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Meningococcal conjugate vaccine safety surveillance in the Vaccine Safety Datalink using a tree-temporal scan data mining method

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Abstract

Purpose: The objective of our study was to conduct a data mining analysis to identify potential adverse events (AEs) following MENACWY-D using the tree-temporal scan statistic in the Vaccine Safety Datalink population and demonstrate the feasibility of this method in a large distributed safety data setting.

Methods: Traditional pharmacovigilance techniques used in vaccine safety are generally geared to detecting AEs based on pre-defined sets of conditions or diagnoses. Using a newly developed tree-temporal scan statistic data mining method, we performed a pilot study to evaluate the safety profile of the meningococcal conjugate vaccine Menactra® (MenACWY-D), screening thousands of potential AE diagnoses and diagnosis groupings. The study cohort included enrolled participants in the Vaccine Safety Datalink aged 11 to 18 years who had received MenACWY-D vaccination(s) between 2005 and 2014. The tree-temporal scan statistic was employed to identify statistical associations (signals) of AEs following MENACWY-D at a 0.05 level of significance, adjusted for multiple testing.

Results: We detected signals for 2 groups of outcomes: diseases of the skin and subcutaneous tissue, fever, and urticaria. Both groups are known AEs following MENACWY-D vaccination. We

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CONFLICT OF INTEREST

None declared.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

also identified a statistical signal for pleurisy, but further examination suggested it was likely a false signal. No new MENACWY-D safety concerns were raised.

Conclusions: As a pilot study, we demonstrated that the tree-temporal scan statistic data mining method can be successfully applied to screen broadly for a wide range of vaccine-AE associations within a large health care data network.

Keywords

adverse events; Bell's palsy; Menactra; pharmacoepidemiology; post-licensure

1 | INTRODUCTION

Post-licensure vaccine safety surveillance is an essential component of any vaccination program and has important implications for immunization policy. Although pre-licensure human clinical trials evaluate vaccine safety, these usually have limited sample size, only assess otherwise healthy individuals. Therefore, rare adverse events (AEs), and AEs only occurring in a special sub-population may not be detected until a vaccine is widely used in the general population. For example, in 1999, post-marketing surveillance detected an excess risk of intussusception following the Rotashield® vaccine, which led to the withdrawal of the vaccine from the market shortly after it was licensed and recommended for public use.[1]

Current vaccine safety surveillance systems include both passive and active surveillance activities. The Vaccine Adverse Event Reporting System (VAERS) is a passive surveillance system which routinely provides analysis and data mining reports.[2–4] However, VAERS has important limitations, including under-reporting bias and incomplete information inherent to all passive reporting systems.[5,6] Active surveillance using rapid cycle analysis has also been regularly performed within the CDC's Vaccine Safety Datalink (VSD) project to sequentially monitor the safety of new vaccines or the safety of established vaccines when changes are made to Advisory Committee on Immunization Practices recommendations for that vaccine.[7–9] Although rapid cycle analysis has some advantage for near real-time detection of an AE signal, the standard practice has involved pre-specifying a relatively small number of AEs in a fixed risk interval before beginning the surveillance; thus, potential AEs that are not pre-specified for screening or are outside of the predefined risk interval will not be detected.

The tree-temporal scan method was recently developed for vaccine and drug safety surveillance in situations where a wide range of potential AEs defined with different levels of specificity can be actively monitored simultaneously.[10,11] For example, using this method, we can find out whether a vaccine causes a very specific reaction such as febrile convulsion (International Classification of Diseases, Ninth Revision (ICD-9) code 780.31) or a broader group of related AEs such as convulsions (ICD-9 code 780.3). Pilot studies of the tree-temporal scan method have been conducted by the Food and Drug Administration Mini-Sentinel investigators to monitor potential AEs following HPV vaccines,[12] and they found 2 expected statistical signals (cellulitis and abscess of arm, other complication of surgical and medical procedures).

Meningococcal conjugate vaccine (Menactra®, MENACWY-D) was approved for public use by Food and Drug Administration in January 2005. Subsequently, the Advisory Committee on Immunization Practices recommended that this vaccine be given routinely to 11 to 12-year-olds with a booster dose at age 16. In addition to local reactions, there have been reports of GBS occurring within 6 weeks after vaccination with MENACWY-D.[13] One other study found an increased risk for Bell's palsy in subjects receiving concomitant vaccines including MENACWY- CRM.[14] No other potential AEs following Meningococcal conjugate vaccines have been identified.

The objective of our study was to conduct a data mining analysis to identify potential AEs following MENACWY-D using the tree-temporal scan statistic for pre-adolescents and adolescents in the VSD population and demonstrate the feasibility of this method in a large distributed safety data setting like VSD.

2 | METHODS

2.1 | Study population

The study population included individuals aged 11 to 18 years old with a MENACWY-D vaccination record who were continuously enrolled in 1 of 6 VSD sites during January 1, 2005 through December 31, 2014. The 6 participating VSD sites were as follows: Kaiser Permanente of Northern California, Oakland, California (KPNC); Kaiser Permanente of Colorado, Denver, Colorado (KPC); Marshfield Clinic Research Foundation, Marshfield, Wisconsin (MFC); Northwest Kaiser Permanente, Portland, Oregon (NWK); Group Health Cooperative, Seattle, Washington (GHC); and Kaiser Permanente of Southern California, Pasadena, California (SCK). Members must have been enrolled for at least 183 consecutive days prior to vaccination and 56 days after vaccination to be eligible for this study.

2.2 | Exposure

MENACWY-D vaccination was identified using the standard CVX code "114." For the reason of simplicity, only the first vaccine dose for each eligible individual was included in the analysis. We considered a MENACWY-D dose to be a first dose if there was no prior record of a MENACWY-D dose for that individual as far back as his/her 11th birthday.

2.3 | Diagnosis tree

The tree-temporal scan data mining method is conducted based on a predefined tree structure. In this study, we used a hierarchical tree structure defined by the Multi-Level Clinical Classification Software (MLCCS) (https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp). The MLCCS is a diagnosis and procedure categorization scheme for ICD-9 codes. Four levels exist in this version of MLCCS. The first and broadest of the 4 levels contains 18 body-system categories. We added a fifth level containing the individual ICD-9 diagnosis codes. The fourth MLCCS level was linked to particular ICD-9 codes. In other words, we used a hybrid of the structure imposed by both ICD-9 and MLCCS. With the tree-temporal scan method, we performed the temporal scan statistic testing for each of the many overlapping branches of the tree and for each risk interval of the outcome, adjusting for multiple testing.

2.4 | Incident diagnoses

The outcomes of interest were any incident adverse event diagnosis or diagnosis grouping following MENACWY-D vaccination. A diagnosis was considered to be an incident diagnosis if it was observed either in the inpatient, outpatient, or emergency department setting during the 1 to 56 days following vaccination and if there was no other similar diagnosis (ie, same diagnosis code in the third-level branch of the MLCCS diagnosis tree) in any setting during the 183 days prior to the AE occurrence. We defined risk windows as any possible combinations of intervals that start 1 to 21 days after vaccination and end 2 to 42 days later, with a minimum window length of 2 days and a maximum window length of 28 days. We excluded day zero (day of vaccination) from the analysis in order to remove the diagnoses that are often recorded by the health care provider on the same day as the vaccination day to note pre-existing conditions. The comparison window comprised those remaining days within the 1 to 56 follow-up period but outside of the risk window. The diagram in Figure 1 shows 2 examples of possible risk windows and comparison windows.

2.5 | Conditional tree-temporal scan statistic

The conditional tree-temporal scan statistic[12] was used to identify any potential AEs following MENACWY-D vaccination in any potential risk window. With this method, under the null hypothesis, conditioned on the total number of cases for each AE in the follow-up period, we assume all AEs have the same probability of occurring on any particular day. The probability for an AE to occur on a day equals the total number of AEs on that day divided by the total number of AEs during the entire follow-up period. This method makes within-person comparisons, and therefore all time-invariant confounders (such as race, sex, site, etc.) were self-adjusted. The conditional tree-temporal scan test statistic is analogous to a Poisson generalized log likelihood ratio (LLR) test statistic. The formula is presented as

$$\mathrm{LLR} = \mathrm{I}(c > u)\,(c \ln[c/u] + (N - c) \ln[(N - c)/(N - u)])$$

where n is the number of observed cases for a specific AE, c is the number of observed cases in the risk window for that AE, and N is the total number of cases in the follow-up period summed over all AEs. u is the expected number of cases under the null hypothesis, which is u = nz/N, where z is the number of cases in the risk interval summed over all AEs. I() is an indicator function which is equal to 1 if the number of observed cases is greater than the expected, or 0 otherwise.

This test statistic was calculated for each AE and each possible risk interval. Because the distribution of the test statistic is unknown analytically, there is no mathematical formula available to calculate a P-value. Instead, we used Monte Carlo simulation to generate 99 999 random datasets to obtain the empirical distribution of the test statistic under the null hypothesis. Datasets were generated in a way that the total number of AEs on any specific day, summed over all ICD-9 codes, in each dataset was the same as in the real data set. Randomization was conducted by randomly permuting the days and the ICD-9 code, keeping the total number of AE cases fixed on each day.[12,15] For each generated dataset, we calculated the LLR for each AE and each possible risk interval in the same way as we calculated it using the real dataset. The maximum LLR was found for each AE among

all possible risk intervals calculated from real data and generated data. We then ranked the maximum test statistic from real dataset among all datasets. The Monte Carlo *P*-value was obtained by the formula $P = R/(99999 + 1)$, where R indicated the rank. Because we compare the test statistic generated from real dataset with test statistics generated from all other random datasets under the null hypothesis, this method inherently adjusts for the multiple testing due to evaluating many potential AEs, AE groupings, and risk intervals.[12]

The ratio of observed to expected (O/E) of AE outcome occurrences was also derived using this method. The analysis was implemented using treeScan software.[16]

2.6 | Signal evaluation and validation

We conducted post-hoc tree-temporal scan analyses for AEs following well-care visits as control outcomes when MENACWY-D was not administered. The rationale behind this is that common minor symptoms such as skin or eye-related problems are often revealed and generate referrals during the same well-care visits for adolescents, whether or not MENACWY-D is administered. If we found a signal for an AE following well-care visits when MENACWY-D was not given, this AE was excluded in the primary analyses. In other words, we can use signals following well-care visits without MENACWY-D administered to better understand the baseline expectation for AEs that were detected.

We identified well-care visits for children aged 11 to 18 years via ICD-9 codes V20.2, V70.0, V70.3, V70.5, and V70.9. The risk and comparison windows following well-care visits were the same as defined earlier.

3 | RESULTS

A total of 1 253 403 first doses of MENACWY-D were included in the analysis. Results for AEs following MENACWY-D are presented in Table 1. Out of 2 209 116 (4046 AEs × 546 risk intervals) AE-risk interval combinations, 38 were significant with *P*-values <0.05. Based on the MLCCS tree structure, those 38 significant outcomes belong to these broad groups: (1) disease of the nervous system and sense organs (Figure 2; branch 6); (2) disease of the skin and subcutaneous tissue (Figure 3; branch 12); (3) signs and ill-defined conditions and factors influencing health status (Figure 4; branch 17); (4) diseases of the respiratory system (Figure 5; branch 8); and others (including infectious and parasitic disease, diseases of digestive system, disorders of lipid metabolism, and other abnormal clinical findings). Among the 38 significant outcomes, a majority had a ratio of observed to expected (O/E) AE outcome occurrences between 1 and 3, except for unspecified erythematous condition (ICD-9 code 695.9) with an O/E ratio of 23.62, cellulitis, and abscess of upper arm and forearm (ICD-9 code 682.3 and its corresponding upper level MLCCS code 12.1.1.3) with an O/E ratio of 19.42, and other ill-defined and unknown causes of morbidity and mortality (ICD-9 code 799.8) with an O/E ratio of 8.69.

A subset of Table 1 results designated with a star sign (*) beside the MLCCS or ICD-9 code represents signals following MENACWY-D vaccination but not following well-care visits (without MENACWY-D vaccination). Only 10 outcomes were significant with *P*-values <0.05. According to the MLCCS hierarchical tree, those 10 outcomes belong to 1 of these

categories: diseases of the skin and subcutaneous tissue (Figure 3; branch 12), signs and ill-defined conditions and factors influencing health status (Figure 4; branch 17), and diseases of respiratory system (Figure 5; branch 8). More specific descriptions of the signals in these 3 groups are listed below.

3.1 | Diseases of the skin and subcutaneous tissue (branch 12)

Within branch 12, "diseases of the skin and subcutaneous tissue," there were signals at 4 different levels (Table 1) with *P*-values ≤0.001. All these signals occurred during a risk window of 2 to 3 days after MENACWY-D vaccination. Results are identical for ICD-9 code 682.3 and MLCCS code 12.1.1.3. The majority of cases for 12.1.1.7 came from ICD-9 code 682.9 (157 out of 162 cases). Therefore, 209 cases on the finest level with ICD-9 code 682.3 and 682.9 appear to be driving the branch 12 signals. ICD-9 codes 695.9 and 682.3 have the highest O/E ratio, 23.6 and 19.4, respectively.

3.2 | Signs and ill-defined conditions and factors influencing health status (branch 17)

We observed 47 cases of fever (780.6) on days 1 to 2 following MENACWY-D with an O/E of 3.33. However, the broader upper level 17.1.2.00, "fever of unknown origin" which includes ICD-9 codes 780.6, 780.60, and 780.61 did not signal. In addition, urticaria signaled with 229 cases on days 4 to 14, with an O/E ratio of 1.71 and a *P*-value <0.001. However, the upper level 17.1.9.00 "allergic reactions," which includes 72 finer level ICD-9 codes, did not signal.

3.3 | Diseases of respiratory system (branch 8)

Only 1 node (8.5; "pleurisy, pulmonary collapse") within branch 8 signaled (*P*-value = 0.023, O/E ratio = 3.1). Forty-eight cases in the window 21 to 32 days after MENACWY-D vaccination contributed to this signal. ICD-9 codes 511.0 ("pleurisy without effusion or current tuberculosis"), 518.0 ("atelectasis"), and 512.8 ("pneumothorax, spontaneous") contributed the majority of cases. However, none of the codes on the lower levels with more specific symptoms in this branch, such as 8.5.1, 8.5.2, and ICD-9 codes of 511.0, 518.0, and 512.8, signaled (Figure 5).

4 | DISCUSSION

In this study, we demonstrated that the tree-temporal scan data mining technique can be successfully used in a large electronic database, such as the VSD, to monitor vaccine safety. We examined more than 1.2 million recipients of first dose of MENACWY-D and identified 3 groups of AE signals occurring within 42 days of MENACWY-D vaccination. The first 2 AE groups ("skin and subcutaneous tissue infections", "fever and unspecified urticarial") are expected outcomes following vaccination.[17] For the third AE group which signaled ("pleurisy"), we hypothesized that there may be patients with these diagnostic codes who presented following a traumatic injury to the chest (eg, motor vehicle accident) or other pleurisy-causing conditions such as pneumonia. Therefore, we performed post-hoc exploration and searched for any diagnosis codes 60 days prior to the diagnosis of pleurisy. Among 48 cases, we identified 29 (60%) patients who had ICD-9 diagnosis codes for conditions that could cause pleurisy, including accident-related trauma, pneumonia, asthma,

cardiac disease, bronchitis, abdominal injury, appendicitis, and surgery. It seems plausible that pleurisy is a false signal, considering that there is a lack of biological plausibility for pleurisy to result following this vaccination. However, it may need further investigation in future studies.

The present study has several strengths. First, we identified 2 major groups of signals, and they both were previously identified AE associations with MENACWY-D.[17] The detection of previously observed associations provides support that the conditional tree-temporal scan method potentially can be reliably used to detect specific vaccine-AE associations. Second, whereas previous tree-temporal scan data mining studies only included inpatient data,[18] we included data from inpatient, emergency department, and outpatient files, which improved study power. Third, the VSD distributed data model[19] and the EMR (electronic medical records) database allowed us to extract detailed individual level data to follow up on detected associations. Importantly in the VSD, access to the patient's complete EMR is available for review if we need to validate the patient's diagnosis and to establish that there is an incident outcome. Fourth, we analyzed data for AEs following both vaccination and well-care visits without vaccination, allowing us to understand the baseline rate of the outcomes diagnosed following well-care visits without vaccination and eliminate them from consideration as true signals (eg, eye-related disorders/illnesses).

There are some limitations of this study. First, we only evaluated AEs following the first dose of MENACWY-D vaccine and during the first 6 weeks following vaccination. If there are adverse reactions that follow the booster dose(s) of MENACWY-D or manifest much later, we could not detect that. Second, this method lacks the capability to adjust for all time-varying confounders automatically.[12] However, we consider this data mining method is an approach to generate hypothesis(ses). Further investigation that takes time-varying confounders into account can be performed through rigorous traditional epidemiological studies. Third, patients with and without MENACWY-D vaccination after well-care visit may differ. If these differences are associated with AEs, it may be problematic to use patients without MENACWY-D vaccination as a control cohort for eliminating signals in the main analyses. Fourth, although our study shows the application of the tree temporal scan method as a hypothesis generating tool for MENACWY-D vaccine safety surveillance, applying this method to additional vaccines would provide strong evidence of the reliability of this method. Fifth, the rule we defined for determining incidence diagnosis (no previous diagnosis code on the third level within the past 183 days) may apply poorly to some AEs. Eg, if a patient had a fever 2 days following MENACWY-D, but also had a fever 5 months before this incidence, this AE of fever would be excluded from analysis because it was not considered as a new episode. Therefore, some truly incident cases were not captured using this rule. On the other hand, for certain chronic or long-lasting conditions, there is no guarantee that a prevalent condition will have been mentioned at a visit in the previous 6 months. A potential refinement of this design for the future studies is to tailor the incidence determination rules to each class of outcomes.

In summary, we identified 2 expected safety signals within 42 days of MENACWY-D vaccination using the tree-temporal scan data mining approach. We suspect that the third significant association was not a true signal. Overall, our findings provide reassurance

that there is no evidence to suggest unexpected early onset AEs following MENACWY-D vaccine in the age group we studied. Because this data mining approach mainly serves for hypothesis generation, rigorous epidemiological studies may be needed for further validation of any signals. We also plan to develop and implement routine tree-temporal data mining applications for other vaccines in the VSD.

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KEY POINTS

- Monitoring adverse events (AEs) following vaccination is a critical activity in post-licensure vaccine safety surveillance.
- The tree-temporal scan statistic was used in this study to identify statistical associations of AEs following the meningococcal conjugate vaccine Menactra (MENACWY-D).
- Findings in this study provide reassurance that there is no evidence to suggest unexpected early onset AEs following MENACWY-D vaccine.
- This study demonstrated that the tree-temporal scan data mining method can be applied to screen for a wide range of vaccine-AE associations simultaneously.

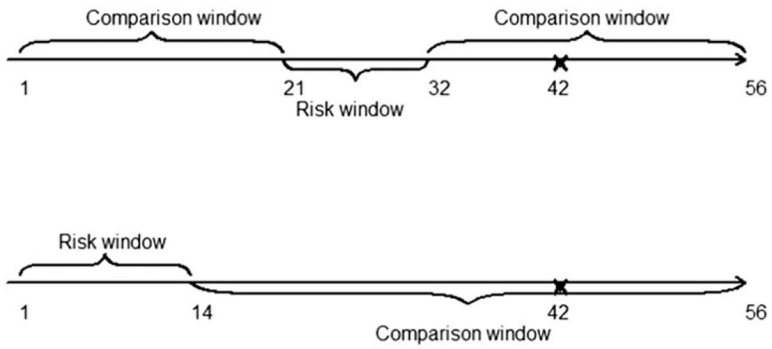

FIGURE 1.

A diagram illustrating possible risk windows and comparison windows during 1 to 56 study period (**X**: maximum day for risk windows)

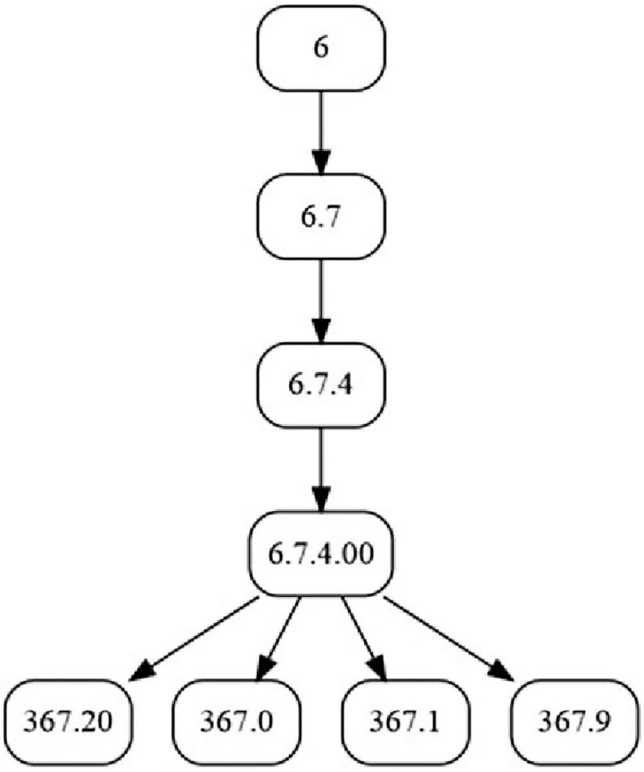

FIGURE 2.
A hierarchical tree for branch 6 (disease of the nervous system and sense organs) that includes statistical signals for nodes in Table 1 (the first 4 levels are MLCCS codes; the last level is ICD-9 code)

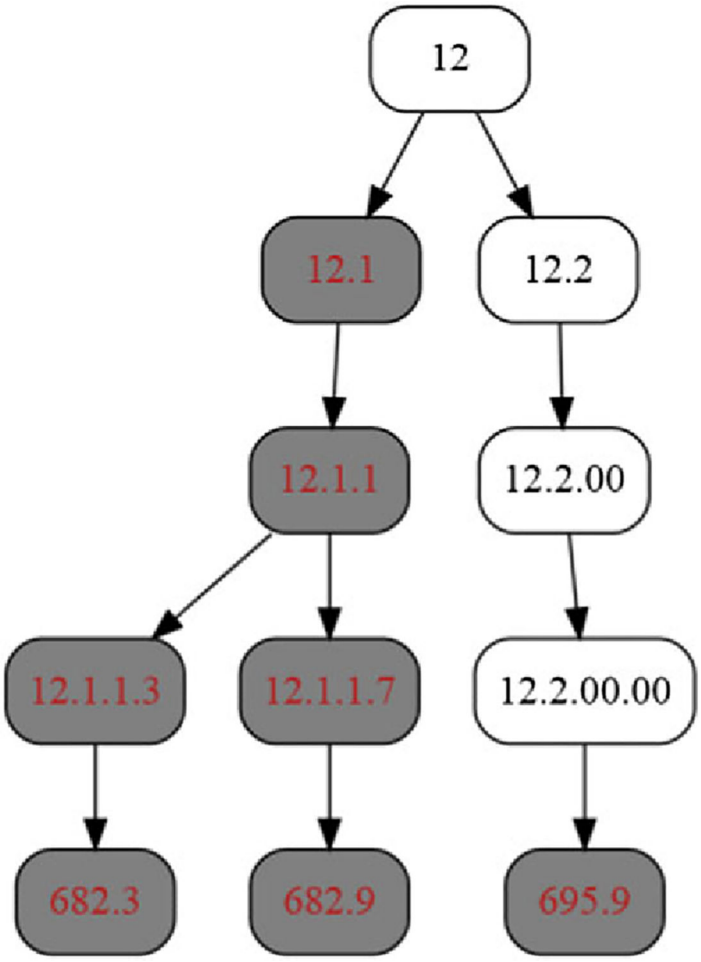

FIGURE 3.

A hierarchical tree for branch 12 (diseases of the skin and subcutaneous tissue) that includes statistical signals for nodes in Table 1 (nodes with gray background indicate AE signals after removing signals following well-care visits; the first 4 levels are MLCCS codes; the last level is ICD-9 code) [Colour figure can be viewed at wileyonlinelibrary.com]

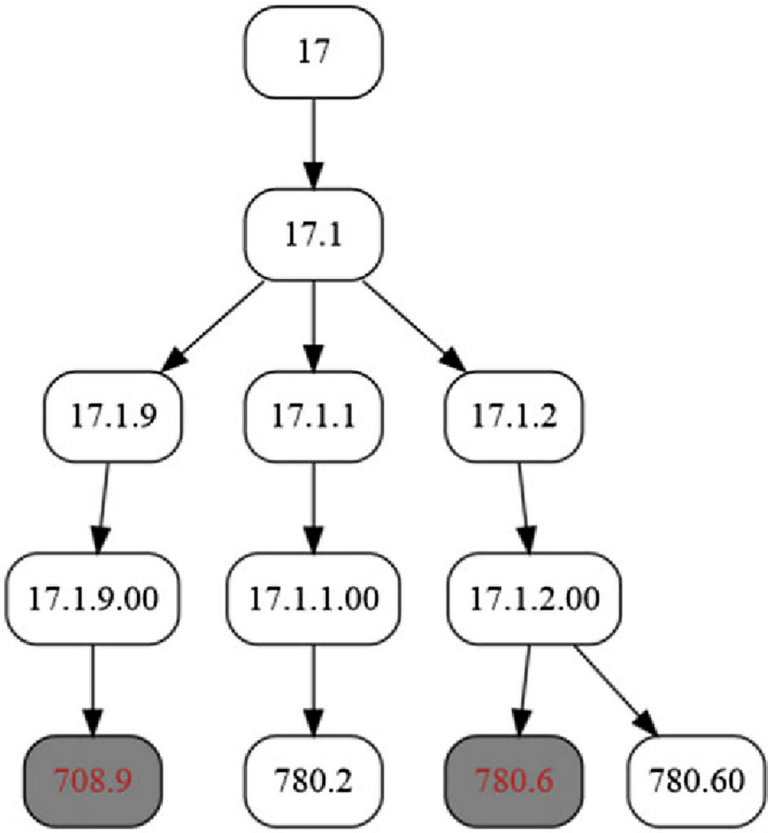

FIGURE 4.

A hierarchical tree for branch 17 (signs and ill-defined conditions and factors influencing health status) that includes statistical signals for nodes in Table 1 (nodes with gray background indicate AE signals after removing signals following well-care visits; the first 4 levels are MLCCS codes; the last level is ICD-9 code) [Colour figure can be viewed at wileyonlinelibrary.com]

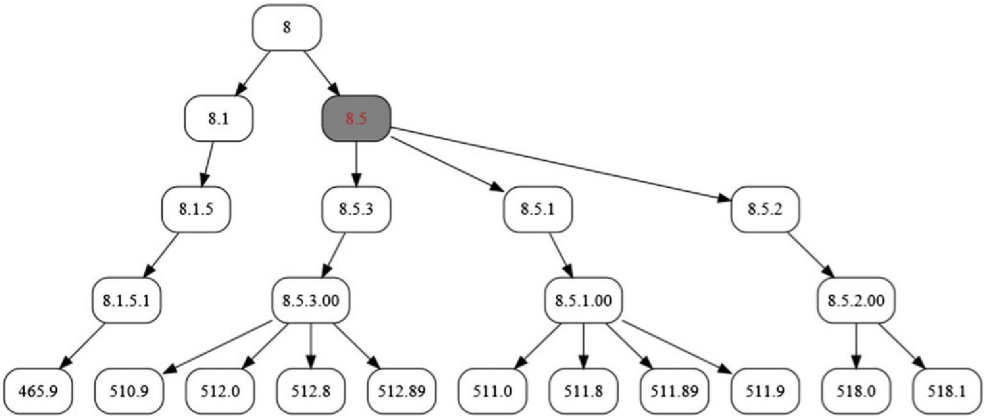

FIGURE 5.

A hierarchical tree for branch 8 (diseases of respiratory system) that includes statistical signals for nodes in Table 1 (nodes with gray background indicate AE signals after removing signals following well-care visits; the first 4 levels are MLCCS codes; the last level is ICD-9 code) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1

List of adverse event outcomes following the first dose of MENACWY-D that generated significant ($P < 0.05$) statistical signals using the tree-temporal scan statistic

MLCCS[&] or ICD9	Diagnosis	Start Window	End Window	Observed Events	Expected Events	O/E	*P*-Values
6	Diseases of the nervous system and sense organs	1	15	17 966	15037.23	1.41	0.001
6.8	Ear conditions	16	41	5296	4946.11	1.14	0.005
6.7	Eye disorders	1	15	13 277	9727.85	1.76	0.001
6.7.4	Blindness and vision defects [89.]	1	15	11 029	7607.73	1.94	0.001
6.7.6	Other eye disorders [91.]	1	17	1099	924.58	1.31	0.001
367.1	Myopia	1	15	6161	4141.89	1.95	0.001
367.0	Hypermetropia	1	8	1120	651.43	2.02	0.001
367.20	Astigmatism, unspecified	1	13	746	448.74	2.12	0.001
367.9	Unspecified disorder of refraction and accommodation	1	15	1820	1418.99	1.46	0.001
12*	Diseases of the skin and subcutaneous tissue	2	3	782	610.63	1.33	0.001
12.1*	Skin and subcutaneous tissue infections [197.]	2	3	292	161.75	1.89	0.001
12.1.1*	Cellulitis and abscess	2	3	250	101.91	2.64	0.001
12.1.1.3*	Cellulitis and abscess of arm	2	3	52	4.45	19.42	0.001
12.1.1.7*	Other cellulitis and abscess	2	3	162	62.97	2.77	0.001
682.3*	Cellulitis and abscess of upper arm and forearm	2	3	52	4.45	19.42	0.001
682.9*	Cellulitis and abscess of unspecified sites	2	3	157	57.81	2.94	0.001
695.9*	Unspecified erythematous condition	1	3	25	2.39	23.62	0.001
17.1.1	Syncope [245.]	1	2	73	37.46	2.04	0.002
17.1.2	Fever of unknown origin [246.]	1	2	153	69.27	2.35	0.001
780.60	Fever, unspecified	1	3	141	75.96	1.97	0.001
780.6*	Fever and other physiologic disturbances of temperature regulation	1	2	47	15.45	3.33	0.001
780.2	Syncope and collapse	1	2	73	37.46	2.04	0.002
708.9*	Urticaria, unspecified	4	13	229	151.41	1.71	0.001
8	Diseases of the respiratory system	21	42	15 587	14707.54	1.13	0.001
8.5*	Pleurisy; pneumothorax; pulmonary collapse [130.]	21	32	48	22.35	3.13	0.023

MLCCS[&] or ICD9	Diagnosis	Start Window	End Window	Observed Events	Expected Events	O/E	*P*-Values
8.1	Respiratory infections	18	42	8027	7469.39	1.16	0.001
8.1.5	Other upper respiratory infections [126.]	18	42	5835	5355.34	1.18	0.001
8.1.5.1	Acute upper respiratory infections of multiple or unspecified sites	17	42	3817	3488.98	1.2	0.001
465.9	Acute upper respiratory infections of unspecified site	17	42	3808	3481.16	1.2	0.001
9.5	Abdominal hernia [143.]	1	12	79	42.77	2.43	0.006
9.5.1	Inguinal hernia	2	12	52	25.45	2.77	0.043
9.5.1.2	Inguinal hernia without obstruction or gangrene	2	12	52	25.25	2.81	0.033
1	Infectious and parasitic diseases	2	3	548	410.19	1.38	0.001
1.1	Bacterial infection	2	5	86	45.93	2	0.001
3.6	Disorders of lipid metabolism [53.]	2	14	174	115.72	1.81	0.004
799.8	Other ill-defined and unknown causes of morbidity and mortality	2	5	46	8.06	8.69	0.001
796.4	Other abnormal clinical findings	1	15	146	93.73	2.01	0.005
999	Complications of medical care not elsewhere classified	1	6	20	4.21	8.71	0.001

[&]Multi-Level Clinical Classifications Software; ICD-9, International Classification of Diseases, Ninth Revision, Clinical Modification; O/E, a ratio of observed to expected.

[*]Signals that remained after removing the ones also identified following well-care visits.