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Surveillance for Adverse Events Following Receipt of Pandemic 2009 H1N1 Vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009–2010

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The Post-Licensure Rapid Immunization Safety Monitoring (PRISM) system is a cohort-based active surveillance network initiated by the US Department of Health and Human Services to supplement preexisting and other vaccine safety monitoring systems in tracking the safety of monovalent pandemic 2009 H1N1 influenza vaccine in the United States during 2009–2010. PRISM investigators conducted retrospective analysis to determine whether 2009 H1N1 vaccination was associated with increased risk of any of 14 prespecified outcomes. Five health insurance and associated companies with 38 million members and 9 state/city immunization registries contributed records on more than 2.6 million doses of 2009 H1N1 vaccine. Data on outcomes came from insurance claims. Complementary designs (self-controlled risk interval, case-centered, and current-vs.-historical comparison) were used to optimize control for confounding and statistical power. The self-controlled risk interval analysis of chart-confirmed Guillain-Barré syndrome found an elevated but not statistically significant incidence rate ratio following receipt of inactivated 2009 H1N1 vaccine (incidence rate ratio = 2.50, 95% confidence interval: 0.42, 15.0) and no cases following live attenuated 2009 H1N1 vaccine. The study did not control for infection prior to Guillain-Barré syndrome, which may have been a confounder. The risks of other health outcomes of interest were generally not significantly elevated after 2009 H1N1 vaccination.

Guillain-Barré syndrome; influenza A virus; influenza A virus, H1N1 subtype; influenza vaccines; population surveillance; safety; vaccines

Abbreviations: CI, confidence interval; GBS, Guillain-Barré syndrome; ICD-9, *International Classification of Diseases*, Ninth Revision; IRR, incidence rate ratio; LAMV, live attenuated monovalent influenza vaccine; MIV, monovalent inactivated influenza vaccine; PRISM, Post-Licensure Rapid Immunization Safety Monitoring; SCRI, self-controlled risk interval; TIV, trivalent inactivated influenza vaccine.

Editor's note: *An invited commentary on this article appears on page 1129.*

The emergence of the novel influenza A H1N1 virus in April 2009 impelled the development of monovalent 2009 H1N1 vaccines. In view of the large number of prospective vaccinees and the increased risk of Guillain-Barré syndrome (GBS) associated with swine flu vaccination in 1976 (1), the federal government developed a comprehensive plan for vaccine safety surveillance and established several new monitoring systems to complement existing systems (2).

One new system was the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program, a cohort-based active surveillance network created by the US Department of Health and Human Services. PRISM investigators monitored a large representative health-insured population and incorporated immunization records through linkage with state/city immunization registries. During the pandemic season, PRISM investigators prospectively evaluated the risks of prespecified

health outcomes following 2009 H1N1 vaccination using sequential analysis methods developed by the Vaccine Safety Datalink Project (3–8) and found no potential safety problems. Afterwards, GBS cases were chart-validated, and retrospective analyses for all outcomes were conducted. Results of those analyses are described here.

MATERIALS AND METHODS

Study population

The PRISM system included 5 data partners with a total of 38 million members, chosen for their size, geographic reach, and ability to provide timely data. The data partners were Aetna, CIGNA, HealthCore, Inc. (the evaluation group for WellPoint/Blue Cross in California and WellPoint/Blue Cross Blue Shield in Colorado and New York), Blue Care Network of Michigan and Blue Cross Blue Shield of Michigan, and Humana. The study population consisted of health plan members whose records indicated receipt of 2009 H1N1 or seasonal influenza vaccine between August 2009 and April 2010 or receipt of inactivated or not-otherwise-specified seasonal influenza vaccine during either the 2007–2008 or 2008–2009 influenza season. The Department of Health and Human Services Office for Human Research Protections determined that PRISM was not subject to Department of Health and Human Services human subject protection regulations (Code of Federal Regulations, Title 45, Part 46).

Exposures

Vaccination data were obtained from data partner claims from 2007–2010 and city-/state-based immunization registries for the 2009–2010 season. Immunization registries were selected on the basis of population size, anticipated completeness and timeliness of 2009 H1N1 vaccine data, and experience exchanging data with health plans. Registries in Arizona, Florida, Georgia, Michigan, Minnesota, New York State, New York City, Pennsylvania, and Wisconsin participated. Data were successfully exchanged for 26 of 28 planned data partner-registry linkages. The registries provided information on vaccine code and vaccination date to the data partners for their specific health plan members.

Seasonal influenza vaccines, including trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine, were identified in 2007–2010. Monovalent inactivated 2009 H1N1 influenza vaccine (MIV) and live attenuated monovalent influenza vaccine (LAMV) were identified in the 2009–2010 season. The 2009 H1N1 codes available in claims data during the surveillance period did not distinguish between MIV and LAMV (see Web Table 1, which is posted on the *Journal*'s website (http://aje.oxfordjournals.org/)). Influenza vaccines not otherwise specified were classified as inactivated.

Outcomes

Health insurance claims data and *International Classification of Diseases*, Ninth Revision (ICD-9), code algorithms were used to identify health outcomes following influenza vaccination (Web Table 2). The outcomes monitored were similar to those monitored by the Vaccine Safety Datalink Project (6) and were selected in consultation with the Centers for Disease Control and Prevention and the Food and Drug Administration based on epidemiologic associations with vaccines or on biologic plausibility. The 12 outcomes studied for both MIV and LAMV were GBS, demyelinating disease, peripheral nervous system disorders, seizures, encephalitis/myelitis/encephalomyelitis, Bell's palsy, other cranial nerve disorders, ataxia, anaphylaxis, allergic reactions, hemorrhagic stroke, and ischemic stroke. For LAMV, myocarditis/pericarditis and wheezing were also monitored.

Preanalysis data processing

PRISM employed a distributed data-analysis approach (9, 10). Data partners extracted patient-level data into standard-format files, which remained confidential, and used standardized programs to aggregate counts of vaccine doses and outcomes by week of vaccination, age, sex, vaccine type, and dose number.

To avoid bias related to time lag in the accrual of health insurance claims data, we used outcome data only for vaccinations given up to dates in January or February, ensuring nearly complete follow-up through both the risk and control periods (Web Appendix).

GBS case validation

Two of the 5 data partners, which contributed more than 80% of the potential GBS cases, participated in GBS medical record review. Data partners mailed letters to health-care providers, explaining the public health importance of the surveillance effort and addressing confidentiality issues. An on-site clinician reviewed medical records to distinguish between potential and miscoded GBS cases. For potential GBS cases, de-identified relevant clinical information was abstracted for GBS case validation. Miscoded GBS charts were not abstracted. Cases for which records were unobtainable were considered inconclusive.

A team of 3 neurologists with expertise in demyelinating disease reviewed the abstracted data and classified each potential GBS case according to Brighton Collaboration criteria (11). Cases reported as GBS by a physician but with insufficient evidence to meet the case definition were labeled "probable." If it could not be determined from the available information whether a case was acute inflammatory demyelinating polyneuropathy (i.e., GBS) or chronic inflammatory demyelinating polyneuropathy, the case was considered "indeterminate." The onset date of each case was determined from clinical notes, as detailed in the Web Appendix.

Vaccine exposure groups studied

Our primary vaccination group for analysis was all first-dose recipients of 2009 H1N1 influenza vaccine, regardless of whether seasonal influenza vaccination had also been received. We also studied 2 subsets of this group: persons who had received MIV without any overlapping exposure to seasonal influenza vaccine (in Figure 1, set "a" for self-controlled risk interval (SCRI) analyses and set "a" + set "b" for current-vs.-historical analyses) and those who had received MIV and seasonal influenza vaccine concomitantly (Figure 1, set "d").

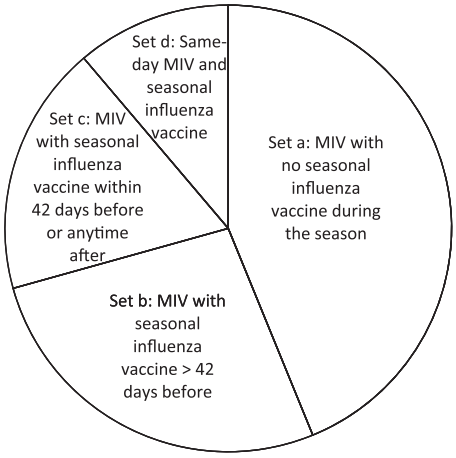

Figure 1. Vaccination groups analyzed in a PRISM (Post-Licensure Rapid Immunization Safety Monitoring) study of 2009 H1N1 influenza vaccine safety, United States, 2009–2010. The whole pie represents the primary vaccination group analyzed: recipients of a first dose of monovalent inactivated or not-otherwise-specified 2009 H1N1 influenza vaccine (MIV), without regard to receipt of seasonal influenza vaccine. The subgroup that received MIV without any overlapping exposure to seasonal influenza vaccine, whose results are presented in the middle section of Table 1, consisted of set "a" for the self-controlled risk interval analyses and set "a" + set "b" for the current-vs.-historical analyses. The other subgroup analyzed, the vaccinees who received MIV and seasonal influenza vaccine concomitantly, is represented by set "d." Separate analyses were not conducted for the subgroup that received seasonal influenza vaccine within 42 days before MIV vaccination or anytime after MIV vaccination (set "c") due to the complexity of quantifying their exposure status over the course of the various risk and control intervals.

Separate analyses were not conducted for the subgroup that received seasonal influenza vaccine within 42 days before MIV vaccination or anytime after MIV vaccination (Figure 1, set "c") because of the complexity of quantifying exposure status over the course of the various risk and control intervals. Because of low numbers, subsets of the primary vaccination group were not analyzed for chart-confirmed Guillain-Barré syndrome or for live attenuated 2009 H1N1 vaccine.

Study design and analysis

For GBS and most other outcomes, the SCRI design (6, 7, 12, 13) was prespecified as primary because of its ability to control for individual confounders and its greater statistical power in comparison with the case-centered approach. The latter, used to adjust for seasonality, was prespecified as secondary for GBS. For selected rare outcomes, we used the current-vs.-historical comparison method instead, because of its greater statistical power.

In SCRI analysis, the risk of the outcome in a predefined "risk" interval immediately following immunization was compared with the risk in an unexposed control interval either before vaccination ("prevaccination control interval") or after the risk interval ("postvaccination control interval") (Web Table 2). We used the postvaccination control interval rather than the prevaccination control interval for outcomes for which we were concerned about bias due to indication or contraindication. We estimated the incidence rate ratio (IRR) for each outcome by fitting a conditional Poisson regression model using data from cases only.

For GBS, we conducted a season-adjusted analysis using the case-centered method of Fireman et al. (14, 15). This approach evaluates the probability that persons with the outcome received the vaccine of interest within a prior specified time period, based on the timing of vaccination in the general study population. Logistic regression models were used, with the offset term based on the probability that a person had been vaccinated during the 42 days prior to GBS onset, adjusted for data partner, sex, and age group.

In current-vs.-historical comparisons, rates of potential adverse events among MIV and LAMV vaccinees during the 2009–2010 season were compared with event rates among recipients of TIV during the prior 2 influenza seasons. We conducted logistic regression analysis in which the outcome was whether the adverse event of interest had occurred within the risk interval, and the predictor was whether the person had received the vaccine of interest (MIV or LAMV) during the 2009–2010 season or had received TIV during historical seasons. Analyses were adjusted for data partner, sex, and age group.

For GBS, the confirmed cases were the main group analyzed. In order to understand the range of plausible risk estimates, we conducted sensitivity analyses including 1) the probable and indeterminate cases and 2) the inconclusive cases as well.

Prior to analysis, a decision was made to reject the null hypothesis with a type 1 error rate of 0.05 for the analyses of GBS and anaphylaxis, the 2 outcomes of greatest concern, and 0.01 for all other outcomes, the latter to minimize false-positive findings due to multiple testing.

In investigating statistically significant findings for which case counts were high enough and postvaccination observation periods long enough, we applied a temporal scan statistic (16) to the distribution of cases during the weeks after vaccination among MIV-only vaccinees, to determine whether there was any statistically significant temporal clustering, adjusting for the many potential cluster locations and sizes. Freely available SaTScan software (www.satscan.org) was used.

RESULTS

Vaccine doses

PRISM captured 3,040,363 first doses of 2009 H1N1 vaccine, of which 2,880,797 were MIV, 156,899 were LAMV administered at the recommended ages of 2–49 years, and an additional 2,667 were LAMV given outside of this age range. More than 90% of 2009 H1N1 doses were retained for analysis after truncation of data to avoid bias due to data lag (Web Appendix). Among subjects for whom registry data were potentially available, registries contributed 63% of 2009 H1N1 first doses, but apparent vaccine coverage was 11%, lower than the national estimate of 27% (17).

Medical record review of potential GBS cases

No potential GBS cases were identified after more than 150,000 identified LAMV immunizations, so all GBS analyses described here concern MIV only.

Table 1. Risks of Health Outcomes of Interest Occurring After Receipt of a First Dose of Inactivated or Not-Otherwise-Specified 2009 H1N1 Influenza Vaccine, United States, 2009–2010

Vaccination Group, Analytical Design, and Outcome[a]	Age Range	Risk Interval, days	Control Interval, days	No. of Events in Risk Interval	Expected No. of Events[b]	Risk Estimate[c]	99% CI or 95% CI[d]	*P* Value[e]
2009 H1N1 Vaccinees With or Without Seasonal Influenza Vaccine During the 2009–2010 Season (Sets a + b + c + d in Figure 1)								
SCRI analysis								
Demyelinating disease	≥25 years	1–42	Pre, −98 to −15	348	344	1.01	0.86, 1.20	0.84
Peripheral nervous system disorders	6 months–24 years	1–42	Pre, −98 to −15	95	82	1.17	0.84, 1.63	0.24
	≥25 years	1–42	Pre, −98 to −15	2,232	2,262	0.99	0.92, 1.05	0.61
Bell's palsy	6 months–24 years	1–42	Pre, −56 to −15	23	19	1.21	0.54, 2.69	0.54
	≥25 years	1–42	Pre, −56 to −15	128	104	1.23	0.88, 1.73	0.12
Other cranial nerve disorders	≥25 years	1–42	Pre, −98 to −15	304	285	1.07	0.89, 1.28	0.35
Allergic reactions	≥6 months	1–2	Post, 8–9	244	209	1.17	0.92, 1.49	0.10
Hemorrhagic stroke	6 months–24 years	1–42	Post, 43–84	17	15	1.13	0.46, 2.82	0.72
	≥25 years	1–42	Post, 43–84	125	147	0.85	0.62, 1.16	0.18
Ischemic stroke	6 months–24 years	1–42	Post, 43–84	13	6	2.17	0.61, 7.73	0.12
	≥25 years	1–42	Post, 43–84	404	439	0.92	0.77, 1.10	0.23
Seizures	6 months–24 years	0–1	Post, 7–8	12	22	0.55	0.22, 1.37	0.09
	≥25 years	0–1	Post, 7–8	7	14	0.50	0.15, 1.65	0.13
Current-vs.-historical analysis								
Demyelinating disease	6 months–24 years	1–42	1–42	31	32.6	0.95	0.54, 1.68	0.82
Encephalitis/myelitis/encephalomyelitis	≥6 months	1–21	1–21	7	8.2	0.85	0.28, 2.54	0.69
Other cranial nerve disorders	6 months–24 years	1–42	1–42	48	56.5	0.85	0.55, 1.32	0.35
Ataxia	≥6 months	1–42	1–42	25	34.7	0.72	0.41, 1.28	0.14
Anaphylaxis	≥6 months	0–2	0–2	6	8.0	0.75	0.29, 1.90	0.54
2009 H1N1 Vaccinees Without Proximate Seasonal Influenza Vaccine								
SCRI analysis (set a in Figure 1)								
Demyelinating disease	≥25 years	1–42	Pre, −98 to −15	171	171	1.00	0.79, 1.28	0.98
Peripheral nervous system disorders	6 months–24 years	1–42	Pre, −98 to −15	30	34	0.88	0.50, 1.55	0.57
	≥25 years	1–42	Pre, −98 to −15	1,099	984	1.12	1.01, 1.23	0.003
Bell's palsy	6 months–24 years	1–42	Pre, −56 to −15	10	8	1.25	0.37, 4.24	0.64
	≥25 years	1–42	Pre, −56 to −15	79	48	1.65	1.03, 2.64	0.006
Other cranial nerve disorders	≥25 years	1–42	Pre, −98 to −15	144	135	1.07	0.82, 1.40	0.51
Allergic reactions	≥6 months	1–2	Post, 8–9	82	77	1.06	0.71, 1.60	0.69
Hemorrhagic stroke	6 months–24 years	1–42	Post, 43–84	6	6	1.00	0.23, 4.42	1.00
	≥25 years	1–42	Post, 43–84	64	69	0.93	0.59, 1.45	0.66
Ischemic stroke	6 months–24 years	1–42	Post, 43–84	5	2	2.50	0.29, 21.6	0.27
	≥25 years	1–42	Post, 43–84	204	232	0.88	0.69, 1.13	0.18
Seizures	6 months–24 years	0–1	Post, 7–8	2	8	0.25	0.03, 1.92	0.08
	≥25 years	0–1	Post, 7–8	4	9	0.44	0.09, 2.09	0.18

Table continues

Table 1. Continued

Vaccination Group, Analytical Design, and Outcome[a]	Age Range	Risk Interval, days	Control Interval, days	No. of Events in Risk Interval	Expected No. of Events[b]	Risk Estimate[c]	99% CI or 95% CI[d]	*P* Value[e]
Current-vs.-historical analysis (sets a + b in Figure 1)								
Demyelinating disease	6 months–24 years	1–42	1–42	17	20.7	0.82	0.40, 1.68	0.47
Encephalitis/myelitis/encephalomyelitis	≥6 months	1–21	1–21	4	6.5	0.62	0.15, 2.49	0.37
Other cranial nerve disorders	6 months–24 years	1–42	1–42	29	33.3	0.87	0.51, 1.49	0.52
Ataxia	≥6 months	1–42	1–42	19	28.4	0.67	0.35, 1.29	0.12
Anaphylaxis	≥6 months	0–2	0–2	4	6.0	0.67	0.22, 2.00	0.47
2009 H1N1 Vaccinees With Concomitantly Administered Seasonal Influenza Vaccine (Set d in Figure 1)								
SCRI analysis								
Demyelinating disease	≥25 years	1–42	Pre, −98 to −15	31	21	1.48	0.80, 2.72	0.10
Peripheral nervous system disorders	6 months–24 years	1–42	Pre, −98 to −15	12	8	1.50	0.56, 4.01	0.29
	≥25 years	1–42	Pre, −98 to −15	174	155	1.12	0.88, 1.43	0.22
Bell's palsy	6 months–24 years	1–42	Pre, −56 to −15	4	1	4.00	0.22, 71.2	0.21
	≥25 years	1–42	Pre, −56 to −15	12	9	1.33	0.43, 4.15	0.51
Other cranial nerve disorders	≥25 years	1–42	Pre, −98 to −15	37	22	1.72	0.97, 3.07	0.02
Allergic reactions	≥6 months	1–2	Post, 8–9	41	17	2.41	1.15, 5.07	0.002
Hemorrhagic stroke	6 months–24 years	1–42	Post, 43–84	4	2	2.00	0.21, 18.6	0.42
	≥25 years	1–42	Post, 43–84	9	8	1.13	0.32, 3.93	0.81
Ischemic stroke	6 months–24 years	1–42	Post, 43–84	2	1	2.00	0.09, 46. 9	0.57
	≥25 years	1–42	Post, 43–84	23	22	1.05	0.49, 2.25	0.88
Seizures	6 months–24 years	0–1	Post, 7–8	3	3	1.00	0.12, 8.19	1.00
	≥25 years	0–1	Post, 7–8	1	0			
Current-vs.-historical analysis								
Demyelinating disease	6 months–24 years	1–42	1–42	5	4.8	1.04	0.31, 3.45	0.93
Encephalitis/myelitis/encephalomyelitis	≥6 months	1–21	1–21	3	0.9	3.45	0.70, 17.0	0.05
Other cranial nerve disorders	6 months–24 years	1–42	1–42	7	8.1	0.86	0.32, 2.34	0.70
Ataxia	≥6 months	1–42	1–42	3	3.0	1.01	0.22, 4.60	0.98
Anaphylaxis	≥6 months	0–2	0–2	1	0.8	1.20	0.16, 9.04	0.86

Abbreviations: CI, confidence interval; Post, postvaccination control interval; Pre, prevaccination control interval; SCRI, self-controlled risk interval.

[a] All outcomes shown were based on *International Classification of Diseases*, Ninth Revision, codes observed in computerized claims data and were not validated by chart review.

[b] For the current-vs.-historical analysis, the expected number of events was based on historical rates; for the SCRI analysis, it was scaled to a control interval of the same length as the risk interval.

[c] Incidence rate ratio for SCRI analyses; odds ratio for current-vs.-historical analyses.

[d] A 95% CI was used for anaphylaxis; 99% CIs were used for all other outcomes shown in the table, to account for multiple testing.

[e] All *P* values are 2-sided.

Between the 2 data partners participating in medical record review, 50 potential GBS cases occurring after MIV dose 1 were identified via ICD-9 codes in claims data. Of these, 32 (64%) were ruled out before abstraction based on either a local clinician's review of the medical record ($n = 29$) or a PRISM clinician's review of the claims pattern ($n = 3$), 2 (4%) were instances of a provider misfiling claims attributing GBS to a different family member, 5 (10%) were inconclusive because of unobtainable charts, and 11 (22%) were abstracted and adjudicated. The proportions of cases abstracted and adjudicated were similar for the risk and control intervals.

Of the 11 abstracted and adjudicated cases, 5 were confirmed, all at Brighton level 2; 2 were considered probable by virtue of documentation of a GBS diagnosis by a physician (a neurologist in both cases); 3 were ruled out; and 1 was classified as indeterminate.

The positive predictive value of the ICD-9-code-based GBS algorithm was 5/42 or 12%, excluding the inconclusive, indeterminate, and probable cases. If the probable cases are included with the confirmed cases, this figure becomes 7/44 or 16%. Three of the 7 cases (43%) in the risk interval and 2 of the 4 cases (50%) in the control interval were confirmed.

Of the 5 confirmed cases, 4 persons were white and 1 was of unknown race. Two of the 3 persons with confirmed cases in the risk interval were female and the other was male; both cases in the control interval were male. Of the 3 cases in the risk interval, 1 was under 18 years of age, 1 was in the age group 18–49 years, and 1 was in the age group ≥65 years; both cases in the control interval were under age 18 years. One of the 3 cases in the risk interval and 1 of the 2 cases in the control interval had received seasonal influenza vaccine within the 6 weeks prior to MIV vaccination. One of the 3 cases in the risk interval and 1 of the 2 cases in the control interval had had a respiratory or gastrointestinal illness within the 6 weeks prior to GBS onset.

Analyses of confirmed GBS cases

In the SCRI analysis, with 3 cases in the 42-day risk interval and 2 cases in the 70-day control interval, the IRR was 2.50 (95% confidence interval (CI): 0.42, 15.0). In the case-centered analysis of the same 5 cases, the odds ratio was 1.15 (95% CI: 0.07, 18.6).

The first sensitivity analysis included the 3 probable and indeterminate cases, with 5 in the risk interval and 3 in the control interval. The risk estimate in the SCRI analysis changed to 2.78 (95% CI: 0.66, 11.6), and in the case-centered analysis it changed to 2.53 (95% CI: 0.38, 16.8). The second sensitivity analysis included, in addition, the 5 inconclusive cases, with 7 cases in the risk interval and 6 in the control interval, and it produced risk estimates of 1.94 (95% CI: 0.65, 5.79) for the SCRI analysis and 2.27 (95% CI: 0.57, 9.05) for the case-centered analysis.

Analyses of ICD-9-code-identified outcomes after immunization with MIV

Results for other outcomes occurring after receipt of MIV are shown in Table 1. In analyses of the primary vaccination group, MIV with or without seasonal influenza vaccine, none of the risk estimates were statistically significant. For MIV administered without overlapping exposure to seasonal influenza vaccine, there were 2 instances of statistically significant elevated risk, for peripheral nervous system disorders in persons aged ≥25 years (IRR = 1.12, 99% CI: 1.01, 1.23; $P = 0.003$) and for Bell's palsy in persons aged ≥25 years (IRR = 1.65, 99% CI: 1.03, 2.64; $P = 0.006$). For MIV and seasonal influenza vaccine doses administered concomitantly, the IRR for allergic reactions (excluding anaphylaxis) was 2.41 (99% CI: 1.15, 5.07; $P = 0.002$).

For these 3 outcomes, we compared risk estimates across several categories of vaccinees, including TIV only. For peripheral nervous system disorders, the IRR among all MIV vaccinees was 0.99 (99% CI: 0.92, 1.05), compared with the above-mentioned IRR of 1.12 (99% CI: 1.01, 1.23) for MIV-only recipients and 1.01 (99% CI: 0.97, 1.06) for TIV-only recipients. For Bell's palsy, the IRR among all MIV vaccinees was 1.23 (99% CI: 0.88, 1.73), in the same direction but not as high as the 1.65 seen in the MIV-only vaccinees; the IRR among TIV-only recipients was 1.03 (99% CI: 0.86, 1.24). For allergic reactions, in the MIV-only group, there was no evidence of an elevated risk (IRR = 1.06, 99% CI: 0.71, 1.60). In the TIV-only group, however, there were 463 cases in the risk interval and 334 in the control interval, for a statistically significant IRR of 1.39 (99% CI: 1.15, 1.67; $P < 0.0001$).

Applying the temporal scan statistic in MIV-only recipients, we found no significant temporal clustering during the 42 days after vaccination for peripheral nervous system disorders in persons aged ≥25 years or during the 60 days after vaccination for Bell's palsy in persons aged ≥25 years ($P = 0.13$ and $P = 0.35$, respectively).

Analyses of ICD-9-code-identified outcomes after immunization with LAMV

In LAMV analyses, the 1 statistically significant elevated risk was for wheezing in the age group 2–24 years. There were 46 cases in the risk interval and 21 in the control interval, for an IRR of 2.19 (99% CI: 1.11, 4.32; $P = 0.003$).

DISCUSSION

Major findings

We observed an elevated but nonsignificant risk of GBS after MIV vaccination, using chart-confirmed data. When evaluated in terms of published background rates, which in the United States are in the range of 1–2 cases per 100,000 person-years (18), the observed IRR of 2.5, *if true*, would translate to approximately 2–3 excess cases per million vaccinations, well under the 8.8 excess cases per million vaccinations observed during the swine flu vaccination program of 1976 (1). (Note that there is uncertainty in the background rate because of the rarity of GBS, possible variation in the age structures of the populations studied, and differences in case-finding among study methods (prospective vs. retrospective, etc.).) Evaluations pooling data from multiple systems that monitored 2009 H1N1 vaccine safety in the United States and other countries are needed to develop more precise risk estimates.

Recent European studies have suggested that prior respiratory infection is a confounder that may lead to spurious associations between influenza vaccination and GBS (19, 20). In the Vaccine Safety Datalink evaluation, there was some evidence to support this hypothesis (15). Our study did not evaluate prior respiratory infection as a confounding factor, and the results should be interpreted with this limitation in mind.

Other health outcomes

For the other prespecified outcomes examined, our results did not suggest clinically significant safety concerns using ICD-9 data. Three of the 54 analyses identified a statistically significant elevated risk of an adverse health outcome after receipt of MIV, but this does not take into account the multiple testing: If the null hypothesis of no excess risk for any of the outcomes is true, then statistically, the expected number of statistically significant results using our selected type 1 error rates is 0.66. With such an expected value, it would not be surprising to see a few statistically significant results due to chance alone. For each of the 3 analyses, we discuss our interpretation of the findings below.

For peripheral nervous system disorders in the age group $\geq$25 years, we identified an IRR of 1.12 (99% CI: 1.01, 1.23) after administration of MIV alone. However, we do not consider this finding clinically meaningful, mainly because of the small incremental risk identified. In addition, the temporal scan statistic analysis did not find significant clustering of cases after vaccination.

For Bell's palsy in the age group $\geq$25 years, the statistically significant increase in risk observed after MIV alone might have been due to confounding by seasonality. The Vaccine Safety Datalink Project also found a statistically significant excess risk of Bell's palsy after MIV in its SCRI analysis, but further analysis using the temporal scan statistic as well as the case-centered method failed to provide evidence for a true association (6). There is published evidence of seasonality in Bell's palsy, with a significantly higher rate during cold months versus warm months, possibly related to reactivation of herpes simplex infection due to seasonally varying stressors (21), and this may have played a role in our findings. Most MIV recipients were vaccinated between October 2009 and January 2010, and for many vaccinees the long prevaccination control interval could have occurred at a time of quite different conditions than those prevailing during the risk interval. The data elements available for non-chart-confirmed outcomes did not enable us to control for seasonality, but the temporal scan statistic did not find statistically significant clusters.

For allergic reactions, the risk was elevated for MIV administered concomitantly with seasonal influenza vaccine but not for MIV alone. Analysis of TIV alone found a slight but highly statistically significant increase in risk. Concomitant administration of these 2 vaccines *might* result in an increased risk of allergic reactions. However, the Vaccine Safety Datalink Project found no statistically significant increase in the risk of allergic reactions after concomitant administration of MIV and seasonal influenza vaccine (unpublished data; available from G. M. L.).

We found 1 statistically significant elevated risk after LAMV, for wheezing in the age group 2–24 years. Indeed, in prelicensure trials, an increased risk of wheezing after LAMV was seen in children under 2 years of age, and there is a precaution against its use in people with a history of asthma (22). However, our result should be treated with skepticism, because of the lack of chart confirmation, inclusion of persons with a history of asthma, and inability to adjust for seasonality. No statistically significant increased risk was apparent in the Vaccine Safety Datalink Project's end-of-surveillance analysis, with more than 270,000 LAMV first doses administered (unpublished data).

Strengths and limitations

This study used multiple analysis methods, allowing us to select the most appropriate analysis for each outcome. Each method had advantages and disadvantages. The strength of the SCRI method is its ability to control for individual confounders that do not vary over the observation period, including sex, genetic factors, socioeconomic factors, and underlying chronic disease. This is accomplished by comparing numbers of events in risk and control periods within vaccinees. However, time-varying confounders, such as seasonality in both vaccination and outcome, can affect SCRI risk estimates and require explicit adjustment, which our temporal aggregate data elements were insufficiently detailed to permit. The main strength of the current-vs.-historical comparison is its statistical power, obtained from multiple years of historical data. Thus, it is helpful in the analysis of rare outcomes. However, vaccinated cohorts in current and historical periods may differ from each other, contributing to confounding. An advantage of the case-centered approach as compared with the SCRI approach is adjustment for confounding due to seasonality, achieved by incorporating information on the timing of vaccination in the general study population. However, disadvantages in comparison with the SCRI method are that it is not self-controlled and that it has less statistical power.

One limitation of our study was that the only chart-validated outcome was GBS. For unvalidated outcome definitions with low positive predictive value, this could have led to attenuation and lower statistical power, and possibly missed true excess risks.

The percentage of potential GBS cases identified by ICD-9 codes that were eventually confirmed after medical record review was 12%, lower than in other studies. This was most likely because PRISM used health insurance claims data from hundreds of clinical locations. In addition, our study's requirement for a potential GBS case to undergo a medical record review was deliberately set low, at $\geq$1 events with GBS diagnoses, in order to maximize sensitivity, while in other evaluations the requirement has been set at $\geq$2 events with GBS diagnoses (P. Velentgas, Outcome Sciences, Inc. (Cambridge, Massachusetts), personal communication, 2010).

In conclusion, in this surveillance effort, we observed a possibly elevated but not statistically significantly increased risk of GBS after receipt of inactivated 2009 H1N1 vaccine. Our other findings provided reassurance that the risks of other health outcomes of interest were, in general, not elevated after 2009 H1N1 vaccination. In future studies, investigators should combine data on GBS from multiple systems to achieve

better statistical power and should attempt to control for confounding by prior respiratory or gastrointestinal infection.

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