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ORIGINAL RESEARCH ARTICLE

Data Mining for Prospective Early Detection of Safety Signals in the Vaccine Adverse Event Reporting System (VAERS): A Case Study of Febrile Seizures after a 2010–2011 Seasonal Influenza Virus Vaccine

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Abstract

Background Reports of data mining results as an initial indication of a prospectively detected safety signal in the US Vaccine Adverse Event Reporting System (VAERS) have been limited. In April 2010 a vaccine safety signal for febrile seizures after Fluvax® and Fluvax® Junior was identified in Australia without the aid of data mining. In order to refine Northern Hemisphere influenza vaccine safety surveillance, VAERS data mining analyses based on vaccine brand name were initiated during the 2010–2011 influenza season.

Objective We describe the strategies that led to the finding of a novel safety signal using empirical Bayesian data mining.

Methods The primary US VAERS analysis calculated an empirical Bayesian geometric mean (EBGM), which was adjusted for age group, sex and year received. A secondary age-stratified analysis calculated a separate EBGM for 11 pre-defined age subsets. These bi-weekly analyses were generated with database restrictions that separated live and inactivated vaccines as well as with the US VAERS database. A cutoff of 2.0 at the fifth percentile of the confidence interval (CI) for the EBGM, the EB05, was used to identify vaccine adverse event combinations for further evaluation. Examination of potential interactions among concomitantly administered vaccines is based on the Interaction Signal Score (INTSS), which is a relative measure of how much excess disproportionality is present in the three-dimensional combination of two vaccines and one adverse event term. An INTSS >1 indicates that the CI for the three-dimensional analysis is larger than and does not overlap with the CI from the highest two-dimensional analysis. We subsequently examined the possibility of masking by removing all 2,095 Fluzone®$_{2010\text{-}2011}$ reports from the 10 December 2010 version of the VAERS database. In addition, we calculated relative reporting ratios to observe the relative contribution of adjustment and the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm to EBGM values.

Results On 10 December 2010, US VAERS analyses we found an EB05 >2 for Fluzone®$_{2010\text{-}2011}$ and the Medical Dictionary for Regulatory Activities (MedDRA®) term "febrile seizure". MedDRA® terminology is the medical terminology developed under the auspices of the International Conference on Harmonization of technical requirements for Registration of Pharmaceuticals for Human Use (ICH). No other vaccine products had independent vaccine-febrile seizure combinations with an EB05 >2. Three-dimensional analyses to examine possible interactions among vaccine products concomitantly administered with Fluzone®$_{2010\text{-}2011}$ yielded Interaction Signal Score values <1. Removal of all Fluzone®$_{2010\text{-}2011}$ reports from the VAERS database failed to demonstrate a previously masked vaccine adverse event pair with an EB05 >2. The inactivated vaccine database restriction resulted in a 41 % reduction in background VAERS reports and a 24 % reduction in foreground VAERS reports.

Conclusion Empirical Bayesian data mining in VAERS prospectively detected the safety signal for febrile seizures after Fluzone®$_{2010\text{-}2011}$ in young children. The EB05 threshold, database restrictions, adjustment and baseline data mining were strategies adopted *a priori* to enhance the specificity of the 2010–2011 influenza vaccine data mining analyses. A database restriction used to separate live

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vaccines resulted in a reduced EB05. Adjustment of data mining analyses had a larger effect on estimates of disproportionality than the MGPS algorithm. Masking did not appear to influence our findings. This case study illustrates the value of VAERS data mining for vaccine safety monitoring.

1 Introduction

The US Food and Drug Administration (FDA) defines a signal as "a concern about an excess of adverse events compared to what would be expected to be associated with a product's use" [1]. However, rates cannot be calculated from the Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting system. Data mining addresses the inherent limitation of absent denominator data by screening the VAERS database for higher than expected proportions of vaccine-event combinations [2, 3]. In order to determine if a vaccine-event combination of interest represents a signal, additional scientific review is necessary. Data mining may be used to contribute to a variety of pharmacovigilance objectives including: signal detection, strengthening or weakening of existing safety signals detected by data mining, providing evidence for or against existing safety concerns not previously evaluated using data mining, evaluation of vaccine-vaccine interactions, and identification of novel signals related to a known signal (e.g., multiple adverse events in a syndrome) [4].

A variety of quantitative methods can be used to detect disproportionality among spontaneous adverse event reports. Such methods and their statistical outputs include the proportional reporting ratio (PRR), reporting odds ratio (ROR) and the empirical Bayesian geometric mean (EBGM), and they are described elsewhere [5–8]. An advantage of Bayesian data mining over other methods is its minimization of false-positive signals due to "shrinkage" towards the null with low observed or expected counts. The utility of applying empirical Bayesian data mining to vaccine safety monitoring has been previously demonstrated retrospectively in a study indicating that a signal for intussusception after a rotavirus vaccine could have theoretically been detected months earlier [9]. Subsequently, data mining findings of vaccine-associated adverse events were reported including photophobia after smallpox vaccine [10], Guillain Barré syndrome after trivalent influenza vaccine [11] and syncope after quadrivalent human papillomavirus vaccine [12]. Data mining in VAERS has been used to screen vaccine-event combinations from the point of view of a specific adverse event (e.g., thrombocytopenia [13]) or a single vaccine (e.g., anthrax vaccine [14]). In most of these previously reported data mining findings, the information was supportive of findings from other monitoring methods, rather than the first indication of a novel safety signal.

In the 2010–2011 Northern Hemisphere influenza season, influenza vaccination was recommended in the USA for all adults as well as all children aged 6 months and older [15]. To match circulating influenza strains the influenza vaccine is typically changed each year, and in 2010 the influenza A (H1N1) pandemic strain was added to the seasonal influenza vaccine products distributed in the USA. Estimated coverage among children aged 6 months to 4 years for the 2010–2011 season was 63.6 % (95 % confidence interval [CI] 61.9–65.3) based on the National Immunization Survey [16].

Because prudent pharmacovigilance necessitates strategies for detecting novel safety signals for different seasonal formulations of specific influenza vaccine products, adoption of data mining by influenza vaccine brand name rather than product class was planned in early 2010. This product-specific approach provided consistency with the FDA's product-focused mission and gained added impetus after April 2010 when the Australian Therapeutic Goods Administration identified a safety signal for febrile seizures in young children following vaccination with Fluvax® and Fluvax® Junior (CSL, Parkeville, VIC, Australia). An increased risk was not documented with other seasonal trivalent influenza products distributed in Australia at the time [17]. This example highlighted the need to differentiate data mining findings by specific vaccine product in order to refine signal identification. Consequently, routine influenza vaccine data mining during the 2010–2011 Northern Hemisphere influenza season was conducted separately for each of the eight then US-licensed and -marketed seasonal trivalent influenza vaccines, each of which contained antigenically equivalent influenza strains to those present in the CSL influenza vaccine formulation associated with febrile seizures [18]. We report the methods of and findings from this surveillance effort resulting in the initial detection of a new important safety signal.

2 Methods

The VAERS is the US national surveillance system for monitoring vaccine safety. VAERS accepts spontaneous reports of post-vaccination adverse events from a variety of sources including vaccine manufacturers, healthcare providers and the public. In 2010, VAERS received ~38,000 reports of ~37,000 events, ~5,000 of which were serious (characterized by death, hospitalization, prolonged hospitalization, disability, life-threatening-illness or birth defect) [19]. VAERS has many limitations including under-reporting, variable degree of individual report detail and accuracy, duplicate reports, lack of control groups for

comparison and lack of denominator data (i.e., number of vaccine doses administered), as well as strengths including its national scope and the timeliness of reported events (enabling near real-time capturing of data) [20]. Although it is generally not possible to establish causality from VAERS reports alone, VAERS can be helpful in identifying and generating hypotheses about potential rare vaccine-associated adverse events that may be undetectable in pre-marketing clinical trials (e.g., due to sample size limitations or selection criteria).

Among other routine product-specific safety surveillance duties, medical epidemiologists in the FDA's Center for Biologics Evaluation and Research (CBER) review data mining output from Empirica® data mining software (Version 7.2, Oracle), which is generally refreshed biweekly. Empirica® draws upon a background of all VAERS reports since establishment of the database in 1990, and it provides an adjusted ratio of observed to expected counts of vaccine-adverse event combinations that is derived exclusively from "numerator" (i.e., number of events reported for each vaccine-event pair) data. Reports without a brand name are excluded from these analyses. Adverse events are encoded from the text of VAERS reports using Medical Dictionary for Regulatory Activities (MedDRA®, Version 13.0) preferred terms (PTs). Initially, Empirica® calculates the relative reporting ratio, which is the observed number of reports containing a specific vaccine-adverse event PT pair divided by the expected number of reports containing this pair. The expected count of this pair (if the vaccine and adverse event PT were independent) is calculated by multiplying the proportion of reports with the specific vaccine, the proportion of reports with the specific PT, and the total number of reports in the database. The relative reporting ratio can be adjusted for one or more categorically defined potential confounders by calculating stratum-specific expected counts. The proportion of reports within a specific stratum for a specific vaccine is multiplied by the proportion of reports within this stratum with a specific PT and the total number of reports in the stratum. The adjusted relative reporting ratio is the observed number of a specific vaccine-adverse event PT combination divided by the sum of the stratum-specific expected counts. After calculating a relative reporting ratio or an adjusted relative reporting ratio, Empirica® uses the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm to calculate the EBGM. The MGPS algorithm addresses the multiple-comparisons concern stemming from the determination of relative reporting ratios for thousands of vaccine-adverse event pairs [21]. We routinely use a cutoff value of 2 at the lower bound (EB05) of the 90 % CI surrounding the EBGM to identify vaccine-event combinations of interest since this threshold has been shown to indicate sufficient specificity to warrant further evaluation [22]. The upper bound of this CI is referred to as the EB95. An EB05 >2 provides a high degree of confidence that a vaccine-event pair has been reported at least twice as frequently as would be expected when compared with reports for the same adverse event and other vaccines in the background database.

In addition to adjusting the calculation of the relative reporting ratio for potential confounders, we routinely customize our data mining strategies through database restrictions and subsets. Two routine vaccine product-specific data mining analyses were used prior to and during the 2010–2011 Northern Hemisphere influenza season. The primary analysis (Fig. 1) is restricted to USA or unknown country reports and is adjusted for age group, sex and year the FDA received the report. The majority of the reports with missing country data originate in the USA. Hereafter, this analysis is referred to as the "US VAERS" analysis. In addition, a secondary analysis (Fig. 2), "US VAERS by age group," calculated a separate EBGM adjusted for sex and year received for 11 pre-defined age subsets of the VAERS database for each vaccine product. The 11 pre-defined data mining age groups identified by Empirica® include 0 to <18 months, 18 to <54 months, 54 months to <12.5 years, 12.5 years to <16.5 years, 16.5 years to <29.5 years, 29.5 years to <45.5 years, 45.5 years to <64.5 years, 64.5 years to <75.5 years, 75.5 years to <85.5 years, 85.5 years and above, and age unknown. The effects of data-mining stratification (through MGPS subsets) in VAERS are discussed elsewhere [23–25]. Prior to 2010, influenza product class (rather than vaccine brand name) analyses were used. In addition, prior to and during the 2010–2011 Northern Hemisphere influenza season, the VAERS database was segregated to enable the live attenuated influenza vaccine product to be assessed against a background of live viral vaccine adverse event reports and to enable the inactivated influenza vaccines to be assessed against a background containing only inactivated vaccines [26]. As a consequence of this database restriction, any VAERS report with a live vaccine whether or not it also contains an inactivated vaccine is excluded from the inactivated vaccine data mining background. Hereafter, primary and secondary analyses utilizing this database restriction will be followed by the term "inactivated" in parentheses.

When data mining analyses are conducted for a specific vaccine brand name, the data mining outcome measure of interest incorporates the entire post-marketing period for the vaccine from initial licensure through the current review period. Since influenza vaccines generally contain new strains compared to prior seasons, they are considered for data mining purposes to be "new" products at the beginning of the influenza season and carry a suffix for that influenza season. Reports with a vaccination date prior to 1

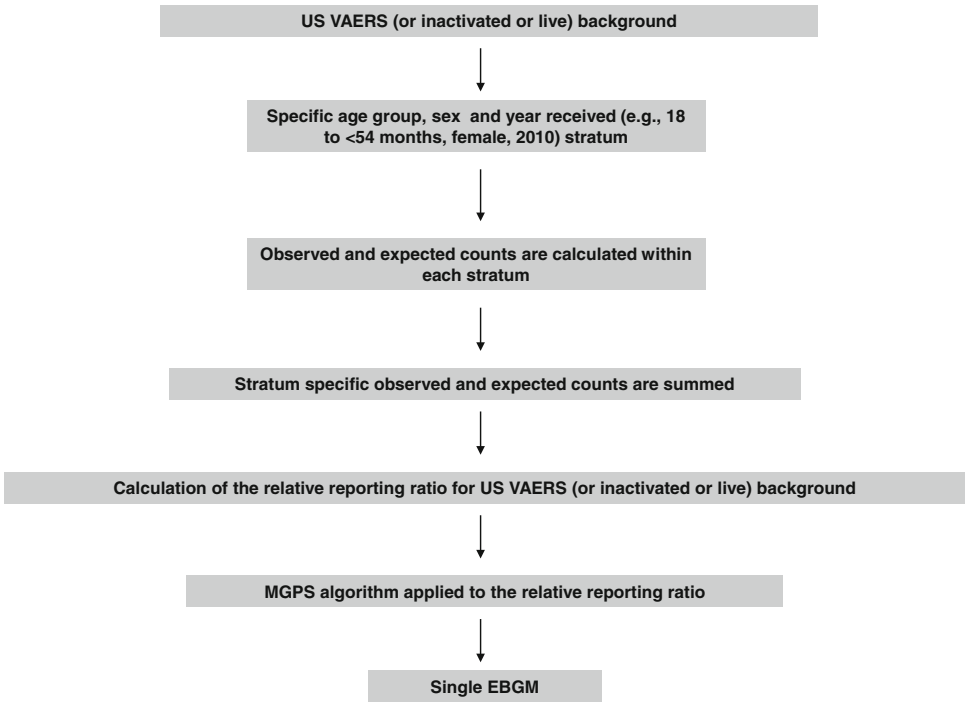

Fig. 1 Schematic overview of the US Vaccine Adverse Event Reporting System (VAERS) analysis. Although only one stratum is depicted, data from reports within each unique combination of age group, sex and year received form multiple strata. After the observed and expected counts from all strata are summed a single empirical Bayesian geometric mean (EBGM) is calculated. *MGPS* multi-item gamma poisson shrinker

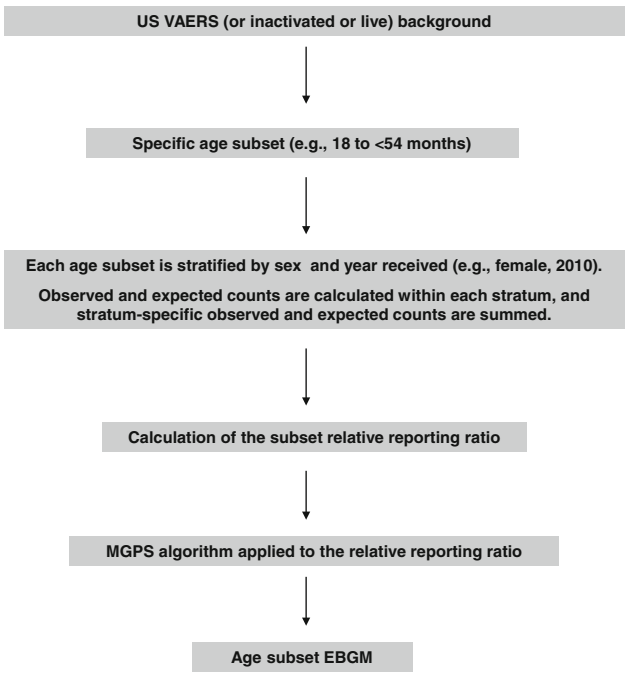

Fig. 2 Schematic view of the US Vaccine Adverse Event Reporting System (VAERS) by age group analysis. Although only one age group is depicted, a separate empirical Bayesian geometric mean (EBGM; stratified by sex and year received) is calculated for each age group

July 2010 were regrouped by product name, and reviewers conducted "baseline" data mining analyses at the beginning of the influenza season using these composite product-specific variables to enable comparisons with 2010–2011 product analyses.

Examination of potential interactions among concomitantly administered vaccines is undertaken in a three-dimensional analysis (i.e., two vaccines and one adverse event PT). This analysis applies the MGPS algorithm, which is adjusted for age group, sex and year received, but

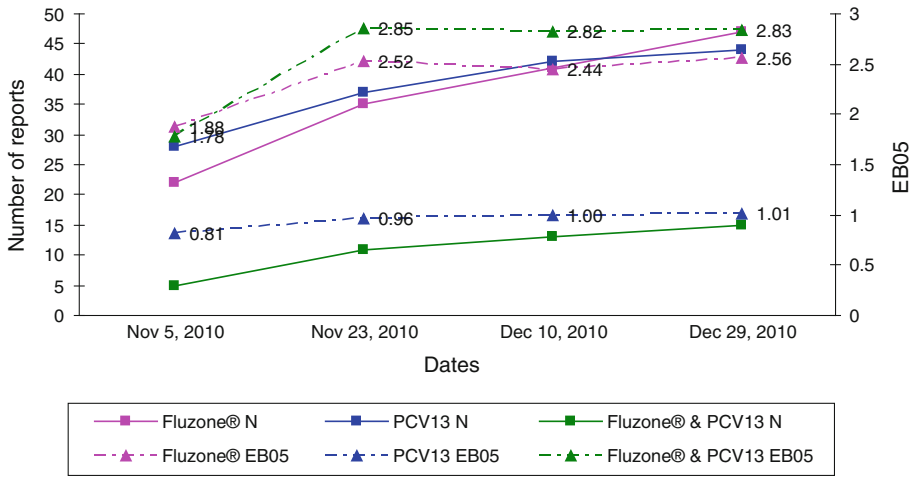

Fig. 3 US Vaccine Adverse Event Reporting System (VAERS). Febrile convulsions after Fluzone®$_{2010\text{-}2011}$, Prevnar 13® (PCV13) and both vaccines given concomitantly. *EB05* fifth percentile of the confidence interval for the empirical Bayesian geometric mean

it allows three items per combination. The EB05 derived from this higher order combination calculation is then divided by the EB95 from the highest two-dimensional (e.g., one vaccine and one adverse event PT) analysis. The quotient is the Interaction Signal Score (INTSS), and an INTSS >1 is the threshold for higher order disproportionality involving two vaccines and an adverse event PT that cannot be explained solely by a single pairwise vaccine-PT association. An INTSS >1 indicates that the CI for the three-dimensional analysis is larger than and does not overlap with the CI from the highest two-dimensional analysis. Thus, the INTSS is a relative measure of how much excess disproportionality is present in the three-dimensional combination [27].

3 Results

The routine US VAERS (inactivated) by age group analysis (based on the 23 November 2010 version of the VAERS database) revealed an EB05 = 2.50 (EBGM = 4.08, EB95 = 6.25, $n = 15$) for the "febrile convulsion" PT paired with Fluzone®$_{2010\text{-}2011}$ (Sanofi Pasteur Inc., Bridgewater, NJ, USA) trivalent inactivated influenza virus vaccine in the 0- to 18-month age group. The US VAERS (inactivated) analysis combining all ages did not have an EB05 value that exceeded our predetermined threshold of 2 for any other vaccine including Fluzone®$_{2010\text{-}2011}$. In addition, the same runs conducted for Fluzone® using all prior seasons combined (i.e., "baseline" data mining), did not reveal an EB05 >2 for the "febrile convulsion" PT. Given this new finding, we expanded our data mining evaluation of Fluzone®$_{2010\text{-}2011}$ to the US VAERS analysis, which included both live and inactivated vaccines. In the US VAERS analysis (Fig. 3) we found an EB05 = 2.52 (EBGM = 3.66, EB95 = 5.12, $n = 35$), and in the US VAERS by age group analysis we found an EB05 = 2.68 (EBGM = 4.10, EB95 = 5.85, $n = 22$) in the 0- to 18-month age group. Clinical review confirmed 21 cases of febrile seizure (using a case definition of a healthcare provider diagnosis of febrile seizure) after Fluzone®$_{2010\text{-}2011}$ in 0- to 18-month age stratum and 13 additional (mostly children 18–23 months old) cases of febrile seizure identified in US VAERS analysis. These cases were characterized by age, sex, time to onset, concomitant vaccinations, seriousness, geographic location and vaccine lot (data not shown). No other US licensed vaccine in routine US VAERS analyses, including the other licensed influenza vaccines available in the 2010–2011 season, had an EB05 >2 for the "febrile convulsion" PT.

The 10 December 2010 version of the VAERS database was used for additional two-dimensional analyses to see if the Fluzone®$_{2010\text{-}2011}$ febrile seizure signal persisted. The results of the two-dimensional analyses were similar to those from 23 November 2010. In the US VAERS analysis for all age groups we found an EB05 = 2.44 (EBGM = 3.36, EB95 = 4.60, $n = 41$) and in the US VAERS by age group analysis we found an EB05 = 2.92 (EBGM = 4.15, EB95 = 5.66, $n = 28$) in the 0- to 18-month age group. No other vaccine products had independent vaccine-febrile seizure combinations with an EB05 >2.0, and Table 1 depicts results for those vaccines concomitantly administered with Fluzone®$_{2010\text{-}2011}$. We also conducted three-dimensional analyses to examine possible interactions among vaccines concomitantly administered with Fluzone®$_{2010\text{-}2011}$. There was no evidence for synergy because the INTSS values for these products were all <1.0 (Table 1).

The Fluzone®$_{2010\text{-}2011}$ febrile seizure signal persisted over time. Data mining findings from the 29 December 2010 version of the VAERS database were similar to those from 10 December 2010. In the US VAERS analysis we found an EB05 = 2.56 (EBGM = 3.46, EB95 = 4.60, $n = 47$) and in the US VAERS by age group analysis we

Table 1 US Vaccine Adverse Event Reporting System as of 10 December 2010: data mining results for the paired (febrile convulsion-vaccine product) analysis and for the three-dimensional analysis including febrile convulsion combined with Fluzone®$_{2010\text{-}2011}$ and concomitantly administered vaccines

Vaccine	Paired analysis			Three-dimensional analysis	
	N	EB05	EBGM	*N*	INTSS
Fluzone®$_{2010\text{-}2011}$	41	2.44	3.36		
Prevnar 13®	42	1.00	1.29	13	0.59
M-M-R® II	1060	1.64	1.72	7	0.53
ActCTHIB®	333	0.94	1.03	7	0.53
Recombivax HB®	134	0.57	0.66	3	0.49
VAQTA®	75	1.39	1.68	4	0.48
ProQuad®	72	1.64	1.98	2	0.46
VARIVAX®	540	1.00	1.07	6	0.46
HAVRIX®	120	1.31	1.52	4	0.45
DAPTACEL®	139	1.02	1.17	2	0.43
PedvaxHIB®	152	0.90	1.03	2	0.43
INFANRIX®	172	0.82	0.93	2	0.42
Tripedia®	236	0.94	1.05	1	0.40
Prevnar®	568	1.05	1.12	3	0.39
Pentacel®	41	0.55	0.70	1	0.29

EB05 fifth percentile of the confidence interval for the EBGM, *EBGM* empirical Bayesian geometric mean, *INTSS* Interaction Signal Score

found an EB05 = 2.98 (EBGM = 4.11, EB95 = 5.48, $n = 32$) in the 0- to 18-month age group. Vaccines reported to VAERS as concomitantly administered with Fluzone®$_{2010\text{-}2011}$ continued to have no independent findings for febrile seizure. Subsequently, the US Centers for Disease Control and Prevention (CDC) and FDA shared the Fluzone®$_{2010\text{-}2011}$ febrile seizure VAERS findings publicly via a press release and web postings [28, 29].

Prevnar 13® (Pfizer Inc., New York, NY, USA) was the only newly licensed and recommended vaccine (other than the 2010–2011 influenza strain change) for children under the age of 5 years during the 2010–2011 influenza season [30]. To ensure that we did not overlook a possible signal from Prevnar 13®, we examined the possible contribution of observed values, stratification and shrinkage to the finding that the Prevnar 13®-febrile seizure combination did not exceed our predetermined threshold in the US VAERS analysis. The crude relative reporting ratio for the Fluzone®-febrile seizure combination (2.28) was lower than that for the Prevnar 13®-febrile seizure combination (3.75) (Tables 2, 3). However, adjustment nearly tripled the expected value for the Prevnar 13®-febrile seizure combination from 11.2 to 31.3, and the resulting relative reporting ratio for this combination was reduced to 1.34 (Table 4). MGPS shrinkage played a smaller role in the reduction of the point estimate of disproportionate reporting than adjustment, and the EBGM for the Prevnar 13®-febrile convulsion combination was 1.29 with an EB05 of 1.00 (Table 4).

We examined the possibility that a signal from Prevnar 13® was masked by removing all 2,095 Fluzone®$_{2010\text{-}2011}$ reports from the 10 December 2010 version of the VAERS database. This sensitivity analysis necessarily resulted in the removal of all concomitant vaccination reports listed in Table 2. In spite of the removal of the Fluzone®$_{2010\text{-}2011}$ reports, no vaccine had a two-dimensional combination with an EB05 >2. Indeed, measures of disproportionate reporting actually decreased after Fluzone®$_{2010\text{-}2011}$ reports were removed (Table 5).

Because the US VAERS (inactivated) analysis did not have an EB05 value that exceeded our predetermined threshold of 2 while the 0- to 18-month age subset of the US VAERS (inactivated) by age group analysis exceed this threshold, we examined the effect of our database restriction (Table 6). In the US VAERS analysis there were 41 reports with Fluzone®$_{2010\text{-}2011}$ and the PT "febrile convulsion", and the EB05 was 2.44. The inactivated vaccine database restriction resulted in a 41 % reduction in background VAERS reports. Although foreground VAERS reports (i.e., those with Fluzone®$_{2010\text{-}2011}$ and the PT "febrile convulsion") were only reduced by 24 %, the resulting EB05 of 1.89 did not reach our threshold. In the 0- to 18-month age group, nearly half of the Fluzone®$_{2010\text{-}2011}$ "febrile convulsion" PT pairs were preserved in the foreground while there was a simultaneous 92 % reduction in the size of the VAERS background. This reduced the expected count within the 0- to 18-month stratum, and the resulting EB05 was 2.62.

4 Discussion and Conclusion

This report describes the initial identification of a vaccine safety signal using empirical Bayesian data mining of the VAERS database rather than traditional pharmacovigilance methods such as expert review and calculation of reporting rates. Despite advances in population-based active surveillance, passive surveillance systems remain an important component of post-marketing safety monitoring efforts in order to detect unexpected adverse events that have not been prespecified in active surveillance systems. To date, demonstration that VAERS data mining methods can prospectively identify important safety signals in a timely fashion has been limited. Conducting clinical and epidemiological evaluations of disproportional vaccine event pairs is resource intensive [31], and this case study demonstrates the value of optimizing the application of data mining to spontaneous reporting system databases. For influenza products, the EB05 threshold, adjustment and

Table 2 Fluzone®$_{2010\text{-}2011}$ crude relative reporting ratio in the 10 December 2010 US Vaccine Adverse Event Reporting System analysis*

Adverse event	Reports with Fluzone®$_{2010\text{-}2011}$	All other reports	Total
Febrile convulsion	41	2,532	2,573
All other adverse events	2,054	294,936	296,990
Total	*2,095*	*297,468*	*299,563*

* The observed value (N) = 41, the expected value (E) = (2,573)(2,095)/299,563 = 17.9, and the crude relative reporting ratio = N/E = 41/17.9 = 2.28

Table 3 Prevnar 13® crude relative reporting ratio in the 10 December 2010 US Vaccine Adverse Event Reporting System analysis*

Adverse event	Reports with Prevnar 13®	All other reports	Total
Febrile convulsion	42	2,531	2,573
All other adverse events	1,262	295,728	296,990
Total	*1,304*	*298,259*	*299,563*

* The observed value (N) = 42, the expected value (E) = (2,573)(1,304)/299,563 = 11.2, and the crude relative reporting ratio = N/E = 41/17.9 = 3.75

Table 4 Comparison of the US Vaccine Adverse Event Reporting System (VAERS) analysis (10 December 2010 version of the VAERS database) for Fluzone®$_{2010\text{-}2011}$ and Prevnar 13®

	Expected value		Relative reporting ratio		EBGM	EB05
	Crude	Adjusted	Crude	Adjusted		
Fluzone®$_{2010\text{-}2011}$	17.9	10.7	2.28	3.84	3.36	2.44
Prevnar 13®	11.2	31.3	3.75	1.34	1.29	1.00

EB05 fifth percentile of the confidence interval for the EBGM, *EBGM* empirical Bayesian geometric mean

Table 5 US Vaccine Adverse Event Reporting System (excluding Fluzone®$_{2010\text{-}2011}$ reports) as of 10 December 2010: two-dimensional "febrile convulsion" preferred term results for vaccines given concomitantly with Fluzone®$_{2010\text{-}2011}$

Vaccine	EB05	EBGM
Prevnar 13®	0.88	1.18
M-M-R® II	1.65	1.74
ActHIB®	0.94	1.03
Recombivax HB®	0.56	0.65
VAQTA®	1.40	1.70
ProQuad®	1.61	1.96
VARIVAX®	1.01	1.08
HAVRIX®	1.34	1.56
DAPTACEL®	1.03	1.18
PedvaxHIB®	0.90	1.03
INFANRIX®	0.82	0.92
Tripedia®	0.94	1.05
Prevnar®	1.06	1.14
Pentacel®	0.60	0.77

EB05 fifth percentile of the confidence interval for the EBGM, *EBGM* empirical Bayesian geometric mean

baseline data mining (which served as an additional gauge of unexpectedness), were strategies adopted *a priori* to enhance the specificity of the 2010–2011 data mining surveillance plan.

The signal for febrile seizures after Fluzone®$_{2010\text{-}2011}$ identified in the 0- to 18-month age group of the US VAERS (inactivated) by age group analysis was not observed in the US VAERS (inactivated) analysis with all ages combined. Two elements might have contributed to a decrease in the relative reporting ratio and the empirical Bayesian geometric mean in the US VAERS (inactivated) analysis relative to the US VAERS analysis. First, this analysis excluded cases that had concomitant live vaccines, and the relative reporting ratio is sensitive to decreases in vaccine-event combination counts. Second, it has been noted that relative reporting ratios are proportional to the total number of reports in the database when all other factors are held constant [32]. The US VAERS analysis had more cases and more reports than the US VAERS (inactivated) analysis. The US VAERS (inactivated) by age group analysis met the EB05 >2 threshold because the expected count was dramatically reduced in the 0- to 18-month age subset (Table 6), while the majority (58 %) of inactivated US VAERS cases were retained. Beginning with the 2011–2012 Northern Hemisphere influenza season, FDA CBER utilized the overall US VAERS background for influenza vaccine data mining. This harmonized our data mining architecture with the architecture utilized for non-influenza vaccine data mining, and it allowed our pharmacovigilance group to avoid the limitations of database restrictions.

Data mining in VAERS detected an independent signal for febrile seizures after Fluzone®$_{2010\text{-}2011}$ with no independent signal after any concomitant vaccines. Nearly

Table 6 Influence of the inactivated background on report counts and resulting EBGM and EB05 values

	US VAERS	Inactivated US VAERS	Inactivated US VAERS by age group: 0–18 months
Total reports	299,563	177,353 (−41 %)	24,047 (−92 %)
Reports with Fluzone®$_{2010\text{-}2011}$ and febrile convulsion	41	31 (−24 %)	18 (−56 %)
EBGM	3.36	2.72	3.95
EB05	2.44	1.89	2.62

EB05 fifth percentile of the confidence interval for the EBGM, *EBGM* empirical Bayesian geometric mean, *VAERS* Vaccine Adverse Event Reporting System

identical crude counts of vaccine "febrile convulsion" PT pairs were noted for Prevnar 13® and Fluzone®$_{2010\text{-}2011}$, and there were 1,304 Prevnar 13® reports and 2,095 Fluzone®$_{2010\text{-}2011}$ reports. This resulted in a crude relative reporting ratio that was actually higher for the Prevnar 13®-febrile seizure pair than for the Fluzone®-febrile seizure pair. Comparison of the crude and adjusted relative reporting ratios demonstrates that adjustment played an important role in the calculation of the final EBGM. Since both vaccines were licensed and recommended for similar periods of time and there were no sex-specific usage differences, we infer that age was the strongest contributor to the adjustment. This finding demonstrates the value of a disproportionality reporting method that is able to adjust for a confounder that is associated with both administration of Prevnar 13® (and Fluzone®$_{2010\text{-}2011}$ to a lesser extent) and febrile seizures.

Due to concerns about febrile seizures after a southern hemisphere influenza vaccine, active surveillance in the US CDC Vaccine Safety Datalink (VSD) for febrile seizures was already underway [33]. As a result of the data mining finding in VAERS and a concurrent signal for febrile seizures after trivalent inactivated influenza vaccine in the VSD, additional VSD analyses were planned to determine attributable risks for febrile seizures and to examine the possible contribution of concomitant vaccinations. A subsequent joint signal evaluation in the VSD indicated an association with febrile seizures that was strongest when Fluzone®$_{2010\text{-}2011}$ and Prevnar 13® were concomitantly administered to children aged 12–23 months [34]. Potential explanations for differential results in the VSD and VAERS include possible under-reporting in VAERS, masking in VAERS data mining, and differential patterns of Fluzone®$_{2010\text{-}2011}$ and Prevnar 13® utilization in the VSD population relative to the source population for VAERS. Under-reporting and differential patterns of utilization in the source population for VAERS cannot be empirically tested in this passive surveillance database alone. However, when Fluzone®$_{2010\text{-}2011}$ reports were removed from the database, the independent Prevnar 13®-febrile seizure combination EB05 decreased from 1.00 to 0.88. Since the measures of disproportionate reporting did not increase with removal of Fluzone®$_{2010\text{-}2011}$, we conclude that masking did not play a significant role in our findings. Likewise, removal of Prevnar 13® from the database did not increase the EB05 for Fluzone®$_{2010\text{-}2011}$.

Data mining in VAERS has multiple limitations. False disproportionality findings could arise in VAERS from stimulated reporting (e.g., due to a publication) as well as from unique characteristics of products (e.g., recent licensure) or product-adverse event pairs (e.g., confounding by indication). Influenza vaccines may be additionally subject to a seasonality bias if an adverse event such as febrile seizures disproportionally occurs during the influenza season. Data mining findings may be further limited by several factors related to the use of coding terms as proxies for underlying events. PTs reflecting more readily identifiable symptoms/diagnoses (e.g., "mental status changes" rather than "acute disseminated encephalomyelitis" in the same patient) are more likely to be coded after VAERS data obtained early in the evolution of an adverse event is reviewed. Additional medical records that may result in revised coding are sought for VAERS reports associated with administration of any vaccine if the clinical situation is consistent with the regulatory definition of a serious adverse experience [35]. Enhanced surveillance processing activities enabling collection of additional medical records for certain products, product classes or adverse events without regard to the regulatory definition may introduce measurement bias through differential coding practices. Finally, MedDRA® hierarchy constraints may preclude identification of a common underlying pathophysiological process or components thereof. For example, a product might be associated with thrombosis, yet data mining EB05s for deep venous thrombosis or pulmonary embolism might not exceed 2.0.

Data mining analysis plans have been integrated into surveillance activities for all CBER-regulated vaccines. As our data mining capabilities evolve, we hope to have more precise and robust search strategies that can improve specificity and answer specialized questions. Our evaluation of febrile seizures could have been enhanced if we were able to define more appropriate age strata (e.g., a 6- to 24-month-old stratum, in which a large majority of febrile seizures occurred). Ongoing work will provide this capability in the near future. Furthermore, we could benefit from the ability to adjust analyses for symptom-onset interval (e.g., minimizing potential confounding from a

concomitantly administered measles-mumps-rubella-varicella vaccine known to also have an association with febrile seizures at a longer onset interval). Ideally, data mining could one day reliably enable further important *ad hoc* subset analyses using other data fields from the VAERS form to better characterize potential signals. Potential limitations notwithstanding, routine automated data mining can be an important hypothesis-generating tool that has demonstrated the capacity to enable the rapid detection of signals that might otherwise be missed by other pharmacovigilance practices. This case study describing the identification of a novel signal for febrile seizures after an influenza vaccine illustrates that Bayesian data mining can be used to detect a vaccine-adverse event signal as well as an age-specific signal for a given vaccine.

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