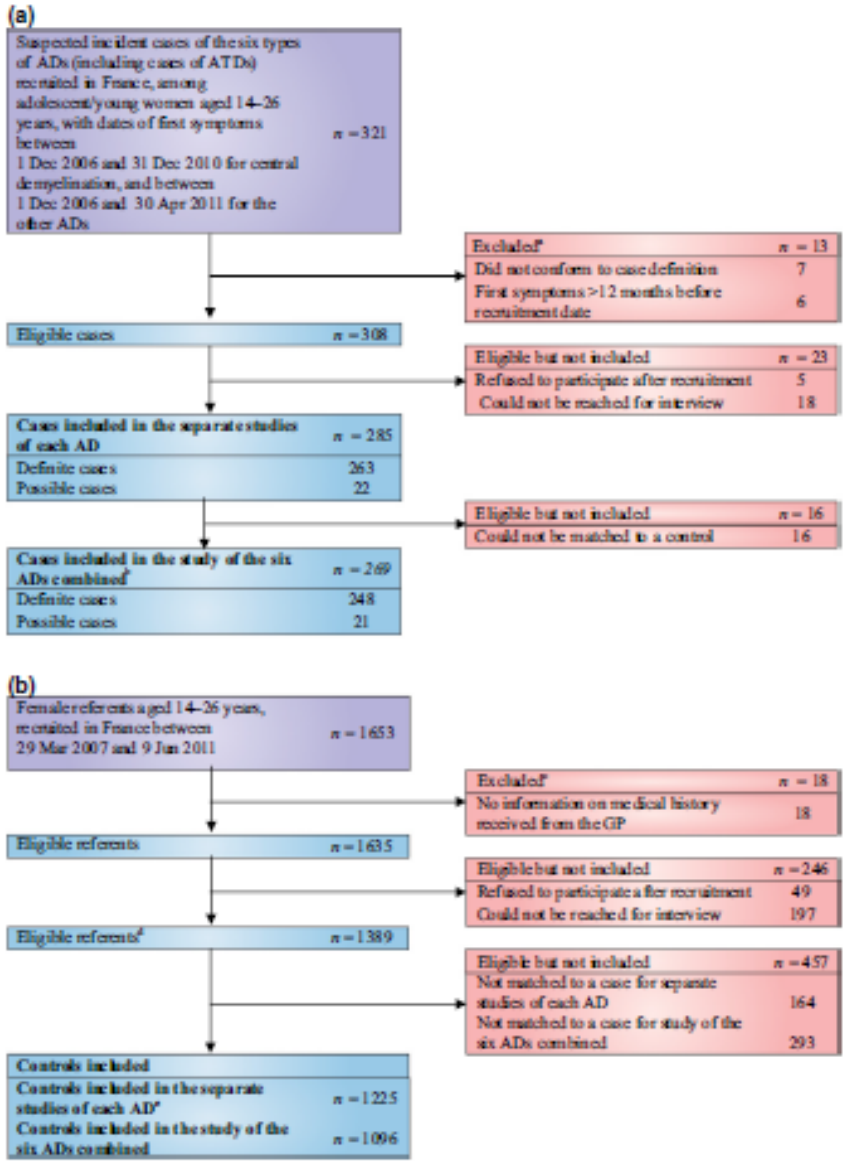


Fig. 1 *Flow charts describing the recruitment of cases (a) and control subjects (b). AD, autoimmune disorder; ATD, autoimmune thyroid disorder; GP, general practitioner.* [a]*Vaccination with Gardasil in excluded cases: of the seven not conforming to the case definition, none was vaccinated; of the six not included with first symptoms > 12 months before recruitment, one was vaccinated; of the 23 not interviewed, medical records were obtained for 15 (four were vaccinated); of the 16 not matched to a control, none was vaccinated.* [b]*The study of the ADs combined included fewer cases than the separate studies of each AD. Each control could only be matched to one case for the combined study, so 16 cases could not be matched. For the separate studies of each AD, a control could be matched to more than one case if the cases had different ADs.* [c]*Vaccination with Gardasil in excluded referents: of the 18 excluded with no information on medical history, 10 were interviewed (four were vaccinated); of the 197 not reached for the interview, medical records were obtained for 187 (31 were vaccinated).* [d]*The pool of eligible referents included patients with a history of AD. For each AD case, only referents with no history of that AD were selected as potential controls. In referents, a history of AD was defined as ADs reported by the recruiting GP or a treatment consistent with AD reported by the patient (list of treatments available upon request).* [e]*For the separate studies of each AD, a control could be matched to more than one case if the cases had different ADs. Thus, some controls were included for several ADs.*

Figure 5 Flow chart for the Grimaldi-Bensouda study

Exposure to the Gardasil vaccine was defined according to predefined time windows before the index date. The primary time windows considered were ≤6 months before the index date for ITP, ≤2 months for Guillain–Barre syndrome and ≤24 months for the other ADs. Other time windows were used in sensitivity analyses. If a patient was vaccinated at least once within a time window, she was considered to be exposed for that analysis.

Multivariate conditional logistic regression analysis; factors included age, geographical origin smoking, alcohol consumption, use of oral contraceptive(s) or vaccine(s) other than Gardasil received within 24 months before the index date and personal/ family history of ADs.

Three analyses were performed, first for all studied ADs except autoimmune thyroid disorders (ATDs) (i.e. ITP, connective tissue disorders, central demyelination and MS, Guillain-Barre syndrome and type 1 diabetes mellitus) combined and then for each of the five ADs separately, if the sample size allowed. Cases of ATDs were included in the descriptive analyses, but not in the case–control analysis because of uncertainty regarding the date of first symptoms in many cases, which led to doubts concerning their definition as incident diagnoses. First, only definite cases and their matched controls were compared for confirmed exposure to the vaccine during the primary time window. Secondly, these analyses were repeated using different time windows. Thirdly, sensitivity analyses were performed by also including possible cases and their matched controls and unconfirmed vaccine exposure during the primary time window.

Table 17 Description of cases and controls for the six types of ADs combined.

Characteristics[a]	Definite and possible cases (n = 269) (%)	Controls[b] (n = 1096) (%)	P-value
Age, years			
14–17	24.2	25.5	NA
18–26	75.8	74.5	
Mean (standard deviation)	21.4 (3.8)	21.2 (3.8)	
Region of residence in France			
North	57.2	57.2	NA
South	42.8	42.8	
Geographical origin[c]			
Northern Europe and North America	83.6	90.9	<0.001
Other	11.2	3.4	
Missing	5.2	5.7	
Smoking			
Smoker	36.8	33.7	0.61
Former smoker (stopped smoking for ≥1 year)	5.2	4.9	
Never smoked	58.0	61.4	
Alcohol consumption			
Daily or almost daily	0.4	0.0	0.71
A few times per week	8.9	8.5	
Occasionally or never	90.7	91.5	
Number of medicines (any) taken within 24 months before recruitment date			
0–6	27.5	27.1	0.57
7+	72.5	72.9	
Use of oral contraceptive(s) within 24 months before index date			
Yes	49.4	58.6	0.01
Vaccine(s) other than Gardasil received within 24 months before index date			
Yes	31.2	38.2	0.05
At least one chronic comorbidity[d]			
Yes	12.6	15.4	0.32
Personal history of previous AD[e]			
Yes	4.5	0.6	0.001
No	95.5	99.4	
Family history of AD[f]			
Yes	10.4	5.0	0.02
No	64.3	70.3	
Unknown or missing	25.3	24.6	
Previous personal history or familial history of AD			
Yes	14.1	5.6	<0.001
No	61.0	70.1	
Unknown or missing	24.9	24.4	

AD, autoimmune disorder; ATD, autoimmune thyroid disorder; NA, not applicable.
[a]All information obtained from the patient interview. [b]Proportions weighted by the number of matched controls per case. [c]Global geographical origin was defined as follows: Region of birth of the patient was categorized as 'N' (within Northern Europe or North America), 'other' (outside N) or 'missing'. Region of birth of the patient's parents was also categorized as 'N', 'other' or 'missing': if the region of birth for one parent was 'N' and for the second parent was 'other', the parents' region of birth was classified as 'other'; if one or both parents had a missing region of birth, overall parents' region of birth was classified as 'missing'. Next, (i) if either the patient's or both parents' region of birth was 'N', then the geographical origin was classified as 'N', (ii) if the patient's and both parents' region of birth was 'other', then the geographical origin was classified as 'other', and (iii) if the patient's and/or both parents' region of birth was 'missing' and condition (i) did not apply, then the geographical origin was classified as 'missing'. [d]At least one of the following comorbidities: diabetes, obesity, Crohn's disease, ulcerative colitis, cirrhosis, cancer, epilepsy, multiple sclerosis, migraine, rheumatoid arthritis, chronic renal failure, asthma and chronic obstructive pulmonary disease. [e]Not including the AD of the case, includes the following: multiple sclerosis, lupus, rheumatoid arthritis, Crohn's disease, ulcerative colitis and autoimmune thyroiditis. [f]Includes the above ADs (listed in e) in first-degree relatives; only available for patients interviewed after 11 September 2008.

Overall, 211 definite cases of ADs were matched to 875 controls. The adjusted odds ratio (OR) for any quadrivalent HPV vaccine use was 0.9 [95% confidence interval (CI) 0.5–1.5].

The individual ORs were

- (95% CI 0.4–2.6) for ITP,
- 0.3 (95% CI 0.1–0.9) for MS,
- 0.8 (95% CI 0.3–2.4) for connective disorders and
- 1.2 (95% CI 0.4–3.6) for type 1 diabetes.

No exposure to HPV vaccine was observed in cases with either Guillain–Barre syndrome or thyroiditis.

Table 18 Associations between Gardasil vaccination and ADs (excluding ATDs)

Analysis (*n* cases/*n* controls)	Cases exposed *n* (%)	Controls exposed *n* (%)	Crude OR[b] (95% CI)	Adjusted OR[b] (95% CI)
For definite cases and confirmed Gardasil vaccinations in primary time window[a]:				
All ADs combined				
211 of 875	25 (11.8)	192 (21.9)	0.5 (0.3–0.7)[c]	0.9 (0.5–1.5)[c]
With personal or family history of AD: 20 of 55	3 (15.0)	15 (27.3)	0.5 (0.1–1.9)[d]	1.1 (0.2–5.9)[d]
Without personal or family history of AD: 137 of 602	19 (13.9)	139 (23.1)	0.5 (0.3–0.9)[d]	0.8 (0.5–1.5)[d]
ADs separately				
Idiopathic thrombocytopenic purpura: 40 of 183	6 (15.0)	33 (18.0)	0.8 (0.3–2.2)[c]	1.0 (0.4–2.6)[c]
Connective tissue disorders: 49 of 200	6 (12.2)	37 (18.5)	0.6 (0.2–1.5)[c]	0.8 (0.3–2.4)[c]
Central demyelination: 83 of 290	4 (4.8)	48 (16.6)	0.3 (0.1–0.7)[c]	0.3 (0.1–0.9)[c]
Guillain–Barré syndrome: 15 of 91	0 (0.0)	7 (7.7)	–	–
Type 1 diabetes: 38 of 202	9 (23.7)	41 (20.3)	1.2 (0.5–2.9)[c]	1.2 (0.4–3.6)[c]

AD, autoimmune disorder; ATD, autoimmune thyroid disorder; OR, odds ratio; CI, confidence interval.
[a]Primary time window A was ≤6 months before the index date for ITP, ≤2 months for Guillain–Barré syndrome and ≤24 months for the other ADs. For each case–control set, the relevant time window was used according to the AD. [b]ORs were calculated whenever there were three or more patients in each cell considered. [c]Crude ORs were calculated using unconditional logistic regression; adjusted ORs were calculated using conditional logistic regression and controlled for the multivariate risk score and a personal or family history of AD. [d]Crude and adjusted ORs were calculated using unconditional logistic regression; adjusted ORs controlled for the multivariate risk score and matching factors.

No evidence of an increase in the risk of the studied ADs was observable following vaccination with Gardasil within the time periods studied. There was insufficient statistical power to allow conclusions to be drawn regarding individual ADs.

Assuming 95% confidence and 80% power, the minimum detectable ORs for the numbers of definite and possible cases were 1.6 for the five Ads (excluding ATDs) combined (229 cases) and between 2.2 and 2.8 for the ADs individually except for Guillain–Barre syndrome. For the latter, no exposed case was reported, thus suggesting no risk; however, the study had limited statistical power, so that a definite conclusion could not be drawn regarding this syndrome.

There was no evidence of an increase in the risk of the studied ADs following vaccination with Gardasil within the time windows set a priori for each of the ADs in this age group. Using different time windows in sensitivity analyses did not affect the main results. From a monitoring viewpoint, no unusual patterns of accrual of incident cases of any of the ADs were observed in a large series of AD specialist centres, at a time when one-third of the girls/young women in the survey were being vaccinated against HPV, mainly with Gardasil.

Comments

The result of no association between autoimmune disease and Gardasil vaccination is consistent with the other observational studies. The study was underpowered to exclude a small increase in risk but could exclude larger increases in risk.

3.2.6 Langer-Gould[18]

This study was conducted to determine whether HPV (or Hep B) vaccine increases the risk of MS or other CNS autoimmune diseases. A nested case control study was conducted using data obtained from the electronic records of Kaiser Permanente Southern California (KPSC) members. Cases were identified between 1 Jan 2008 and 31 Dec 2011, which included extensive review of medical records by an MS specialist. Five controls per case were matched on age, sex and zip code. Patients with less than 6 months membership prior to onset of symptoms were excluded.

Table 19 Distribution of baseline characteristics between cases and controls

Characteristic	No. (%)		*P* Value
	Cases (n = 780)	Controls (n = 3885)	
Age at onset, y			
≤10	16 (2.1)	77 (2.0)	.97
11-18	52 (6.7)	260 (6.7)	
19-49	520 (66.7)	2590 (66.7)	
≥50	192 (24.6)	958 (24.7)	
Mean (range)	39.3 (2.2-85.8)	39.3 (2.2-85.9)	
Sex			
Male	239 (30.6)	1192 (30.7)	.98
Female	541 (69.4)	2693 (69.3)	
Race/ethnicity			
White	334 (42.8)	1227 (31.6)	<.01
Black	142 (18.2)	430 (11.1)	
Hispanic	233 (29.9)	1442 (37.1)	
Native American/Alaskan	2 (0.3)	10 (0.3)	
Asian/Pacific Islander	33 (4.2)	350 (9.0)	
Multiple/other/unknown	36 (4.6)	426 (11.0)	
No. of hospitalizations in 6 mo before index date			
0	703 (90.1)	3743 (96.3)	<.01
≥1	77 (9.9)	142 (3.7)	
No. of emergency department visits in 6 mo before the index date			
0	616 (79.0)	3546 (91.3)	<.01
≥1	164 (21.0)	339 (8.7)	
No. of physician or nurse practitioner visits in 6 mo before index date			
0	171 (21.9)	1513 (38.9)	<.01
1-4	464 (59.5)	1981 (51.0)	
≥5	145 (18.6)	391 (10.1)	
Infectious/parasitic diseases			
No	690 (88.5)	3546 (91.3)	.01
Yes	90 (11.5)	339 (8.7)	
Comorbidity[a]			
No	728 (93.3)	3643 (93.8)	.65
Yes	52 (6.7)	242 (6.2)	
Length of membership before onset of symptoms (index date), mean (range), y	7.72 (0.51-19.15)	7.23 (0.51-19.14)	.03

[18] Langer-Gould A, Qian L, Tartof SY et al 2014 'Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating disease' JAMA Neurol 71: 1506-1513

Vaccination of any type within 3 years of the index date (but particularly HepB and HPV) were identified through the electronic vaccination records system.

All forms of CNS acquired demyelinating syndromes (CNS ADS) were analysed using conditional logistic regression adjusted for race/ethnicity, health care utilisation, comorbid disease and infectious illness before symptom onset.

Conditional logistic regression was used to estimate the matched odds ratio. When 10 or more exposed individuals were identified the models were adjusted for race/ethnicity, hospitalisations, outpatient visits, emergency department visits comorbid chronic disease and infections within 6 months before symptom onset/index date.

The authors identified 780 incident cases of CNS ADS and 3885 controls. 92 cases and 459 controls were female and aged between 9-26 years, the indicated age for HPV vaccination.

The most common form of incident CNS ADS during the study period was MS (427 patients [54.7%]) followed by optic neuritis (ON) (177 [22.7%]), transverse myelitis ™ (122 [15.6%]), other forms of clinically isolated syndrome (CIS) (33 [4.2%]), and ADEM (21 [2.7%]).Most cases of CNS ADS were diagnosed within 300 days of symptom onset (median, 83.5 days; 25% by 13.0 days and 75% by 299.5 days). Correspondingly, most cases (718 [92.1%]) had an onset of symptoms between 2007 and 2011.

The baseline demographic and clinical characteristics of case patients and controls are presented in the Table 16. Case patients were more likely to have been hospitalized, been seen in the emergency department, and used outpatient services in the 6 months before symptom onset/index date than were the controls (Table). In addition, the cases were more likely to have had a visit for an infectious illness in the 6 months before symptom onset than were the controls.

There were no associations with an increased risk of CNS ADS up to three years later: hep B vaccination OR 1.12 (0.72-7.73), HPV OR 1.05 (0.62-1.78) any vaccination OR 1.03 (0.86-1.22). Vaccination of any type was associated with an increased risk of CNS ADS onset within the first 30 days after vaccination only in younger (<50 years) individuals OR 2.32 (1.18-4.57).

Of the 24 younger individuals who developed their first symptoms of CNS ADS within 30 days following vaccination, 11 had MS. Among these 11 patients, 1 woman had 3 other MS risk factors: previously diagnosed radiologically isolated syndrome, a family history of MS, and comorbid ulcerative colitis. Nine individuals developed ON (including 1 woman who was 2 weeks post partum), 3 developed TM, and 1 child developed ADEM. All new-onset MS cases made a full recovery from their first attack, as did 8 of the patients with ON, 2 with TM, and the child with ADEM. Of the 12 patients with ON and TM, 9 did not have any asymptomatic lesions identified on brain magnetic resonance imaging, indicating a very low long-term risk of conversion to MS.23 The most common type of vaccine received by these 24 cases and their 74 matched controls were influenza (14 cases and 36 controls) and tetanus, pertussis, and diphtheria (8 cases and 14 controls).

Infections are known to accelerate the onset of overt CNS ADS in children. The authors found that vaccines may have a similar effect, since they detected an increased risk of ADS symptoms shortly after vaccination in younger individuals. This effect was not vaccine specific, was similar for MS and CIS, was rare (4% of younger cases), and resulted in a monophasic, self-limited illness in almost half of the cases. In contrast, there was no increased risk of CNS ADS 30 days after vaccination. This argues against causality because the risk in the vaccinated group should remain elevated regardless of whether the time window between exposure and clinical disease expression is defined as 15 days or 3 years. However, the findings are consistent with vaccines acting as a proinflammatory cofactor in Individuals with subclinical autoimmunity because this mechanism would be expected to hasten symptom onset but not change the long-term risk of developing MS or CIS.

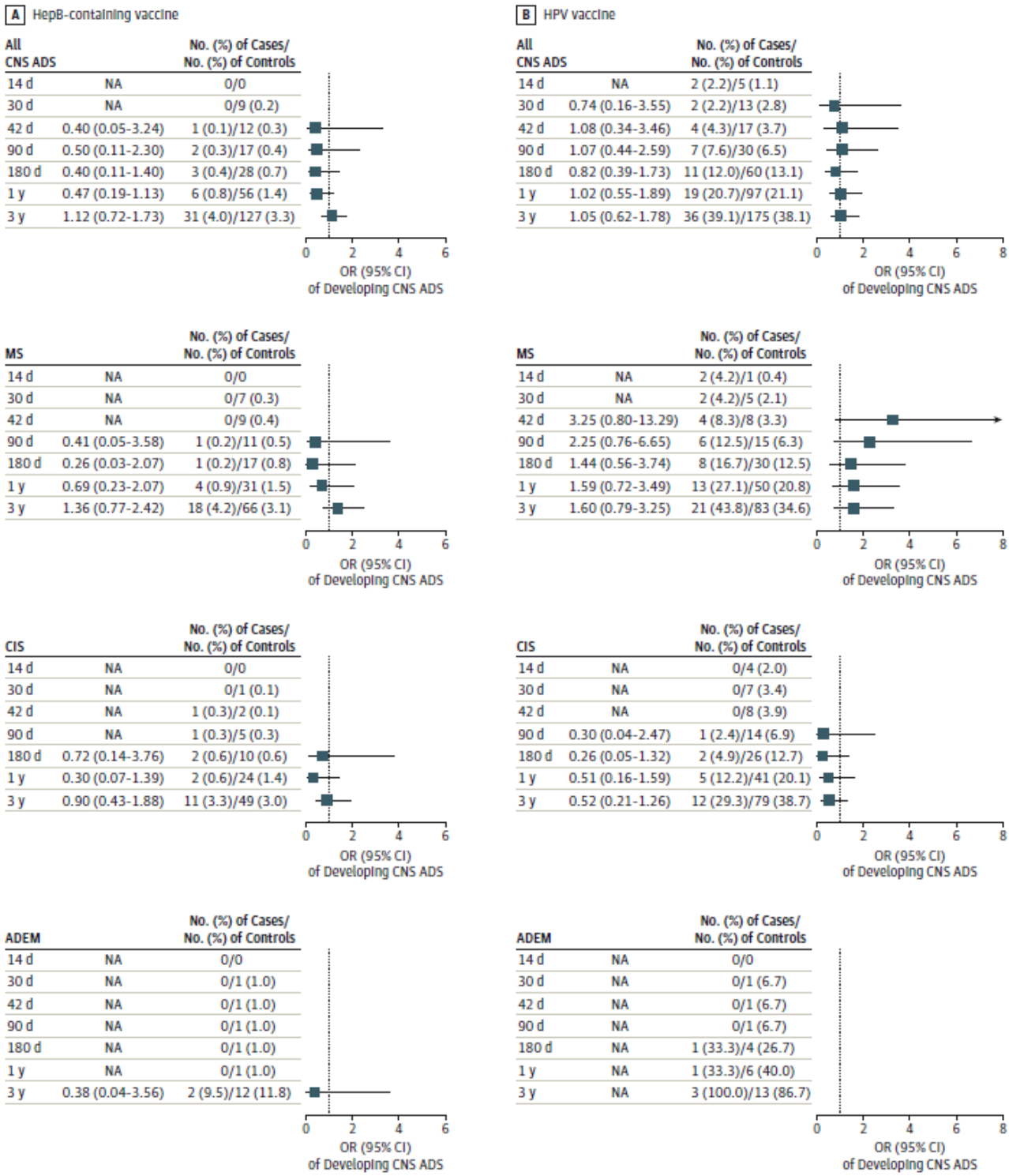


Figure 6 Association between hepatitis B and HPV vaccines and acquired central nervous system demyelinating syndrome by time since vaccination

The case reports of young females presenting with fulminant onset of ADEM or MS 2 to 4weeks following administration of HPV vaccine are difficult to interpret, since young women are the highest MS risk group. Several of these women had mild symptoms of CNS ADS at the time of vaccination, and several occurred after the second or third dose. An earlier study of HPV vaccine and MS, ADEM, and ON found no association, but only 11 cases were identified, making it difficult to draw conclusions. This study, using more comprehensive and accurate case-finding methods, identified 92 women with incident CNS ADS. The authors found a small, non-significant increase in the risk of MS

but not its potential precursors (CIS or ADEM), which suggests a spurious finding. Larger studies are needed to completely rule out an effect.

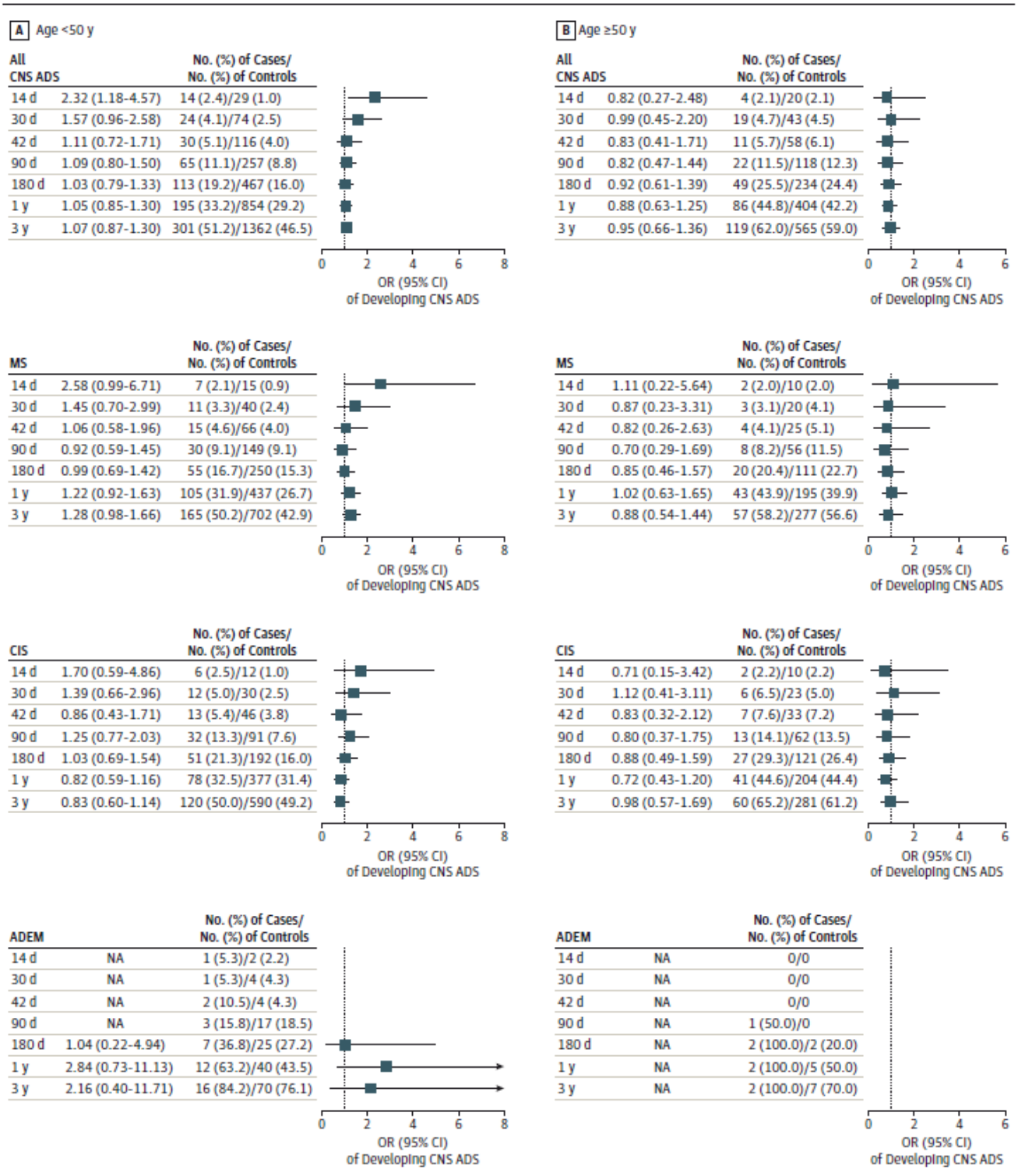


Figure 7 Association between any vaccination and acquired central nervous system demyelinating syndromes by age and time since vaccination.

The authors note that the study remains underpowered, particularly for detecting associations with rare forms of CNS ADS (paediatric ADS and ADEM), uncommon exposures (single-antigen HepB vaccine), and small select subgroups (symptom onset within 180 days following HPV vaccine in young women). In addition, the number of older individuals was relatively small. Other limitations include

the inability to examine high-risk subgroups, such as those with a family history of MS or carriers of MS risk alleles, and the inability to examine the potential influence of vaccine preservatives.

The authors concluded that they found no longer-term association of vaccines with MS or any other CNS ADS which argues against a causal association. The short-term increase in risk suggests that vaccines may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease. Our findings support clinical anecdotes of CNS ADS symptom onset shortly after vaccination but do not suggest a need for a change in vaccine policy.

Comments
The finding of increase in risk in the first 30 days of vaccination may also reflect unmasking as described above.

3.2.7 Scheller[19]

The objective of this study was to investigate if qHPV vaccination is associated with an increased risk of multiple sclerosis and other demyelinating diseases.

The authors used the nationwide registers in Denmark and Sweden to identify a cohort of all females aged 10 years to 44 years. The cohort was followed from 1 Oct 2006 to 1 July 2013. Information on qHPV vaccination and incident diagnoses of multiple sclerosis and other demyelinating diseases were collected. Other diseases of interest were: optic neuritis, neuromyelitis optica, transverse myelitis, acute disseminated encephalomyelitis, other central demyelinating disease.

The primary analysis used a cohort design including vaccinated and unvaccinated study participants. A secondary analysis used a self-controlled case series design including only cases. Both analyses used a 2 year risk period following vaccination.

The primary outcomes were MS and a composite end point of other demyelinating disease. Incidence rate ratios were estimated using Poisson regression, comparing rates of events in the 2 years risk periods following vaccination and in unvaccinated time periods.

The following sensitivity analyses were performed. Four alternative risk windows were evaluated in the cohort study- 0-179, 180-364, 365-729 and >729. An analysis stratified by age- 10-29 years and 30-44 years. Analyses stratified by country. In the case controlled series if becoming a case contraindicates or delays vaccination in a significant number of participants the results can be biased. Therefore 2 additional analyses were performed, one excluding a 30 day pre-vaccination period and one including only vaccinated cases.

The study included 3,983,824 females, among whom 789,082 received a total of 1,927,581 qHPV vaccine doses. 5553 individuals were excluded because of prevalent MS and 3108 were excluded as they had a history of the other demyelinating diseases.

During follow up 4322 MS cases and 3300 cases of other demyelinating disease were identified, of which 73 and 90 respectively occurred within the risk period.

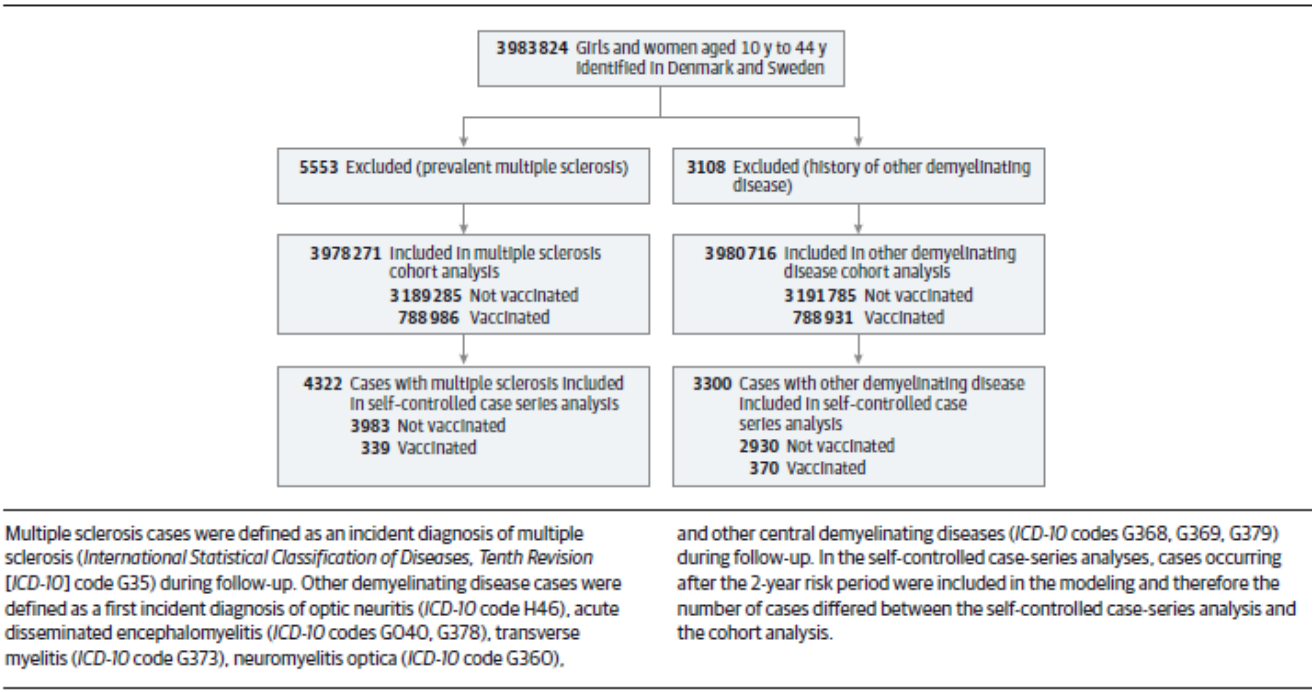
[19] Scheller NM, Svanstroem H, Pasternak B et al 2015 'Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating disease of the central nervous system' JAMA 313: 54-61

Table 20 Selected characteristics of the 3,983,924 subjects in the background population

Characteristics	No.		
	Denmark	Sweden	Combined
Participants	1 565 964	2 417 860	3 983 824
Follow-up, person-years	8 595 477	12 737 145	21 332 622
Age at entry, mean (SD), y	25.4 (11.3)	25.5 (11.1)	25.5 (11.2)
Year of study entry			
2006	1 351 157	2 133 569	3 484 726
2007	34 329	47 670	81 999
2008	33 483	46 616	80 099
2009	33 379	46 407	79 786
2010	33 508	47 060	80 568
2011	32 551	47 208	79 759
2012	31 770	49 330	81 100
2013	15 787	0	15 787
Age at vaccination, mean (SD), y	18.5 (6.6)	15.3 (3.2)	17.3 (5.8)
Age at first vaccine dose, y			
10-14	224 118	145 664	369 782
15-19	68 199	138 458	206 657
20-24	112 466	7616	120 082
25-29	66 641	2481	69 122
30-34	8879	731	9610
35-39	7559	627	8186
40-44	5140	503	5643
Total vaccine doses	1 177 603	749 978	1 927 581
1	493 002	296 080	789 082
2	406 357	264 330	670 687
3	278 244	189 568	467 812
Year of first vaccine dose			
2006	391	406	797
2007	10 481	21 504	31 985
2008	25 343	34 278	59 621
2009	147 565	41 379	188 944
2010	43 654	27 769	71 423
2011	43 668	13 397	57 065
2012	150 107	157 347	307 454
2013	71 793	0	71 793

In the cohort analysis there was no increased risk of multiple sclerosis or other demyelinating disease associated with qHPV vaccination. Similarly no increased risk was found using the self-controlled case-series design.

Consistent with the cohort analysis, the self-controlled case-series analysis showed no increased risk of multiple sclerosis (IR, 1.05 [95% CI, 0.79-1.38]) or other demyelinating diseases (IR, 1.14 [95% CI, 0.88-1.47]). Excluding a pre-vaccination risk period of 30 days from the unexposed group did not significantly change the results of the self-controlled case-series analysis (IR for multiple sclerosis, 1.12 [95% CI, 0.84-1.49] ; IR for other demyelinating diseases, 1.16 [95% CI, 0.89-1.51]). Similarly, using only exposed cases did not significantly change the results of the self-controlled case-series analysis (IR for multiple sclerosis, 1.07 [95% CI, 0.80-1.43]; IR for other demyelinating diseases, 1.14 [95% CI, 0.88-1.48]).



Multiple sclerosis cases were defined as an incident diagnosis of multiple sclerosis (*International Statistical Classification of Diseases, Tenth Revision* [*ICD-10*] code G35) during follow-up. Other demyelinating disease cases were defined as a first incident diagnosis of optic neuritis (*ICD-10* code H46), acute disseminated encephalomyelitis (*ICD-10* codes G040, G378), transverse myelitis (*ICD-10* code G373), neuromyelitis optica (*ICD-10* code G360), and other central demyelinating diseases (*ICD-10* codes G368, G369, G379) during follow-up. In the self-controlled case-series analyses, cases occurring after the 2-year risk period were included in the modeling and therefore the number of cases differed between the self-controlled case-series analysis and the cohort analysis.

Figure 8 Inclusion of subjects in the cohort analysis and in the self controlled case series analysis

The authors consider that the study has a number of strengths. First, it was based on individual and complete records of vaccination and outcome diagnoses ascertained prospectively and independently in well-defined geographical areas. Correspondingly, concern over recall and ascertainment bias has been minimized. Second, by combining data from Sweden and Denmark, countries with comparable public health systems and registers, the study had statistical power to exclude meaningful increases in risk, which is reflected in the narrow 95% CIs. Third, the nationwide nature of the study allows for a high degree of generalizability of the results; this includes rates of demyelinating diseases based on true background rates.

The study limitations as outlined by the authors were.

- First, information on ethnicity, socioeconomic status, lifestyle factors, and family history was not available, and potential confounding was therefore a possibility in the cohort analysis. However, the self-controlled case-series analysis, which implicitly controls for time-independent confounders, suggested that bias attributable to such unmeasured confounders was minimal and confirmed the results from the cohort analysis of no risk of multiple sclerosis and other demyelinating diseases following qHPV vaccination.
- Second there may have been miscoding of ICD10 codes in the national patient registries.
- Third the unmasking phenomenon is relevant to MS, however the null results are unlikely to reflect such a bias.
- Fourth the date of diagnosis rather than disease was used, random misclassification would bias the results to no association. To account for any delay from onset to diagnosis the authors chose a 2-year risk period. Analyses subdividing post-vaccination time into a number of different risk intervals did not reveal any temporal patterns suggestive of bias or the presence of risk increases masked by the 2-year risk period.
- Fifth if becoming a case contraindicates or delays vaccination in a significant number of participants the self-controlled case series can be biased. This was addressed by the supplementary analyses.

Table 21 Adjusted rate ratios of MS and other demyelinating disease in qHPV vaccinated and unvaccinated girls and women

Outcome	Unvaccinated			Vaccinated			Adjusted RR (95% CI)[a]	*P* Value
	No. of Cases	Person-Years	Crude Incidence Rate (95% CI), Events/100 000 Person-Years	No. of Cases	Person-Years	Crude Incidence Rate (95% CI), Events/100 000 Person-Years		
Multiple Sclerosis								
Main analysis	4208	19 532 311	21.54 (20.90-22.20)	73	1 193 703	6.12 (4.86-7.69)	0.90 (0.70-1.15)	
Analysis by age, y								
10-29	1374	10 095 340	13.61 (12.91-14.35)	62	1 166 450	5.32 (4.14-6.82)	0.77 (0.58-1.02)	.15[c]
30-44	2834	9 436 971	30.03 (28.95-31.16)	11	27 253	40.36 (22.35-72.88)	1.28 (0.71-2.33)	
Analysis by country								
Denmark	1807	7 410 041	24.39 (23.29-25.54)	57	774 158	7.36 (5.68-9.55)	1.02 (0.76-1.36)	.16[c]
Sweden	2401	12 122 270	19.81 (19.03-20.61)	16	419 545	3.81 (2.34-6.23)	0.68 (0.41-1.13)	
Analysis of different risk windows, d								
0-179	4208[b]	19 532 311[b]	21.54 (20.90-22.20)[b]	47	595 851	7.89 (5.93-10.50)	1.06 (0.78-1.43)	
180-364				14	224 952	6.22 (3.69-10.51)	1.10 (0.65-1.87)	
365-729				12	372 900	3.22 (1.83-5.67)	0.50 (0.28-0.88)	
>729				41	565 225	7.25 (5.34-9.85)	0.75 (0.54-1.03)	
Other Demyelinating Diseases								
Main analysis	3154	19 546 190	16.14 (15.58-16.71)	90	1 193 591	7.54 (6.13-9.27)	1.00 (0.80-1.26)	
Analysis by age, y								
10-29	1175	10 095 490	11.64 (10.99-12.32)	85	1 166 289	7.29 (5.89-9.01)	1.00 (0.78-1.28)	.51[c]
30-44	1979	9 450 700	20.94 (20.04-21.88)	5	27 302	18.31 (7.62-44.00)	0.75 (0.31-1.80)	
Analysis by country								
Denmark	1369	7 416 343	18.46 (17.51-19.46)	73	774 095	9.43 (7.50-11.86)	1.10 (0.84-1.44)	.14[c]
Sweden	1785	12 129 846	14.72 (14.05-15.41)	17	419 496	4.05 (2.52-6.52)	0.73 (0.44-1.20)	
Analysis of different risk windows, d								
0-179	3154[b]	19 546 190[b]	16.14 (15.58-16.71)[b]	54	595 804	9.06 (6.94-11.83)	1.13 (0.85-1.51)	
180-364				11	224 930	4.89 (2.71-8.83)	0.73 (0.40-1.33)	
365-729				25	372 857	6.71 (4.53-9.92)	0.91 (0.61-1.37)	
>729				56	565 106	9.91 (7.63-12.88)	1.01 (0.76-1.34)	

Abbreviations: HPV, human papillomavirus; RR, risk ratio.

[a] Model included adjustment for calendar year, age (2-year intervals), and country.

[b] Common unvaccinated reference category for all vaccine-exposed risk windows.

[c] Test for heterogeneity

Comparing crude rates to adjusted RRs, there was substantial influence from adjustment. This derives from the fact that both vaccination and outcomes are age dependent.

The vaccinated group was younger on average than the unvaccinated group, and since the background incidence of demyelinating diseases peaks later among the included age groups, the crude rates were higher in the unvaccinated group compared with the vaccinated group.

The authors concluded that qHPV vaccination was not associated with the development of multiple sclerosis or other demyelinating disease. These findings do not support concerns about a causal relationship between qHPV vaccination and demyelinating diseases.

Comment
This study is an update to the Arnheim-Dahlstroem study. No association between HPV vaccination and demyelinating disease was seen using two different analysis methods.

3.3 Other data

There have been several analyses of the VAERS data, some of the results were published with case reports and are outlined above. Other notable studies are outlined below.

3.3.1 Geier[20]

The authors claim to have undertaken an epidemiology study using the VAERS database looking at adverse event reports for Gardasil between Jan 2006 and Dec 2012.

According to the authors the VAERS is an epidemiological database maintained jointly by CDC and FDA. Specific adverse events following vaccination are required to be reported to this database as mandated by law, but other adverse events are passively reported. The CDC and FDA have repeatedly analysed and published epidemiologic studies based on VAERS. Adverse event reports associated with vaccines administered from Jan 06- Dec 12 to girls aged 18-39 years resident in the USA were used to identify cases and controls. Overall a total of 22,011 adverse event reports were examined.

Table 22 Outcomes examined

Outcome examined (VAERS code)	Number
Serious autoimmune adverse events:	
Gastroenteritis cases (10017888)	12
Controls	21,999
Arthritis (10003246 or 10039073)	56
Controls	21,955
Guillain-Barre syndrome (10018767)	97
Controls	21,914
Thrombocytopenia (10043554 or 10043561)	24
Controls	21,987
Systemic lupus erythematosus (10042945)	13
Controls	21,998
Vasculitis (10047115)	11
Controls	22,000
Alopecia (10001760)	56
Controls	21,955
CNS conditions (10028245 or 10012305 or 10030942 or 10028524 or 10028527)	75
Controls	21,936
General health adverse events:	
Infection (10021789)	39
Controls	21,972
Conjunctivitis (10010741)	19
Controls	21,992
Diarrhea (10012735)	639
Controls	21,372

[20] Geier DA, Geier MR 2014 'A case-control study of quadrivalent human papillomavirus vaccine-associated autoimmune adverse events' Clin Rheumatol doi:10.1007/s10067-014-2846-1

Cases were those with the following outcomes: gastroenteritis, arthritis, GBS, thrombocytopenia, SLE, vasculitis, alopecia, central nervous system conditions (5 different unspecified terms). In addition general health outcome cases were selected from the 22011 reports and were defined with outcomes specified as infection, conjunctivitis and diarrhoea.

Controls were selected from the 22011 reports for each type of case outcome examined by including only those adverse event reports that did not include the specific type of case outcome under study.

Exposure was determined based on HPV vaccine administration, it was presumed that adverse event reports that included HPV vaccine were exposed and reports that did not include HPV vaccine were unexposed.

Fisher's exact test was used for statistical analyses and a two sided p value < 0.05 was considered to be statistically significant. The null hypothesis was that there would be no difference in exposure to HPV vaccine among cases and controls.

The authors state that the following adverse events were associated with Gardasil.

- Gastroenteritis OR 4.6 (1.3-18.5).
- Arthritis OR 2.5 (1.4-4.3).
- SLE OR 4 (1.01-16.4).
- Alopecia OR 8.3 (4.5-15.9).
- CNS conditions OR 1.8 (1.04-2.9).

The median onset of symptoms was 6-55 days post vaccination.

Cases of GBS and thrombocytopenia were no more likely than controls to have received HPV vaccine.

Previous case series and biological plausibility support the observed results. The present study provides epidemiological evidence to support an association between HPV vaccine and specific serious autoimmune side effects. Additional studies should be conducted to further evaluate the potential biological mechanisms involved and to examine the potential epidemiological relationship between HPV4 vaccine and serious autoimmune adverse events in other databases and populations.

Comments

Case control studies conducted in spontaneous report databases can be used for signal detection. However, the VAERS database is not a source of unbiased data comparable with a medical claims database and therefore cannot be used to perform a case control study to assess an association between a medicine and event.

This study is at best hypothesis generating; it does not provide evidence of an association.

To note also that Geier was removed from the practising register in all US states where he was practising medicine for his unethical treatment of children with autism.

3.3.2 Souayah[21]

The authors used data from VAERS to identify 69 reports of GBS occurring after vaccination in the US between 2006 and 2009. The onset of symptoms was within 6 weeks after vaccination in 70% of the patients in whom the date of vaccination was known. The estimated weekly reporting rate within the first 6 weeks was 6.6/10,000,000, higher than that of the general population. This rate was also higher than that seen after vaccination for Menactra and influenza.

[21] Souayah N, Michas-Martin PA, Nasar A et al 2011 'Guillain-Barre syndrome after Gardasil vaccination: Data from Vaccine Adverse Event Reporting System 2006-2009' Vaccine 29: 886-889

Comments

This publication was criticised[22] as follows.

- VAERS data are subject to reporting biases such as under reporting or stimulated reporting
- The temporal association of an adverse event with vaccination also does not prove a causal relationship, VAERS cannot usually assess causality.
- The information provided if ofter incomplete, without additaionl review of medical records it is difficult to verify the reported diagnoses
- The publication sis not adequately address the limitation of VAERS data and made inaccurate assumptions in their calculations, for example they assumed everyone had 3 vaccinations inflating the reporting rate.
- The peak onet was during the first 2 weeks following vaccination, which only partially overlaps the period of time of increased GBS risk found following the swine flu vaccine in 1976. In fact most reports (14/15) of those reported with onset in the first week had an onset<3 days. The IOM considers the plausible onset time to range from 5 days to 6 weeks.

3.4 CARM data

Table 23 outlines cases of possible autoimmune conditions in females, reported to CARM following HPV vaccination

Table 23 Summary of CARM reports of possible autoimmune conditions

CARM Ref	Age	Event (s)	Other medicines	Comments
091291	14	Henoch-Schonlein purpura	Not reported	22 day onset
105826	18	Idiopathic thrombocytopenia	Not reported	Platelet count 69 on day of second vaccination. Continues to recur since
085633	15	Bell's Palsy Face oedema	Lamotrigine Fluticasone Dalbutamol antibiotics	Onset day after vaccination
101714	16	Bell's Palsy	malathion	Onset day after vaccination
115471	13	Encephalitis psychosis	Not reported	Onset around 7 months
101935	14	GBS	Not reported	Onset 49 days
084523	17	Neuropathy rash	Not reported	Onset same day
089100	17	Leg pain Neuropathy Headache Chest pain syncope	Microgynon 20ED	Onset was 25 days
090702	16	Neuropathy Headache Concentration impaired	Citalopram metoclopromide	Onset time unclear – within 2 weeks

[22] Slade BA, Gee J, Broder KR et al 2011 'Comment on the contribution by Souayah et al …'Vaccine 29: 865-6

		Behaviour abnormal lethargy		
082890	18	Arthropathy Hypertension Myalgia Diabetes aggravated uveitis	Not reported	Onset time unclear

Comments

No safety concern has been raised following CARM analysis of these reports. The number of reports is low considering the expected background incidence and the number of people vaccinated.

4.0 DISCUSSION AND CONCLUSIONS

Both GBS and ADEM are listed adverse effects of Gardasil.

The observational studies completed to date have concluded that there is no association between HPV vaccination and the development of autoimmune conditions. However, there are difficulties in conducting these studies due to the non-specific initial symptoms of disease and thus determining the timing of onset and/or diagnosis. In addition some of these conditions are rare so the power of the studies to conclusively eliminate any association is limited.

The low number of reported case reports in comparison to both the expected rate of temporal association and the estimated exposure also suggest a lack of association.

Abiding by the strict criteria of the Institute of medicine there is insufficient evidence to confirm or refute an association with individual conditions. However the balance of evidence suggests that an association is very unlikely.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- There is a safety concern relating to development of autoimmune conditions after HPV vaccination

6.0 ANNEXES

1. Gardasil data sheet
2. Chao C, Klein NP, Velicer CM et al 2011 'Surveillance of autoimmune conditions following routine se of quadrivalent human papillomavirus vaccine' J Int Med 271: 193-203
3. Arnheim-Dahlstroem L, Pasternak B, Svanstroem H et al 2013 'Autoimmune, neurological and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study' BMJ 247:f5906
4. Grimaldi-Bensouda L, Guillemot D, Godeau B et al 2014 'Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects' J Int Med 275: 398-408
5. Langer-Gould A, Qian L, Tartof SY et al 2014 'Vaccines and the risk of multiple sclerosis and other central nervous system demyelinating disease' JAMA Neurol 71: 1506-1513
6. Scheller NM, Svanstroem H, Pasternak B et al 2015 'Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating disease of the central nervous system' JAMA 313: 54-61