

## NATIONAL VACCINE INFORMATION CENTER

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### HUMAN PAPILLOMA VIRUS VACCINE SAFETY

#### Analysis of Vaccine Adverse Events Reporting System Reports: Part III

August 14, 2007 (revised 08/15/07)

As of May 31, 2007, 2,227 reports of adverse events following administration of Gardasil have been submitted to the FDA's Vaccine Adverse Event Reporting System (VAERS). This document serves as a follow-up to reports previously issued by the National Vaccine Information Center (NVIC) on this topic.<sup>1</sup> Readers are encouraged to review the previously released reports. Recommendations and limitations have already been described and remain relevant concerns. Issues include a number of clinical and patient safety problems arising from co-administration of Gardasil with other vaccines not evaluated by the manufacturer, which were discussed in the previous reports.

Also, readers are referred to the VAERS website for cautions related to use of VAERS data.<sup>2</sup> The information in this report does not prove a cause and effect relationship between any of the reactions and administration of Gardasil. This document only summarizes the information in VAERS as it relates to use of Gardasil, either alone or in combination with other vaccines. Even though causal relationships between adverse events and Gardasil are not proved in this report, VAERS serves as an important alerting mechanism and the data described in this report provide substantive evidence warranting serious and immediate attention on the part of parents, clinicians, government regulators and policymakers and others.

This report reviews the adverse events reports submitted through May 31, 2007.

#### Overview and Patient Demographics Through May 31, 2007

Since licensure of Gardasil in June 2006, the number of monthly reports increased as would be expected in response to increased use of the vaccine by a growing number of people. Specifically, in July 2006, two reports were filed but in May 2007, 473 reports

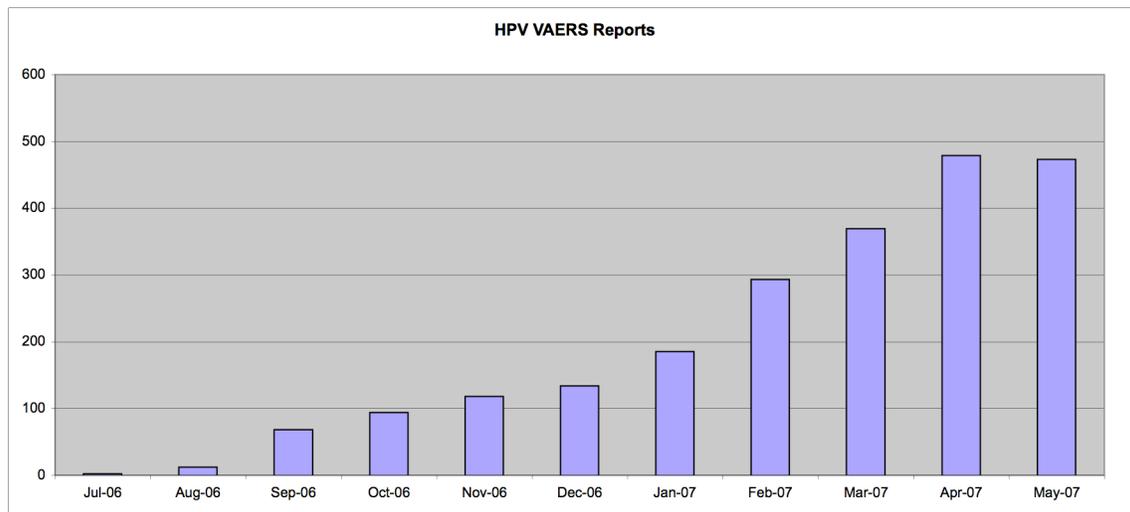
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<sup>1</sup> Previous reports and press releases issued by NVIC include: Merck's Gardasil Vaccine Not Proven Safe for Little Girls, June 27, 2006 <http://www.nvic.org/PressReleases/pr62706gardasil.htm>; NVIC Private Pediatrician Office Survey: Northern Virginia HPV Vaccine Costs, January 2007 <http://www.nvic.org/Diseases/HPV/docsurvey.htm>; Human Papilloma Virus Vaccine Safety, Analysis of Vaccine Adverse Events Reporting System Reports: Part I, February 1, 2007 <http://www.nvic.org/Diseases/HPV/HPVrpt.htm>; HPV Mandates Risky and Expensive, February 1, 2007 <http://www.nvic.org/PressReleases/pr020107HPV.htm>; HPV Infection Facts, <http://www.nvic.org/Diseases/HPV/HPVInfection.htm>; Human Papilloma Virus Vaccine Safety, Analysis of Vaccine Adverse Events Reporting System Reports: Part II, February 18, 2007 <http://www.nvic.org/Diseases/HPV/HPVRPT2.htm>; Vaccine Safety Group Releases Gardasil Report: Calls on FDA and CDC to Warn Doctors and Parents to Report to VAERS, February 21, 2007 <http://www.nvic.org/Diseases/HPV/pr022107HPV.htm>.

<sup>2</sup> Information about the VAERS reporting system can be found at <http://vaers.hhs.gov>. The government has issued the following warning to people using VAERS data: When evaluating data from VAERS, it is important to note that for any reported event, no cause and effect relationship has been established. VAERS is interested in all potential associations between vaccines and adverse events. Therefore, VAERS collects data on any adverse event following vaccination, be it coincidental or truly caused by a vaccine. The report of an adverse event to VAERS is not documentation that a vaccine caused the event.

were filed. The change in number of monthly reports is shown in Figure 1.<sup>3</sup> In December 2006, 3.97 reports per day were filed. In May 2007, 15.3 reports per day were filed. Additionally, 43 percent of all HPV VAERS reports were filed in April and May 2007; almost as many as were filed over the previous nine months since the Gardasil was licensed June 8, 2006 and recommended for inclusion in the national vaccination schedule on June 29, 2006.

**Figure 1. Number of Gardasil VAERS Vaccine Reports by Month of Submission**



Also increasing is the proportion of total VAERS reports that consist of Gardasil reports. **Depending on how the analysis is performed, VAERS reports that involve Gardasil are now 15 to 20 percent of all VAERS reports filed.** This is noteworthy because, considering the number of mandatory and routinely administered vaccines given to infants and influenza vaccines given to adults, it is unlikely that Gardasil accounts for 15 to 20 percent of all vaccinations.

**State of Residence.** VAERS reports following receipt of Gardasil have been filed from all 50 states and the District of Columbia. Over one-quarter of VAERS reports do not list a state of residence for the individual reporting a reaction. The number of reports per state ranged from two to 194. Reports from five states - California, New York, Pennsylvania, Florida and Texas – comprise 40 percent of reports. **California residents accounted for the highest number of reports (194, 11.8 percent), followed by New York (166, 10.1 percent), Pennsylvania (132, 8.0 percent), Florida (101, 6.2 percent) and Texas (78, 4.8 percent).**

**Age.** The age of persons for whom VAERS reports were submitted following receipt of Gardasil ranged from 3 months to 77 years (see Figure 2). Readers should note that the vaccine is only licensed by the Food and Drug Administration (FDA) for use in females

<sup>3</sup> Reports per month were: July (2), August (12), September (68), October (94), November (118), December (134), January (185), February (293), March (369), April (466) and May (473). Duplicate reports previously accounted for 2.3 percent of reports. Duplicate reports were removed for some but not all of the analyses contained in this report.



- Four-month-old twins from North Carolina who had diarrhea for over a week (VAERS ID 276227 and 276238)
- A one-year-old from West Virginia who had fever and contracted chickenpox nine days after vaccination (VAERS ID 277591)
- A one-year-old from Michigan with no symptoms noted - only classified as “unevaluable event” (VAERS ID 265338)
- An 18-month-old from North Carolina with no symptoms noted- only classified as “medication error” (VAERS ID 263024)
- A four-year-old from North Dakota with severe cellulitis, gait disturbance, injection site induration, shock, skin discoloration, severe swelling and compromised circulation (VAERS ID 274432)
- A seven-year-old from North Carolina with redness, swelling and warmth at the injection site (VAERS ID 270921)
- An 11-year-old from New Jersey with asthenia (weakness), fatigue, nausea and pain (VAERS ID 274209)
- A 12-year-old from Colorado who is enrolled in a Gardasil study and the morning after receipt of the third dose was given he experienced abasia (inability to walk due to impaired muscle coordination), gait disturbance, headache, muscular weakness, pyrexia (fever), sensation of heaviness and trouble walking (VAERS ID 268161)

Male adults given Gardasil included:

- An 18-year-old from New York who experienced arthralgia (joint pain) and fever (VAERS ID 263231)
- An 18-year-old from Texas who experienced dizziness, fatigue, nausea and vomiting (VAERS ID 278506)
- A 45-year-old from California who experienced a rash over his entire body (VAERS ID 279599)
- A 53-year-old (state not identified) who experienced asthenia (weakness) dizziness and nausea that persisted for over six weeks (VAERS ID 271136)
- A 64-year-old from Florida who was given Gardasil instead of Zostavax – no symptoms noted (VAERS ID 276152)
- A 77-year-old from California who was given Gardasil instead of Zostavax - no symptoms noted (VAERS ID 275023)

## Symptoms Reported Following Vaccination with Gardasil

A total of 887 unique “symptoms” were identified in case records submitted to VAERS. Items classified as “symptoms” include illness symptoms such as chest pain, rash, and fever, as well as tests and procedures such as blood tests and electrocardiograms and sometimes whether the results of such test were normal or abnormal. A total of 6,276 symptoms, tests and procedures (symptoms) were associated with the 2,227 VAERS reports. The number of symptoms per VAERS report ranged from 1 to 20 with 95 percent of reports containing five or fewer symptoms.

To simplify the analysis, 625 of the 887 symptoms (70 percent), primarily illness symptoms or diagnoses, were sorted into 32 categories of symptoms and other issues as noted in Table 1. Some of the categories were divided into additional sub-categories. For example, in the paralysis and sensory issue category, Guillain-Barre Syndrome, paralysis and sensory disturbances were evaluated separately. Also, in the cardiac and cardiovascular category, major cardiac adverse events were evaluated separately. Within the injury category, falls and head and neck injuries were evaluated separately.

There are a number of different ways that these items could have been sorted. The categories chosen were selected to evaluate specific concerns.

**Table 1. Categories of VAERS Symptoms and Miscellaneous Items\***

Allergic Reactions (N=280)	allergy to vaccine, anaphylactic reaction, anaphylactoid reaction, angioedema, angioneurotic oedema, choking sensation, face oedema, lip swelling, oedema, oedema peripheral, pharyngeal oedema, sneezing, swelling, swelling face, swollen tongue, throat tightness, tongue oedema, urticaria
Arthritis and Joints (N=68)	arthralgia, arthritis, joint range of motion decreased, joint stiffness, joint swelling, juvenile arthritis, rheumatoid arthritis
Autoimmune (N=31)	anaemia haemolytic autoimmune, autoimmune thrombocytopenia, demyelination, disseminated intravascular coagulation, Evan's syndrome, Henoch-Schonlein purpura, idiopathic thrombocytopenic purpura, Stevens-Johnson syndrome, uveitis, antinuclear antibody increased, antinuclear antibody positive, autoimmune disorder, haemorrhage, immune system disorder, scleroderma, systemic lupus erythematosus
Breast (N=7)	biopsy breast abnormal, breast cancer, breast disorder female, breast mass, breast swelling, mammogram abnormal, mastectomy
Cardiac and Cardiovascular (N=173)	autonomic nervous system imbalance, bradycardia, cardiomyopathy, cor pulmonale, coronary artery thrombosis, death, multi-organ failure, myocarditis, sepsis shock, sudden cardiac death, thrombosis, ventricular tachycardia, viral myocarditis, arrhythmia, atrioventricular block first degree, blood pressure decreased, blood pressure fluctuation, blood pressure increased, blood pressure orthostatic, cardiac disorder, cardiac murmur, diastolic dysfunction, echocardiogram abnormal, electrocardiogram abnormal, electrocardiogram ambulatory abnormal, fluid retention, heart rate decreased, heart rate increased, heart rate irregular, hypertension, hypotension, mitral valve incompetence, orthostatic hypotension, orthostatic intolerance, pallor, palpitations, peripheral coldness, postural orthostatic tachycardia syndrome, pulse pressure decreased, respiratory arrest, sinus arrhythmia, sinus tachycardia, tachycardia, tachycardia paroxysmal, tricuspid valve incompetence
Challenge/Rechallenge Evidence (N=34)	reaction to previous exposure to any vaccine, similar reaction on previous exposure to drug, vaccine positive rechallenge

Convulsions and Central Nervous System (N=143)	convulsion, grand mal convulsion, partial seizures, postictal state, seizure anoxic, tonic clonic movements, cerebral disorder, complicated migraine, dyskinesia, electroencephalogram abnormal, encephalitis, extensor plantar response, gaze palsy, meningism, meningitis viral, myoclonic epilepsy, nervous system disorder, posturing, psychomotor hyperactivity, sleep disorder, somnolence, staring, tic, Tourette's disorder, tremor
Ear and Hearing (N=14)	auricular swelling, deafness, hearing impaired, otitis media, otitis media acute, sudden hearing loss, tinnitus, tympanic membrane hyperaemia
Eye and Vision (N=71)	blepharospasm, blindness transient, choroidal naevus, chromatopsia, corneal deposits, diplopia, dry eye, eye disorder, eye haemorrhage, eye infection, eye irritation, eye movement disorder, eye oedema, eye rolling, eye swelling, eyelid disorder, eyelid oedema, hordeolum, lacrimation increased, macular oedema, mydriasis, ocular hyperaemia, ophthalmological examination abnormal, optic neuritis, panophthalmitis, papilloedema, photophobia, photopsia, photosensitivity reaction, vision blurred, visual disturbance
Fever, Pyrexia, Chills, and Flushing (N=266)	body temperature increased, chills, cold sweat, feeling hot, flushing, hot flush, night sweats, pyrexia
Gastrointestinal (N=69)	constipation, Crohn's disease, dehydration, diarrhoea, diarrhoea haemorrhagic, faeces discoloured, gastritis, gastroenteritis rotavirus, gastrointestinal disorder, gastrooesophageal reflux disease, haematochezia, hepatitis, hepatitis acute, irritable bowel syndrome, liver function test abnormal, rectal haemorrhage, stomach discomfort
Guillain-Barre Syndrome, Paralysis and Sensory (N=206)	Guillain-Barre syndrome, Miller Fisher syndrome, diplegia, facial palsy, facial paresis, hemiparesis, monoplegia, paralysis, dysaesthesia, hyperaesthesia, hypersensitivity, hypoaesthesia, hypoaesthesia facial, hypoaesthesia oral, paraesthesia, paraesthesia oral, pharyngeal hypoaesthesia, sensory disturbance, sensory loss, facial nerve disorder
Injection Site (N=621)	injection site abscess, injection site anaesthesia, injection site bruising, injection site calcification, injection site cellulites, injection site cyst, injection site discolouration, injection site discomfort, injection site erythema, injection site extravasation, injection site haematoma, injection site haemorrhage, injection site hypersensitivity, injection site induration, injection site inflammation, injection site irritation, injection site mass, injection site nerve damage, injection site nodule, injection site oedema, injection site pain, injection site pruritus, injection site pustule, injection site rash, injection site reaction, injection site scar, injection site swelling, injection site urticaria, injection site vesicles, injection site warmth, local reaction, local swelling, localized infection
Injuries (N=106)	fall, face injury, fracture, head injury, neck injury, subarachnoid haemorrhage, subdural haematoma, concussion, contusion, injury, laceration, nerve injury, road traffic accident, sciatic nerve injury
Kidney and Bladder (N=17)	congenital cystic kidney disease, dysuria, renal failure, urinary bladder rupture, urinary incontinence, urinary tract infection, urine analysis abnormal
Lethargy, Fatigue and Malaise (N=168)	activities of daily living impaired, fatigue, feeling abnormal, influenza like illness, lethargy, malaise
Loss of Consciousness, Syncope and Pre-syncope (N=660)	loss of consciousness, unresponsive to stimuli, syncope, syncope vasovagal, dizziness, dizziness postural, presyncope, vertigo
Medical Errors (n=184)	accidental exposure, drug administered at inappropriate site, drug exposure during pregnancy, expired drug administered, inappropriate schedule of drug administration, incorrect dose administered, incorrect drug dosage form administered, incorrect route of drug administration, medication error, underdose, wrong drug administered, wrong technique in drug usage process

Menstruation (N=56)	amenorrhoea, dysfunctional uterine bleeding, dysmenorrhoea, menorrhagia, menstrual disorder, menstruation delayed, menstruation irregular, metrorrhagia
Mental Status (N=51)	agitation, amnesia, coma, confusional state, delirium, disorientation, disturbance in attention, hallucination, high-pitched crying, hypersomnia, incoherent, mental impairment, mental status changes
Miscellaneous (N=66)	adverse drug reaction, adverse event, autopsy, immediate post-injection reaction, intensive care, medical device complication, post vaccination syndrome, serum sickness, unevaluable event, vaccination complication
Mouth, Nose, Tongue and Throat (N=74)	aphthous stomatitis, chapped lips, dry mouth, dysgeusia, dysphagia, epistaxis, gingival bleeding, glossitis, glossodynia, laryngitis, mouth ulceration, nasal congestion, nasopharyngitis, oral mucosal blistering, oral pain, pharyngolaryngeal discomfort, rhinorrhoea, sinus congestion, sinusitis, stomatitis, throat irritation, tongue disorder, tonsillar hypertrophy, tonsillitis, tooth repair, torticollis, upper respiratory tract infection
Nausea, Vomiting, Appetite and Weight (N=343)	decreased appetite, eating disorder, feeding disorder, nausea, oral intake reduced, retching, vomiting, weight decreased, weight increased
Neuromuscular and Coordination (N=205)	abasia, areflexia, asthenia, balance disorder, clumsiness, coordination abnormal, decreased activity, difficulty in walking, dysarthria, dysstasia, dystonia, gait disturbance, hypertonia, hypokinesia, hyporeflexia, hypotonia, injected limb mobility decreased, mobility decreased, movement disorder, muscle atrophy, muscle contractions involuntary, muscle contracture, muscle disorder, muscle rigidity, muscle spasms, muscle tightness, muscle twitching, muscular weakness, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myositis, neuropathy, posture abnormal, radiculitis brachial, sciatic nerve neuropathy, sciatica, sensation of heaviness
Pain and Discomfort (N=629)	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, adnexa uteri pain, axillary pain, back pain, basilar migraine, bone pain, breast pain, burning sensation, chest discomfort, chest pain complex regional pain syndrome, discomfort, ear pain, epigastric discomfort, flank pain, groin pain, headache, limb discomfort, lymph node pain, migraine, myalgia, neck pain, neuralgia, pain, pain in extremity, pain in jaw, pain of skin, pelvic pain, pharyngolaryngeal pain, shoulder pain, tenderness, tendonitis
Pregnancy, Fertility and Obstetrical/Gynecological (N=108)	abortion spontaneous, intra-uterine death, alpha 1 foetoprotein abnormal, benign hydatidiform mole, blighted ovum, ectopic pregnancy, foetal disorder, foetal heart rate abnormal, foetal movements decreased, neural tube defect, premature baby, umbilical cord abnormality, abortion, abortion induced, abortion threatened, antepartum haemorrhage, blood human chorionic gonadotropin abnormal, blood human chorionic gonadotropin increased, blood human chorionic gonadotropin positive, infertility female, ovarian cyst, ovarian cyst ruptured, pelvic inflammatory disease, pregnancy, pregnancy induced hypertension, pregnancy test false positive, pregnancy test positive, pregnancy test urine positive, prenatal care, unintended pregnancy, urine human chorionic gonadotropin positive, uterine dilation and curettage, uterine haemorrhage, vaginal discharge, vaginal haemorrhage, vaginal infection, vaginal odour, vaginal pain, vaginal swelling, vaginitis bacterial, vulval disorder, vulvovaginal pruritus
Psychological and Affect (N=47)	abnormal behaviour, affect lability, anger, anxiety, depressed mood, depression, euphoric mood, fear, irritability, mental disorder, mood swings, nervousness, panic attack, panic reaction, schizophrenia, screaming, stress, suicide attempt, tension

Respiratory (N=130)	acute respiratory distress syndrome, dyspnoea, mechanical ventilation, oxygen supplementation, pulmonary embolism, pulmonary infarction, pulmonary oedema, respiratory distress, respiratory failure, asthma, asthma exercise induced, bronchial disorder, bronchitis, bronchospasm, cough, cyanosis, extubation, hyperventilation, hypoventilation, hypoxia, inspiratory capacity decreased, intubation, pleural effusion, pneumonia, productive cough, pulmonary congestion, rales, respiratory rate increased, wheezing
Sexually Transmitted Disease and Other Infections (N=79)	genital herpes, gonorrhoea, herpes simplex, herpes virus infection, HIV test positive, syphilis test positive, trichomoniasis, Epstein-Barr virus test positive, fungal infection, haemophilus infection, herpes zoster, herpes zoster oticus, infection, infectious mononucleosis, influenza, lyme disease, molluscum contagiosum, mycoplasma serology positive, pneumonia staphylococcal, pyelonephritis, staphylococcal infection, streptococcal identification test positive, streptococcal infection, vaginal candidiasis, varicella, viral infection
Skin (N=578)	acne, alopecia, blister, dermatitis allergic, dermatitis contact, dermatographism, dry skin, eczema, erythema, erythema multiforme, erythema nodosum, genital pruritus female, genital rash, guttate psoriasis, hypotrichosis, induration, melanocytic naevus, petechiae, pigmentation disorder, pityriasis rosea, pruritus, pruritus generalized, pruritus genital, pseudomononucleosis, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash popular, rash pruritic, rash pustular, rash vesicular, skin burning sensation, skin depigmentation, skin discolouration, skin disorder, skin exfoliation, skin hyperpigmentation, skin irritation, skin laceration, skin lesion, skin nodule, skin papilloma, skin reaction, skin tightness, skin ulcer, skin warm
Speech (N=8)	aphasia, dysphonia, lack of spontaneous speech, speech disorder
Vaccine Effectiveness Concerns (N=58)	anogenital warts, cervical dysplasia, drug ineffective, dysplasia, human papilloma virus test positive, papilloma viral infection, smear cervix abnormal

\* N for the symptom category identifies the number of times one or more symptoms from the category were specified in VAERS reports.

**Syncope and Injuries.** As is clear from the table of symptoms and issues, the VAERS reports reflect a large number of routine and expected issues as well as some that merit special attention. **Syncope and vasovagal syncope (fainting with temporary loss of consciousness and posture) was reported 239 times, the second most commonly reported adverse event, and it was sometimes combined with various injuries. In total, injuries were reported 106 times and some of them were very serious including head injuries, fractures and subarachnoid and subdural hematomas.**

For example, VAERS ID 275712 reported that a 13-year-old girl from Florida:

*Fainted within 10 minutes of receiving vaccines and fell backward and hit head on carpeted floor was unresponsive for 20-30 seconds. Complained of headache and neck pain. Transported to ER – CT showed traumatic subarachnoid hemorrhage. Transferred to the PICU [Pediatric Intensive Care Unit].*

NVIC previously addressed the issue of immediate vasovagal post-vaccination syncope as well as atypical syncopal episodes where fainting occurred 10-15 minutes or longer after vaccination. Immediate attention to this issue is required to avoid further

unnecessary and preventable injuries such as noted above. Many children are sustaining serious injuries because providers are not vaccinating children in a supine position and are not requiring them to stay in a supine position for an additional 30 minutes. Sudden loss of consciousness within 24 hours of vaccination is at least the 10<sup>th</sup> most frequently reported symptom, and the medical community, parents and vaccine recipients should be made aware of this fact, particularly with regard to driving or activities requiring constant attention.

**Guillain-Barre Syndrome.** Among the symptoms and illnesses reported to VAERS of greatest concern are death and Guillain-Barre Syndrome (GBS). According to the National Institute for Neurological Disorders and Stroke:

*GBS is a serious disorder in which the body's immune system attacks part of the peripheral nervous system. The first symptoms of this disorder include varying degrees of weakness or tingling sensations in the legs. In many instances, the weakness and abnormal sensations spread to the arms and upper body. These symptoms can increase in intensity until certain muscles cannot be used at all and, when severe, the patient is almost totally paralyzed. ... Vaccinations can trigger onset of GBS.<sup>5</sup>*

In NVIC's February 1, 2007 analysis of VAERS reports submitted following vaccination with Gardasil, two cases of GBS were described both of which were filed by December 2006, and in both cases the girls had also been vaccinated with Menactra. One of these cases was reviewed in the CDC's Morbidity and Mortality Weekly Report and confirmed as GBS.<sup>6</sup>

In the second analysis released February 18, 2007, an additional three GBS reports were submitted to VAERS. Three days later, a newspaper story reported, "health officials have been cautiously watching for reports of Guillain-Barre syndrome, a paralyzing side effect that has been associated with a few other vaccines. In the reporting period, there were three such cases." In the newspaper story, a CDC official was quoted, "*based on these numbers, it's not worrisome to us that there's any sort of association between the vaccine and Guillain-Barre.*"<sup>7</sup>

**Six months later, as of May 31, 2007, there are at least 13 suspected or confirmed GBS reports following vaccination with Gardasil in the VAERS database. In June 2007, an additional two reports have been received, raising total GBS reports to 15.<sup>8</sup>**

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<sup>5</sup> National Institute of Neurological Disorders and Stroke. *Guillain-Barre Fact Sheet* [http://www.ninds.nih.gov/disorders/gbs/detail\\_gbs.htm](http://www.ninds.nih.gov/disorders/gbs/detail_gbs.htm). Accessed January 31, 2007.

<sup>6</sup> Centers for Disease Control and Prevention. (October 20, 2006). Update: Guillain-Barre syndrome among recipients of Menactra Meningococcal Conjugate Vaccine --- United States, June 2005---September 2006, 55(41):1120-1124 [www.cdc.gov/mmwr/preview/mmwrhtml/mm5541a2.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5541a2.htm) (accessed August 5, 2007).

<sup>7</sup> Stobbe, M. (February 21, 2007). U.S. health officials say side effects from new cancer vaccine merit no additional warnings. Associated Press. <http://www.newsvine.com/news/2007/02/21/579711-cdc-says-cancer-vaccine-problems-minor> (accessed August 14, 2007)

<sup>8</sup> VAERS reports for vaccine = HPV4 and symptoms = guillain <http://tinyurl.com/2dsfmm> (Note: the MedAlerts search engine retrieves reports for symptoms from two areas – the symptom list and narrative. In this case, two reports would be discarded because of the way the report was coded: VAERS ID 277815 and 279407. Additionally, with VAERS ID 277815, GBS was ruled out as a diagnosis.)

Additionally, there was a noteworthy report of a 16-year-old girl from Missouri who had been diagnosed with GBS and released from the neurologist's care in March. The teenager was vaccinated with Gardasil and Menactra on May 16, 2007 and two days later began experiencing pain and weakness in her legs. The report was filed with VAERS on May 23 and her condition is being monitored. According to the report, the child's neurologist indicated that she should not have been vaccinated. The report stated that, "*Clinic never gave patient any information on vaccine reactions until after vaccine was given. Clinic is patient's primary care physician so they are aware of her previous condition of GBS.*" This report is not included in the 13 VAERS reports because of the way the report was coded (GBS was not specifically listed as a symptom).

The children for whom GBS reports were filed were between the ages of 13 and 17 and from Ohio, Arkansas, Arizona, Nevada, Mississippi, Illinois, Louisiana, Connecticut, Florida and California (age was not noted in one case and state was not noted in two reports). The symptoms and clinical descriptions of the course of illness were very similar for most of the children: numbness and tingling as well as decreased sensation in the hands and feet, weakness and difficulty walking, and in some cases, paralysis.

**Death.** On May 23, 2007 a public interest group, Judicial Watch, released a statement indicating it had received from the FDA VAERS reports within which were reports for three children who died as of May 11, 2007.<sup>9</sup>

Following the Judicial Watch press release, CDC posted a document on its website dated June 4, 2007 in a section titled, "For Health Professionals, Questions and Answers about HPV Vaccine Safety & Efficacy" and posted the same document on June 7, 2007 in a section titled "For the Media." This document states:

*Since the vaccine was licensed, there have been three deaths reported among persons who received Gardasil: One involving a pulmonary embolism; one involving myocarditis due to influenza A infection; and one from a blood clot. These deaths are being fully investigated. Since more than 5 million doses have been distributed, some deaths will occur coincidentally following vaccination (but not due to vaccination).*<sup>10</sup>

Three weeks later, a document was posted for the public on June 28, 2007 in a section of the website titled, "What You Should Know", "Vaccine Safety", "Qs and As for the Public on the Safety and Effectiveness of HPV Vaccine (June 28, 2007)".<sup>11</sup> Using data from May 8, 2007, CDC reported the following:

*There also have been four deaths reported among females who received the HPV vaccine: One involving a blood clot in the lungs (pulmonary embolism); one*

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<sup>9</sup> Judicial Watch Uncovers Three Deaths Relating to HPV Vaccine: Event Reports Obtained from FDA Detail 1,637 Adverse Reactions to Gardasil. May 23, 2007. [http://www.judicialwatch.org/printer\\_6299.shtml](http://www.judicialwatch.org/printer_6299.shtml)

<sup>10</sup> Centers for Disease Control and Prevention, CDC Question and Answers Concerning the Safety and Efficacy of Gardasil, June 4, 2007, <http://www.cdc.gov/vaccines/vpd-vac/hpv/default.htm> (accessed August, 6, 2007).

<sup>11</sup> Centers for Disease Control and Prevention, HPV Vaccine – Questions & Answers For the Public, June 28, 2007, <http://www.cdc.gov/vaccines/vpd-vac/hpv/default.htm> (accessed August, 6, 2007).

*involving inflammation of the health muscle due to influenza; one from a blood clot; and one from multiorgan system failure due to influenza infection unrelated to vaccination. Preliminary data indicate that the two women who died of blood clots were taking birth control pills, and blood clots are a known risk association with birth control pills. All four deaths are being fully investigated but none appear to be caused by vaccination.*

**Currently, there are seven deaths following vaccination with Gardasil noted in the VAERS database.**<sup>12</sup> CDC has not commented on the three additional deaths reported.

### Co-administration of Vaccines

VAERS reports were filed for people who received different numbers of vaccines at the time of vaccination. The number of vaccines received ranged from one to five. Even though 87 percent only received Gardasil, during a single office visit, two vaccines were administered to 179 persons (8 percent), three vaccines were given to 77 persons (3 percent), four vaccines to 35 persons (2 percent) and five vaccines to six people.

Although Gardasil's manufacturer only evaluated the safety of administration of Gardasil with Hepatitis B vaccine, 26 additional vaccines have been administered along with Gardasil among recipients reporting adverse events.<sup>13</sup> **Over 80 percent of Gardasil adverse event reports to VAERS involving two or more vaccines involved simultaneous administration of Gardasil with either one or more of five particular vaccines or were vaccines not recommended for combined use with Gardasil by the Centers for Disease Control such as typhoid, smallpox and anthrax. The five most frequently administered vaccines not evaluated for safety were:**

- MNQ - meningococcal conjugate (Sanofi-Aventis Pasteur) - 135 reports (29 percent)
- TDAP (Tdap) - tetanus, diphtheria and acellular pertussis (GlaxoSmithKline; Sanofi-Aventis Pasteur) 75 reports (16 percent)
- HEPA - hepatitis A (GlaxoSmithKline; Merck, Sharp & Dohme) - 73 reports (16 percent)
- VARCEL – Varicella (chickenpox) (Merck, Sharp & Dohme) - 57 reports (12 percent)
- FLU – influenza (Various) 38 reports – (Wyeth, Connaught, Lederle, GlaxoSmithKline, Sanofi-Aventis Pasteur, Chiron) 38 reports (8 percent)

<sup>12</sup>VAERS reports for vaccine = HPV4 and died? = <http://tinyurl.com/2sabor>

<sup>13</sup> The vaccines administered and the number of adverse reports submitted include: ANTH - anthrax (2), DTaP – diphtheria and tetanus toxoids and acellular pertussis (12), DTaPH - diphtheria and tetanus toxoids and acellular pertussis and haemophilus (1), DTOX - diphtheria toxoid (1), DPT - diphtheria and tetanus toxoids whole-cell pertussis (2), FLU – influenza (38), FLUN – influenza (nasal spray) (2), HEP – hepatitis B (8), HEPA – hepatitis A (73), HEPAB – hepatitis A and hepatitis B (1), HIBV – haemophilus B conjugate (3), IPV – inactivated poliovirus (4), MEN – meningococcal polysaccharide (4), MMR – measles, mumps, rubella (6), MMRV – measles, mumps, rubella and varicella (3), MNC – meningococcal conjugate (2), MNQ – meningococcal conjugate (135), OPV – live oral poliovirus trivalent (2), PNC – pneumococcal 7-valent conjugate (3), PPV – pneumococcal polyvalent (2), SMALL – smallpox (3), TD – tetanus and diphtheria toxoids (adult) (3), TDAP – Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (75), TTOX – tetanus toxoid (4), TYP – typhoid (2), VARCEL – varivax-varicella (57), VARZOS - varicella-zoster (4) and unknown (9).

None of these five vaccines was explicitly evaluated for co-administration safety and efficacy by Gardasil's manufacturer prior to licensure. Specifically, on the Gardasil package insert Merck states the following:<sup>14</sup>

*Studies with Other Vaccines*

*The safety and immunogenicity of co-administration of Gardasil with hepatitis B vaccine (recombinant) (same visit, injections at separate sites) were evaluated in a randomized study of 1,871 women aged 18 to 24 years at enrollment. Immune response to both hepatitis B vaccine (recombinant) and Gardasil was non-inferior whether they were administered at the same visit or at a different visit.*

*Use with Other Vaccines*

*Results from clinical studies indicate that Gardasil may be administered concomitantly (at a separate injection site) with hepatitis B vaccine (recombinant) (see CLINICAL PHARMACOLOGY, Studies with Other Vaccines). Co-administration of Gardasil with other vaccines has not been studied.*

It should be noted that Gardasil's manufacturer indicated that the "immune response" was similar when Gardasil was administered with Hepatitis B. It did not comment on safety or rates of adverse reactions. The inability to do so was likely a function of the small sample (N=1,871), which lacks the statistical power to allow the detection of relatively rare adverse events. Therefore, **there is no published literature that has sufficiently evaluated the safety of co-administration of Gardasil with any other vaccine.**

Of particular note is that more than one-quarter of adverse reaction reports that involve two or more vaccines involved adverse events when Gardasil was also administered with MNQ – Menactra - a meningococcal vaccine — manufactured by Sanofi-Aventis Pasteur. Both the FDA and CDC have issued advisories to clinicians regarding Menactra and a serious neurological disorder, Guillain-Barre Syndrome.<sup>15</sup>

## Medical Errors and Patient Safety Issues

More than seven years ago, the Institute of Medicine (IOM) published a landmark document, *To Err Is Human: Building a Safer Health System*, which estimated that as many as 98,000 hospitalized Americans die each year not because of their illness or disease, but because of errors in the care provided to them.<sup>16</sup> As a result, medical errors have been estimated to be the 8<sup>th</sup> leading cause of death in the US. Although the IOM focused primarily on health care delivered in hospitals, concerns about errors and

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<sup>14</sup> Merck & Co., Inc. (2006). GARDASIL [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]. [http://www.merck.com/product/usa/pi\\_circulars/g/gardasil/gardasil\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf)

<sup>15</sup> Food and Drug Administration, FDA and CDC Issue Alert on Menactra Meningococcal Vaccine and Guillain Barre Syndrome, September 30, 2005, <http://www.fda.gov/bbs/topics/NEWS/2005/NEW01238.html> (accessed August 5, 2007).

<sup>16</sup> IOM (Institute of Medicine). 2000. *To Err is Human: Building a Safer Health System*. Washington, DC: National Academy Press.

their effects on health outcomes and costs apply to ambulatory settings where vaccines are administered to children and adults.

According to the Quality Interagency Coordination Task Force, appropriate efforts to improve patient safety include those designed to prevent adverse health outcomes arising from medical errors. Such efforts tend to involve preventing errors, making errors visible and mitigating the effects of errors.

A medical error is defined by the Institute of Medicine as:

*Error - Failure of a planned action to be completed as intended or use of a wrong plan to achieve an aim; the accumulation of errors results in accidents.*

Additionally, questions about appropriate care arise when drugs and products are not administered in accordance with FDA licensing directives.

To evaluate the extent to which Gardasil VAERS reports could be classified as either medical errors, the following “symptoms” that reflect errors in care were evaluated:

- Accidental exposure
- Drug administered at inappropriate site
- Drug exposure during pregnancy
- Expired drug administered
- Inappropriate schedule of drug administration
- Incorrect dose administered
- Incorrect drug dosage form administered
- Incorrect route of drug administration
- Medication error
- Under-dose
- Wrong drug administered
- Wrong technique in drug usage process

Also, as noted earlier, despite FDA licensing directives, Gardasil was administered to males and to females who were under nine or over 26 years of age. Although prescribing a drug in a way that is not consistent with licensing directives may not constitute a medical error, per se, in some cases it does.

Of the 2,227 VAERS reports, 162 (7.3 percent) contained one or more of the types of errors listed above. Within this group, 42 were filed on behalf of patients who were given Gardasil outside the prescribing limits established by the FDA; either the patient was under 9 or over 26 years of age or was a male. An additional 50 reports were filed for these same types of patients but no medical error was identified in the VAERS report.

**In total, 212 reports, 9.5 percent of all VAERS reports, reflected care that was either classified as a medical error or involved patient care that was inconsistent with FDA licensing directives or both.**

Not included in this analysis are other instances of questionably inappropriate care. For example, use of Gardasil after evidence of previous vaccine reactions; failure to provide safe care that would prevent injuries such as those following syncopal episodes; and co-

administration of Gardasil with vaccines for which efficacy and safety of co-administration have not been explicitly evaluated. Regarding the first examples – use of Gardasil after evidence of previous vaccine reactions - there are dozens of examples of “challenge-rechallenge” evidence suggesting that patients who have certain reactions after the first dose of vaccine should not be given a second or third dose. A challenge-rechallenge test is when a drug is given and a reaction occurs (challenge) and the drug is given a second time and the same (or more severe) reaction occurs (rechallenge).

**Challenge-rechallenge reactions reported include: convulsions; swollen lymph nodes; persistent vertigo; numbness, tingling and weakness in non-injected limbs; joint pain; allergic rashes; hallucinations requiring emergency care; urticaria (hives); wheezing; vision problems; and loss of balance. These are examples of reactions that should be considered contraindications to receiving additional doses of vaccine.**

[With regard to acknowledging the importance of challenge-rechallenge, clinicians should ask themselves: If an antibiotic was administered and the patient broke out into a head-to-toe rash, urticaria, or began wheezing, would a reasonable clinician prescribe the drug a second time?]

Gardasil's manufacturer states in the product insert that, “*Individuals who develop symptoms indicative of hypersensitivity after receiving a dose of Gardasil should not receive further doses of Gardasil.*”<sup>17</sup> CDC's Vaccine Information Statement (VIS), however, only notes that, “*Anyone who has ever had a life-threatening allergic reaction to yeast, to any other component of HPV vaccine, or to a previous dose of HPV vaccine should not get the vaccine.*”<sup>18</sup>

A number of the challenge-rechallenge reactions reported after receipt of Gardasil are life-threatening, yet physicians continued to re-vaccinate despite the serious nature of the adverse events being experienced by the patient. **The CDC's list of contraindications to Gardasil use is not specific and the CDC Vaccine Information Statement (VIS) does not adequately warn vaccine providers, patients and parents about the risk of re-vaccination after a serious adverse event has been experienced. A vaccine reaction should not have to be life-threatening to be contraindicated for further vaccine exposures.**

The gap between what is recommended by the manufacturer, CDC and actual clinical practice is an example of a “systems” problem that permits errors in care to occur and results in preventable adverse health outcomes. Improvements in vaccine administration systems used within ambulatory care settings (physician offices and public health clinics) could benefit from adoption of a number of principles and systems designed to reduce medication errors. The resources available through the Institute for Safe Medication Practices <http://www.ismp.org/> should be used to improve routine vaccination practice.

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<sup>17</sup> Merck & Co., Inc. (2006). GARDASIL [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine]. [http://www.merck.com/product/usa/pi\\_circulars/g/gardasil/gardasil\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf)

<sup>18</sup> Centers for Disease Control and Prevention, Vaccine Information Statement (Interim) Human Papillomavirus (HPV) Vaccine, 2/2/07, <http://www.cdc.gov/vaccines/pubs/vis/default.htm#hpv> (accessed August 7, 2007).

Explicit adoption of the principles, which acknowledge the value of “patient-centered care” as a way to reduce preventable adverse events and improve health outcomes, would require:

- provider-patient relationships reframed as a partnership with shared decision-making and open communication; and
- patients taking an active role in the process of care and design of safety mechanisms to prevent errors.<sup>19</sup>

A number of the medication errors could have been eliminated by double-checking the vaccine against the recommended vaccination schedule; showing patients the vial/syringe of vaccine to be given; making sure that the correct vaccine was selected for administration; explaining the vaccine’s purpose, risks, contraindications and benefits to the patient/parent making sure that the vaccine was not contraindicated; double-checking dose and proper route of administration; and obtaining meaningful parent/patient informed consent prior to administration. Additionally, routine use of the “Five Rights” taught to nursing students --- right patient, right drug, right dose, right schedule, right site --- could have substantially reduced administration errors reported to VAERS in addition to preventing dozens of adverse health outcomes and their associated costs.

### **Adverse Events and Co-administration of Vaccines**

Six months ago, NVIC raised concerns about the safety of co-administration of Gardasil with other vaccines. VAERS data had already alerted federal health officials to a potential association between Guillain-Barre Syndrome and Menactra, to which the FDA and CDC had responded appropriately by issuing an alert to vaccine providers and the public for special monitoring of GBS following receipt of Menactra. However, in response to reports in VAERS of GBS following receipt of Gardasil, Centers for Disease Control (CDC) officials issued a statement reassuring the public that *“there’s no evidence Gardasil is harmful in combination with other vaccines.”*<sup>20</sup>

One month later, acknowledging a lack of evidence on safety of co-administering Gardasil with other vaccines, in the March 12, 2007 Morbidity and Mortality Weekly Report, CDC stated that *“no data exist on administration of quadrivalent HPV vaccine*

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<sup>19</sup> Michigan State Commission on Patient Safety. (2005). *Call to Action: A Plan to Improve Patient Safety in Michigan’s Health Care System*. Southfield, MI: Michigan Health and Safety Coalition. Citing the following recommended resources: Joint Commission on Accreditation of Healthcare Organizations (2005). *Facts About the 2006 National Patient Safety Goals*. Washington, DC: Joint Commission on Accreditation of Healthcare Organizations. Retrieved 07/23/05 from [http://www.jcaho.org/accredited+organizations/patient+safety/06\\_facts.htm](http://www.jcaho.org/accredited+organizations/patient+safety/06_facts.htm); Kohn LT, Corrigan JM & Donaldson MS (Eds.). Committee on Quality of Health Care in America, Institute of Medicine (2001). *Crossing the Quality Chasm: A New Health System for the 21<sup>st</sup> Century*. Washington, DC: National Academy Press.; Aspden P, Corrigan JM, Wolcott J & Erickson SM (Eds.) Committee on Data Standards for Patient Safety, Board on Health Care Services, Institute of Medicine (2004). *Patient Safety: Achieving a New Standard of Care*. Washington, DC: National Academy Press.; Kizer KW. (2001). *Patient Safety: A Call to Action*. Washington, DC: The National Forum for Health Care Quality Measurement and Reporting. <http://www.qualityforum.org>.; National Patient Safety Foundation Patient and Family Advisory Council (2003). *National Agenda for Action: Patients and Families in Patient Safety, Nothing About Me, Without Me*. Executive Summary. Washington, DC: The National Patient Safety Foundation. <http://www.npsf.org/html>

<sup>20</sup> Stobbe, M. (February 21, 2007). U.S. health officials say side effects from new cancer vaccine merit no additional warnings. Associated Press. <http://www.newsvine.com/news/2007/02/21/579711-cdc-says-cancer-vaccine-problems-minor> (accessed August 14, 2007)

with vaccines other than hepatitis B” and “studies are planned to evaluate concomitant administration with meningococcal conjugate vaccine and with the adolescent/adult formulation of tetanus, diphtheria and acellular pertussis (Tdap) vaccine.”<sup>21</sup> As stated earlier, the evaluation of co-administration of Gardasil with hepatitis B vaccine by Gardasil’s manufacturer, Merck, focused on immune system response and not adverse events.

**There is no published peer-reviewed evidence that establishes the safety of administering Gardasil at the same time other vaccines are given.**

CDC reasoned that because Gardasil “is not a live virus vaccine and has no components that adversely impact safety or efficacy of other vaccinations,” it “can be administered at the same visit as other age appropriate vaccines, such as the Tdap and quadrivalent meningococcal conjugate (MCV4) vaccines.”<sup>22</sup> Menactra is a quadrivalent meningococcal conjugate (MCV4) vaccine. **CDC did not provide empirical evidence that evaluated the safety of giving Gardasil with other vaccines.**

To evaluate whether there is evidence that co-administering Gardasil with other vaccines, including Menactra, is safe, an analysis of the VAERS data submitted through May 31, 2007 was conducted. Specifically, a number of bivariate comparisons were performed to determine whether evidence of an association between different types of vaccine exposures and reported adverse events exists.

As described earlier, the symptoms contained in the VAERS reports were divided into a 32 categories and sub-categories. A VAERS report was coded as containing an adverse event category if one or more symptoms within the category were recorded in a symptom field of the VAERS records.

Additionally, VAERS reports were sorted into three different vaccine exposure groups:

- Group 1 = VAERS reports where individuals received only Gardasil.
- Group 2 = VAERS reports where individuals received Gardasil and any/all other vaccines including combinations without Menactra.

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<sup>21</sup> “GMT’s (geometric mean titers) after concomitant administration of quadrivalent HPV vaccine and hepatitis B vaccine at all 3 doses were noninferior to GMT’s after administration at separate visits. Studies are planned to evaluate concomitant administration with meningococcal conjugate vaccine and with the adolescent/adult formulation of tetanus, diphtheria and acellular pertussis (Tdap) vaccine.” (p. 12). Centers for Disease Control and Prevention. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report (MMWR) Early Release 2007*;56 March 12, 2007:1-24.

<sup>22</sup> “Although no data exist on administration of quadrivalent HPV vaccine with vaccines other than hepatitis B vaccine, quadrivalent HPV vaccine is not a live vaccine and has no components that adversely impact safety or efficacy of other vaccination. Quadrivalent HPV vaccine can be administered at the same visit as other age appropriate vaccines, such as the Tdap and quadrivalent meningococcal conjugate (MCV4) vaccines. Administering all indicated vaccines together at a single visit increases the likelihood that adolescents and young adults will receive each of the vaccines on schedule. Each vaccine should be administered using a separate syringe at a different anatomic site.” (p. 17) Centers for Disease Control and Prevention. Quadrivalent Human Papillomavirus Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report (MMWR) Early Release 2007*;56 March 12, 2007:1-24.

- Group 3 = VAERS reports where individuals received only combinations with Gardasil and Menactra (48 percent of this group, N = 65) received only Gardasil and Menactra; the remainder also received one or more of 10 different vaccines).<sup>23</sup>

The percentages of each group that reported experiencing various categories of adverse events were compared. Chi-square statistics, and in cases where cell sizes were small, Fisher's Exact Test statistics, using SAS 9.1 and Epi Info 3.4 were computed to determine whether the differences in proportions observed across Group 1 and Group 3 were statistically significant. The results from this analysis are shown in Table 2.

Using one of the adverse outcome categories as an example -- neuromuscular and coordination problems -- the data in Table 2 show that among the 1,930 VAERS reports where only Gardasil was given, 120 (6.2 percent) experienced neuromuscular and coordination problems. In comparison, among the 135 VAERS reports where Gardasil and Menactra were given at the same time, 28 (20.7 percent) experienced neuromuscular and coordination problems. The chi-square statistic was computed to determine whether the difference in these proportions was statistically significant and the computed relative risk was 3.34 (with a 95 percent confidence interval of 2.30 to 4.84 and p-value of <0.0001).

**These are highly statistically significant findings which suggest that among people who reported adverse events to VAERS following vaccination with Gardasil, the risk of a reported neuromuscular and coordination problem was increased by 234 percent when Gardasil was given in combination with Menactra rather than given alone. In other words, Gardasil recipients who reported an adverse reaction were 3.3 times more likely to report a neuromuscular and coordination problem if they were injected with Gardasil and Menactra at the same time rather than only receiving Gardasil.**

**For most comparisons, the rates of reported adverse events were higher when Gardasil was combined with other vaccines rather than when given alone, but was highest when Menactra was part of the combination of vaccines given along with Gardasil. Thus, the rates between Group 1 and Group 3 were compared. As shown in Table 2, the results of this analysis indicate that there is a statistically significant increase in reported adverse events when Gardasil is given in combination with other vaccines, such as Menactra.**

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<sup>23</sup> Additional vaccines included (see footnote 13 for definitions): TDAP (36 doses), HEPA (28 doses), VARCEL (17 doses), FLU (11 doses), DTAP (3 doses), HEPB (2 doses), PPV (2 doses), TTOX (1 dose), HIBV (1 dose), and MMR (1 dose).

**Table 2. Adverse Events and Co-administration of Gardasil and Menactra**

Symptom Category	Gardasil N=1930 <sup>24</sup>	Gardasil with Menactra N=135 <sup>25</sup>	Relative Risk Ratio	95% Confidence Interval	p value
Allergic Reactions	204 (10.6%)	20 (14.8)	1.40	(0.92, 2.14)	0.1252
Arthritis and Joints	54 (2.8%)	4 (3.0%)	1.06	(0.39, 2.88)	0.7889*
Autoimmune	27 (1.4%)	2 (1.5%)	1.06	(0.25, 4.40)	0.7144*
• Major Autoimmune Adverse Events	12 (0.6%)	1 (0.7%)	1.19	(0.16, 9.09)	0.5859*
Breast	2 (0.1%)	0 (0%)	N/A <sup>a</sup>		
Cardiac and Cardiovascular	92 (4.8%)	14 (10.4%)	2.18	(1.27, 3.71)	0.0043
• Major Cardiac Adverse Events	9 (0.5%)	0 (0%)	N/A <sup>a</sup>		
Challenge/Rechallenge Evidence	29 (1.5%)	2 (1.5%)	0.99	(0.24, 4.09)	>0.999
Convulsions and Central Nervous System	82 (4.2%)	23 (17.0%)	4.01	(2.61, 6.15)	<0.0001
• Convulsions	39 (2.0%)	9 (6.7%)	3.30	(1.63, 6.67)	0.0031*
Ear and Hearing	10 (0.5%)	0 (0%)	N/A <sup>a</sup>		
Eye and Vision	47 (2.4%)	5(3.7%)	1.52	(0.62, 3.76)	0.3847*
Fever, Pyrexia, Chills, and Flushing	175 (9.1%)	26 (19.3%)	2.12	(1.46, 3.08)	0.0001
Gastrointestinal	49 (2.5%)	6 (4.4%)	1.75	(0.76, 4.01)	0.1689*
Guillain-Barre Syndrome, Paralysis and Sensory	125 (6.5%)	17 (12.6%)	1.94	(1.21, 3.13)	0.0066
• Guillain-Barre Syndrome	7 (0.4%)	6 (4.4%)	12.3	(4.18, 36.7)	<0.0001*
• Paralysis	13 (0.7%)	3 (2.2%)	3.30	(0.95, 11.4)	0.0818*
• Sensory Disturbance	114 (5.9%)	15 (11.1%)	1.88	(1.13, 3.13)	0.0157
Injuries	56 (2.9%)	16 (11.9%)	4.08	(2.41, 6.92)	<0.0001
• Falls	24 (1.2%)	13 (9.6%)	7.74	(4.03, 14.9)	<0.0001
• Head and Neck Injuries	20 (1.0%)	7 (5.2%)	5.0	(2.15, 11.6)	0.0013*
Injection Site	347 (2.5%)	28 (20.7%)	1.15	(0.82, 1.63)	0.4210
Kidney and Bladder	12 (0.6%)	2 (1.5%)	2.38	(0.54, 10.5)	0.2317*
Lethargy, Fatigue and Malaise	126 (6.5%)	14 (10.4%)	1.59	(0.94, 2.68)	0.0861
Loss of Consciousness, Syncope and Pre-syncope	484 (25.1%)	32 (23.7%)	0.95	(0.69, 1.29)	0.7215
• Loss of Consciousness	104 (5.4%)	11 (8.1%)	1.51	(0.83, 2.75)	0.1765
• Syncope	201 (10.4%)	13 (9.6%)	0.92	(0.54, 1.58)	0.7724
• Pre-syncope	233 (12.1%)	17 (12.6%)	1.04	(0.66, 1.65)	0.8579
Medical Errors	136 (7.0%)	10 (7.4%)	1.05	(0.57, 1.95)	0.8744
Menstruation	50 (2.6%)	1 (0.7%)	0.29	(0.04, 2.05)	0.2435*
Mental Status	35 (1.8%)	5 (3.7%)	2.04	(0.81, 5.13)	0.1810*
Miscellaneous complication	55 (2.8%)	2 (1.5%)	0.52	(0.13, 2.11)	0.5823*
Mouth, Nose, Tongue and Throat	51 (2.6%)	9 (6.7%)	2.52	(1.27, 5.01)	0.0141*
Nausea, Vomiting, Appetite and Weight	243 (12.6%)	18 (13.3%)	1.06	(0.68, 1.65)	0.8018
Neuromuscular and Coordination	120 (6.2%)	28 (20.7%)	3.34	(2.30, 4.84)	<0.0001
Pain and Discomfort	416 (21.6%)	45( 33.3%)	1.55	(1.20, 1.99)	0.0015
Pregnancy, Fertility and Obstetrical/Gynecological	66 (3.4%)	1 (0.7%)	0.22	(0.03, 1.55)	0.1254*
• Spontaneous Abortion, Fetal Loss	14 (0.7%)	0 (0%)	N/A <sup>a</sup>		
• Pregnancy/Fetal Adverse Outcomes	7 (0.4%)	1 (0.7%)	2.04	(0.25, 16.5)	0.4183*
Psychological and Affect	34 <sup>26</sup> (1.8%)	5 (3.7%)	2.10	(0.84, 5.29)	0.1067*
Respiratory	80 (4.1%)	12 (8.9%)	2.14	(1.20, 3.83)	0.0098
• Major Respiratory Adverse Events	56 (2.9%)	6 (4.4%)	1.53	(0.67, 3.49)	0.3931*
Sexually Transmitted Disease and Other Infections	57 (3.0%)	6 (4.4%)	1.50	(0.66, 3.43)	0.2997*
• Sexually Transmitted Disease	12 (0.6%)	1 (0.7%)	1.19	(0.16, 9.09)	0.5859*
Skin	336 (17.4%)	33 (24.4%)	1.40	(1.03, 1.92)	0.0391
Speech	6 (0.3%)	2 (1.5%)	4.77	(0.97, 23.4)	0.0916*
Vaccine Effectiveness Concerns	43 (2.2%)	1 (0.7%)	0.33	(0.05, 2.40)	0.3611*

\*Fisher's Exact test used to compute p value due to small cell size.

<sup>a</sup> Not applicable because one of the cells contained a value of zero, computation could not be performed.

<sup>24</sup> Total number of VAERS case records through May 31, 2007 in which only Gardasil was administered.

<sup>25</sup> Total number of VAERS cases records through May 31, 2007 in which Gardasil was administered in combination with Menactra and possibly other vaccines.

<sup>26</sup> For each of the symptom categories, the number of VAERS case records that contained one or more symptoms assigned to the category.

The findings reported in Table 2 show that highly significant differences in reported adverse outcome risks were identified across the two types of vaccine exposures. The rows highlighted in dark gray are statistically significant with p values <0.05. Specifically, among persons who reported adverse events to VAERS following vaccination with Gardasil alone compared to persons given Gardasil in combination with Menactra, the increased risk of reported adverse outcomes when Gardasil and Menactra are given simultaneously are as follows:

- **Cardiac and cardiovascular problems**
  - 118% or 2.2 times more likely to be reported
- **Convulsion and central nervous system problems**
  - 301% or 4.0 times more likely to be reported
  - Convulsions (only) 230% increased risk or 3.3 times more likely to be reported
- **Fever, chills and flushing**
  - 112% or 2.1 times more likely to be reported
- **Guillain-Barre Syndrome, paralysis and sensory problems**
  - 94% or 1.9 times more likely to be reported
  - **GBS (only) 1,130% or 12.3 times more likely to be reported**<sup>27</sup>
  - Sensory disturbance (only) 88% or 1.8 times more likely to be reported
- **Injuries, overall**
  - 308% or 4.0 times more likely to be reported
  - **falls (only) 674% or 7.7 times more likely to be reported**
  - head or neck injury (only) 400% or 5.0 times more likely to be reported
- **Mouth, nose, throat and tongue problems**
  - 152% or 2.5 times more likely to be reported
- **Neuromuscular and coordination problems**
  - 234% or 3.3 times more likely to be reported
- **Pain and Discomfort**
  - 55% or 1.5 times more likely to be reported
- **Respiratory problems**
  - 114% or 2.1 times more likely to be reported

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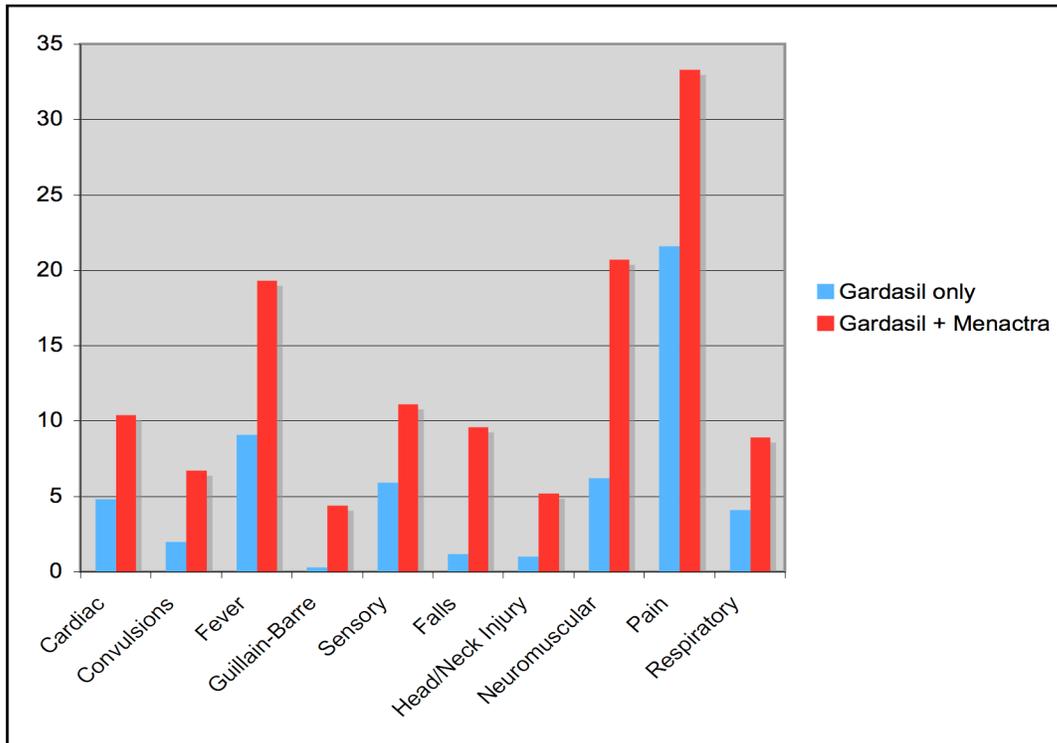
<sup>27</sup> For the GBS analysis, 13 cases were included in the computation including VAERS ID 269328, which was in the VAERS database but is not any longer. VAERS ID 279407 was not included. Nor were the two new reports for VAERS ID 280394 and 282746 that are in the June 2007 data. Supplementary analyses including removing the one VAERS report where an additional vaccine was administered along with Menactra (VAERS ID 279082) and limiting the denominator to 65 (only those VAERS reports reflecting Gardasil with Menactra and no other vaccines). The net effect was to increase the relative risk to 21.2 (95% CI 6.91-65.1), p <0.0001.

The differences between percent of reported adverse events which were statistically significant across the two vaccine exposure groups are shown in Figure 3. The p values for these comparisons ranged from  $p < 0.0001$  to  $p = 0.0157$ .

Additionally, there are findings that may be clinically significant although they don't meet the strict definition of statistically significant for hypothesis testing. The high upper limit point estimates for the relative risk ratios are important.<sup>28</sup> Specifically,

- **Allergic reactions**
  - 40% or 1.4 times more likely to be reported
- **Lethargy, fatigue and malaise**
  - 59% or 1.5 times more likely to be reported
- **Loss of consciousness**
  - 51% or 1.5 times more likely to be reported
- **Skin-related problems**
  - 40% or 1.4 times more likely to be reported

**Figure 3. Percent of VAERS Reports with Adverse Events by Vaccine Exposure**



<sup>28</sup> Values at either end of the confidence intervals (see Table 2) are less likely to occur than is the relative risk estimate. Take allergic reactions, for example, where the confidence interval is 0.92 to 2.14. It is equally probable that the true estimate is 0.92 (the lower limit) as it is 2.14 (the upper limit). Assuming that no systematic error is present, because most of the p-value function falls above the null hypothesis, the true association is more likely to have a value greater than 1.0 than less than or equal to one.

**Taken as a whole, these findings suggest there is an additional risk of experiencing and reporting various adverse health outcomes when Gardasil is administered with other vaccines, especially Menactra. Causation cannot be established using epidemiological methods and administrative data of this type. However, even though these findings do not prove that Gardasil or Gardasil combined with Menactra and other vaccines cause any of these outcomes, they do provide an important signal that should be further investigated.**

Limitations in this analysis include assumption of no systematic error, no selection bias and no confounding. It was not possible to assess the effect of non-random sources of error. Some of the cell sizes for of the analyses were small and could produce unstable statistics. In addition, because the VAERS database does not include information on the total number of persons given each vaccine and vaccine combination, the Gardasil and Gardasil-combined-with-Menactra-specific risks of reported adverse events could not be computed among all persons exposed to (a) Gardasil alone and (b) Gardasil combined with Menactra.

**Until the safety of co-administration of Gardasil with Menactra and other vaccines is demonstrated, sensible adherence to the precautionary principle dictates that Gardasil should not be administered simultaneously with other vaccines, especially Menactra.**

This precaution does not suggest that taking Gardasil alone is risk-free, only that co-administration of Gardasil with other vaccines appears to increase the number of serious adverse events reported to VAERS. To reiterate what the data show, the June 2007 VAERS data that there have been 15 reports of GBS following administration of Gardasil. So far, eight of the reports have followed receiving Gardasil alone, five following Gardasil and Menactra, and two following Gardasil, Menactra and Hepatitis A.

### **CDC Statements on Guillain-Barre Syndrome and Vaccines**

As stated earlier, CDC has previously commented on the potential association between Gardasil and Guillain-Barre Syndrome. Specifically, in a newspaper article CDC officials stated, *“based on these numbers [three cases of GBS], it’s not worrisome to us that there’s any sort of association between the vaccine” and Guillain-Barre.*<sup>29</sup>

**Guillain-Barre Syndrome and Gardasil.** CDC posted a document on it’s website dated June 4, 2007 in a section titled, “For Health Professionals, Questions and Answers about HPV Vaccine Safety & Efficacy” and posted the same document on June 7, 2007 in a section titled “For the Media.” This document states:

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<sup>29</sup> Stobbe, M. (February 21, 2007). U.S. health officials say side effects from new cancer vaccine merit no additional warnings. Associated Press. <http://www.newsvine.com/news/2007/02/21/579711-cdc-says-cancer-vaccine-problems-minor> (accessed August 14, 2007)

*Since the vaccine was licensed, there have been 13 reports of Guillain-Barre Syndrome (GBS) among persons who received Gardasil. CDC investigators are in the process of confirming GBS. Of the 13 reports, six individuals received Gardasil given alone, five received Gardasil and Menactra, one received Gardasil, Menactra and Hepatitis A vaccine, and one received Gardasil and Pneumococcal Polysacchride Vaccine given within 30 days of one another. At least one media article has incorrectly reported the number of GBS cases as forty. Because GBS occurs at a rate of 1-2/100,000 person years during the second decade of life, some cases will occur by coincidence following vaccination (but not due to vaccination).<sup>30</sup>*

In this document CDC describes the VAERS system and said that it is “*working closely with the FDA to closely monitor the safety of the HPV vaccine.*” It reviewed pre-licensure data and stated that there appeared to be “*no serious side effects.*” Additionally, the document states:

*It is important to know that many adverse events reported to VAERS may not be caused by vaccines. Reports to VAERS may be submitted by anyone, including healthcare providers, patients and family members. Because of this, VAERS is subject to several limitations including underreporting and incomplete information.*

*VAERS receives reports of many events that occur after immunization. Some of these events may occur coincidentally following vaccination, while others may be caused by vaccination. The fact that an adverse event occurred following immunization is not conclusive evidence that the event was caused by a vaccine. Factors such as medical history and other medications taken near the time of the vaccination must be examined to determine if they could have caused the adverse event.*

Note that, in contrast to what occurred when concerns were raised two years earlier related to GBS and other adverse events following receipt of Menactra, physicians and others were not encouraged to carefully monitor patients or informed of their obligation to report GBS and other adverse events following receipt of Gardasil to VAERS.

An additional document was posted by CDC on June 28, 2007 in a section of the website titled, “What You Should Know”, “Vaccine Safety”, “Qs and As for the Public on the Safety and Effectiveness of HPV Vaccine (June 28, 2007)”.<sup>31</sup> In this document, CDC appears to be using VAERS data current as of May 8, 2007 and with respect to concerns about Gardasil and GBS, CDC stated:

***Is the HPV vaccine safe?***

*The vaccine has been licensed as safe.*

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<sup>30</sup> Centers for Disease Control and Prevention, CDC Question and Answers Concerning the Safety and Efficacy of Gardasil, June 4, 2007, <http://www.cdc.gov/vaccines/vpd-vac/hpv/default.htm> (accessed August, 6, 2007).

<sup>31</sup> Centers for Disease Control and Prevention, HPV Vaccine – Questions & Answers For the Public, June 28, 2007, <http://www.cdc.gov/vaccines/vpd-vac/hpv/default.htm> (accessed August, 6, 2007).

***Have any reports of serious events been received?***

*Of the total VAERS reports, 94 (5 percent) are defined as serious. They include 13 unconfirmed reports of Guillain-Barre Syndrome (GBS), a neurological illness resulting in muscle weakness and sometimes in paralysis. It is important to know that some cases of GBS will occur by coincidence following vaccination but not because of vaccination.*

It's not clear what criteria CDC uses to define a "serious" event but in a document containing VAERS reports obtained under a Freedom of Information Act request<sup>32</sup> from roughly the same time period, 371 events were defined as "serious." A review of those events show that records labeled as "non-serious" contained many of the same symptoms as those defined as "serious" including: convulsions, facial paralysis, syncope, loss of consciousness, head injury, anaphylactic reaction. It would appear that little comfort can be derived from knowing that only 5 percent of cases were defined as "serious" when life-threatening conditions are defined as "non-serious."

CDC also produces the Vaccine Information Statements (VIS) that are supposed to be provided to parents prior to vaccination as part of the informed consent process and to make parents aware of potential side effects to watch for and report. The VIS for HPV vaccine only mentions the possibility of "severe allergic reactions" along with "mild problems" (injection site pain, redness or swelling, and itching and mild to moderate fever).<sup>33</sup>

In the section of the HPV vaccine VIS titled, "What if there is a severe reaction" the document recommends that the doctor be called in the event of "*High fever or behavior changes, difficulty breathing, hoarseness or wheezing, hives, paleness, weakness, a fast heart beat or dizziness.*"

This list of symptoms are incomplete and do not reflect the full range of adverse events being reported that require medical attention and investigation.

**Guillain-Barre Syndrome and Menactra.** When concerns about GBS and Menactra surfaced in September 2005, seven months after ACIP recommended adding Menactra to the national vaccination schedule, the FDA and CDC issued an Alert to the public and stated it was "*sharing this information with the public now and actively investigating the situation because of its potentially serious nature.*"<sup>34</sup> The alert also stated, "*Because of the potentially serious nature of these matters, FDA and CDC are asking any persons with knowledge of any possible cases of GBS occurring after Menactra to report them to the Vaccine Adverse Event Reporting System (VAERS) to help the agencies further evaluate the matter*" and then provided instructions on reporting to VAERS.

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<sup>32</sup> Judicial Watch Uncovers Three Deaths Relating to HPV Vaccine: Event Reports Obtained from FDA Detail 1,637 Adverse Reactions to Gardasil. May 23, 2007. [http://www.judicialwatch.org/printer\\_6299.shtml](http://www.judicialwatch.org/printer_6299.shtml).

<sup>33</sup> Centers for Disease Control and Prevention, Vaccine Information Statement (Interim) Human Papillomavirus (HPV) Vaccine, 2/2/07, <http://www.cdc.gov/vaccines/pubs/vis/default.htm#hpv> (accessed August 7, 2007).

<sup>34</sup> Food and Drug Administration, FDA and CDC Issue Alert on Menactra Meningococcal Vaccine and Guillain Barre Syndrome, September 30, 2005, <http://www.fda.gov/bbs/topics/NEWS/2005/NEW01238.html> (accessed August 5, 2007).

Following this Alert, the American Academy of Pediatrics issued a document that provided physicians with guidance for handling Menactra concerns.<sup>35</sup> By that time, six cases of GBS following receipt of Menactra vaccine were being investigated and physicians were cautioned:

*“Until the potential relationship between MCV4 and Guillain-Barre syndrome is clarified, delay of MCV4 immunization of children who have a history of previous Guillain-Barre Syndrome is prudent. Adolescents and their caregivers should be informed of the ongoing investigation as part of the consent process for immunization with MCV4. The vaccine information sheet for meningococcal vaccine was modified on October 7, 2005 to state: “Anyone who has ever had Guillain-Barre syndrome should talk with their doctor before getting MCV4.” This updated VIS should be used.*

*All providers should report possible cases of Guillain-Barre syndrome or other clinically significant events associated with use of MCV4 to VAERS...”*

By October 20, 2005 nine reports of GBS had been filed with VAERS and were reported in the Morbidity and Mortality Weekly Report including the 16-year-old girl from Mississippi who had been vaccinated with Menactra and Gardasil whose GBS diagnosis was confirmed.<sup>36</sup> In this report, the CDC stated that it *“recommends that persons with a history of GBS not receive MCV4.”*

Additional MMWR reports on this topic have been issued.<sup>37</sup> The CDC also has a website titled, “Frequently Asked Questions about Guillain-Barre Syndrome and Menactra Meningococcal Vaccine” updated January 8, 2007.<sup>38</sup> CDC is making the public aware of the concern so they will report cases of GBS occurring after Menactra to VAERS. The document also stated that *“A few cases of Guillain-Barre Syndrome, a serious nervous system disorder, have been reported among people who received Menactra vaccine. There is not enough evidence yet to tell whether any of these cases were caused by the vaccine.”*

In contrast to the manner in which CDC addressed adverse event reports related to Menactra and GBS, there has been very little effort to address the possibility that Gardasil alone, or in combination with Menactra and possibly other vaccines, is a potential causal factor in development of GBS in more than a dozen children.

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<sup>35</sup> American Academy of Pediatrics, Guillain-Barre Cases Among Recipients of Meningococcal Conjugate Vaccine: Interim Guidance for Physicians, (undated) <http://www.cdc.gov/od/science/iso/concerns/gbsfactsheet.htm> (accessed August 5, 2007).

<sup>36</sup> Centers for Disease Control and Prevention. (October 20, 2006). Update: Guillain-Barre syndrome among recipients of Menactra Meningococcal Conjugate Vaccine --- United States, June 2005---September 2006, 55(41);1120-1124 [www.cdc.gov/mmwr/preview/mmwrhtml/mm5541a2.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5541a2.htm) (accessed August 5, 2007).

<sup>37</sup> Centers for Disease Control and Prevention. (April 7, 2006). Update: Guillain-Barre syndrome among recipients of Menactra Meningococcal Conjugate Vaccine --- United States, October 2005---February 2006, 55(13);364-366 <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5513a2.htm> (accessed August 5, 2007).

<sup>38</sup> Centers for Disease Control and Prevention, Frequently Asked Questions about Guillain-Barre Syndrome and Menactra Meningococcal Vaccine, October 19, 2006, [http://www.cdc.gov/od/science/iso/concerns/faq\\_guillainbarre.htm](http://www.cdc.gov/od/science/iso/concerns/faq_guillainbarre.htm) (accessed August 6, 2007).

**Federal health agencies have not actively addressed or informed vaccine providers and the public about reported adverse events involving Guillain-Barre Syndrome (GBS) and Gardasil with the same diligence that was applied to reported adverse events involving GBS following receipt of Menactra and other vaccines. The lack of scientific evidence demonstrating the safety of co-administration of Gardasil with Menactra and other vaccines pre-licensure or before the CDC publicly recommended Gardasil be co-administered with other vaccines, including Menactra, raises serious questions about the scientific integrity of federal HPV vaccine policy recommendations issued by the Advisory Committee on Immunization Practices (ACIP) of the CDC.**

### **Coincidence and Adverse Events Following Vaccination**

The available data in VAERS raise legitimate concerns about the routine administration of Gardasil vaccine, particularly co-administration of Gardasil with other vaccines such as Menactra. This analysis of Gardasil adverse events reported to VAERS demonstrates a statistically significant increase in reports of GBS in girls who receive Gardasil in combination with Menactra and other vaccines, an increase which cannot be dismissed as coincidental.

These data show that for those who experience a Gardasil-related adverse event reported to VAERS, reports of serious adverse events consistent with neurological damage – including convulsions, paralysis, Guillain-Barre Syndrome, falls, head and neck injuries, neuromuscular and coordination problems – are more likely to occur in those who received Gardasil and Menactra together than in those who received only Gardasil. This reported increased risk is statistically significant under standards universally accepted in the scientific community.

For example, of those patients who had a reported a Gardasil adverse event, the percentage who reported falls after being vaccinated only with Gardasil was 1.2%. The rate of falls for those who received both Gardasil and Menactra, however, was 9.6%.<sup>39</sup> If a fall after being vaccinated was merely coincidence – that is, if the fall was unrelated to the vaccination – one would expect the rates of falls to be roughly the same for the two groups. But the odds that this large difference in the rate of falls was due merely to chance is less than 1 in 10,000 (*i.e.*,  $p < 0.0001$ ).

A  $p$  value of 0.05 – making the odds 1 in 20 – is widely recognized as evidence that the difference between the two groups is statistically significant. In other words, the relationship between an increased risk of falls after receipt of Gardasil and Menactra versus receipt of Gardasil alone cannot be dismissed as mere coincidence.

These newly available results raise a number of important questions that can only be answered with additional data. For example:

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<sup>39</sup> The reported rates of adverse effects for those simultaneously receiving Gardasil and Menactra include persons who received only those two vaccines (9 persons) and those who received those two vaccines plus at least one other (4 persons).

- What percentage of all persons receiving the Gardasil vaccine experienced one or more of the adverse events reported in the VAERS database? (The available data identify only some of those who experienced an adverse event – *i.e.*, those for whom an adverse event was voluntarily reported – and the total number of persons receiving Gardasil each month is not included.); and
- How do such adverse event reporting rates compare to those for persons who received Menactra or other vaccines along with Gardasil? How do they compare to the reporting rates of each symptom (*e.g.*, an unexplained fall) in the general population?

Such data would help determine the relative risks of administering Gardasil, either alone or in combination with other vaccines.

Underreporting of vaccine adverse events that occur after vaccination by physicians and other health care providers who administer vaccines is a problem that has been acknowledged for more than 20 years. A decade ago, citing a 1986 study, CDC scientists stated that, “*Reporting of adverse events appears to depend on a number of factors, such as clinical seriousness, temporal proximity to vaccination, and health care workers’ awareness of and obligation to report particular adverse events.*” *Federal health agencies should be monitoring and enforcing adverse event reporting requirements.*<sup>40</sup>

Federal health agencies should be collecting and disseminating all relevant data so co-administration and other risks can properly be identified and evaluated by health officials, vaccine providers and patients receiving the vaccine. Unfortunately, with regard to Gardasil, it appears that no effort was made by vaccine policymaking committees to determine, prior to issuing public vaccine policy recommendations, the possible adverse effects of co-administering Gardasil with other vaccines such as Menactra.<sup>41</sup>

**Dismissing the importance of implementing evidence-based vaccine policies by making assumptions of safety in the absence of scientific certainty is not the standard of care American health care consumers expect from federal health officials. Federal vaccine policy recommendations are carried out by pediatricians and other vaccine providers, who do not question the scientific evidence upon which federal health officials made the recommendation. The burden should not be on consumers to prove recommended use of a new drug or vaccine is unsafe; the legal and ethical burden is properly on federal health officials to prove to consumers and prescribing physicians recommended use of a new drug or vaccine is safe.**

<sup>40</sup> Rosenthal S, Chen R. (1995). The reporting sensitivities of two passive surveillance systems for vaccine adverse events. *American Journal of Public Health* 85:12; 1706-1709 citing Sills JM, Tanner LA, Milstien JB. (1986). Food and Drug Administration monitoring of adverse drug reactions. *Am J Hosp Pharm* 43:2764-2770.

<sup>41</sup> Although the CDC has asserted that “Quadrivalent HPV vaccine can be administered at the same visit as other age appropriate vaccines, such as the Tdap and quadrivalent meningococcal conjugate (MCV4) vaccines,” it acknowledges that this advice is based only on *assumptions* about how vaccines might interact when given at the same time. MMWR (Morbidity and Mortality Weekly Report) March 12, 2007, Vol. 56 at 17 (explaining that “quadrivalent HPV vaccine is not a live vaccine and has no components that adversely impact safety or efficacy of other vaccination”). The CDC concedes that “no data exist on administration of quadrivalent HPV vaccine with vaccines other than hepatitis B vaccine[.]” *Id.* The CDC has proposed studies to evaluate concomitant administration of the HPV vaccine with meningococcal conjugate vaccine and with the adolescent/adult formulation of tetanus, diphtheria and acellular pertussis (Tdap) vaccine, *id.* at 12, but it does not appear that such studies have been conducted and published.

Those responsible for manufacturing, distributing and approving the use of a new pharmaceutical product – whether the product will be used alone or in combination with other products – have an obligation to determine the risks and, at a minimum, inform the consumer of those risks before the consumer consents to using that product. This basic quality control standard to insure safe use of a new pharmaceutical product is all the more important with vaccines, which are (1) given to healthy persons; (2) often required by state governments for children and adults to attend school and engage in other social activities; and (3) are frequently co-administered with other vaccines by doctors and other vaccine providers without any consideration about whether co-administration is safe.

**The available data in this VAERS analysis indicate that Gardasil should not be given with other vaccines until the government has gathered and publicly disseminated the data required to demonstrate the relative risks of co-administering Gardasil with other vaccines.**

## Conclusions and Recommendations

- 1. Simultaneous Administration of Gardasil And Menactra Indicates Increased Risk of Reports For GBS and Other Serious Adverse Events:** There have been 15 reports of GBS following receipt of Gardasil to VAERS. Our analysis indicates there is a statistically significant increased risk for reports of GBS and other serious adverse events following administration of Gardasil and Menactra simultaneously and that this increased risk cannot be dismissed as "coincidence."
- 2. CDC Failed To Confirm Co-Administration Safety:** There are no published studies confirming the safety of giving Gardasil in combination with other vaccines. The CDC's March 12, 2007 MMWR recommendations for Gardasil acknowledged a lack of evidence proving that it is safe to administer Gardasil in combination with other vaccines, except hepatitis B, and encouraged simultaneous vaccination based on "assumption" of safety. Assumptions about vaccine safety are not a responsible substitute for scientific evidence.
- 3. CDC Should Issue a Public Advisory:** The CDC should amend the March 12, 2007 MMWR Gardasil recommendations for co-administration use and issue a public Advisory to doctors, parents and vaccine recipients that Gardasil should be administered alone and not simultaneously with any other vaccine, especially Menactra, until simultaneous administration is proven safe.
- 4. Medical Errors Can And Should Be Eliminated:** Reduction of preventable adverse events and medical errors in health care that eliminate unnecessary mortality and morbidity is defined as a national priority in American health care quality control standards. Nearly 10 percent of VAERS Gardasil reports contained medical errors, many of which could have been avoided if commonly available medication safety practices were used.

The FDA and CDC should develop and promote vaccination safety standards as a national priority and work with the medical community to aggressively monitor vaccine

administration errors in order to improve the safety of patient care when vaccines are administered singly or simultaneously. Federal health authorities should also inform the public of the urgent need for a patient-physician partnership in preventing vaccine reactions, injuries and deaths.

The CDC's HPV Vaccine Information Statement (VIS) provided to parents and consumers and other information materials provided to physicians should clearly state that there is a reported association between Gardasil and development of Guillain-Barre Syndrome when given alone or in combination with other vaccines. This information should also state that if life-threatening and other severe challenge-rechallenge reactions have occurred, further vaccination is contraindicated.

**5. Basic Science Research Needed:** Epidemiological studies and analyses may “infer” but cannot “prove” causal relationships between receipt of a vaccine and a specific biological adverse outcome. There is urgent need for basic science research which examines biological mechanisms for vaccine-induced GBS and other reported serious vaccine adverse events, as well as the pathological effects on the human brain and immune system when multiple vaccines are administered simultaneously. Pathological profiles that separate out what is and is not vaccine-induced versus what can be dismissed as “coincidence” can only be developed by utilizing advanced technology to investigate underlying mechanisms for vaccine injury and death. This basic science research will also generate information which can be used to identify genetic and other high risk factors for vaccine reactions and create healing therapies for the vaccine injured.

**6. VAERS Reporting Requirement Should Be Enforced:** Although in 1986, the U.S. Congress passed the National Childhood Vaccine Injury Act, which included a mandate for all doctors and other vaccine providers to report hospitalizations, injuries and deaths following vaccination to the federal government, there are no legal sanctions for non-compliance. Therefore, VAERS has functioned as a passive surveillance system which depends upon voluntary reporting of serious health problems following vaccination. There have been estimates that fewer than 10 percent, even as low as 1 to 4 percent, of adverse events which occur after prescription drug or vaccine use are ever reported to passive government adverse event reporting systems.<sup>42</sup>

Unacceptably low rates of vaccine provider reporting of serious health problems following vaccination creates potential reporting bias in VAERS, which may confound conclusions of this and other analyses of VAERS data. Without knowing (1) the total number of doses of vaccine administered and (2) the total number of adverse events which occur following vaccination, all VAERS analyses are compromised to some degree by insufficient data and potential reporting bias.

Doctors and other health care providers who administer vaccines should be required to obey federal law and report adverse health outcomes following vaccination or suffer

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<sup>42</sup> Scott HD, Rosenbaum SE et al. [Rhode Island physicians' recognition and reporting of adverse drug reactions](#). RI Med J 1987; 70:311-316; Rosenthal S, Chen R. [The reporting sensitivities of two passive surveillance systems for vaccine adverse events](#). Am J Public Health 1995; 85:1706-9; <sup>1</sup> Braun M. [Vaccine adverse event reporting system \(VAERS\): usefulness and limitations](#). John's Hopkins Bloomberg School of Public Health. [www.vaccinesafety.edu/VAERS.htm](http://www.vaccinesafety.edu/VAERS.htm); Food and Drug Administration, Center for Drug Evaluation and Research. [The clinical impact of adverse event reporting](#). MedWatch. October 1996.

legal sanctions, such as temporary or permanent loss of the right to administer vaccines. Effective post-licensure monitoring of new vaccine adverse events, such as those reported after receipt of Gardasil, would be measurably improved by a high rate of vaccine provider compliance with VAERS reporting requirements.

### Summary

As of May 31, 2007, 2,227 reports of adverse events following administration of Gardasil vaccine have been submitted to the FDA's Vaccine Adverse Event Reporting System (VAERS). There are at least 13 suspected or confirmed GBS reports and in June 2007, an additional two GBS reports were filed, bringing the total to 15. Syncope and vasovagal syncope (fainting with temporary loss of consciousness and posture) was reported 239 times, the second most commonly reported adverse event, and 106 reports were associated with injury such as head injuries, fractures and subarachnoid and subdural hematomas. Seven deaths have been filed with VAERS in association with receipt of Gardasil. Nearly 10 percent of VAERS Gardasil reports contained medical errors, many of which could have been avoided if commonly available medication safety practices were used.

On Feb. 21, 2007, the National Vaccine Information Center reported concerns about potential increased risk for serious adverse events after co-administration of Gardasil with other vaccines based on lack of pre-licensure proof that co-administration was safe. As of May 31, 2007, a total of 1,930 adverse events have been reported to VAERS following administration of Gardasil alone and an additional 135 adverse events have been reported following administration of Gardasil and Menactra simultaneously. The above analysis suggests that among those who reported Gardasil adverse events, there was a two to 12 times increased risk for reports of serious adverse events when Gardasil was given in combination with Menactra rather than given alone.

When Gardasil was given in combination with Menactra rather than alone, the relative risk of reports involving respiratory problems increased by 114 percent; cardiac problems increased by 118 percent; neuromuscular and coordination problems increased 234 percent; convulsions and central nervous system problems increased 301 percent; injuries from falls after unconsciousness increased 674 percent and GBS increased 1,130 percent. Accepted scientific standards indicate that these findings are statistically significant and cannot be dismissed as coincidence.

VAERS is a passive reporting system that may provide warning of potentially important associations between new vaccine use and serious adverse health outcomes. This analysis strongly suggests that there is an association with GBS and receipt of Gardasil and that there is a statistically significant increased risk of reported GBS and other serious adverse events when Gardasil and Menactra are co-administered compared to when Gardasil is administered alone.

**The precautionary principle dictates that good science should precede vaccine policy recommendations by federal health officials. The CDC should immediately issue a public advisory to doctors, parents, and vaccine recipients that Gardasil is associated with 15 reports of GBS in VAERS. Further, the March 12, 2007 ACIP recommendation for Gardasil use should be amended to state that, in the absence of scientific evidence demonstrating safety of co-administration of other vaccines,**

**Gardasil should be administered alone and not in combination with Menactra or other vaccines.**