"SERIOUS" UNDER-REPORTING? AN EXAMINATION OF VACCINE ADVERSE EVENT REPORTING AFTER QUADRIVALENT HUMAN PAPILLOMAVIRUS (qHPV) VACCINATION

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ABSTRACT

The World Health Organization, the Centers for Disease Control and Prevention, and other governmental health agencies strongly recommend the human papillomavirus (HPV) vaccine to prevent high risk HPV infection associated with certain cancers. Quadrivalent HPV (qHPV) was initially licensed by the FDA in June 2006 to prevent cervical cancer. Broad recommendations for the vaccine rest, in part, on a 2009 FDA/CDC postlicensure safety study of the qHPV vaccine that Merck, Inc. has marketed under the trade name Gardasil. *The 2009 Slade et al. safety study reported that 6.2% of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS) were "serious," a rate that did not signal a safety concern. The Slade et al. 2009 study defined "serious adverse events" more narrowly, though, than its statutory definition in the US Code of Federal Regulations (CFR).*

The authors set out to test whether the conclusions of the 2009 study authors would be similar to those of independent physicians regarding adverse events judged to be "serious" and "non-serious." They used both the 2009 study definition and the more inclusive CFR definition for the same data pool. Strikingly, the independent physicians rated 12% of the adverse reports as "serious" using the 2009 study definition and 24.2% of the adverse reports as "serious" using the CFR one. This empirical evidence suggests that VAERS may be significantly under-reporting serious adverse events related to the qHPV vaccine. Given VAERS' critical role in vaccine safety surveillance, it is imperative that it accurately record serious adverse events. If it fails to do so, it potentially puts individuals at risk of serious harm, including death.

I. INTRODUCTION

The recombinant human papillomavirus vaccine (qHPV) Gardasil was licensed by the United States Food and Drug Administration (FDA) on June 8, 2006 for routine vaccination of females aged 9 to 26 to prevent infection with genital HPV types 6, 11, 16 and 18.[2] Following the introduction of a new vaccine, the FDA and the Center for Disease Control and Prevention

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(CDC) monitor systems designed to track adverse events in the general population. One such system is the Vaccine Adverse Event Reporting System (VAERS) which was created in 1986 as a result of the National Childhood Vaccine Injury Act (NCVIA).[3] The VAERS is a single system in the United States for the collection and analysis of reports of Adverse Events Following Immunization (AEFI).[4] The FDA and CDC jointly implement the system and a contractor hired by the CDC operates the system to distribute and collect forms for AEFIs. NCVIA stipulated that health care providers who administer vaccines and vaccine manufacturers licensed in the US must report AEFIs following specific vaccinations to the FDA and CDC~~n~~ Nonetheless, VAERS is still regarded as a passive system and reporting by the general public is voluntary. Indeed, under-reporting of AEFIs is one of the well acknowledged limitations of the VAERS database.[5] When AEFIs are reported to VAERS, they are reviewed and are assessed as to whether or not they fall into a serious or non-serious category. Specific outcomes such as seizures are assigned standardized codes from the Medical Dictionary for Regulatory Activities (MedDRA) and the data are then entered into a computer database.[6]

In addition to VAERS, the CDC has two other systems in place to monitor the safety of all licensed vaccines, the Vaccine Safety Datalink (VSD) and the Clinical Immunization Safety Assessment (CISA) Network. The VSD is a collaborative project between CDC and nine managed care organizations that monitors vaccine safety while the CISA Network is a collaboration including six academic centers in the US whose purpose is to conduct clinical research on vaccine-associated adverse events.[7,8] The VSD examines possible associations by comparing the number of AEFIs reported by the VAERS for selected outcomes with background rates for these events from the large VSD database.[9,10,11] A methodology used by the VSD since

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[2] Dunne EF, Datta SD, E. Markowitz L. A review of prophylactic human papillomavirus vaccines: recommendations and monitoring in the US. *Cancer* 2008; 113:2995-3003.

[3] National Childhood Vaccine Injury Act, 42 U.S.C. 300aa-1 *et seq*.

[4] Chen RT, Rastogi SC, Mullen JR, Hayes SW, Cochi SL, Donlon JA, Wassilak SG. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994; 12:542-50.

[5] Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, Izurieta HS, Ball R, Miller N, Braun MM, Markowitz LE, Iskander J. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 2009; 302:750-7.

[6] Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, Chen RT. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 2004; 23:287-94.

[7] Baggs J, Gee J, Lewis E, Fowler G, Benson P, Lieu T, Naleway A, Klein NP, Baxter R, Belongia E, Glanz J, Hambidge SJ, Jacobsen SJ, Jackson L, Nordin J, Weintraub E. The Vaccine Safety Datalink: a model for monitoring immunization safety. *Pediatrics* 2011; 127 Suppl 1:S45-53.

[8] LaRussa PS, Edwards KM, Dekker CL, Klein NP, Halsey NA, Marchant C, Baxter R, Engler RJ, Kissner J, Slade BA. Understanding the role of human variation in vaccine adverse events: the Clinical Immunization Safety Assessment Network. *Pediatrics* 2011; 127 Suppl 1:S65-73.

2007 to provide active assessment of potential vaccine-safety signals is rapid cycle analysis.[12] However, the surveillance performed by the VSD is only for *selected* outcomes. In particular, rapid cycle analysis studies routinely extract and aggregate counts of electronic data on vaccinations from Managed Care Organizations (MCO) patient records only for *prespecified* outcomes that occur during a *prespecified* post-vaccination observation window. [13,14] The preselected outcomes are identified on the basis of data from prelicensure trials, early reports from VAERS, literature on similar vaccines, known biological properties of the vaccine, or some combination of these factors. While the role of the VSD is to investigate the epidemiologic and statistical significance of potential AEFIs, such AEFIs may not be investigated if VAERS has not identified them as potential safety signals.

Based on VAERS data on AEFIs following quadrivalent human papilloma virus vaccine (qHPV) vaccination, the CDC and the FDA published a postlicensure safety surveillance report on August 19, 2009. This report, authored by Slade et al.[15], provided information on the number and type of AEFIs that were reported to VAERS during two and a half years following the introduction of the qHPV vaccine into the US vaccination schedule. In particular, between June 1, 2006 and December 31, 2008, VAERS received 12,424 AEFIs attributed to qHPV vaccination. Of these, 772 or 6.2% were determined to be serious, including 32 deaths. The authors thus concluded that most AEFIs did not meet the definition of serious, a result which did not signal a safety concern. They did acknowledge several limitations in addition to underreporting such as inconsistency in the quality and completeness of reported data, stimulated reporting due to extensive news coverage, reporting biases, and the fact that not all reports were systematically validated. Indeed, a large proportion (68%) of the VAERS reports for qHPV came from the vaccine manufacturers, and 89% of those did not include sufficient identifying information to allow for independent medical review of individual cases.[16] Although the authors found a disproportional reporting of the specific outcomes of syncope and venous

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[9] Baggs, et al. *supra* note 5.

[10] Salmon DA, Pavia A, Gellin B. Editors' introduction: Vaccine safety throughout the product life cycle. *Pediatrics* 2011; 127 Suppl 1:S1-4.

[11] Yih WK, Kulldorff M, Fireman BH, Shui IM, Lewis EM, Klein NP, Baggs J, Weintraub ES, Belongia EA, Naleway A, Gee J, Platt R, Lieu TA. Active surveillance for adverse events: the experience of the Vaccine Safety Datalink project. *Pediatrics* 2011; 127 Suppl 1:S54-64.

[12] *Ibid.*

[13] *Ibid.*

[14] Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, Kulldorff M, Lewis E, Fireman B, Daley MF, Klein NP, Weintraub ES. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. *Vaccine* 2011; 29:8279-84.

[15] Slade, et al. *supra* note 3.

[16] *Id.* at 756.

thromboembolic events, they found that most of the AEFI rates were not greater than the background rates compared to other vaccines.[17]

The only qHPV-related outcomes analyzed by Slade et al.[18] and later by the VSD[19] were the prespecified outcomes, namely: seizures, syncope, stroke, anaphylaxis, appendicitis, Guillain-Barré Syndrome (GBS), and venous thromboembolic events (VTE). This list was based in part on early reports from VAERS in a narrow window of time. Namely, the post-vaccination window for GBS and VTE was 1-42 days; for appendicitis, stroke, or seizures 0-42 days; for anaphylaxis, 0-2 days; and for syncope, 0 day. Once the prespecified upper limit on length of surveillance is reached without a signal, surveillance stops. [20,21] It is clear then, that VAERS reports of serious AEFIs following qHPV vaccination that were filed within two and a half years postlicensure were key to determining what selected outcomes VSD would ~~be~~ investigate. While the system is designed to rule out if a signal is real or not, it is not designed to monitor whether or not VAERS is failing to detect serious safety signals.

The CDC established the third safety system, the CISA Network, in 2001.[22] The CISA Network conducts research of specific AEFI at the individual or clinical level to determine possible genetic and other risk factors that may predispose people to a higher risk for vaccine adverse reactions. The Network conducts research around a series of specific immunization safety topics which are referred to them. However, the CISA Network, like the VSD, does not provide oversight of VAERS and it is not designed to detect signals nor to monitor whether or not VAERS is failing to detect serious safety signals.

We were thus interested in exploring in more detail the process of classification of the early serious AEFI reports to VAERS related to the qHPV vaccine as this process obviously played a critical role in determining possible safety concerns and the direction of investigation for the other systems. The reference for our exploration was the Slade et al. study on postlicensure safety surveillance for qHPV. This report defined "serious adverse event" as

> one that is life threatening; results in death, permanent disability, congenital anomaly, hospitalization or prolonged hospitalization; or necessitates medical or surgical intervention to preclude one of these outcomes. [23]

This definition purports to be based on the Code of Federal Regulations, 21 CFR 314.80.

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17 *Ibid.*

18 *Id.*

19 Gee, et al. *supra* note 12.

20 Yih et al. *supra* note 9.

21 Gee et al. *supra* note 12.

22 LaRussa et al. *supra* note 6.

23 Slade et al. *supra* note 3.

The authors also referenced the definition of a "serious adverse event" from Chen et al. According to this study,

> For an adverse event to be categorized as serious by the FDA, it must have resulted in one of the following: (1) death; (2) permanent disability; (3) hospitalization; (4) prolongation of hospitalization; or (5) have been determined to be life-threatening.[24]

The definition of a serious adverse event by Chen et al.[25] and Slade et al.[26] are comparable; both cite the Code of Federal Regulations 21 CFR 314.80 as the authoritative source for their definitions.[27,28]

The Code of Federal Regulations, 21 CFR 314.80, however, defines a serious adverse event as follows:

> 1. death;
> 2. a life-threatening adverse drug experience;
> 3. hospitalization;
> 4. prolongation of existing hospitalization;
> 5. A persistent or significant disability/incapacity; or
> 6. a congenital anomaly/birth defect.[29]
>
> Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

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[24] Chen, et al. *supra* note 2.

[25] *Ibid*.

[26] Slade, et al. *supra* note 3.

[27] Food and Drug Administration (FDA) Vaccines, Blood and Biologics. Draft Guidance for Industry: Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines. IV Type of Adverse Experiences, 3 Serious Adverse Experiences. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074850.htm#WHATDOIREPORT.

[28] CFR – Code of Federal Regulations Title 21, Volume 5: Part 314; section 314.80. Postmarketing reporting of adverse drug experiences. (a) Definitions. www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.80.

[29] *Ibid.*

We found that the Federal Code actually describes a serious condition that is absent or truncated in both the Slade et al.[30] and Chen et al.[31] reports. That condition is "a persistent or significant disability/incapacity." Although Slade et al.[32] claim to have used the criteria defined in the Code of Federal Regulations to evaluate whether or not an adverse event was serious or non-serious, the #5 criteria was truncated. While there certainly is overlap between "permanent disability" and "a persistent or significant disability/incapacity," these two criteria are however not the same. Had the Federal Regulation 21 CFR 314.80 been changed? The history of 21 CFR 314.80 revealed that the criteria defining a serious adverse event was initially established in 1986 and is consistent with the definition cited by Chen et al.,[33] including the criterion "permanent disability."[34] The original definition was amended in 1998, however, and "permanent disability" was changed to "a persistent or significant disability or incapacity."[35] The broader definition is also the one delineated in the current Federal Regulations.[36]

Thus, while the truncated definition was correctly quoted in the 1994 Chen et al.[37] article, it has been changed to a broader definition since 1998. The broader definition is then the one which *should have been used* in the 2009 analysis by Slade et al.[38] In addition, both the current CDC website and the VAERS reporting form also inaccurately use the truncated.[39] If regulatory authorities are not providing the accurate criteria regarding the definition of a serious AEFI, how will those reporting or rating vaccine AEFIs know what to rate as a serious event? Did the exclusion or truncating of the criteria for a serious AEFI compromise the identification of potentially serious events? Moreover, did the possible exclusion of such events affect the coding and early calculation rates of serious AEFIs following qHPV vaccinations and therefore affect detection of a possible safety warning signal?

The purpose of this paper was to investigate these questions by reexamining VAERS data from the same data pool Slade et al.[40] utilized to generate their 2009 postlicensure safety surveillance

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30 Slade, et al. *supra* note3.

31 Chen, et al. *supra* note 2.

32 Slade,et al. *supra* note 3.

33 Chen, et al. *supra* note 2.

34 FDA Postmarketing Reporting of Adverse Drug Experiences, 21 C.F.R. § 314.80 (1986).

35 FDA Postmarketing Reporting of Adverse Drug Experiences, 21 C.F.R. § 314.80 (1998).

36 FDA Postmarketing Reporting of Adverse Drug Experiences, 21 C.F.R. § 314.80 (2015).

37 Chen, et al. s*upra* note 2.

38 Slade, et al. *supra* note 3.

39 Centers for Disease Control and Prevention (CDC). Vaccine Adverse Event Reporting System (VAERS). http://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/.

40 Slade et al. *supra* note 3.

report on the qHPV vaccine Gardasil. The lead author conducted a preliminary pilot assessment to rate 2000 randomly selected VAERS reports according to the legal criteria. The outcome from this preliminary assessment suggested that the rate of serious AEs was much higher when one applied the legal criteria for a serious AE. The details of this preliminary assessment are described under Materials and Methods. Since the authors are not medical doctors, it was determined that the cases should be reevaluated by a team of medically trained and licensed doctors. In particular, we sought to estimate the rate at which independent physicians (those with no ties to the vaccine manufacturer or the CDC) would designate qHPV-related AEFIs reported to VAERS as serious, based on the event descriptions entered into the VAERS system and the definitions provided by Slade et al.[41] and the Code of Federal Regulations[42] respectively. The statistical objectives of the study were as follows:

1. To estimate the percent of AEFI reports that independent physicians would rate as serious if they were to assess all qHPV vaccine cases in VAERS' records, according to the truncated Federal Regulations criteria outlined in Definition 1 (Table 1);

2. To estimate the percent of AEFI reports physicians would rate as serious using the complete Federal Regulations criterion as per Definition 2 (Table 1);

3. To assess the statistical evidence that the percent of AEFI rated as serious by VAERS and by independent physicians are different (for either or both of Definition 1 and Definition 2).

41 *Ibid.*

42 FDA, *supra* note 33.

Table 1
AEFI Criteria

Criteria for categorizing a vaccine related AEFI as serious according to two definitions, both reportedly based on the Code of Federal Regulations 21CFR 314.80 (Food & Drug Administration, 2014; Code of Federal Regulations, 2016). The more inclusive Definition 2 is directly sourced from the CFR, while the less inclusive Definition 1 was used in the Slade et al. (2009) postlicensure safety surveillance report on the qHPV vaccine Gardasil.

Definition 1	Definition 2
Death	Death
Permanent disability	A life-threatening adverse drug experience
Hospitalization or prolongation of hospitalization	Inpatient hospitalization or prolongation of existing hospitalization
Have been determined to be life-threatening	A persistent or significant disability/incapacity
Congenital anomaly	A congenital anomaly/birth defect
	Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

II. MATERIALS AND METHODS

A. Data collection and preliminary assessment

Reports of AEFIs, including serious events, can be publicly accessed at wonder.cdc.gov. From a pool of approximately 15,356 AEFI reports for qHPV recorded between June 1, 2006 and December 31, 2009, two thousand cases were randomly selected using a random-number generator. As stated earlier, the lead author did a preliminary review of the reports and classified the cases as serious or non-serious according to Definition 2. In the time required by the author to do the review, 12 cases were delisted from the VAERS, leaving 1988 cases in the analysis. The 1988 cases were categorized into four groups according to their designation as either serious or non-serious by the author and the VAERS respectively (Table 2). The author agreed with the VAERS ratings regarding 1673 cases which were determined to be non-serious and 138 cases which were determined to be serious. However, there were 166 cases which the author determined were serious while the VAERS designated them as non-serious. Additionally, the author rated as non-serious 11 cases which the VAERS rated as serious.

B. Sampling of VAERS reports for independent rating by a panel of 10 physicians and statistical analyses

The lead author's preliminary examination of the sampled cases found more cases rated "Serious" than VAERS found, but it was determined that independent physicians should be the assessors of record. Therefore the authors sought to have a team of medically trained and licensed doctors reevaluate the cases, particularly those cases where there were discrepancies regarding designation between VAERS and the lead author. A physician volunteer who did not himself participate in the study asked among his professional colleagues for volunteers to rate cases based on the given criteria. Of those who did agree to participate in the study, we accepted those who were licensed and who indicated that they had no conflict of interest with respect to the CDC or the vaccine manufacturer. The physician raters were blinded as to the purpose of the study. To the extent possible, raters were unknown to the authors. Ten licensed physicians from different disciplines volunteered to rate cases. These volunteers included one pediatrician, one family practitioner, one geriatrician, one neurologist, two psychiatrists, one gynecologist, one otolaryngologist, and two internists, one of whom also has a degree in epidemiology.

C. Statistical strategy

If limitless resources had been available, the most straightforward study design to address the statistical objectives given above would be to have several independent physicians assess a large sample of VAERS cases. However, we had a small number of independent physicians (10) who each had limited time available to review a small number of cases (20) for a total of 200 cases.- Therefore, for statistical efficiency, we applied a strategy used in survey sampling: divide the population of cases into groups (or "strata"), some of which are expected to be more heterogeneous than others, and sample the heterogeneous groups with higher probability than the others. As the sampling probabilities are known, a weighted average can be constructed that is an unbiased estimate, and which has a smaller standard error than the estimate based on proportional sampling. (If one's expectations are wrong, the estimate remains unbiased, but the standard error is larger.)

In our case, sampling strata were formed by the lead author assessing all cases identified for physician review as "serious" or "non serious." Using the VAERS assessment on record and the author's assessment, every case falls into one of four categories, as given in the first three columns of Table 2. The groups for which VAERS and the author's assessment disagree (rows 2 and 3) are anticipated to be more mixed than those where they agree (rows 1 and 4). Hence the design spends proportionately more of the limited samples available on groups 2 and 3 than on 1 and 4. In other words, an effort was made to over sample the strata representing those cases where the VAERS and the author disagreed.

It should be noted that partitioning the cases into strata has no impact on the expected value of the resulting estimate. It does reduce the estimate's standard error if the stratification usefully classifies heterogeneous and homogenous subgroups (and can increase standard errors if the stratification is ineffective).

Data from this stratified sampling design can be used to calculate estimates of all combinations of VAERS assessment, lead author's initial assessment, and independent physician's rating (a 2 × 2 × 2 contingency table). Then any other probability estimate, such as the probability of

"serious" rating by independent physicians, is easily obtained by summing over the levels of the other two factors.

Each physician was given a block of 20 cases to review, for a total of 200 cases. Each block of 20 contained representatives from each stratum. Table 2 shows how the intended number of cases per stratum were selected for each block. The stratum counts are given in the third column. The sampling probabilities per stratum were selected as study design parameters. Given these sampling probabilities per stratum, and the selection of 200 total sampled cases, the expected number of sampled cases is given in the fifth column. For each stratum, the given number of cases were randomly selected. The task remained to allocate these 200 selected cases in 10 similar blocks of 20.

The sixth column gives the proportion of stratum representatives among the 200 sampled cases. Supposing these proportions are perfectly preserved for every block of 20, column seven gives the expected number of stratum representatives per block. It is not required that every physician see representatives of every block, but having a mix in each block might keep the reviewer alert, and also fairness argues for similar blocks. The selected cases were allocated to blocks such that counts of strata per block approximated column seven, although of course perfect matching was impossible. For example, one stratum sample had only six cases, so not all 10 blocks could have a representative of that stratum.

The percent of cases that would be rated as "serious" by independent physicians (for each definition), had physicians rated all cases, was estimated as described in Hawkins et. al.[43] Statistical inference on the estimate was made by Bayesian methods and credible sets (an analog to confidence intervals) for the proportion estimate was obtained using Monte Carlo methods, in order to avoid distributional assumptions and large-sample approximations. Statistical inference on the ratio of proportions rated serious (independent physicians / VAERS) was made similarly.

Our statistician assigned to the doctors a coded identity and randomly assigned to each a block of cases as described above. All communications were conducted online on a secure server. Physicians were given verbatim copies of the same information that had been available to the initial VAERS data entry person. There was no reason to believe that physicians would be biased one way or the other knowing that the case was an AEFI report since their task was not to determine if the vaccine caused the event, but rather to determine if the event was serious or not according to the criteria. This was the same task that the initial VAERS data entry persons encountered also knowing the event followed vaccination.

Table 2
Parameters of Analysis

Rating of1988 cases of AEFIs related to the qHPV Gardasil by VAERS and the author (L.T.) and the pattern of case sampling and allocation to physicians. The column headed "Count" denotes the number of cases rated as either serious or non-serious by VAERS and the author. The column headed "Sampling Probabilities" gives the proportion

[43] Hawkins DM,, Garrett JA, Stephenson B. Some issues in resolution of diagnostic tests using an imperfect gold standard. *Statistics in Medicine* 2001; 20:1987-2001.

of the stratum that was selected to be sampled. We vastly under sampled the stratum designated non-serious by both sources. This proportion is important however for statistical inference, because to estimate rates in the full population, one must use the sampling rates to give more weight to the under-sampled strata, and less weight to the over-sampled strata. The column headed "Sampled" shows the expected number of cases that were sampled from the stratum, given the desired proportion of the stratum. "% block" shows the expected prevalence of strata in sample blocks. "N per block" shows the expected count of cases for each stratum in a block size of 20 cases.

VAERS	Author	Count	Sampling probabilities	N Sampled	Fraction of block (%)	Expected N per block
Non-serious	Non-serious	1673	0.02	33	16.5	3.3
Serious	Non-serious	11	0.50	6	3.0	0.6
Non-serious	Serious	166	0.80	133	66.5	13.3
Serious	Serious	138	0.20	28	14.0	2.8
Total		1988	1.00	200	100.0	20.0

Physicians rated their respective 20 cases independently and were blinded to the VAERS case numbers, the VAERS ratings and the author's ratings. Physicians were given exact copies of AEFI reports as they appeared in the VAERS database, and they received exact copies of the two definitions outlining the criteria for a designating an AEFI as serious as shown in Table 1.

Namely, both definitions are based on the Code of Federal Regulations 21 CFR 314.80.[44] however, Definition 1 excluded the condition of "a persistent or significant disability or incapacity" (and is the same one used by Slade et al.[45] and Chen et al.,[46] while Definition 2 included this condition and is thus identical to the one outlined in the 21CFR 314.80 since 1988). Physicians were asked to evaluate each case and based on the respective criteria according to each of the two definitions, to determine if the event was serious. It was emphasized that their task was not to determine if the event was caused by the vaccine. The physicians recorded their ratings online on a secure server and forwarded them to the author (J.G.) for further statistical analyses.

III. RESULTS

A. Rates of rating an AEFI as serious by the panel of physicians

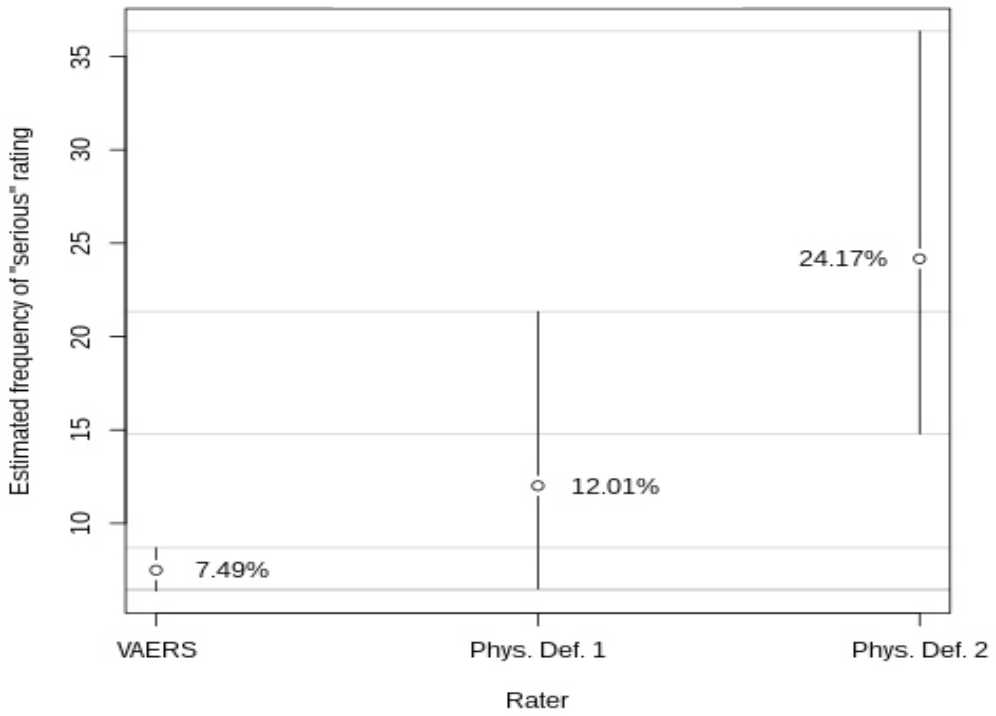
Overall, the author designated 15.29% of qHPV-related reports to the VAERS as serious under the Definition 2 criteria. Under the VAERS' rating scheme, only 7.5% of these AEFIs were designated as serious. According to stratified-sampling estimates (obtained by weighting stratum-specific rates according to stratum prevalence in the sample), independent physicians would rate 12% of cases as serious by Definition 1 had they rated all cases, and would rate 24.2% as serious by Definition 2.

[44] CFR. s*upra* note 26.

[45] Slade, et al. *supra* note 3.

[46] Chen, et al. *supra* note 2.

Figure 1



Estimate of rating AEFIs as serious by different rating sources (VAERS and the panel of physicians using Definition 1 or Definition 2), with 95% CI. CIs for the physician's ratings (using either definition) are much wider than those for VAERS because the VAERS estimate is based directly on the 1988 cases, while the physicians' estimates are based on a reweighted estimate from the 200 cases rated by the physicians.

As shown in Figure 1 above, the 95% credible set for the physicians' rate of designating an AEFI as serious, using Definition 1, is wide and contains the interval from VAERS. When the physicians used Definition 2, however, they gave a serious designation to qHPV vaccine-related AEFIs at an much higher rate than when using Definition 1, and the 95% credible set for this rate did not overlap with that of VAERS, indicating that there was statistically significant evidence that these rates are different. Credible sets for rates of serious assessments are quantiles of the Bayesian posterior distributions for the rates. The means of these distributions also serve as point estimates; they are 13.2% and 25.0% for the Definitions 1 and 2, respectively.

Comparing credible sets (or confidence intervals) is not the most statistically efficient way to compare two proportions, however. In order to directly compare the rates of serious assessments (physicians' versus VAERS') we show in Table 3 point estimates and 95% credible sets for ratios of proportions. The ratio for Definition 1 includes 1.0, indicating that a hypothesis of equality cannot be discarded. The point estimate for the ratio (1.6) is substantially higher than 1.0, so it is not the case that the data clearly support equality; more data is needed to estimate this proportion more precisely. For Definition 2, however, the credible set for the ratio (3.2), is well removed from 1.0, so the hypothesis of equality between proportions is strongly inconsistent with the data. This pattern is also clear in Figure 1, thereby supporting the conclusion that the frequency with

which physicians rated AEFIs as serious by Definitions 2 was significantly higher than that of VAERS.

Table 3
Estimates and 95% CI for ratio of physicians' to VAERS' rates of serious assessments by Definition

Definition	Estimate	Lower	Upper
1	1.6024	0.8481	2.9030
2	3.2246	1.9037	4.9780

Physicians' rates for Definitions 1 and 2 can be compared in a more powerful way since physicians rated the same cases using both definitions. Table 4 below shows the cross-tabulation between each physician's assessment according to the two definitions. Since there were 51 cases assessed as serious by Definition 2 but not by Definition 1, yet 0 cases in the converse direction, the difference in assessments has a clear direction which is not consistent with random differences. An exact version of McNemar's test was carried out by applying an exact two-sided binomial test to the hypothesis that the rate of one off-diagonal cell is not equal to 0.5. The test yielded p=0. Since Definition 2 is uniformly more inclusive than Definition 1, this demonstrates that physicians are logically consistent.

Table 4
Cross-tabulation of physicians' serious and non-serious assessments according to Definition 1 and 2

	Definition 2	
Definition 1	Non-serious	Serious
Non-serious	99	51
Serious	0	50

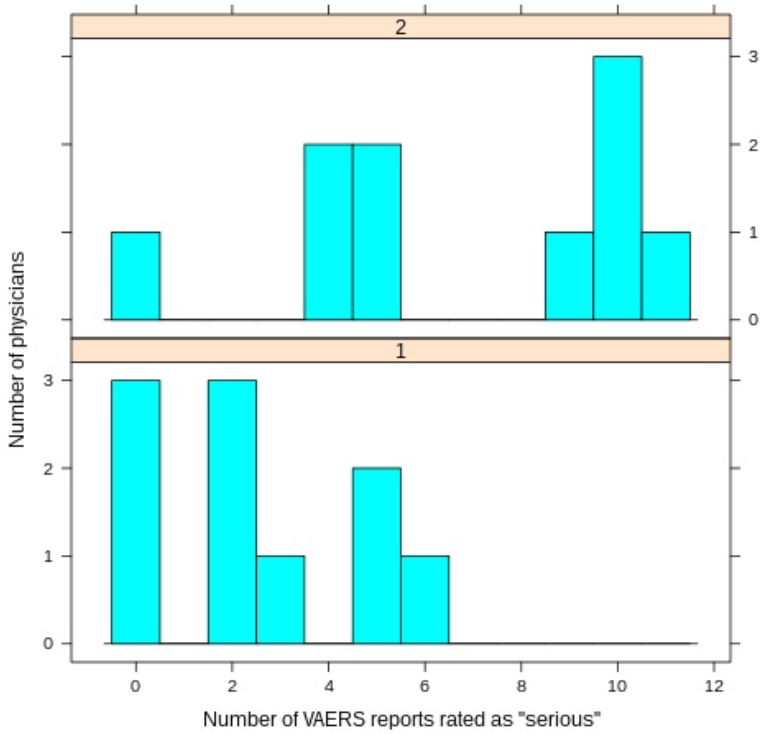
B. Variation among physicians

Since the number of available assessments from physicians was small, it was not possible to allocate specific cases to multiple physicians. With only 200 assessment opportunities available, the secondary goal of estimating physician variability was sacrificed in favor of the primary goal, e.g., estimating the proportion of cases that a typical independent physician would rate as serious. However, within each of the four strata, cases were randomly allocated to physicians, and so if some physicians were consistently more likely than others to give serious assessments for patients within the same stratum, this would more likely be due to differences among the physicians, rather than an artifact of the study design. Variation in the physicians' serious rate can be detected using Fisher's Exact Test of equality of proportions within each stratum.

For Definition 1, Fisher's Exact Test only identified variation among physicians for the stratum which VAERS rated non-serious and the lead author rated serious (p = 0.0038). In this stratum, each physician assessed 13 cases. The next-lowest p-value was 0.9391. For Definition 2, the outcome was similar, namely, the same stratum was again the only stratum to show evidence of a significant difference by the Fisher's Exact Test (p = 1e-05). The next-lowest p-value was 1. Figure 2 shows the distribution of serious assessments per physician, for Definitions 1 and 2. This indicates that there is a type of case for which independent physicians have substantial consensus, and another type for which there is less consensus. In our study these classes were iden-

tified via the lead author's judgment; a repeatable, explicit identification would require textual analysis of the case descriptions. Still, even with some variation among physicians, the independent physicians in our study gave "serious" ratings more often than VAERS.

Figure 2



Distributions of serious assessments per physician for the stratum assessed as non-serious by VAERS but serious by the author, for Definition 1 (lower panel) and 2 (upper panel). For Definition 1, three physicians rated no cases as serious, three rated two cases as serious, one rated three cases as serious etc.

IV. DISCUSSION

The purpose of this study was to estimate the rate at which physicians would designate AEFIs reported following qHPV as serious, by Definitions 1 and 2, and to determine whether their rating was different from that of VAERS. As shown in Figure 1, the results were as follows: 0.0749, or 7.49% (VAERS' rate), 0.1201, or 12.01% (Physicians' rate using Definition 1), and 0.2417, or 24.17% (Physicians' rate using Definition 2). Thus, the discrepancy between VAERS and the physicians rating of AEFI as serious was much greater for Definition 2. It is important to note that Figure 1 does not represent the actual number of cases rated as serious by the physicians, but rather it shows the overall rate at which we estimated physicians would designate AEFIs as serious were they to rate all 1988 reports. The data presented here thus suggest that there is a significant VAERS bias in under-rating the AEFIs following qHPV vaccination as non-serious when they fit the criteria for serious. In particular, our analysis shows that compared to VAERS rating, physicians' rating of serious cases was more than 1.5 times higher for Definition 1 and more than 3 times higher for Definition 2 (Figure 1).

Examples where the VAERS ratings of an AEFI as non-serious were at odds with the ratings by the physicians include reports of post qHPV vaccination cervical cancer, multiple sclerosis, lupus, severe dysplasia, vision loss, Bell's palsy, non-Hodgkin's lymphoma, pulmonary embolism, throat tightness with breathing difficulty and hospitalization, and paralysis (VAERS, 2010a).[47] Descriptions of some of these reports which VAERS rated as non-serious are shown in Table 5.

Table 5
Sample of qHPV-related AEFI reports which VAERS rated as non-serious which were rated as serious by the panel of physicians in this study.

VAERS ID	Event Description
338586	Information has been received from a healthcare worker concerning a 20 year old female patient with no pertinent medical history and with allergic reaction to CECLOR who on 28APR-2008 was vaccinated with the first dose of GARDASIL (lot# 655604/0052X), on 30-JUN-2008 was vaccinated with the second dose of GARDASIL (lot# 0152X) and on 10-Nov-2008 she received third dose of GARDASIL (lot# 0250X). Concomitant therapy included YAZ. It was reported that the patient was diagnosed with Bell's palsy after receiving the third dose of GARDASIL. It was reported that the patient had not recovered at the time of the report. The patient sought medical attention with a different physician. Follow up information was received on 15-DEC-2008 from a medical assistant who stated that the patient went to the emergency room. Follow up information was received on 15-DEC-2008 from the medical assistant who stated that on 10-DEC-2008 went to the emergency room and diagnosed Bell's palsy by the physician. Additional information has been requested.
325193	Autoimmune muscle disease. Dermatomyositis. Muscle weakness, fatigue, purple patches on skin. 9/23/08-records received-office visit 04/27/07-seen for contraception follow up received 1st HPV vaccine. 6/20/07-second HPV vaccine. 10/23/07-3rd HPV vaccine. No office visits documented between vaccinations. 3/14/08-C/O stomach pain after dairy. Continues to use Loestrin 24 BCP. 7/15/08-C/O autoimmune disorder. Muscle pain and weakness. Dermatomyositis. 8/20/08-has been using Yaz BCP now having difficulty with increased bleeding and period lasting longer. 9/11/08-DX dermatomyositis.
298447	"Information has been received from a mother concerning her 21-year old daughter with no known drug allergies who on 17-MAY-2007 was vaccinated with her first dose of Gardasil, injection. Concomitant therapy included hormonal contraceptives (unspecified). In the ""middle of July"" estimated to be approximately 15-JUL-2007, ""about two months"" after the first dose of Gardasil, the patient experienced paralysis of the stomach, slow down of the gallbladder, chest pain and pain in the diaphragm. The chest pain extended to her diaphragm area. At first, the physician thought the patient had acid reflux. Further testing showed that she had paralysis of the stomach and a slow down of the gallbladder. The patient started to ""get better"" about 4 weeks before the third dose, estimated to be 21-OCT-2007. On 21-NOV-2007 the patient received her third dose of Gardasil. The patient's symptoms came back. The patient underwent the following tests: diabetes (results not provided), scleroderma (results not provided), gallbladder (no stones) and liver scan (results not provided). The patient's paralysis of the stomach, slow down of the gallbladder, chest pain and pain in the diaphragm persisted. Unspecified medical attention was sought. OME statement: Upon internal review, paralysis of the stomach was determined to be another important medical event. Additional information has been requested."
364709	Information has been received from a registered nurse concerning her approximately 16-year old

[47] Sample of VAERS reports following vaccination with qHPV, according to VAERS ID #: cervical cancer 350859; muscular sclerosis 353172; severe dysplasia 352921; Lupus 318888, 338386 ; blindness 370051; Bell's Palsy 314140, 329722, 289753; embolisms 339415, 276871; non-Hodgkins lymphoma 364709; throat tightness with breathing difficulty 292869, 356463 and hospitalization 329701; chronic severe joint pain, numbness 353070, 318759, respectively. Sourced from: wonder.cdc.gov. Accessed 6/6/2010.

	sister in law's daughter who on an unspecified date was vaccinated with a dose of GARDASIL (Lot number unspecified). The registered nurse reported that the patient was diagnosed with Non-Hodgkin's lymphoma after vaccination with GARDASIL. At the time of the report the status of the patient was unspecified. The patient sought medical attention. Upon internal review, Non-Hodgkin's lymphoma is considered to be another important medical event. All telephone attempts to obtain follow-up information have been unsuccessful. Additional information has been requested.
352921	After first gardasil shot on 03/27/08 my symptoms included: Pain in my arm, dizziness, acute pharyngitis, sore joints and mucles. After my 2nd Gardasil shot on 05/27/08 my symptoms were arm was sore, dizzy, weak, fatigued, whole body ached, severe lower pelvic pain a couple times, Flue off and on, colds, acute pharyngitis a few times, ear aches and infections, sore joints, back and neck pain, headaches off and on, IBS with constipation and bouts of diarrhea, had colonoscopy done, frequent UTI's, kidney infection, hard to concentrate, confusion, had rash on left shoulder for a while then went away, sensitivity to light, racing heart sometimes, when dizzy my palms sweat, I become clumsy and heart races, grinding teeth, and on 05/29/09 went to OBGYN for Yearly Pap smear and every year it has been normal, no problems but this year, one year after I had my second Gardasil shot the results came back as abnormal. Showed HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION moderate dysplasia CIN 2. Doctor then gave me a colposcopy on 6/26/09 my protein level in urine was high +3 as well said I had ACUTE CERVICITIS. Then had Leep Biopsy done on 7/15/09 for the HIGH GRADE SIL the results were, I had HIGH GRADE SQUAMOUS INTRAPITHELIAL LESION CIN 3 SEVERE DYSPLASIA. They removed all abnormal cells. now bleeding on and off. Been on antibiotics 6 different times in one year time since I had the Vaccine. Never got sick before the shot. I believe these symptoms are caused by the Gardasil Vaccine. I believe I might have something wrong with my immune system or nervous system now. 8/5/09 PCP medical records received DOS 08/16/06 to 7/20/09. Assessment: Acute Cervicitis. High Grade Squamous Intraepithelial Lesion (CIN 3, Severe Dysplasia of Cervix. Patient presents with sore throat, productive cough, and sinus drainage. Oral contraceptives. Pharyngitis. Ear ache. Hurts to swallow. Neck anterior lymphadenopathy. Strep throat. Fatigue, headaches, needing more sleep at night. Bronchitis, chest discomfort with hx of rib contusions. Constipation, bloody stools, stomach cramps. Anal fissure. Runny nose, itchy skin. Allergy symptoms. Irritable bowel syndrome symptoms. Dysuria, flank pain, pyelonephritis. Lightheaded with dizziness. Serous otitis. Abdominal pain. LEEP procedure
338386	Information has been received from a physician concerning a female patient who on 25-FEB-2008 was vaccinated with the third dose of GARDASIL. No lot number was provided. The physician reported that the patient had a positive lab test for lupus about six months (August 2008) after the date of the third dose of GARDASIL. Physician does not wish to be contacted. The patient sought unspecified medical attention. Upon internal review, lupus was determined to be another important medical event. No further information is available.

In our random sample, we also found 23 cases of spontaneous miscarriage (VAERS, 2010b),[48] three reports of infant deaths at birth,[49] and one report of infant congenital anomaly[50] in cases

[48] VAERS reports of spontaneous miscarriage following qHPV vaccination. VAERS ID#: 284390, 306354, 300961, 342700, 313380, 311564, 310279, 311457, 374776, 301933, 371293, 356980, 284195, 313382, 291686, 270302, 363343, 341208, 291285, 290872, 301933, 295177, 304880. Sourced from: wonder.cdc.gov. Accessed 6/6/2010.

[49] VAERS reports of infant deaths following delivery from qHPV vaccinated mothers, VAERS ID#: 346965, 325593, 346965. Sourced from: wonder.cdc.gov. Accessed 6/6/2010.

[50] VAERS report of infant birth anomalies following delivery from qHPV vaccinated mothers, VAERS ID#: 348547. (This report was originally recorded by VAERS as "not serious" but was later changed by the VAERS to “serious”). Sourced from: wonder.cdc.gov. Accessed 6/6/2010.

where the mothers of these infants received the qHPV vaccine. While we cannot say these AEFIs were caused by the vaccine, they do meet the criteria of being rated as serious according to both definitions. However, all of these events were designated as non-serious by VAERS. Examples of some of these pregnancy-related events are shown in Table 6. Further, what is notable is that there are reports of spontaneous abortions and congenital anomalies similar to those shown in Table 6, which VAERS rated as serious. These are shown in Table 7.

Table 6
Sample of qHPV-related AEFI reports of spontaneous miscarriage, infant deaths at birth and infant congenital anomalies which VAERS rated as non-serious.

VAERS ID	Event Description
304880	Information has been received for the Merck Pregnancy Registry for Gardasil from an 18-year old female with no pertinent medical history or drug reactions/allergies who on 31-JAN-2008 was vaccinated with a first dose of Gardasil injection. There was no concomitant medication. On 03-FEB-2008 or 04-FEB-2008 (3 to 4 days) after receiving the first dose of Gardasil the patient miscarried. The patient was approximately 2 weeks pregnant. The patient was unaware she was pregnant until she miscarried. The physician stated to the patient that her left ovary was swollen. The patient was in a lot of pain. The patient was scheduled for a CT scan next week. At the time of reporting the patient has not recovered. On approximately 20-JAN-2008 was the patient's date of last menstrual period. The patient's estimated date of delivery was 26-OCT-2008. No additional information was provided. Upon internal review miscarriage was considered to be another medical event. Additional information is not expected.
317119	"Information has been received from the mother of a consumer and a health professional for the pregnancy registry for GARDASIL, concerning a 17-year old female with pertinent medical history reported as unremarkable, who on an unspecified date in April 2008, was vaccinated with the first dose of GARDASIL, IM in the arm. There was no concomitant medication. On 22-MAY-2008 the patient received the second dose of GARDASIL. Subsequently, she became pregnant. The patient sought unspecified medical attention and had blood work. No results were provided. On 29-MAY-2008, the patient had a fetal ultrasound which revealed that the fetal pole was not identified and there was ""no gestational sac."" The patient's last menstrual period or weeks of gestation were not reported. The patient had a miscarriage on 11-JUN-2008. At the time of the report, the daughter was still having clots and bleeding due to the miscarriage, and was emotionally distressed. No other information was provided. Upon internal review it was determined that miscarriage was another important medical event. Additional information has been requested.
291686	Information has been received from Merck Pregnancy Registry for the Gardasil vaccine from a health professional concerning a 17-year old female patient who on 31-MAY-2007 was vaccinated with a dose of Gardasil. Concomitant therapy included hormonal contraceptives (unspecified) and antimicrobial (unspecified). The reporter reported that patient miscarried on 18-AUG-2007 after receiving the dose of Gardasil. The estimated date of conception was about 06-JUN-2007. On an unspecified day laboratory test serum beta-human chorionic gonadotropin test was done. Unspecified medical attention was sought. The outcome was unknown. Upon internal review, miscarried was considered another important medical event. Additional information has been requested.
284707	Information has been received from a nurse practitioner as part of the pregnancy registry for Gardasil concerning a 17-year old female with no history of drug reactions/allergy who on 16-FEB-2007 was vaccinated with a first dose of Gardasil (lot # 656049/0187U) 0.5 ml IM. On 06-JUN-2007, was vaccinated with a second dose of Gardasil (lot # 657736/0389U). There was no concomitant medication. Medical attention was sought. It was reported that the patient did not know she was pregnant until a baby was delivered on the patient's bathroom floor on 21-JUN-2007 at an approximated gestation of 30 weeks. Estimated date of delivery September 2007. The baby died eight days later on 29-JUN-2007 of schizencephaly. The patient claimed to be

	unaware of her pregnancy because she had her menstrual periods throughout her pregnancy and did not gain weight. The patient had no prenatal care. No other information was available at the time of reporting. Additional information has been requested

Table 7
Sample of qHPV-related AEFI reports of spontaneous miscarriage, infant deaths at birth and infant congenital anomalies which VAERS rated as serious.

VAERS ID	Event Description
293065	"Information has been received from a physician concerning a 22-year old female with a history of abnormal papanicolaou smears with no treatment who on 30-NOV-2006 was vaccinated with a first dose of Gardasil. On 07-JAN-2007, the patient tested positive for pregnancy (type unspecified). The date of her last menstrual period was not reported. Medical attention was sought. On an unspecified date in 2007, at 19 weeks gestation, the mother's ""water broke"", and she was taken to the hospital where labor was induced. The baby did not live. At the time of reporting, the status of the mother was unspecified. Additional information has been requested."
326806	Information has been received from a 24-year old female who in February 2008 received her first dose of GARDASIL (lot # not provided) and on 02-Apr-2008 received the second dose of GARDASIL (lot # not provided) without knowing she was pregnant. The patient had no medical history or concurrent condition. Concomitant therapy included vitamins (unspecified). The patient's LMP was reported as 07-MAR-2008. The patient was scheduled to be due in December however when she went in for a Ultra Sound on 17-Sep-2008 the baby had no heart beat and was dead. The patient delivered the baby on 18-Sep-2008 and was hospitalized for 12 hours after giving birth. Additional information has been requested.
335489	Information has been received from a licensed practical nurse concerning a 20-year old female patient who in June 2008, was vaccinated with the first dose of GARDASI, lot # was not reported. It was reported that the patient became pregnant with twins and had a miscarriage about one week ago. Patient was hospitalized. LMP was 25-JUL-2008. Additional information has been requested.
353081	"Information has been received from a physician and a certified medical assistant, for GARDASIL, a Pregnancy Registry Product, concerning her 17-year old niece no pertinent medical history and no known allergies who on 14-NOV-2007 was vaccinated (injection) with a first dose of GARDASIL (lot# (lot# 659437/1266U) a second dose on 16-JAN-2008 (lot# 659439/1267U), and a third dose was administered on 21-MAY-2008 (lot# 660389/1968U). There was no concomitant medication. In June 2008 the patient found out she was pregnant. The patient then had her baby in March 2009 and the baby was born with brain swelling. The baby then had surgery (name of hospital, address and phone number unspecified) to have the fluid around the brain drained and once the fluid was drained the physician noticed that the baby's brain was not fully developed in the frontal cortex. The certified medical assistant reported that the patient and baby were under care with the patient's Obstetrician/Gynecologist (OBGYN). The patient's last menstrual period (LMP) was reported as ""around June 2008"". The patient was determined to be pregnant in December 2008 when she was 6 months gestation. The patient delivered a male infant on 23-MAR-2009. The infant was diagnosed with hydranencephaly at birth (also reported by the physician as 2 months after birth). Unspecified medical attention was sought. At the time of the report, the patient had not recovered. The physician reported that she was unsure about the patient's prenatal care. Follow up information was received on 28-JUL-2009 via telephone call from a registered nurse who reported that concomitant therapy included MENACTRA (lot# U2538AA) and influenza virus vaccine (unspecified) (lot# U2475KA). The nurse confirmed that there was no pertinent medical history and no known drug allergies (NKDA) and the only therapy taken by the patient was pm naproxen for menses. The nurse was not certain, but believed it was the patient's first pregnancy. LMP date and length of gestation were not available from the nurse's of"

The Slade et al.[51] post-licensure safety surveillance report stated that there were 10 AEFI reports for hospitalization due to miscarriage and an additional 143 reports from the Merck Pregnancy Registry for qHPV "were coded as miscarriage (spontaneous abortion)". Yet the 32 deaths noted in the Slade post-licensure report appear not to include any of these fetal deaths. Our search in September 2014 of the VAERS database for reports of fetal deaths from females who received the qHPV from 6/01/2006 through 12/31/2008 showed that there were 0 deaths, yet as noted above, such deaths were reported. This outcome begs the question as to whether or not a significant number of miscarriages and stillbirths may have been inaccurately discounted as non-serious?

Given that VAERS reports are not standardized and that submission of reports is voluntary, the quantity and quality of information provided varies widely. For example, when reviewing the AEFI reports, physicians were allowed to make comments. These comments sometimes indicated that the synopsis provided in the VAERS records was insufficient to make a firm determination and in such cases, physicians were inclined to give a non-serious assessment. As one might expect, there was variability among the raters as discussed earlier (Figure 2). Overall, however, there was a notable difference in outcome between physicians and the VAERS as to the number of AEFIs rated as serious when applying the criteria for either of the two definitions (Figure 1).

The disparity between VAERS and the physicians in their ratings was especially significant when applying Definition 2, which includes the criterion of "a persistent or significant disability/ incapacity." This suggests that many such cases may not have been accurately rated by VAERS. Indeed, the VAERS form[52] itself narrows this condition to "permanent disability" on a checklist of outcomes to be reported, thereby potentially shrinking the number of serious reports (VAERS online form).

Since AEFIs are also coded and classified for specific outcomes based on terms from the Medical Dictionary for Regulatory Activities (MedDRA), one might argue that the possible inaccuracy of serious/non-serious classification should not impact signal detection.[53] MedDRA is an internationally utilized database of terminology used for converting an adverse event report into a hierarchical, biomedical framework with standardized codes. Once adverse events have been properly coded, frequencies and incidences of adverse events can be analyzed for safety signals. However, proper coding is a challenge and there can be great uncertainty on how AEFIs should be coded, which can result in misinterpretation and misclassification.

Scholl et al.[54] conducted a systematic review of studies on intra- and inter- coder variation and other potential problems related to interpretation and translation of adverse events into coding

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[51] Slade, et al. *supra* note 3.

[52] VAERS form. https://vaers.hhs.gov/resources/vaers_form.pdf.

[53] Medical Dictionary for Regulatory Activities, https://www.meddra.org/.

[54] Schroll JB, Maund E, Gotzsche PC. Challenges in coding adverse events in clinical trials: a systematic review. *PLoS One* 2012; 7:e41174.

terms. They concluded: "There is a lack of evidence that coding of adverse events is a reliable, unbiased and reproducible process." A study by Toneatti et al.[55] found that two blinded coders using MedDRA coded the same adverse events differently 12% of the time at preferred term level and 13% of the adverse events were assessed by experts to be "non-accurate."[56] The accuracy level of the initial coding will obviously affect the accuracy of the overall analysis. In an effort to increase more objective coding, MedDRA is constantly developing additional terms that might be more exact matches to the verbatim adverse event report, and it is updated biannually. Consequently, there are now more than 72,000 Lowest Level Terms (LLT) and more than 20,000 Preferred Terms (PT) including, for example, 50 LLTs for headache.[57] As the amount of terms increases, however, events are split into subcategories. This can result in signal dilution, thereby making it harder to statistically detect adverse events. This can in turn potentially compromise safety.[58]

Regarding specific outcomes, Souayah et al.[59] identified 69 VAERS reports of GBS associated with the qHPV vaccine Gardasil in the U.S between 2006 and 2009. The estimated weekly reporting rate of post-Gardasil GBS within the first 6 weeks was higher than that of the general population, and higher than post-Menactra and post-influenza vaccinations. In particular, there was nearly a 2.5 to 10 time greater risk of acquiring GBS within 6 weeks after Gardasil vaccination when compared with the general population. Additionally, Gardasil vaccination was associated with approximately 8.5 times more emergency department visits, 12.5 times more hospitalizations, 10 times more life-threatening events and 26.5 times more disability than the Menactra vaccine. One criticism of the finding by Souayah et al.,[60] which was addressed by Slade et al.,[61] is that the authors took the doses distributed and divided by three (for three doses) to estimate the number of persons at risk for an adverse event following qHPV. However, it has been reported that only 60% of the girls who were immunized received all three doses.[62] The assumption that all vaccinees received three doses thus reduces the denominator and falsely

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55 Toneatti C, Saidi Y, Meiffredy V, Tangre P, Harel M, Eliette V, Dormont J, Pierre Aboulker J. Experience using MedDRA for global events coding in HIV clinical trials. *Contemporary clinical trials* 2006; 27:13-22

56 *Ibid*.

57 Mozzicato P. MedDRA: An Overview of the Medical Dictionary for Regulatory Activities. *Pharmaceutical Medicine* 2009; 23:65-75

58 Schroll, et al. *supra* note 49.

59 Souayah N, Michas-Martin PA, Nasar A, Krivitskaya N, Yacoub HA, Khan H, Qureshi AI. Guillain-Barre syndrome after Gardasil vaccination: data from Vaccine Adverse Event Reporting System 2006-2009. *Vaccine* 2011; 29:886-9.

60 *Ibid.*

61 Slade BA, Gee J, Broder KR, Vellozzi C. Comment on the contribution by Souayah et al., "Guillain-Barre syndrome after Gardasil vaccination: data from Vaccine Adverse Event Reporting System 2006-2009". *Vaccine* 2011; 29:865-6.

inflates the reporting rate. On the other hand, Slade et al.[63] also made inaccurate calculations to determine reporting rates. They used the number of qHPV vaccine doses distributed rather than the number of vaccine doses administered, and they likewise did not adjust the distributed doses to account for the fact that 60% of the vaccinees received three doses and at least some of the remaining 40% received two doses. The assumption that all doses distributed were actually used and that all vaccinees received only one dose inflates the denominator and falsely deflates the reporting rate.

Another issue relevant to the detection of safety concerns is that an inaccurately rated VAERS report as a non-serious event might not be reviewed. For example, in a report regarding the increased number of post-vaccination syncope reports to VAERS between January 2005 and July 2007 primarily among females aged 11-18 years for newly licensed adolescent vaccines, the CDC acknowledged the findings were subject to several limitations "including the fact that MedDRA coding terms might not accurately reflect the diagnosis of syncope" and that the "clinical details of non-serious reports were not reviewed."[64] This suggests that errors in rating VAERS reports as non-serious can affect coding and review, which in turn could skew the interpretation of the safety profile. Consequently, it is not necessarily true that MedDRA would detect safety signals regardless of the inaccuracy of serious/non-serious classifications due to acknowledged problems regarding differences in the medical aptitude of coders, consistency concerns, the accuracy of terms, discrepancies among different versions of MedDRA, bias, and signal dilution.[65]

Since the primary function of VAERS is to identify early signals of potential safety concern, it is important that potential safety signals are correctly identified. The process of condensing and recording data from thousands of reports is vulnerable to error at multiple levels, however. How reliable is the data, particularly at the entry level? Schroll et al.[66] expressed surprise that "the system that forms the basis for all regulatory safety reporting has been subject to so little publicly available research on the topic." The International Federation of Pharmaceutical Manufacturers and Associations is a Trustee of the International Conference on Harmonisation (ICH) Steering Committee and holds the intellectual property right to MedDRA with technical and financial oversight.[67] One could pose the question as to whether the manufacturer who creates and profits from the sale of the vaccine and the government body who licenses, promotes, and profits from the vaccine should be the same entities that oversee its post-licensure safety?

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[62] Centers for Disease C, Prevention. National, state, and local area vaccination coverage among adolescents aged 13-17 years --- United States, 2009. *MMWR Morb Mortal Wkly Rep* 2010; 59:1018-23.

[63] Slade, et al. *supra* note 3.

[64] Centers for Disease C, Prevention. Syncope after vaccination--United States, January 2005-July 2007. *MMWR Morb Mortal Wkly Rep* 2008; 57:457-60.

[65] Schroll, et al. *supra* note 49.

[66] *Ibid.*

[67] Qureshi, S. Adverse Event and Drug Coding in Clinical Research. J Clin Res Best Practices 2012; 3(8). http://oprs.usc.edu/files/2013/01/1203_Coding.pdf.

For decades there has been broad acknowledgment and passive acceptance of the many limitations of VAERS. Given the importance of the need for reliable reporting and recording of AEFIs, focused research efforts to improve the system seem warranted. The results of our study, for example, not surprisingly show a much higher figure of reported serious AEFIs when cases are assessed according to the complete legal criteria for a serious AEFI as opposed to a truncated definition. So why does the legal definition not universally apply? Given that the truncated criteria for evaluating AEFIs appear to be utilized by the VAERS system, it is likely that serious events possibly related to vaccines other than HPV may also be underrated.

At the reporting level, there are no standardized questions or checklists regarding pre- and post-vaccine adverse events. Such a checklist would be particularly relevant and helpful in assessing the safety of the qHPV vaccine because this vaccine was given in three doses over a relatively short period of time, so the subject could thus become his or her own baseline for examining pre- and post-injection AEFIs (note that the current general recommendation is either two or three doses depending on age). Other improvements might be to use the number of vaccines administered as the denominator to determine the rate of AEFIs rather than using the number of vaccines distributed and to adjust the denominator proportionally depending on the number of vaccinations per person. Also, while medical records are obtained to validate some reports, it would seem appropriate to ensure personal follow-up for individuals who experience serious post-vaccination events, such as death, to obtain from their family members or them more detailed information. Such follow up is not a part of the current VAERS protocol, however.

Recently a thorough monitoring and follow-up of AEFIs following HPV vaccination was conducted by the Japanese Ministry of Health, Labor and Welfare (MHLW). The Ministry found that the rate of AEFIs related to HPV vaccines exceeded greatly that reported in relation to other routine vaccinations. The vaccinations with HPV in Japan commenced in December 2009 and by December 2012, a total of 8.29 million people had been vaccinated. According to the MHLW panel, 1,968 AEFIs were reported by the end of March 2013. Of these, 106 were rated as serious and related to cases of pain or body convulsions, joint pain or difficulty in walking. This figure translates into a rate of 12.8 serious AEFIs per 1 million vaccinations, which is 6.1 times higher than that reported for the inactivated polio vaccine (2.1 serious cases per million vaccinations) and 14.2 times higher than that reported for the influenza vaccine (0.9 serious cases per million vaccinations).[68,69] Ultimately, on June 14, 2013, the Japanese MHLW suspended its active recommendation for HPV vaccination due to increasing public concerns regarding serious AEFIs.

Throughout 2014, diseases with intense symptoms related to HPV vaccination continued to be reported in Japan. The symptoms were so severe as to cause significant disability in the patients.

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[68] Medscape. Japan Withdraws HPV Vaccine Recommendation for Girls. June 25, 2013. http://www.medscape.com/viewarticle/806645#vp_1.

[69] The Japan Times. Editorial: HPV vaccine raises questions. June 14, 2013. http://www.japantimes.co.jp/opinion/2013/06/14/editorials/hpv-vaccine-raises-questions/#.VilWwH6nvIV.

As of September 2014, more than two hundred such serious cases had been reported.[70] In order to investigate the causes of neurological manifestations in girls vaccinated with HPV vaccine, Kinoshita et al.[71] conducted studies on 40 young women patients, aged 11 to 17 years who exhibited headaches, general fatigue, coldness of the legs, limb pain, and weakness after receiving the first dose of the vaccine with a mean incubation period after the first dose of 5.47±5.00 months. The limb symptoms of four girls were compatible with the Japanese clinical diagnostic criteria for complex regional pain syndrome (CRPS), while those in the other 14 girls were consistent with foreign diagnostic criteria for CRPS. Moreover, eight patients were diagnosed with orthostatic hypotension and four patients with postural orthostatic tachycardia syndrome. The patients diagnosed with CRPS and orthostatic intolerance suffered from transient violent tremors and persistent asthenia. Electron-microscopic examinations of the intradermal nerves showed an abnormal pathology in the unmyelinated fibers in two of the three girls examined. The authors concluded that the symptoms observed in their study could be explained by abnormal peripheral sympathetic responses following HPV immunizations and that it was unlikely that the Japanese environment played a role in the pathogenesis of this unique autonomic disorder. Their conclusions are supported by reports of similar symptoms related to HPV vaccine administration worldwide, namely Denmark,[72,73] US[74,75] Australia,[76] and

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[70] Hama, R. Harm of HPV vaccine: The latest information and examination of epidemiological studies. Medcheck, The Informed Prescriber 2015; 1(1): 9-13. http://www.npojip.org/english/MedCheck/Med%20Check-TIP%2001-4-25.pdf.

[71] Kinoshita T, Abe RT, Hineno A, Tsunekawa K, Nakane S, Ikeda S. Peripheral sympathetic nerve dysfunction in adolescent Japanese girls following immunization with the human papillomavirus vaccine. *Intern Med* 2014; 53:2185-200.

[72] Brinth LS, Pors K, Theibel AC, Mehlsen J. Orthostatic intolerance and postural tachycardia syndrome as suspected adverse effects of vaccination against human papilloma virus. *Vaccine* 2015; 33:2602-5.

[73] Brinth L, Theibel AC, Pors K, Mehlsen J. Suspected side effects to the quadrivalent human papilloma vaccine. *Danish medical journal* 2015; 62:A5064.

[74] Blitshteyn S. Postural tachycardia syndrome following human papillomavirus vaccination. *Eur J Neurol* 2014; 21:135-9.

[75] Tomljenovic L, Colafrancesco S, Perricone C, Shoenfeld Y. Postural Orthostatic Tachycardia With Chronic Fatigue After HPV Vaccination as Part of the "Autoimmune/Auto-inflammatory Syndrome Induced by Adjuvants": Case Report and Literature Review. *J Investig Med High Impact Case Rep* 2014; 2:2324709614527812.

[76] Richards S, Chalkiadis G, Lakshman R, Buttery JP, Crawford NW. Complex regional pain syndrome following immunisation. *Arch Dis Child* 2012; 97:913-5.

elsewhere.[77,78,79] Studies with large scale investigations and experimental approaches are needed to further assess questions raised about serious AEFIs following HPV vaccination as well as the manner in which such reports are recorded and rated.

Notably, consistent with the results obtained by AEFI surveillance in Japan, our analysis of VAERS data showed that AEFIs reported in relation to HPV vaccine administration exceeded greatly those reported for other vaccines. Namely, 59.04 – 76.97% of all serious and 41.63-64.32% of total AEFIs reported to VAERS yearly since 2007 to 2014 in females younger than 30 years were HPV-vaccine related reports (Figure 3). The corresponding percentages for 2006 year reports were much lower since the HPV vaccine has only been licensed by the FDA in June 2006.[80] Furthermore, during that same period (2007 to 2014), of all AEFIs reported for HPV vaccines, 9.25-24.96% were classified by VAERS as serious. By comparison, the yearly percentages of serious AEFIs for all other vaccines combined ranged from 7.4-11.07 (Figure 4), which is approximately 1.3-3.0 lower than the corresponding percentages of HPV vaccine-related serious AEFIs. It is also notable that the percentages of serious AEFIs reported yearly for Menactra, a suitable comparator vaccine since it is routinely given to the same age group as HPV, are in line with those reported for all other vaccines, ranging from 7.2-7.34% for the 2007-2014 period (Figure 4).

Moreover, since Menactra has also been introduced into the US vaccination schedule in 2005,[81] only shortly prior to HPV vaccines (the quadrivalent vaccine Gardasil in 2006[82] and the bivalent vaccine Cervarix in 2009[83]), this latter observation argues against the popular assertion that the increase in HPV vaccine-related AEFIs is merely the result of the "Weber effect." According to that effect, increased publicity generally follows after the introduction of any new drug into the market and presumably causes the adverse event reporting to peak by the end of the second year following introduction, declining thereafter.[84] As shown in Figure 4, the yearly percentages of serious HPV-vaccine related AEFIs for the period since HPV vaccine introduction (2006-2014) do

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[77] Martinez-Lavin M, Martinez-Martinez LA, Reyes-Loyola P. HPV vaccination syndrome. A questionnaire-based study. *Clin Rheumatol* 2015; 34:1981-3.

[78] Martinez-Lavin M. Hypothesis: Human papillomavirus vaccination syndrome-small fiber neuropathy and dysautonomia could be its underlying pathogenesis. *Clin Rheumatol* 2015; 34:1165-9.

[79] Martinez-Lavin M. Fibromyalgia-like illness in 2 girls after human papillomavirus vaccination. *Journal of clinical rheumatology : practical reports on rheumatic & musculoskeletal diseases* 2014; 20:392-3.

[80] Dunne, et al. *supra* note 1.

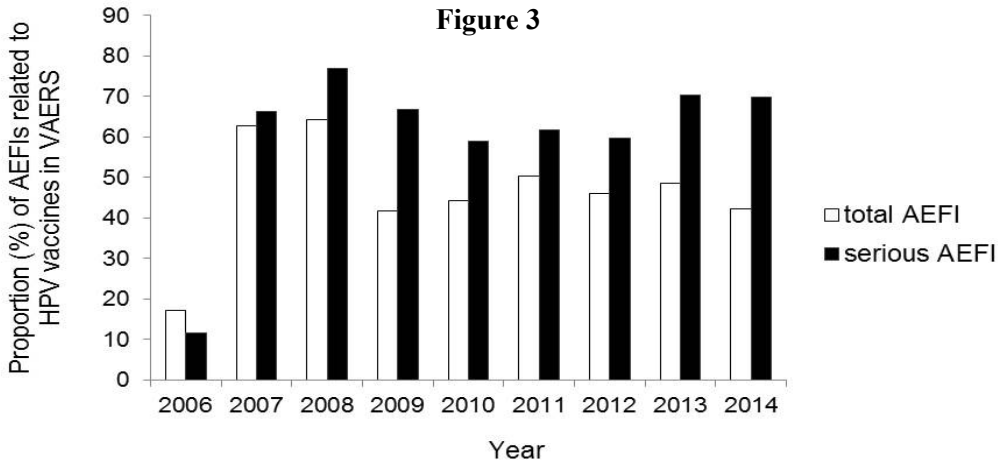
[81] Bilukha OO, Rosenstein N. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2005; 54:1-21.

[82] Slade, et al. *supra* note 3.

[83] Centers for Disease C, Prevention. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2010; 59:626-9.

not follow the expected Weber effect pattern. Namely, although showing a peak in 2009 (approximately three years following HPV vaccine licensure) and then a decline in 2010, the percentages of serious AEFIs linked to HPV vaccination have since increased steadily, and in 2013 and 2014 reached a new peak, higher than that observed in 2009. Of additional relevance, Weber himself noted that the decline in reporting observed after the general second year peak is due to a reduction in the reporting of clinically mild or trivial reactions while the more serious events continue to be reported from year to year in a quite constant manner.[85] We can further conclude that although the number of adverse events reported is expected to increase following introduction of a new drug, it is incorrect to assume that this increase is a simple artifact of increased reporting due to increased public awareness. Rather, the observed increase may point to an actual safety warning signal, especially in instances where after an initial peak, serious AEFIs continue to be reported at the same or increased rate which exceeds the baseline reported for products of a similar class.

Figure 3

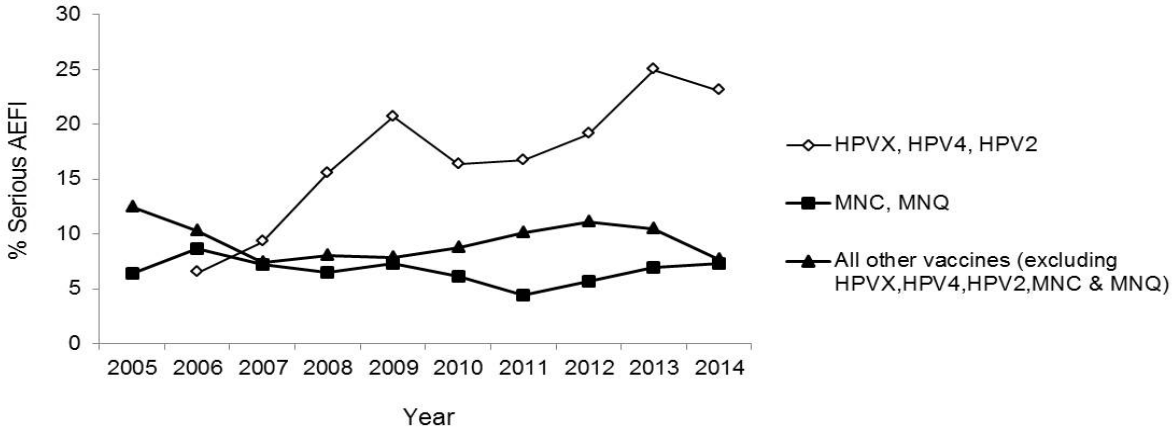


The yearly contribution (in percentages) of AEFIs (total and serious) related to HPV vaccines to all AEFIs reported to VAERS for all vaccines in the period from 2006-2014. The yearly AEFI percentages were calculated as follows: % contribution to total AEFIs (HPV) = (# total (HPV)/# total (all vaccines)) x 100; % contribution to serious AEFIs (HPV) = (# serious (HPV)/# serious (all vaccines)) x 100. The VAERS Internet Database (http://wonder.cdc.gov/controller/datarequest/D8) was searched using the following criteria: 1) Group results by: VAERS ID; 2) Symptoms: All symptoms; 3) Vaccine products: A) HPVX, HPV4, HPV2, B) All vaccine products; 4) Vaccine doses: All doses; 5) Territory: All locations; 6) Age: 6 to 29 years (target age group for HPV vaccines); 7) Gender: female; 8) Event category: A) All events, B) Not serious (Serious events were calculated as A-B); 9) Date report completed: Year intervals from 2006-2014 (Jan 2005-Jan 2006, Jan 2006-Jan 2007, etc.). 10) Date report received: Year intervals from 2005-2014 (Jan 2005-Jan 2006, Jan 2006-Jan 2007, etc.).

[84] Hoffman KB, Dimbil M, Erdman CB, Tatonetti NP, Overstreet BM. The Weber effect and the United States Food and Drug Administration's Adverse Event Reporting System (FAERS): analysis of sixty-two drugs approved from 2006 to 2010. *Drug Saf* 2014; **37**:283-94

[85] 79.Weber JCP. Epidemiology in the United Kingdom of adverse drug reactions from non-steroidal anti-inflammatory drugs. In: Rainsford KD, Velo GP, editors. Side-effects of anti-inflammatory drugs. Springer Netherlands; 1987. p. 27–35

Figure 4



Yearly percentages of serious AEFIs for HPV, Menactra meningococcal vaccines and all other vaccines in the period from 2005-2014. The yearly AEFI percentages were calculated as follows: % serious (HPV) = (# serious (HPV) /# total (HPV)) x 100; % serious (MNC/MNQ) = (# serious (MNC/MNQ) /# total (MNC/MNQ)) x 100; % serious (all other vaccines except HPV and MNC/MNQ) = (# serious (all other vaccines) /# total (all other vaccines)) x 100. VAERS Internet Database (http://wonder.cdc.gov/controller/datarequest/D8) was searched using the following criteria: 1) Group results by: VAERS ID; 2) Symptoms: All symptoms; 3) Vaccine products: A) HPVX, HPV4, HPV2, B) MNC, MNQ, C) All vaccine products except HPVX, HPV4, HPV2, B) MNC, MNQ; 4) Vaccine doses: All doses; 5) Territory: All locations; 6) Age: 6 to 29 years (target age group for HPV vaccines); 7) Gender: female; 8) Event category: A) All events, B) Not serious (Serious events were calculated as A-B); 9) Date report completed: Year intervals from 2005-2014 (Jan 2005-Jan 2006, Jan 2006-Jan 2007, etc.). 10) Date report received: Year intervals from 2005-2014 (Jan 2005-Jan 2006, Jan 2006-Jan 2007, etc.). Abbreviations: HPV4, quadrivalent HPV vaccine Gardasil; HPV2, bivalent HPV vaccine Cervarix; HPVX, HPV vaccine nonspecified; MNC, meningococcal conjugate vaccine, MNQ, meningococcal conjugate vaccine Menactra.

Finally, although the FDA Adverse Event Reporting System (FAERS) database is frequently *assumed* [emphasis added] to suffer from the Weber effect, a recent more elaborate analysis on adverse events for 62 drugs found no evidence to support such a general trend of a second year peak and decrease in adverse event reporting trends. It concluded that such assertions that modern FAERS data are unreliable due to the Weber effect are largely unfounded.[86] In particular, while a few of the 62 drugs analyzed showed a Weber-like trending, the vast majority did not. Based on these observations, the authors noted that the Weber effect should not be assumed when analyzing modern day FAERS reporting.

V. CONCLUSION

Since it is generally acknowledged that the AEFIs related to the qHPV (and other vaccines) are under reported, it becomes all the more important that events that are reported are properly rated. The current study suggests that the criteria for rating AEFIs as serious may be inaccurately applied which may have resulted in under-rating of serious AEFIs. In particular, it appears that the rating criteria used by the US vaccine safety surveillance authorities do not necessarily conform to those stipulated by the Code of Federal Regulations, 21 CFR 314.80. Because of the limited number of physician raters who agreed to volunteer in this study, it was not possible to extend our analysis to vaccines other than HPV. However, given that the truncated criteria for evaluating AEFIs appear to be the standard used by the VAERS, it is likely that serious events

[86] Hoffman, et al. *supra* note 78.

possibly related to other vaccines may also be underrated. Due to the sentinel role of the VAERS in the monitoring of vaccine safety, it is imperative that the possibility of significant bias in under reporting of serious events following qHPV as well as other vaccines be further investigated and that the critical limitations of VAERS be adequately addressed.

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