Real-Time Vaccine Safety Surveillance for the Early Detection of Adverse Events

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Background: Rare but serious adverse events associated with vaccines or drugs are often nearly impossible to detect in prelicensure studies and require monitoring after introduction of the agent in large populations. Sequential testing procedures are needed to detect vaccine or drug safety problems as soon as possible after introduction.

Objective: To develop and evaluate a new real-time surveillance system that uses dynamic data files and sequential analysis for early detection of adverse events after the introduction of new vaccines.

Research Design: The Centers for Disease Control and Prevention (CDC)-sponsored Vaccine Safety Datalink Project developed a real-time surveillance system and initiated its use in an ongoing study of a new meningococcal vaccine for adolescents. Dynamic data files from 8 health plans were updated and aggregated for analysis every week. The analysis used maximized sequential probability ratio testing (maxSPRT), a new signal detection method that supports continuous or time-period analysis of data as they are collected.

Results: Using the new real-time surveillance system, ongoing analyses of meningococcal conjugate vaccine (MCV) safety are being conducted on a weekly basis. Two forms of maxSPRT were implemented: an analysis using concurrent matched controls, and an analysis based on expected counts of the outcomes of interest, which were estimated based on historical data. The analysis highlights both theoretical and operational issues, including how to (1) choose appropriate outcomes and stopping rules, (2) select control groups, and (3) accommodate variation in exposed:unexposed ratios between time periods and study sites.

Conclusions: Real-time surveillance combining dynamic data files, aggregation of data, and sequential analysis methods offers a useful and highly adaptable approach to early detection of adverse events after the introduction of new vaccines.

Key Words: vaccine safety, active surveillance, sequential analysis, meningococcal vaccine, drug safety

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Concerns about the safety of vaccines and drugs introduced in recent years have highlighted the need to enhance systems for early detection of potential adverse events. Uncommon but serious adverse events have led to the withdrawal of both biologic and pharmacologic agents from the market. Examples include the discontinuation of rotavirus vaccine after reports of intussusception (a rare but serious form of bowel obstruction) in 1999 and discontinuation of rofecoxib after its association with cardiovascular events in 2004.[1–3]

Traditional postlicensure monitoring has entailed unavoidable delays between the first reports of a potential adverse event and the studies that formally evaluate whether vaccine recipients or drug users are at elevated risk. Reports are made to passive surveillance systems, including the Vaccine Adverse Events Reporting System (VAERS) of the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) and, for drugs, the FDA Adverse Event Reporting System. However, passive surveillance systems are prone to underascertainment and reporting bias, and rates of disease among vaccinated or unvaccinated persons cannot be calculated. Once a potential problem is identified, months if not years may be required before definitive studies can be completed.[4]

Population-based networks such as the CDC-sponsored Vaccine Safety Datalink (VSD) Project, the nation's active surveillance system for vaccine adverse events, hold promise to allow earlier identification of adverse events. Ideally, data that address safety questions should be tested as soon as they become available, and all available data should be used in every analysis. However, repeated statistical testing of accumulating data requires special methods. Sequential analysis

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methods are needed to detect safety problems as soon as possible with minimal false alarms.

Recent concerns about a new meningococcal conjugate vaccine (MCV) have added impetus to efforts to establish a real-time system for active vaccine safety surveillance. In early 2005, MCV was introduced for routine use nationally in all children age 11–12 years and adolescents age 14–15 years. By summer 2005, VAERS had received 4 reports of Guillain-Barre syndrome, a form of paralysis that is usually temporary, after MCV immunization. National alerts were issued and the Vaccine Information Statement used to educate parents about meningococcal vaccine was revised to mention these events.[5] As of September 2006, 15 cases in the 11–19 year age group had been reported to VAERS, and a comparison with background rates from the Healthcare Cost and Utilization Project suggested a small increased risk of GBS after MCV immunization.[6] These events have underscored the importance of timely, population-based safety monitoring for rare events after the introduction of new vaccines.

The aims of this article are to: (1) describe an ongoing real-time surveillance system in a health maintenance organization (HMO) with weekly generation and analysis of data; (2) describe how analyses are conducted using maximized sequential probability ratio testing (maxSPRT), a new statistical method; and (3) discuss this new surveillance system's potential in vaccine safety monitoring. We address the strengths and limitations of the system and highlight operational decisions for users of these types of systems, including the choice of appropriate outcomes and comparison groups.

METHODS

Design and Study Population

This section describes how the real-time vaccine safety surveillance system has been applied in an ongoing study of the safety of MCV. The study uses a prospective cohort design and includes all 8 VSD sites, which are geographically diverse HMOs or provider groups whose combined population includes approximately 1.7% of all US children younger than 6 years.[7] This article reports on the first 2 years of observation, during which approximately 120,000 doses of MCV were administered. Surveillance for the rarer outcomes of GBS and thrombocytopenia is expected to continue until 230,000 persons age 11-17.99 years in these health plans have been immunized, likely in late 2008 or early 2009.

Data Collection

All VSD sites use automated systems that track immunizations administered to members and can consistently capture health care use and diagnostic codes in outpatient, emergency department, and hospital settings. In 2005, each VSD site began creating dynamic data files that were updated weekly with vaccine, and outpatient and inpatient diagnosis information. For the current study, the VSD's Rapid Cycle Analysis Coordinating Center uses these dynamic files to create aggregate weekly files detailing: (1) MCV exposure, (2) preventive visit exposure, and (3) outcomes of interest (ie, all designated diagnoses received in either the outpatient or inpatient setting within 42 days after either exposure). The aggregated files contain the counts of MCV administrations, preventive visits, or prespecified outcomes that have occurred since the beginning of the study period in the following strata: calendar week of observation, patient age in years, sex, and VSD site.

Vaccinated and Control Groups

The time window of interest is 42 days after either MCV administration or a preventive visit. Receipt of MCV, either alone or concomitantly with other vaccines, results in a vaccinated (exposed) time window. A preventive visit at which MCV is not administered (even when other vaccines are administered) results in a control (unexposed) time window. An individual may undergo both a meningococcal vaccination and a preventive visit during the study and may thus contribute time windows to both the vaccinated and control groups.

Outcomes

We identified outcomes of interest by reviewing data from several sources: analyses from VAERS of adverse events after meningococcal polysaccharide vaccine (Jane Woo, MD, unpublished data, February 4, 2005); and articles on adverse events after meningococcal conjugate vaccine in other countries,[8] pneumococcal conjugate vaccine,[9] and MCV.[10–12] We selected outcomes meeting the following criteria:

1. Clinically well-defined; for example, "seizures" have relatively clear criteria for diagnosis, whereas "dizziness" is a symptom with only a vague clinical definition. Experience in previous pilot analyses suggested that vaguely defined outcomes would lead to false signaling;
2. Serious, causing potential harm significant enough to result in hospital-based use or follow-up visits to specialists;
3. Already observed via passive surveillance, so that the current maxSPRT analyses would be hypothesis testing rather than hypothesis generating;
4. Plausible as a consequence of vaccination based on either past associations with similar vaccines or biologic plausibility.

In this analysis, we evaluate 2 outcomes that meet all the above criteria: Guillain-Barre syndrome and facial paralysis (Bell palsy). For the purposes of evaluating our surveillance system and testing outcome definitions for future vaccine safety studies, we also evaluate 2 other outcomes: seizures and thrombocytopenia (low platelet count). However, a priori, we do not hypothesize that seizures or thrombocytopenia are biologically plausible consequences of MCV.

The Maximized Sequential Probability Ratio Test

Sequential analysis methods are needed to adjust for the multiple testing that occurs with weekly or continuous surveillance. Our surveillance system uses the new statistical method maxSPRT, which was developed as a refinement of sequential probability ratio testing (SPRT) for use in safety monitoring. Details are available in a working paper by Kulldorff et al[13] available upon request.

The classic SPRT method, developed by Wald in 1945, involves continuous or time-periodic statistical analysis of data as they are collected and tests the hypothesis that the relative risk (RR) is equal to 1, compared with an alternative hypothesis where the RR is a prespecified number different from 1.[14] Davis et al[7] at CDC tested SPRT for possible use in vaccine safety studies in 2002–2003. An important limitation of SPRT is that it requires the user to specify the RR to be tested in the alternative hypothesis as a single alternative (eg, RR = 10). A poor choice of RR may result in failure to support the alternative hypothesis, or a delay in signaling, even when the true RR differs from 1.[13,15]

To address this problem, VSD team members developed the maxSPRT.[13,16] With maxSPRT, the alternative hypothesis is that RR is more than one (a composite alternative). The log likelihood ratio (LLR) test statistic at time t is calculated as:

$$\mathrm{LLR}(t) = \max_{r>1} \ln\left(\frac{P(c_t|RR = r)}{P(c_t|RR = 1)}\right)$$

where c_t is the observed number of adverse events up until and including time t. The user must specify alpha, the usual measure of incorrectly finding a significant signal when there is no increased risk, and an upper limit on the length of surveillance, when the surveillance will be stopped if a signal has not yet been identified.

Analysis Using Matched Controls

We used 2 forms of maxSPRT in this study. The first compares outcomes in the vaccinated group (exposed time window) with those in a concurrent matched control group (unexposed time window), and estimates critical values based on a Bernoulli probability distribution. Our preliminary analyses found that strict matching by sex, age, health plan, and week of index event would result in about half of the vaccinated time windows being unmatched. So that the study data would yield a 1:1 ratio of observations (time windows) between the vaccinated and control groups, we matched control time windows to vaccinated time windows using hierarchical rules as follows: age within 2 years; week within 8 weeks; geographically proximate health plan; either sex; any health plan. In the analysis at week 106, which included all events cumulatively from week 1, approximately 99% of the vaccinated time windows were matched to control time windows.

Using Historical Data as the Reference

The second analysis uses historical expected counts based on historical data and estimates critical values based on a Poisson distribution. For this analysis, we used existing information to estimate the numbers of outcomes that would occur among exposed persons if there were no increase in risk. For Guillain-Barre syndrome, we used a rate of 1.4 cases per 100,000 person-years based on analyses of data from the Vaccine Safety Datalink Project and the Hospital Cost and Utilization Project.[17] For facial paralysis and thrombocytopenia, we analyzed VSD historical data to estimate incidence rates. We did not include seizures in the analysis using historical expected counts. Because seizures are more common than the other outcomes studied, the matched control analysis was felt to be sufficient to evaluate them. For each outcome, we calculated a 42-day incidence rate and multiplied this by the number of MCVs actually administered to generate expected counts.

Study Parameters and Critical Values

The null hypothesis is rejected the first time the LLR exceeds a critical value, B (ie, when $\mathrm{LLR}(t) > B$). To establish the critical value, it is necessary to specify: 1-tailed versus 2-tailed test, the alpha level (ie, 0.05, 0.01, or 0.001), the upper limit on the length of surveillance, and for the analysis using matched controls, the ratio of exposed to unexposed observations (ie, 1:1, 1:2, or 1:3). Critical values were generated via simulations and are available from tables provided by Kulldorff et al.[13]

For the analysis using matched controls, the upper limit, T, on the length of surveillance is specified in terms of the observed number of adverse events in the exposed and unexposed groups combined. With the historical comparison group, the upper limit instead is defined in terms of the expected number of adverse events under the null. Surveillance ends when either the LLR exceeds the critical value, at which time the null hypothesis is rejected, or when the upper limit T is reached, in which case the null hypothesis is not rejected.

In the current study of MCV, we specified an alpha of 0.05 for a 1-sided test. We chose upper limits on the length of surveillance by roughly estimating the number of adverse events that would be observed or expected in a 2-year period, based on the reasoning that serious adverse events after a new vaccine is introduced are usually identified within the first 2 years of its use. The upper limits for the concurrent analysis ranged from 10 observed adverse events for Guillain-Barre syndrome and thrombocytopenia to 15 for facial paralysis and 30 for seizures. For the historical analysis, the upper limits ranged from 1 expected event for Guillain-Barre syndrome and thrombocytopenia to 8 for facial paralysis. We chose a ratio of 1:1 exposed versus unexposed observations because there were not enough unexposed observations to yield a higher ratio. The resulting critical values ranged from 2.77 to 3.42.

Evaluation Using Historical Data

To illustrate how the system may perform, we applied the technique to historical data on rotavirus vaccination and intussusception, mimicking a real-time surveillance system. Figure 1 shows how LLR test value for intussusception in children younger than 8 months old would have changed during each week of surveillance. The critical value of 3.3 was based on an upper limit of 5 expected cases. The LLR would have exceeded the critical value in May 1999 after the 16th week of surveillance. This would have resulted in a signal at approximately the same time that more intussusception reports were first being recognized via the VAERS passive surveillance system.

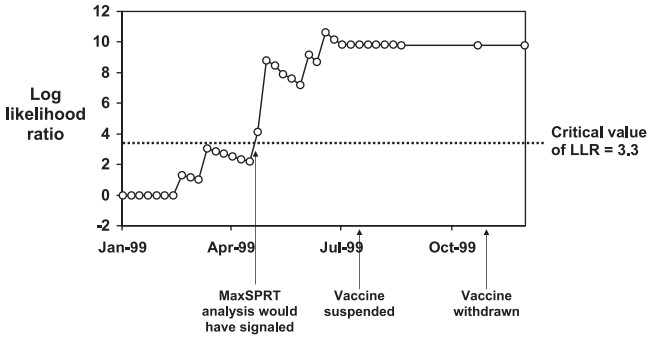

FIGURE 1. Example of signal detection using maximized sequential probability ratio testing to evaluate historical data on the risk of intussusception after Rotashield vaccination. The analysis compares the observed number of cases to the expected number of cases based on historical incidence. The *x-axis* shows how the LLR changes each week during the analysis. The critical value of 3.3 is calculated using a stopping limit of 5 cases. A signal would have been detected when the LLR exceeded the critical value in May 1999, about the same time as more reports of intussusception were first being recognized via passive surveillance systems.

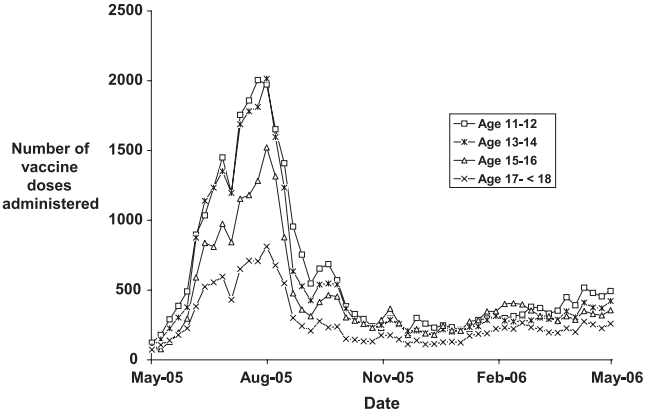

FIGURE 2. Number of meningococcal conjugate vaccine doses administered to 11- to 17-year-olds in health plans participating in the Vaccine Safety Datalink Project between May 1, 2005 and April 30, 2006.

RESULTS

Patterns of Vaccine Exposure and Preventive Visit Use

After 106 weeks of observation, 119,972 doses of MCV had been administered to children and adolescents age 11–17 years from the 8 health plans in the VSD Project. In the first year of surveillance, the numbers of MCVs administered were highest in July and August (Fig. 2). In age-stratified analyses, children age 11–12 years were administered the highest number of vaccinations, followed by adolescents age 13–14 years. In general, the seasonality of exposure was similar across the 8 VSD sites. Preventive visit use among those age 11–17 years followed a seasonal pattern similar to that of meningococcal vaccination, with the peak in July and August.

Analysis Using Concurrent Matched Controls

By week 106, no cases of Guillain-Barre syndrome had occurred in the vaccinated group, whereas 1 had occurred in the control group (Table 1). In the vaccinated group, the RR of facial paralysis was 0.83 and the RR of seizures was 0.60. For thrombocytopenia, 2 cases occurred in the vaccinated group and 1 in the control group, resulting in an LLR of 0.17. The LLR at week 106 failed to exceed the critical value at an alpha of 0.05 for any of the 4 outcomes studied.

Analysis Using Historical Expected Counts

By week 106, the number of cases observed in the vaccinated group failed to exceed the number expected for 2 of the 3 outcomes being analyzed (Guillain-Barre syndrome and facial paralysis) (Table 2). Two cases of thrombocytopenia were observed (the expected number was 0.73), resulting in an LLR of 0.74, which was less than the critical value of 2.86.

TABLE 1. Results of Concurrent Matched Control Analysis Using Maximized Sequential Probability Ratio Testing to Evaluate Outcomes After Meningococcal Conjugate Vaccination, Vaccine Safety Datalink Project Health Plans, 2005–2007

Outcome	No. Meningococcal Vaccinations in the Analysis for This Outcome*	Cumulative No. Cases in the 42 d After the Index Event (Meningococcal Vaccination or Preventive Visit) by Week 106		Relative Risk in Vaccinated Group	Log Likelihood Ratio†	Critical Value‡
		Vaccinated Group	Control Group			
Guillain-Barre syndrome	118,343	0	1	0	0	2.77
Facial paralysis	118,352	5	6	0.83	0	2.89
Thrombocytopenia	81,847	2	1	2	0.17	2.77
Seizures	118,364	12	20	0.60	0	3.39

*The number of meningococcal vaccinations in the analysis varied slightly among Guillain-Barre syndrome, facial paralysis, and seizures because the algorithm used to select a matched control for each vaccination was run separately for each outcome. The number of meningococcal vaccinations in the analysis for thrombocytopenia was lower because this outcome required laboratory data, which not all sites were able to contribute.

†One-sided test; when relative risk ≤1, the log likelihood ratio was set to 0.

‡Critical values at alpha = 0.05 were based on the following upper limits: for Guillain-Barre syndrome, 10; for facial paralysis, 15; for thrombocytopenia, 10; and for seizures, 30.

TABLE 2. Results of Historical Expected Count Analysis Using Maximized Sequential Probability Ratio Testing to Evaluate Outcomes After Meningococcal Conjugate Vaccination, Vaccine Safety Datalink Project Health Plans, 2005–2007

Outcome	No. Meningococcal Vaccinations in the Analysis for This Outcome*	Cumulative No. Cases in the 42 d After Meningococcal Vaccination by Week 106		Relative Risk in Vaccinated Group	Log Likelihood Ratio†	Critical Value‡
		Observed	Expected			
Guillain-Barre syndrome	119,972	0	0.18	0	0	2.86
Facial paralysis	119,972	7	7.50	0.93	0	3.42
Thrombocytopenia	83,204	2	0.73	2.73	0.74	2.86

*The number of meningococcal vaccinations in the analysis for thrombocytopenia was lower because this outcome required laboratory data, which not all sites were able to contribute.

†One-sided test; when relative risk ≤1, the log likelihood ratio was set to 0.

‡Critical values at alpha = 0.05 were based on the following upper limits: for Guillain-Barre syndrome, 1; for facial paralysis, 8; and for thrombocytopenia, 1.

TABLE 3. Example of Sequential Changes in Analysis Using Concurrent Matched Controls: Relative Risk and Log Likelihood Ratio for Facial Paralysis at Selected Time Points

Week	Cumulative No. Cases of Facial Paralysis in the 42 d After the Index Event (Meningococcal Vaccination or Preventive Visit)		Relative Risk	Log Likelihood Ratio*
	Vaccinated Group	Control Group		
12	2	0	NC	1.39
14	3	0	NC	2.08
16	3	1	3.0	0.52
28	4	1	4.0	0.96
29	4	2	2.0	0.34
37	4	3	1.33	0.072
44	4	4	1.0	0.00

*One-sided test; when relative risk ≤1, the log likelihood ratio was set to 0. The critical value is 2.89 for alpha = 0.05 and an upper limit of 20.

NC indicates not calculable because it would require dividing a number by zero.

Examples of Sequential Changes in the Analysis

We provide 2 examples to show how the LLR may change over repeated evaluations as the sequential analysis proceeds. In the analysis of facial paralysis using matched controls, the critical value of the LLR was 2.89 at an alpha of 0.05. At week 12, 2 cases occurred in the vaccinated group compared with no cases in the control group, for an LLR of 1.39 (Table 3 and Fig. 3). A third case occurred in the vaccinated group during week 14, with an increase in LLR to 2.08. However, in week 16, a case of facial paralysis occurred in the control group, reducing the LLR to 0.52, and in subsequent weeks, more cases of facial paralysis occurred in the control group than in the vaccinated group, resulting in an LLR of 0 by week 44. Hypothetically, the LLR would have been different if the fourth case of facial paralysis had occurred in the vaccinated group instead of the control group. If this had happened and there had been 4 cases in the vaccinated group and 0 in the control group at any point in time, the LLR would have increased to 2.77. If a fifth case had occurred in the vaccinated group with zero cases in the control group, the LLR would have increased to 3.47, exceeding the critical value.

In the analysis of thrombocytopenia using historical expected counts, 1 case occurred in the vaccinated group during week 12, resulting in an LLR of 1.58 (Table 4). As more weeks elapsed, no additional cases occurred, and the number of expected cases increased, causing the LLR to decrease. Hypothetically, if 2 cases instead of 1 had occurred during week 12, the LLR would have been 4.45, exceeding the critical value at an alpha of 0.05. If 3 cases had occurred during week 12, the LLR would have been 7.86, exceeding the critical value at an alpha of 0.001.

DISCUSSION

This study demonstrates the usefulness of a new system for real-time, active surveillance of vaccine safety in defined populations. We have implemented this system in an ongoing analysis of MCV, for which early detection of a rare and serious adverse event, Guillain-Barre syndrome, has national significance. The advantage of this system, which combines dynamic data files and a new method for sequential analysis, is that it enables weekly or continuous evaluation of accumulating data and looks for any increase in RR.

The unique advantage of using large, linked computerized databases with sequential analysis is this system's ca-

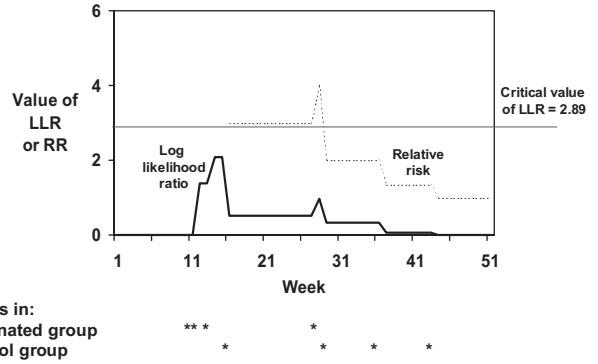

FIGURE 3. Changes in LLRs in the analysis of meningococcal conjugate vaccine using concurrent controls to evaluate the outcome of facial paralysis. The solid line depicts the LLR, which changes as events occur in the vaccinated and control groups as indicated beneath the *x-axis*. The critical value of the LLR is 2.89 at an alpha of 0.05. The dashed line depicts the relative risk.

TABLE 4. Example of Sequential Changes in Analysis Using Historical Expected Counts: Relative Risk and Log Likelihood Ratio for Thrombocytopenia at Selected Time Points

	Cumulative No. Cases of Thrombocytopenia in the 42 d After Vaccination			
Week	Observed	Expected	Relative Risk	Log Likelihood Ratio*
12	1	0.083	12.10	1.576
24	1	0.164	6.08	0.970
36	1	0.205	4.88	0.790
48	1	0.238	4.20	0.674
52	1	0.253	3.96	0.628

*One-sided test; when relative risk ≤1, the log likelihood ratio = 0. The critical value is 2.86 for alpha = 0.05 with an upper limit of 1.

pacity for early detection of adverse events in defined populations where ascertainment of medical events is relatively complete. Events in the approximate range of 1 per 1000 to 1 per 50,000 can be detected. The real-time aggregation of data described here makes the system well-suited to collaborative surveillance efforts by networks of sites, because the only data that must be shared are the weekly (or other periodicity) counts for each of the age, sex, and outcome strata. Thus, concerns about sharing of confidential or proprietary data are largely avoided.

We found that the 2 alternative forms of maxSPRT analysis, using matched controls or historical expected counts, had complementary strengths and weaknesses. Analysis using matched controls allowed us to use concurrent comparison groups, reducing the likelihood of false signaling or missed signals due to secular trends in disease, diagnostic patterns, or coding criteria. However, analysis using matched controls has important limitations. In this study, the number of available controls was limited, and this problem may be worse for vaccines that are adopted more rapidly or in narrower age groups, such as infant vaccines that are administered at 2, 4, and 6 months of age. Defining an appropriate control group required careful evaluation of potential differences from the vaccinated group, as well as testing of many alternative algorithms for matching. The lower risk of seizures in the control group than in the vaccinated group suggests that the control group may have been healthier than the vaccinated group. In addition, for a rare adverse event, analysis using matched controls may not provide the earliest possible signal because it only compares the numbers of events in the exposed and unexposed groups, although the number of rare events observed early in surveillance should be low.

Analysis based on historical expected counts addresses this problem by using information about the projected rate of rare events from existing data. This allows earlier identification of a small number of unusual events among vaccine recipients. However, the use of historical comparisons has important limitations. Secular trends in disease, or in diagnostic or coding practices, may lead to false signaling or failure to identify a true signal. This problem is especially important for exposures such as influenza vaccination, for which both the exposure and the outcomes of interest vary greatly among years and seasons.

This study highlights several other issues surrounding use of real-time surveillance systems. Outcomes that are clearly defined and acute in onset are most appropriate for analysis with maxSPRT, because the method is designed for early detection of potential adverse events. Outcomes that are broadly defined may lead to dampening of true signals, whereas outcomes with insidious onset are likely to require review of medical records to establish whether their onset occurred before or after vaccination. In addition, common adverse events have usually already been identified in prelicensure randomized controlled trials, limiting their appropriateness for analysis with maxSPRT. Another limitation of the surveillance system is that some VSD sites must rely on claims data for hospital-based diagnoses, so the dynamic data files may have lags of up to several months in the completeness of this type of data.

Another limitation of maxSPRT is that it is not designed to provide a definitive answer about whether a vaccine or drug causes an adverse event. Associations identified via maxSPRT will need further study to determine whether they are real or spurious. For example, in the ongoing study of MCV, we have proposed to follow up signals with a minimum RR of 2.0 at an alpha of 0.05. To do this, we will use secondary definitions of exposed and unexposed groups, evaluate temporal clustering of the outcome after vaccination using a temporal scan statistic, conduct analyses stratified by VSD site, conduct reviews of medical records or reviews using clinical experts to evaluate the findings, and/or design and conduct further studies using case-control or other designs.

The maxSPRT method holds promise for broad application. It could be useful not only in vaccine safety studies, but also during drug safety monitoring, when analysts could use it to identify a predetermined set of outcomes of interest for all drugs based on the major adverse reactions that most

commonly lead to drug withdrawals. Each new drug could be monitored for these outcomes and for problems either associated with the drug's class or identified during prelicensure evaluation.

We are currently assessing the use of maxSPRT in drug safety monitoring.[18] Drug safety studies entail several challenges beyond those encountered in vaccine safety studies. These include the need to define patterns of medication use (eg, new, chronic, intermittent); allowance for misclassification of exposure that may arise from various causes (eg, failure to adhere to dosing routine); and adjustment for comorbidities, disease severity, and concurrent medications. In addition, because drugs treat specific conditions, the pool of users for a new medication is limited and unique, and users may differ from nonusers in important ways, both observable and unobservable. Other complications of drug safety studies include use of a drug for multiple indications, off-label drug use, and potential differences between early and late adopters.

We believe that real-time surveillance systems combining dynamic data files, aggregation of data, and sequential analysis methods offer a useful and highly adaptable approach to early detection of potential adverse events after the introduction of new vaccines, and possibly new drugs. Such systems can be applied in widespread settings to allow rapid evaluation of the experiences of many exposed individuals.

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