SHORT COMMUNICATION

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Effects of Stratification on Data Mining in the US Vaccine Adverse Event Reporting System (VAERS)

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Abstract

Background: Vaccines are administered differentially according to age and sex, and disease patterns also vary among people of different age and sex groups. Estimates of disproportionality should be calculated based on comparisons of groups that have a similar likelihood of receiving similar vaccines and experiencing similar adverse events, to prevent false disproportionality from occurring. Stratified empirical Bayesian (EB) methods have been compared with crude, but not stratified, proportional reporting ratios (PRRs) in their performance on adverse event data.

Objectives: (i) to implement stratification of PRR; (ii) to quantify and compare vaccine-event pairs that are highlighted by PRR and EB05 (the lower bound of the 90% CI of the EB geometric mean), for both crude and stratified; and (iii) to evaluate the effects of stratification by age and sex, in identifying adverse events that are accepted to be caused by vaccines.

Methods: We applied EB and PRR data mining methods to data from the US Vaccine Adverse Event Reporting System (VAERS). We stratified PRR and EB05 by age and sex. To study the effects of stratification, we compared the crude PRR and stratified PRR. We also assessed the crude EB05 and stratified EB05, and then compared the effects of stratification on EB05 and PRR.

Results: Stratification not only changed the number of vaccine-event pairs that were highlighted, but also changed which pairs were highlighted. There were 283 vaccine-event pairs that were highlighted by the crude EB05, but not the stratified; 12 that were highlighted by the stratified EB05, but not the crude; and 162 that were highlighted by both. Similarly, there were 701 vaccine-event pairs that were highlighted by the crude PRR, but not the stratified; 139 that were highlighted by the stratified PRR, but not the crude; and 895 that were highlighted by both. There were 1466 vaccine-event pairs in which the effect of stratification was different for EB05 and PRR.

Conclusion: To our knowledge, this is the first published analysis using stratified PRRs. In this analysis of passive surveillance data, stratification revealed and reduced confounding in EB and PRR, and also unmasked some vaccine-event pairs that the crude values did not highlight. Stratification should be applied if confounding is suspected. By decreasing the total number of highlighted vaccine-event pairs, stratification is likely to increase efficiency and therefore might reduce workload.

1. Background

Empirical Bayesian (EB) and proportional reporting ratio (PRR), as applied to vaccine safety monitoring, are data mining methods that attempt to identify adverse events that are reported more commonly for one vaccine than others. PRR compares proportions of reported adverse events for a particular vaccine with proportions for other vaccines.[1] An event with a higher proportion for a particular vaccine than for other vaccines might warrant further investigation. Some of the elevated values might require further evaluation to determine whether they are of sufficient concern to be 'signals' of possible vaccine reactions.[2] The EB methods also provide a measure of disproportionality of vaccine-adverse event pairs while also incorporating certain statistical adjustments.[3] Elevated data mining statistics do not necessarily reflect a causal relationship between a vaccine and an adverse event, but when combined with traditional methods of adverse event evaluation, they may be useful for generating hypotheses that can be tested with controlled study methods.[4-7]

The ability of EB methods to identify some known adverse events of drugs[3,8] and vaccines[9] has been demonstrated. In routine use at the US FDA, PRR has identified events of interest after smallpox,[10] typhoid,[11] and hepatitis A-B combination vaccines[12] from the Vaccine Adverse Event Reporting System (VAERS). Stratified EB values have been compared with crude, but not stratified, PRR in their performance on drug adverse event data.[13] Conclusions drawn from such an evaluation of the performance of one method compared with the other are limited. We sought to contribute to filling this apparent gap in the application of data mining on postmarketing adverse event surveillance data.

2. Objectives

The goals of this study were (i) to implement stratification of PRR; (ii) to quantify and compare vaccine-event pairs that are highlighted by the lower bound of the 90% CI (EB05) of the EB geometric mean (EBGM) and PRR, both crude and stratified; and (iii) to evaluate the effects of stratification by age and sex, in identifying adverse events that are accepted to be caused by vaccines.

3. Study Design

3.1 The Vaccine Adverse Event Reporting System (VAERS)

Established in 1990, VAERS is jointly managed by the FDA and Centers for Disease Control and Prevention (CDC) and receives 10 000–20 000 reports annually of adverse events following immunization. Uses of VAERS include detecting unrecognized adverse events, monitoring known reactions, and vaccine lot surveillance.[4,5] Priorities for analysis of VAERS data include evaluating new vaccines for unexpected adverse events; reports of death and other serious adverse events; and recognition and prevention of adverse effects.[7] Limitations

Count of reports	With COSTART *j*	Without COSTART *j*
With vaccine *i*	*a*	*b*
Without vaccine *i*	*c*	*d*

Fig. 1. Contingency table used to calculate the proportional reporting ratio (PRR) for vaccine *i*, and COSTART *j*. **COSTART** = Coding Symbols for a Thesaurus of Adverse Reaction Terms.

of spontaneous reporting systems, such as VAERS, include the inability to verify reported diagnoses easily, inconsistent data quality, under-reporting, inadequate denominator data and absence of an unvaccinated control group.[4,5] As a result of these limitations, analysis of VAERS data does not usually allow determination of a causal relationship between a vaccine and an adverse event.[6]

The data source used is all VAERS reports (n = 147 011) received from 1 July 1990 to 23 January 2003, encompassing 70 vaccine types and 989 adverse event terms coded using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTARTs).

3.2 Data Mining Methods

The PRR identifies conditions that constitute a larger proportion of reported events for a vaccine of interest, compared with all the other vaccines in the database. PRR is calculated as shown in figure 1.[1,14,15]

In this contingency table notation, the PRR for vaccine *i* and COSTART *j* is:

$$PRR_{ij} = \frac{a/(a+b)}{c/(c+d)}$$

A large PRR for a specific vaccine-COSTART pair indicates that the COSTART has been disproportionately reported for that vaccine.

To define a vaccine-event pair that is highlighted for further evaluation, we applied the screening criteria that Evans et al.[1] have proposed: count *n* (denoted as *a* in the contingency table) ≥3, PRR ≥2 and Yates-corrected χ^2 ≥4.

The EB method starts with the ratio of observed-to-expected adverse events:[14]

$$\frac{a/(a+c)}{(a+b)/(a+b+c+d)}$$

For purposes of detecting vaccine-event pairs that warrant further evaluation, the EBGM is the main statistic generated by DuMouchel's EB algorithm,[3] which 'shrinks' the observed-to-expected ratio, thereby reducing the effect of sampling variation in the data. The shrinkage is greatest when *n* is small. EB provides information about not only the disproportionality of a given association, but also its variability;[3,14] PRR alone provides only the disproportionality. Furthermore, EB takes into account multiple comparisons,[3,14] whereas PRR does not. Szarfman et al.[8] have used the EB05, instead of the EBGM, based on their experience that EB05 ≥2, "ensures with a high degree of confidence that, regardless of count size, the particular drug-event combination is being reported at least twice as often as it would be if there were no association between the drug and the event".[8] We use this cut-off of EB05 ≥2 to define vaccine-event pairs that are highlighted for further evaluation.

3.3 Stratification

Through stratification, traditional epidemiological analysis accounts for factors that are related to both the exposure and the outcome. It is plausible that such adjustment will be needed in data mining analysis. Vaccines are administered differentially according to age (e.g. children receive *Haemophilus influenzae* vaccine, or HIBV, but adults generally do not), and the spectrum of adverse events, signs, symptoms and diseases in children is different from that in adults (e.g. sudden infant death syndrome [SIDS] among children). Similarly, may influence vaccine administration (e.g. more men may receive anthrax vaccine because of their military deployment status), and background disease patterns differ between men and women (e.g. autoimmune condi-

tions are more common among women). These patterns may influence the vaccine-event pairs that are reported to VAERS. Accordingly, estimates of disproportionality should be calculated based on comparisons of groups that have a similar likelihood of receiving similar vaccines and experiencing similar adverse events to prevent false disproportionality from occurring. Stratifying by age and gender partly controls for such factors.[16]

In this paper, we compared the EB05 and PRR, both crude and stratified by age and sex. Methods for calculating summary EB05, including stratification, are described elsewhere.[8] To calculate summary PRRs for stratified analysis, we applied the Mantel-Haenszel method[17] and incorporated it into Statistical Analysis Systems (SAS) code (SAS version 9.1, Cary, NC, USA). For each age-sex stratum, a 2×2 contingency table of exposure (vaccine type) and outcome (COSTART) was created, and counts from all strata were used to calculate the stratified (weighted) value of PRR, as well as a summary χ^2 statistic.[17] Data were stratified by the age (<2, 2–17, 18–64, ≥65 years or unknown) and sex (female, male or unknown) listed on the VAERS report. The age strata were selected on the basis of both vaccine administration and adverse event patterns.

To study the effects of stratification by age and sex, we compared the crude PRR and stratified PRR. We also compared the crude EB05 and stratified EB05 values. We then assessed the effects of stratification on EB05 and PRR by displaying the results for known vaccine-event associations. The Vaccine Injury Table is a list of vaccine adverse event associations that the Institute of Medicine has determined are causal.[18] We operationalized these associations as vaccine-COSTART pairs and compared, for each data mining method, the crude and stratified data mining values for those pairs. Such operationalization is imperfect, since COSTARTs are applied without standardized definitions or diagnostic confirmation (e.g. 'arthritis') may refer to acute or chronic inflammation of joints). However, for the purpose of data mining, COSTARTs have been shown to be useful for highlighting associations that warrant further investigation.[9-12]

4. Results

Of 69 230 theoretical vaccine-event pairs (70 vaccines × 989 event terms), at the time of this analysis, VAERS contained 14 800 vaccine-event pairs with at least one report. Stratification not only changes the number of vaccine-event pairs that are highlighted, but also changes which pairs are identified (figure 2 and figure 3). For example, there are 12 vaccine-event pairs that are highlighted by the stratified EB05, but not the crude; 283 that are highlighted by the crude EB05, but not the stratified; and 162 that are highlighted by both (figure 2; figure 3, rows 2–4). Similarly, there are 139 vaccine-event pairs that are highlighted by the stratified PRR, but not the crude; 701 that are highlighted by the crude PRR, but not the stratified; and 895 that are highlighted by both (figure 2; figure 3, columns 2–4).

Figure 3 displays all 16 possible combinations of highlighting by PRR (both stratified and crude) and EB05 (both stratified and crude). The diagonal that

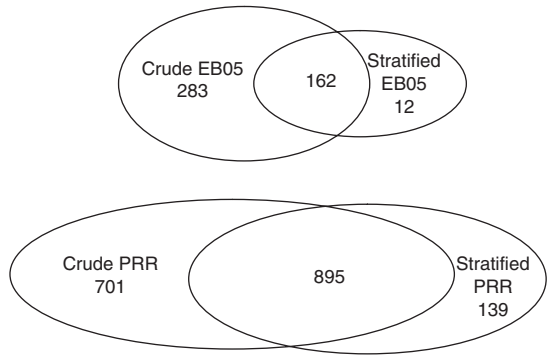

Fig. 2. Number of vaccine-event pairs that each method highlights for further evaluation. At a given threshold, stratification not only changes the number of vaccine-event pairs that are highlighted, but also changes which pairs are highlighted. **EB05** = the lower bound of the 90% CI of the empirical Bayesian geometric mean; **PRR** = proportional reporting ratio.

		PRR				
		Column 1 Crude not highlighted Stratified not highlighted	Column 2 Crude not highlighted Stratified highlighted	Column 3 Crude highlighted Stratified not highlighted	Column 4 Crude highlighted Stratified highlighted	Total
EB05	Row 1 Crude not highlighted Stratified not highlighted	13 065	139	592	547	14 343
	Row 2 Crude not highlighted Stratified highlighted	0	0	0	12	12
	Row 3 Crude highlighted Stratified not highlighted	0	0	108	175	283
	Row 4 Crude highlighted Stratified highlighted	0	0	1	161	162
	Total	13 065	139	701	895	14 800

Fig. 3. Number of vaccine-event pairs that are highlighted by the proportional reporting ratio (PRR) and the lower bound of the 90% CI (EB05) of the empirical Bayesian geometric mean. To define a vaccine-event pair for which the PRR is highlighted for further evaluation, we applied the screening criteria that Evans et al.[1] have proposed: n ≥3, PRR ≥2 and Yates-corrected χ^2 ≥4. To define a vaccine-event pair for which the EB05 is highlighted for further evaluation, we applied the cut-off of EB05 ≥2, as proposed by Szarfman et al.[8]

extends from column 1, row 1 to column 4, row 4 includes a total of 13 334 vaccine-event pairs for which stratification has the same effect on both PRR and EB05; these cells represent 90% of the total 14 800 vaccine-event pairs. For 13 065 (the vast majority), the crude PRR and crude EB05 do not highlight the pair as deserving further investigation, and stratification does not change that result in either method. There are no instances in which both of the stratified values highlight the pair but the two crude values do not (column 2, row 2). Stratification reduces the total number of highlighted pairs from 1596 to 1034 for PRR (35% reduction) and from 445 to 174 for EB05 (61% reduction). In 108 instances (column 3, row 3), the crude PRR and crude EB05 highlight the pair, but in both methods the vaccine-event pair is not highlighted after stratification. In 161 instances (column 4, row 4), crude and stratified PRR, as well as crude and stratified EB05, highlight the vaccine-event pair for further evaluation.

There are 1466 vaccine-event pairs for which either the crude or the stratified results for EB05 or PRR were discordant. In the first row, columns 2–4 reveal that PRR – whether stratified or not – highlights vaccine-event pairs that neither the crude EB05 nor stratified EB05 highlights. In contrast, no such effect is seen in rows 2–4 of the first column. Column 4 reveals that, even when both the crude and stratified PRR highlight a vaccine-event pair, discrepancies among crude EB05 and stratified EB05 exist: there are 12 pairs that the stratified EB05 highlights, but the crude does not, and there are 175 pairs that the crude EB05 highlights, but the stratified does not. Moreover, row 2 illustrates that, for 12 vaccine-event pairs, the stratified EB05 was highlighted, but the crude was not. Similarly, column 2 indicates that, for 139 vaccine-event pairs, the stratified PRR was highlighted, but the crude was not.

Table I lists specific examples of the effects of stratification on EB05 and PRR for vaccine adverse events that the Institute of Medicine has determined are causal.[18] For rotavirus vaccine and intussusception, as well as rubella vaccine and arthritis, both of the stratified values are lower than the crude, but are still highlighted for further evaluation. For diphtheria and tetanus toxoids adsorbed paediatric vaccine and anaphylaxis, as well as measles, mumps and rubella virus vaccine live (MMR) and thrombocytopenia, stratification decreases both EB05 and PRR;

Table I. Effects of stratification on the lower bound of the 90% CI (EB05) of the empirical Bayesian geometric mean and proportional reporting ratio (PRR) on selected vaccine adverse events that the Institute of Medicine has determined are causal[18]

Vaccine adverse event	n	EB05 crude	EB05 stratified	PRR crude	PRR stratified
Anaphylaxis					
DT	14	1.273	1.197	2.227[a]	2.16[a]
DTAP	43	0.474	0.642	0.577	0.791
DTP	38	0.384	0.583	0.464	0.698
HEP	153	1.012	0.931	1.225	1.098
IPV	25	0.415	0.567	0.558	0.767
MMR	98	0.793	0.914	0.928	1.125
TD	28	0.508	0.411	0.683	0.525
Arthritis					
MMR	183	0.721	1.248	0.782	1.548
MR	1	0.207	0.229	1.003	0.634
MUR	1	0.38	0.42	8.959	8.574
R	62	8.595[a]	4.479[a]	11.92[a]	6.532[a]
Brachial neuritis					
TTOX	1	0.407	0.428	26.11	13.42
Encephalitis					
DTAP	37	0.386	0.365	0.472	0.407
DTP	60	0.615	0.584	0.736	0.652
MMR	137	1.096	1.044	1.355	1.309
Encephalopathy					
DTAP	45	0.941	0.708	1.264	0.884
DTP	77	1.582	1.064	2.294[a]	1.468
MMR	61	0.898	0.797	1.153	0.987
Thrombocytopenia purpura					
M	1	0.226	0.321	1.200	1.506
MMR	127	1.894	1.495	3.125[a]	2.49[a]
MR	1	0.334	0.404	3.943	5.473
Poliomyelitis					
OPV	58	4.348[a]	2.619[a]	99.95[a]	185.8[a]
Intussusception					
RV	134	150.8[a]	54.43[a]	1513[a]	564.3[a]

a Highlighted for further evaluation.

DT = diphtheria and tetanus toxoids adsorbed paediatric; **DTAP** = diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed paediatric; **DTP** = diphtheria and tetanus toxoids and pertussis vaccine adsorbed paediatric; **HEP** = hepatitis B vaccine; **IPV** = inactivated polio virus vaccine; **M** = measles virus vaccine live; **MMR** = measles, mumps and rubella virus vaccine live; **MR** = measles and rubella virus vaccine live; **MUR** = mumps and rubella virus vaccine live; **OPV** = oral polio vaccine live; **R** = rubella virus vaccine live; **RV** = oral rhesus-based rotavirus vaccine live; **TD** = tetanus and diphtheria toxoids adsorbed adult; **TTOX** = tetanus toxoid.

both the crude and stratified PRR values are highlighted, but neither the crude nor stratified EB05 is. For diphtheria and tetanus toxoids and pertussis vaccine adsorbed paediatric and encephalopathy, the only data mining value that is highlighted is the crude PRR. For oral polio vaccine live and poliomyelitis, all four values are highlighted, but stratification reduces EB05 and substantially increases PRR.

Table II. Data mining values for individual strata: measles, mumps and rubella virus vaccine live (MMR) and arthritis[a]

Age group (y)	Female			Male			Unknown		
	n	PRR	χ^2	n	PRR	χ^2	n	PRR	χ^2
<2	15	2.997	8.38	13	2.645	5.798	2	1.721	0.031
2–17	22	0.805	0.536	17	0.767	0.603	0		
18–64	90	2.203	49.3	12	1.131	0.067	2	4.361	1.672
≥65	1	8.862	1.313	0			0		
Unknown	5	1.225	0.034	1	0.251	1.433	3	0.991	0.084

a The summary PRR for arthritis and MMR is 1.548 (n = 183, χ^2 = 28.04) and therefore does not meet the screening criteria of n ≥3, PRR ≥2, and χ^2 ≥4. However, for some of the age and sex strata, all three criteria are fulfilled.

PRR = proportional reporting ratio.

Table II displays the data mining values for age and sex strata for MMR vaccine and arthritis. Although the summary PRR does not meet the screening criteria, the values for females and males under 2 years old, as well as women 18–64 years old, fulfil all three screening criteria.

5. Discussion and Conclusions

EB methods have been compared with crude PRR in their performance on drug adverse event data.[13] To our knowledge, this is the first published analysis of the comparative effects of stratification on PRR and EB05 for the analysis of passive surveillance data. The possibility that stratification by potential confounders, such as age and sex, might improve the utility of data mining makes intuitive sense and deserves further exploration.

We sought to describe the effects of stratification on EB05 and PRR. The vast majority of vaccine-event pairs are not highlighted by either method, regardless of stratification. In addition, our results demonstrate concordance for 161 pairs that are highlighted by all four metrics (crude and stratified PRR, and crude and stratified EB05). There were 1466 vaccine-event pairs for which either the crude or stratified results were different for EB05 or PRR. In some cases, such as poliomyelitis after OPV, the effect of stratification on PRR and EB05 was opposite: stratification increased the PRR, but decreased the EB05, even though all four values highlighted the association. This disparity may relate to statistical differences between the methods.[14]

For both EB05 and PRR, stratification reduced the number of pairs that were highlighted. Of those pairs that were highlighted by the crude, more than one-third disappeared after stratification. By decreasing the total number of highlighted vaccine-event pairs, stratification likely increased efficiency and might therefore reduce workload. Stratification revealed and reduced confounding in EB05 and PRR; the disappearance of highlighted vaccine-event pairs after stratification suggests that age and sex are confounders for those associations. The finding that stratification highlighted some vaccine-event pairs that the crude values did not (12 for EB05 and 139 for PRR) suggests that unmasking or negative confounding can occur.

Data mining does not establish causality of adverse events,[2] nor does it always detect accepted vaccine adverse events (table I). PRR and other data mining statistics should not be interpreted or presented as 'relative risks' of specific vaccine adverse events. Data mining statistics should be utilized only for generating hypotheses that can be tested with controlled study methods.[19]

This analysis of passive surveillance data suggests that stratification should be applied to both PRR and EB data mining methods if confounding is suspected. Also, analysis of individual strata may reveal important patterns, particularly if there is a

large imbalance in the administration of vaccines or in the baseline susceptibility to a given condition. As we have demonstrated, the summary value for a data mining metric might fall below a given threshold, while the value for some age and sex strata might be elevated. The importance of periodic analysis and the ability to track changes over time has been emphasized.[20] Stratifying by the year of report may be considered in future analyses. With the recent introduction of several vaccines that are intended for adolescents, the selection of different age strata might also be desirable.

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