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A Broad Safety Assessment of the Recombinant Herpes Zoster Vaccine

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The recombinant herpes zoster vaccine (RZV), approved as a 2-dose series in the United States in October 2017, has proven highly effective and generally safe. However, a small risk of Guillain-Barré syndrome after vaccination was identified after approval, and questions remain about other possible adverse events. This data-mining study assessed RZV safety in the United States using the self-controlled tree-temporal scan statistic, scanning data on thousands of diagnoses recorded during follow-up to detect any statistically unusual temporal clustering of cases within a large hierarchy of diagnoses. IBM MarketScan data on commercially insured persons at least 50 years of age receiving RZV between January 1, 2018, and May 5, 2020, were used, including 56 days of follow-up; 1,014,329 doses were included. Statistically significant clustering was found within a few days of vaccination for unspecified adverse effects, complications, or reactions to immunization or other medical substances/care; fever; unspecified allergy; syncope/collapse; cellulitis; myalgia; and dizziness/giddiness. These findings are consistent with the known safety profile of this and other injected vaccines. No cluster of Guillain-Barré syndrome was detected, possibly due to insufficient sample size. This signal-detection method has now been applied to 5 vaccines, with consistently plausible results, and seems a promising addition to vaccine-safety evaluation methods.

data mining; epidemiologic research design; vaccination; vaccines

Abbreviations: GBS, Guillain-Barré syndrome; ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*; RZV, recombinant herpes zoster vaccine.

Herpes zoster, or shingles, is caused by the reactivation of latent varicella zoster virus in nerve ganglia and can lead to long-lasting, debilitating pain as well as ophthalmic and other complications (1). It occurs quite commonly, particularly among older adults, with a median incidence of 4–4.5 per 1,000 person-years internationally (2). In the United States, about 1 out of every 3 people will develop herpes zoster in their lifetime (3). In October 2017, the Food and Drug Administration approved a recombinant zoster vaccine (RZV) (Shingrix; GlaxoSmithKline, Brentford, United Kingdom) for use in people 50 years of age or older, to be administered as a 2-dose series, with 2–6 months between doses (4). RZV has proven highly effective in preventing herpes zoster and post-herpetic neuralgia (5, 6) and in the United States has replaced the less-effective live attenuated zoster vaccine (Zostavax; Merck & Co., Inc., Kenilworth, New Jersey) approved by the Food and Drug Administration in May 2006 for use in adults aged 60 or older (7). As of 2018, an estimated 24.1% of the US population aged ≥50 years and 34.5% of the population aged ≥60 years had received a vaccine against herpes zoster (8). As of the end of 2020, 41.3 million doses had been distributed in the United States (9), and by the beginning of February 2021, more than 20 million people in the United States had received at least 1 dose.

In the first 3 years after licensure, the only known adverse reactions to RZV were injection-site reactions, allergic reactions, fever, chills, fatigue, and headache within the first few days after vaccination (4, 10, 11). Then, in a study published in 2021, a small increased risk of Guillain-Barré syndrome (GBS) after RZV vaccination in the ≥65-year-old Medicare population was reported (12). Using a self-controlled case series design with a risk window of days 1–42 after vaccination and a control window of days 43–183, the investigators identified an attributable risk of 3.13 (95% confidence interval: 0.62, 5.64) excess cases per million

RZV doses among more than 2 million eligible RZV-vaccinated beneficiaries aged 65 years or older. The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices carefully considered the (pre-publication) results of this study but did not change their recommendations for RZV vaccination in view of the relatively small attributable risk, the public health benefits of RZV in preventing herpes zoster, and a formal risk-benefit analysis (13).

Questions remain about other rare and serious post-RZV vaccination adverse events. For instance, in a pooled analysis of 2 large randomized phase III trials with 14,645 RZV recipients and 14,660 placebo recipients, supraventricular tachycardia and optic ischemic neuropathy were reported in 6 (0.04%) and 3 (0.02%) RZV vaccinees, respectively, compared with 0 of each outcome among placebo recipients (4, 14); all 3 cases of optic ischemic neuropathy occurred within 50 days after vaccination (4). Although less serious, gout (including gouty arthritis) was reported by 27 (0.18%) subjects who received RZV versus 8 (0.05%) placebo recipients within 30 days of vaccination in the same pooled study population (4). In a phase IIIB, nonrandomized study, in which placebo recipients in earlier randomized trials were offered RZV and 8,687 received it, 8.4% of recipients reported at least 1 serious adverse event during the 12-month postvaccination follow-up period. Although there was no comparison group, the clinical investigator considered 2 cases to be causally related to vaccination: a case of reactive arthritis 4 days after dose 1 and a case of polymyalgia rheumatica 41 days after dose 2 (15). The possibility of safety issues such as these led the Food and Drug Administration to request postmarketing commitment studies of 6 prespecified health outcomes, which are currently underway (16).

In this paper, we describe our assessment of the safety of RZV using the self-controlled tree-temporal scan statistic, a data-mining method that evaluates whether any of thousands of health outcomes is associated with receipt of a specific vaccine or drug (17). This method is based on earlier work with tree-based scan statistics (18–20). It does not require preselecting either specific health outcomes of interest or specific postexposure periods of potentially increased risk within the defined postexposure follow-up period. Instead, for an exposed population, data on incident diagnoses recorded within the defined postexposure follow-up period are scanned to detect any statistically unusual clustering of cases within a large hierarchy, or "tree," of diagnoses as well as temporally within the follow-up period. The method adjusts for the multiple overlapping diagnoses and time intervals considered during the construction of the composite null hypothesis that there is no unusual clustering of cases in the tree or across time. Further, the method is self-controlled, eliminating confounding by fixed patient characteristics such as chronic disease status.

When we used this method to study the safety of the earlier (live attenuated) herpes zoster vaccine, statistically significant clusters of local injection-site reactions and other known, generally mild vaccine-associated adverse events were found in the few days immediately following vaccination, with no false alarms (21). We concluded that the method could be useful for assessing the safety of other vaccines for older adults as well.

METHODS

Study population, enrollment criteria, and exposure

We used the IBM MarketScan Research Databases (MarketScan; International Business Machines Corporation, Armonk, New York), among the largest proprietary US claims databases available for health-care research, and likely highly representative of the commercially insured population. The databases capture person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services. Paid claims and encounter data are linked to detailed patient information across sites and types of providers collected from approximately 350 payers (mainly large employers and health plans; predominantly fee-for-service data).

We extracted data on persons aged 50 years or older who were vaccinated from January 1, 2018, through a maximum of May 5, 2020. To be included, an individual had to have been enrolled from 400 days prior through 56 days after RZV vaccination. RZV was identified using Current Procedural Terminology code 90750 and National Drug Codes 58160081912, 58160082311, 58160082801, 58160082803, 58160082901, and 58160082903. RZV doses received within 42 days of a prior dose were excluded.

Hierarchical diagnosis tree

Outcomes were identified using *International Classification of Diseases*, *Tenth Revision*, *Clinical Modification* (ICD-10-CM), codes. ICD-10-CM codes have a hierarchical tree-like structure, starting with 21 broad categories of diagnoses (e.g., diseases of the circulatory system), which progressively branch into more and more specific sets of diagnoses, culminating in a highly specific diagnosis code. The ICD-10-CM tree we used has 6 levels. Table 1 presents an example of the hierarchical classification scheme; this example diagnosis does not use the 6th level. Scanning counts of diagnoses organized in such a tree structure allows clusters of related diagnoses (e.g., within H30, chorioretinal inflammation, whether focal or peripheral or bilateral or not) to be detected, in the event that the exposure of interest is associated with a spectrum of disease rather than a highly specific health outcome.

The composite null hypothesis was constructed to consider clusters in levels 2–5, which contain 88,156 groupings of similar clinical diagnosis codes. (We refer to these groupings as "nodes" of the tree.) We did not look for clusters in the first or sixth level because these groupings are not clinically meaningful—the former are too general, and the latter are too specific (e.g., often only for the purpose of specifying anatomic laterality of a health outcome or distinguishing between initial and subsequent encounters).

Incident diagnoses

The study examined "incident" diagnoses observed in the inpatient or emergency department setting during the

Table 1. Example of Hierarchical Organization in the *International Classification of Diseases*, *Tenth Revision*, Coding System, Showing Levels of Tree Employed

Level	Code or Code Range	Description
1	H00-H59	Diseases of the eye and adnexa
2	H30	Chorioretinal inflammation
3	H30.0	Focal chorioretinal inflammation
4	H30.03	Focal chorioretinal inflammation, peripheral
5	H30.033	Focal chorioretinal inflammation, peripheral, bilateral

follow-up period of 56 days. To be counted as an incident case, the patient must not have been assigned another ICD-10-CM diagnosis code having the same first 3 characters (i.e., in the same second level of the tree) in any setting during the prior 400 days. (We chose 400 days in order to enable ascertainment of preexisting conditions that might have been recorded at a visit roughly 1 year prior, considering that some patients have preventive care visits on an approximately annual basis.) Because incidence was determined using the second level of the tree, above which no analysis of clustering was carried out, no patient could have contributed more than 1 case count to any particular cluster.

Risk and comparison windows

We set the analysis parameters to evaluate every temporal window of potentially increased risk between 2 and 28 days in length that started during days 1–28 after vaccination and ended during days 2–42 after vaccination. There were 665 such windows. The comparison period used to evaluate each eligible potential risk window consisted of all of the days within the 56-day follow-up period that were not in the risk window (Figure 1).

The conditional tree-temporal scan statistic

Since first posited by Joseph Naus in 1965 (22), scan statistics have been used in numerous public health applications (23, 24), including imaging, cancer and other disease surveillance (25–27), and recently genomics (28). They have been widely used to track infectious disease outbreaks in both space and time (29–36). The purpose of a scan statistic is to detect a cluster of nonrandom activity by moving a window of evaluation (e.g., temporal, geospatial) across a data set. Analysis to detect unusual concentrations of activity is typically by means of a generalized likelihood ratio test where the likelihood is governed by parametric assumptions about the underlying data. It is important to note that the word "cluster" is used differently in the scan statistic literature than in cluster analysis in unsupervised machine learning; the objective of the latter is to group like objects together using sophisticated classification algorithms.

A generalized likelihood ratio test is a common statistical hypothesis-testing procedure designed for composite hypothesis-testing problems (i.e., examining many potential models or combinations of data) and maximizes the likelihood ratio function over the multiple potential combinations

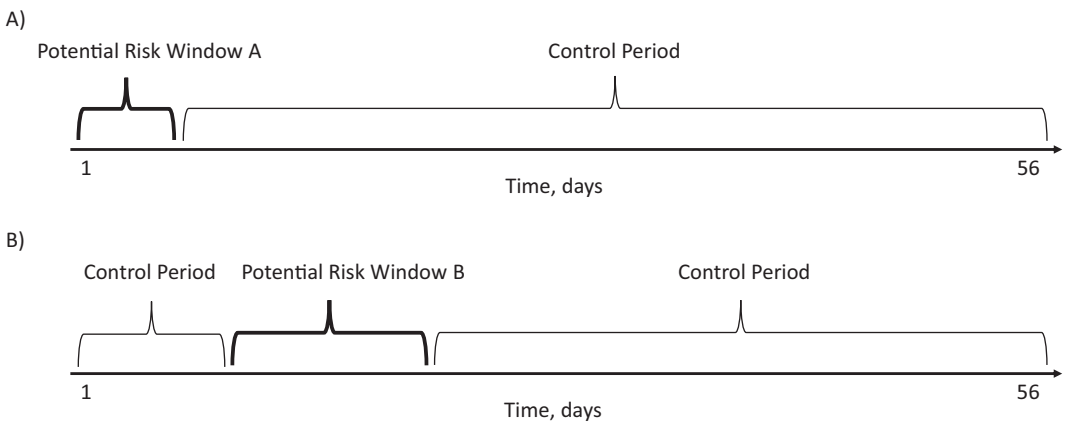

Figure 1. Examples of potential risk windows evaluated at any given instant of analysis, with their control periods. A) A potential risk window that starts on day 1 after vaccination. The corresponding control period starts the day after the end of the potential risk window and extends through day 56. B) A potential risk window situated at neither end of the follow-up period but rather somewhere in between. The corresponding control period consists of the segments of the 56-day follow-up period that are not in the potential risk window being evaluated.

of data analyzed. Generalized likelihood ratio testing has also been used in signal detection using spontaneous reports (37, 38).

With the tree-temporal scan statistic, one considers many potential clusters across 2 dimensions in combination: 1) groups of clinical outcomes across the tree and 2) potential risk windows per clinical outcome group within the predefined postexposure follow-up window (17). Under the composite null hypothesis, there is no unusual temporal clustering of events on any leaf or branch (i.e., within any part of the tree). Under the alternative hypothesis, there is at least 1 leaf or branch of the tree for which there is an unusual temporal cluster of events. Each cluster is evaluated using a log-likelihood ratio test where the observed data are compared with an expected distribution. In a conditional analysis, used for the present study, the expected distribution is conditioned not only on the number of events observed in each node (i.e., clinical outcome group) of the tree during the whole follow-up period but also on the total number of events occurring during the scanning risk window across the entire tree. This adjusts for the type of temporal confounding that would occur if there were differences in the volume of general health care–seeking behavior shortly after compared with longer after the vaccination date.

We used Monte Carlo simulation to generate 9,999 replications of a null data set using a data permutation strategy. The test statistic is calculated for each replication data set plus the real data set and is the maximum of the individual log-likelihood ratios calculated over the 88,156 clinical outcome group and 665 risk window combinations. This technique allows us to rank each potential cluster against the test statistic distribution; given the 9,999 replications, the lowest possible P value is 0.0001. We prespecified the P value cutoff for statistical significance as 0.05.

In using the tree-temporal scan statistic with a self-controlled design, the comparison is within person among time periods. The question being asked is whether there is an elevated occurrence of cases of a particular kind of adverse event during a particular time period postexposure as compared with the rest of the period observed.

The formula for excess cases (attributable risk) is as follows:

$$c - [(n - c)\ (z - c) / (C–n–z + c)],$$

where c is the number of events in the cluster as described by the particular outcome grouping and temporal window, n is the total number of events in the outcome category, z is the number of events in the temporal window summed over the whole tree, and C is the total number of events in the whole tree (17).

Further investigation of potential GBS cases

In view of Goud et al.'s finding on GBS (12), we investigated each of the potential GBS cases ascertained in the follow-up period, not by formal medical record review but by generating and examining a list of all diagnosis, procedure, and medication codes recorded between 183 days before and 56 days after vaccination. A board-certified internal medicine physician blinded to the nature of the study and the exposure of interest distinguished between cases unlikely to be true new-onset cases of GBS and cases that could be true new-onset GBS cases.

Institutional review board approval

The study was approved by the Harvard Pilgrim Health Care Institutional Review Board.

RESULTS

The analysis included 1,014,329 doses of RZV, of which 773,530 (76%) were in persons aged 50–64 years and 240,799 (24%) were in those aged ≥65 years. There were 9 sets of statistically significant clusters (Table 2), where "set" refers to a group of clusters whose ICD-10-CM codes share the same first 3 characters. The sets are presented in decreasing order according to the largest test statistic within the set.

Sets 1, 2, and 4 represent unspecified adverse effects, complications, or reactions to immunization or other medical substances or care. Risk windows of those ranged from 1–2 to 1–5 days after vaccination, and attributable risks ranged from 0.8 to 5.9 cases per 100,000 vaccinations. Set 3 is fever within 2 days after vaccination, with attributable risks of 4.5–5.1 cases per 100,000 vaccinations. Set 5 is adverse effects not classified elsewhere, including unspecified allergy, during the 1–5 days after vaccination, with attributable risks of 2.4–3.1 cases per 100,000 vaccinations. Set 6 is syncope and collapse during days 1–3 after vaccination, with an attributable risk of 4.8 cases per 100,000 vaccinations. Set 7 is cellulitis during days 2–6 after vaccination, driven by cellulitis of the left upper limb during days 2–5, with attributable risks of 1.4–3.0 cases per 100,000 vaccinations. Set 8 is myalgia during days 1–2 after vaccination, with an attributable risk of 1.5 cases per 100,000 vaccinations. Set 9 is dizziness and giddiness during days 1–8 after vaccination, with an attributable risk of 7.8 cases per 100,000 vaccinations.

No evidence was found of any association between RZV and any of the rare serious adverse events about which questions emerged from the clinical trials. There was no signal of any kind for GBS. There were 9 diagnoses of GBS coded in our data during days 1–56 (Figure 2). On assessing the list of diagnosis, procedure, and medication codes for each of the 9 patients, the reviewing internal medicine physician determined that 4 of the 9 cases were likely not true new-onset cases of GBS.

DISCUSSION

In this study of more than 1 million RZV vaccinations, we found statistically significant clustering of cases of unspecified adverse effects, complications, or reactions to immunization or other medical substances or care; fever; unspecified allergy; syncope and collapse; cellulitis; myalgia; and dizziness and giddiness—all within the

Table 2. Details of Statistical Clusters From Tree-Temporal Scan Statistical Analysis of Recombinant Herpes Zoster Vaccination Among Adults ≥50 Years of Age in IBM MarketScan Research Databases (Range of Eligible Vaccination Dates: January 1, 2018 Through May 5, 2020), United States

Row No.	Set No.	ICD-10-CM Code	Text Description	Cases in 56-Day Follow-up Period	Risk Window Detected (Days After Vaccination)	Cases in Risk Window	Excess Cases Per 100,000 Doses	*P* Value
1	1	T50	Poisoning by, adverse effect of, and underdosing of diuretics and other and unspecified drugs, medicaments and biological substances	187	1–4	68	5.9	0.0001
2	1	T50.Z95	Adverse effect of other vaccines and biological substances	40	1–3	33	3.2	0.0001
3	1	T50.B	Poisoning by, adverse effect of, and underdosing of viral vaccines	21	1–4	16	1.5	0.0001
4	1	T50.B95	Adverse effect of other viral vaccines	20	1–4	15	1.4	0.0001
5	2	T88	Other complications of surgical and medical care, not elsewhere classified	66	1–2	26	2.4	0.0001
6	2	T88.1	Other complications following immunization, not elsewhere classified	29	1–2	20	1.9	0.0001
7	3	R50	Fever of other and unknown origin	973	1–2	82	5.1	0.0001
8	3	R50.9	Fever, unspecified	908	1–2	74	4.5	0.0001
9	4	T80	Complications following infusion, transfusion, and therapeutic injection	42	1–5	16	1.4	0.0060
10	4	T80.6	Other serum reactions	11	1–5	11	1.1	0.0001
11	4	T80.62	Other serum reaction due to vaccination	8	1–5	8	0.8	0.0044
12	5	T78	Adverse effects, not elsewhere classified	261	1–5	49	3.1	0.0007
13	5	T78.4	Other and unspecified allergy	152	1–5	34	2.4	0.0017
14	5	T78.40	Allergy, unspecified	139	1–5	33	2.4	0.0006
15	6	R55	Syncope and collapse	1,203	1–3	103	4.8	0.0007
16	7	L03.11	Cellulitis of other parts of limb	310	2–6	51	3.0	0.0108
17	7	L03.114	Cellulitis of left upper limb	64	2–5	17	1.4	0.0088
18	8	M79.1	Myalgia	142	1–2	19	1.5	0.0147
19	9	R42	Dizziness and giddiness	1,448	1–8	251	7.8	0.0232

Abbreviation: ICD-10-CM, *International Classification of Diseases*, *Tenth Revision*, *Clinical Modification*.

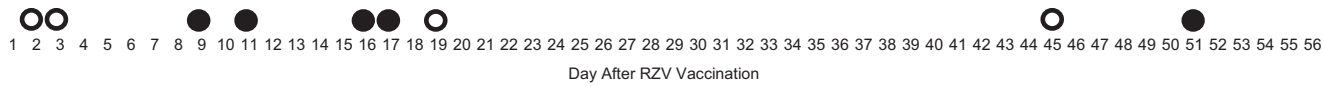

Figure 2. Temporal distribution of potential cases of Guillain-Barré syndrome (GBS) in terms of day after recombinant herpes zoster vaccine (RZV) vaccination that their GBS diagnosis code was recorded in the data source (IBM MarketScan research databases, United States, 2018–2020). Solid circles represent cases of possible new-onset GBS, while hollow circles represent cases of unlikely new-onset GBS, based on review of claims data by an internal medicine physician. Days 2 and 19: ages 70–74 years; day 3: ages 65–69 years; day 9: ages ≥85 years; days 11, 16, 17, and 45: ages 60–64 years; day 51: ages 55–59 years.

first few days of vaccination. All of these seem likely to represent true vaccine-associated adverse events. The unspecified adverse events likely represent such conditions as injection-site reactions, fever, fatigue, and headache, judging from previous case-by-case investigations of similar after-vaccination signals found with this method (39). The only clustered condition that is not noted as an adverse event in the RZV package insert is cellulitis, but skin infections are acknowledged to occur after other injections, including after the quadrivalent human papillomavirus vaccine (40) and the measles-mumps-rubella-varicella combination vaccine (41). No other signals emerged in this analysis.

It is notable that we did not find a signal for GBS. Assuming there is in fact an association between RZV and GBS, insufficient sample size in the older age groups may be a reason that we did not detect it. The Goud et al. (12) study in the Medicare population, which found an attributable risk of 3.13 (95% confidence interval: 0.62, 5.64) excess cases per million RZV doses, included more than 2 million RZV vaccinees 65 years of age or older, who are at higher risk of GBS than younger people, whereas in our study of commercially insured people, only about 241,000 (approximately one-quarter) of the doses were received by people ≥65 years of age. Of the 5 cases deemed possible GBS in our study, 4 were in the second and third weeks after vaccination, like the onsets of the chart-confirmed cases in the Goud et al. study (12).

Notwithstanding this study's possible lack of power to detect signals manifesting in specific subgroups such as the elderly or to detect vaccine-associated adverse events with risks as low as just a few excess cases per million doses, attributable risks as low as 1 excess case per 100,000 vaccinations were seen, indicating good statistical power to detect possible adverse events that are not restricted to subgroups. (In general, the power of this method depends on the number of exposed persons—in this case, vaccinees—and the background rate of the outcome in the affected group (e.g., elderly, women, etc.), as well as the specific features and parameter settings selected for the data extraction and analysis, including the length of the follow-up period, the size and nature of the tree, and the number of risk intervals evaluated.)

There are of course inherent limitations to using administrative claims data for vaccine safety surveillance, including imperfect sensitivity and specificity of diagnosis codes and the fact that a diagnosis date does not necessarily reflect the date of symptom onset. Nonetheless, use of large electronic health-care databases, including claims, has key advantages, including good representation of routine clinical practice and efficient capture of data from large patient populations.

Additional limitations of the approach we used are that any adverse events with an increased risk sustained throughout the follow-up period would not have been detected, and adverse events with long latency periods could have been missed, due to the follow-up period of 56 days and day 42 being the latest day in any potential risk interval evaluated. We chose to limit the follow-up period to 56 days to minimize the possibility of time-varying confounding, which has been seen with longer follow-up (42), but these parameters can be changed in future applications.

Due to our decision to use the conditional tree-temporal scan statistic, which conditions on the total number of outcomes in moving risk windows across the tree, we needed to impose a minimum after-vaccination enrollment requirement, because it is critically important to constructing the composite null hypothesis that all vaccinees have the same opportunity to contribute outcomes. Consequently, vaccinees must have survived the follow-up period, meaning that death during follow-up would not have been captured as a possible outcome. However, as regards the safety of RZV, the pooled clinical trials found no imbalance in the frequency of death between RZV and placebo recipients (4). (Other forms of tree-based scan statistics do not condition on overall temporal distribution and therefore can be used without a postvaccination enrollment requirement. We chose not to use those other tree-based scan statistics for 2 reasons. One reason was that the risk of death from other causes in this population aged 50 years or older is nontrivial and can therefore result in bias and false signaling in unconditional applications of tree-based scan statistics. The other reason we used the conditional method was so as to control for the tendency of preventive-care/vaccination visits to lead to follow-up visits for various conditions or concerns soon thereafter, which could also cause bias and false signaling.)

In conclusion, in this broad assessment of potential adverse events after RZV vaccination, we found no evidence of previously unknown adverse reactions up to 42 days after vaccination. The findings of unspecified adverse effects, fever, unspecified allergy, syncope and collapse, cellulitis, myalgia, and dizziness and giddiness are consistent with the known safety profile of this and other injected vaccines. We did not detect a signal for GBS, possibly as a result of too small a sample size of the older individuals at highest risk of GBS.

With this study, the self-controlled tree-temporal scan statistic has now been applied to 3 vaccines for adolescents

and young adults (39, 42, 43) and 2 herpes zoster vaccines for older adults (21), with consistently plausible results. The prospects for applying this signal-detection method to assess the safety of other vaccines, including coronavirus disease 2019 vaccines, as a complement to approaches that target specific health outcomes (44), thus seem promising.

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Data availability: Aggregated data are available upon request.

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REFERENCES

1. Schmader K. Herpes zoster. *Clin Geriatr Med.* 2016;32(3):539–553.
2. Yawn BP, Gilden D. The global epidemiology of herpes zoster. *Neurology.* 2013;81(10):928–930.
3. Centers for Disease Control and Prevention. About shingles. https://www.cdc.gov/shingles/about/index.html. Accessed January 25, 2022.
4. Shingrix. Package insert. https://www.fda.gov/media/108597/download. Accessed January 25, 2022.
5. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med.* 2015;372(22):2087–2096.
6. Izurieta HS, Wu X, Forshee R, et al. Recombinant zoster vaccine (Shingrix): real-world effectiveness in the first 2 years post-licensure. *Clin Infect Dis.* 2021;73(6):941–948.
7. Zostavax. Package insert. https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm132831.pdf. Accessed January 25, 2022.
8. Lu P, Hung M, Srivastav A, et al. Surveillance of vaccination coverage among adult populations—United States, 2018. *MMWR Surveill Summ.* 2021;70(3):1–26.
9. Lee G. Zoster vaccines session: introduction. *Presented at the Advisory Committee on Immunization Practices Meeting (online)*. 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/24-25/01-Zoster-Vaccines-Lee.pdf. Accessed January 25, 2022.
10. Hesse EM, Shimabukuro TT, Su JR, et al. Postlicensure safety surveillance of recombinant zoster vaccine (Shingrix)—United States, October 2017–June 2018. *MMWR Morb Mortal Wkly Rep.* 2019;68(4):91–94.
11. Tavares-da-Silva F, Co MM, Dessart C, et al. Review of the initial post-marketing safety surveillance for the recombinant zoster vaccine. *Vaccine.* 2020;38(18):3489–3500.
12. Goud R, Lufkin B, Duffy J, et al. Risk of Guillain-Barré syndrome following recombinant zoster vaccine in Medicare beneficiaries. *JAMA Intern Med.* 2021;181(12):1623–1630.
13. Anderson T. Zoster vaccines session: summary of the Herpes Zoster Work Group's interpretation of recombinant zoster vaccine safety data. *Presented at the Advisory Committee on Immunization Practices Meeting (virtual)*, 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/24-25/04-Zoster-Vaccines-Anderson.pdf. Accessed January 25, 2022.
14. López-Fauqued M, Campora L, Delannois F, et al. Safety profile of the adjuvanted recombinant zoster vaccine: pooled analysis of two large randomised phase 3 trials. *Vaccine.* 2019;37(18):2482–2493.
15. Ocran-Appiah J, Boutry C, Hervé C, et al. Safety of the adjuvanted recombinant zoster vaccine in adults aged 50 years or older. A phase IIIB, non-randomized, multinational, open-label study in previous ZOE-50 and ZOE-70 placebo recipients. *Vaccine.* 2021;39(1):6–10.
16. GlaxoSmithKline. Targeted safety study to assess the real-world safety of Shingrix vaccine in adults aged 50 and older in the United States (US). https://www.gsk-studyregister.com/en/trial-details/?id=209452. Accessed January 24, 2022.
17. Kulldorff M, and Information Management Services, Inc. *TreeScan: Software for the Tree-Based Scan Statistic, version 1.4*. Calverton, MD: Information Management Services, Inc.; 2018.
18. Kulldorff M, Dashevsky I, Avery TR, et al. Drug safety data mining with a tree-based scan statistic. *Pharmacoepidemiol Drug Saf.* 2013;22(5):517–523.
19. Kulldorff M, Fang Z, Walsh SJ. A tree-based scan statistic for database disease surveillance. *Biometrics.* 2003;59(2):323–331.
20. Brown JS, Petronis KR, Bate A, et al. Drug adverse event detection in health plan data using the Gamma Poisson Shrinker and comparison to the tree-based scan statistic. *Pharmaceutics.* 2013;5(1):179–200.
21. Yih WK, Kulldorff M, Dashevsky I, et al. Using the self-controlled tree-temporal scan statistic to assess the safety of live attenuated herpes zoster vaccine. *Am J Epidemiol.* 2019;188(7):1383–1388.
22. Naus JL. Clustering of random points in two dimensions. *Biometrika.* 1965;52(1–2):263–266.
23. Glaz J, Koutras MV. *Handbook of Scan Statistics*. New York, NY: Springer New York; 2020.
24. Abolhassani A, Prates MO. An up-to-date review of scan statistics. *Statist Surv.* 2021;15:111–153.
25. Amin R, Hendryx M, Shull M, et al. A cluster analysis of pediatric cancer incidence rates in Florida: 2000–2010. *Stat Public Policy.* 2014;1(1):69–77.
26. Huang L, Pickle LW, Das B. Evaluating spatial methods for investigating global clustering and cluster detection of cancer cases. *Stat Med.* 2008;27(25):5111–5142.
27. Cheung YTD, Spittal MJ, Williamson MK, et al. Application of scan statistics to detect suicide clusters in Australia. *PLoS One.* 2013;8(1):e54168.
28. Nishiyama T, Takahashi K, Tango T, et al. A scan statistic to extract causal gene clusters from case-control genome-wide rare CNV data. *BMC Bioinformatics.* 2011;12(1):205.

29. Huang L, Kulldorff M, Gregorio D. A spatial scan statistic for survival data. *Biometrics.* 2007;63(1):109–118.
30. Kulldorff M, Zhang Z, Hartman J, et al. Benchmark data and power calculations for evaluating disease outbreak detection methods. *MMWR Suppl.* 2004;53:144–151.
31. Kulldorff M, Mostashari F, Duczmal L, et al. Multivariate scan statistics for disease surveillance. *Stat Med.* 2007;26(8): 1824–1833.
32. Viñas M, Tuduri E, Galar A, et al. Laboratory-based prospective surveillance for community outbreaks of *Shigella* spp. in Argentina. *PLoS Negl Trop Dis.* 2013;7(12):e2521.
33. Greene SK, Peterson ER, Kapell D, et al. Daily reportable disease spatiotemporal cluster detection, New York City, New York, USA, 2014–2015. *Emerg Infect Dis.* 2016;22(10): 1808–1812.
34. Latash J, Greene SK, Stavinsky F, et al. Salmonellosis outbreak detected by automated spatiotemporal analysis—New York City, May–June 2019. *MMWR Morb Mortal Wkly Rep.* 2020;69(26):815–819.
35. Greene SK, Peterson ER, Balan D, et al. Detecting COVID-19 clusters at high spatiotemporal resolution, New York City, New York, USA, June–July 2020. *Emerg Infect Dis.* 2021;27(5):1500–1504.
36. Rosillo N, Del Águila-Mejía J, Rojas-Benedicto A, et al. Real time surveillance of COVID-19 space and time clusters during the summer 2020 in Spain. *BMC Public Health.* 2021; 21(1):961.
37. Ding Y, Markatou M, Ball R. An evaluation of statistical approaches to postmarketing surveillance. *Stat Med.* 2020; 39(7):845–874.
38. Hu T, Huang L, Xu J, et al. Spatial-cluster signal detection in medical devices using likelihood ratio test method. *Ther Innov Regul Sci.* 2021;55(1):56–64.
39. Yih WK, Maro JC, Nguyen M, et al. Assessment of quadrivalent human papillomavirus vaccine safety using the self-controlled tree-temporal scan statistic signal-detection method in the Sentinel System. *Am J Epidemiol.* 2018; 187(6):1269–1276.
40. Gardasil. Package insert. https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf. Accessed January 25, 2022.
41. ProQuad. Package insert. https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm123796.pdf. Accessed January 25, 2022.
42. Yih WK, Kulldorff M, Dashevsky I, et al. A broad safety assessment of the 9-valent human papillomavirus vaccine. *Am J Epidemiol.* 2021;190(7):1253–1259.
43. Li R, Weintraub E, McNeil MM, et al. Meningococcal conjugate vaccine safety surveillance in the Vaccine Safety Datalink using a tree-temporal scan data mining method. *Pharmacoepidemiol Drug Saf.* 2018;27(4):391–397.
44. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA.* 2021;326(14):1390–1399.