Evaluation of Cardiovascular Safety of COVID19 Vaccines in VAERS

Matthew Clark (m.clark@elsevier.com)
Elsevier https://orcid.org/0000-0002-9348-3528

Brief Communication

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Abstract

While COVID19 vaccines have been administered to over 100 million patients, a small minority (40,000) have reported adverse events, and an even smaller fraction have reported cardiovascular issues (~500). There have been reporting of a few unusual cardiovascular events associated with some varieties of COVID19 vaccines resulting in pauses of use. Here we analyze the reports of adverse events associated with the COVID19 vaccines in the FDA Vaccine Adverse Event Reporting System (VAERS) database to apply standard methods of detecting safety signals. In this work we apply this methodology to reports in the FDA VAERS database and have identified concerning signals for pulmonary embolism and myocardial infarction associated with COVID19 vaccines. These signals are compared with cardiovascular events reported in connection with influenza (FLU3) vaccines that are administered to a similar population. While signals of these events are higher for COVID19 than other vaccines, the incidence rates are comparable to the normally expected rate for non-vaccinated individuals.

Introduction

In this work we apply this methodology to reports in the FDA VAERS database and have identified concerning signals for pulmonary embolism and myocardial infarction associated with COVID19 vaccines. These signals are compared with cardiovascular events reported in connection with influenza (FLU3) vaccines that are administered to a similar population. While signals of these events are higher for COVID19 than other vaccines, the incidence rates are comparable to the normally expected rate for non-vaccinated individuals.

Methods

The US FDA VAERS reports of vaccine adverse events were downloaded from the FDA website on 9-Apr-2021[5] Data received by VAERS from 11-Dec-2017 to 9-Apr-2021 were used for the analytics. The former date was chosen to provide sufficient data to compare to COVID19 vaccines which became available on 11-Dec-2020. However, the results are somewhat dependent on this choice. Including more historic data tends to amplify the safety signals.

The tables were loaded in to a PostgreSQL database system for convenient linking and querying of the tables with SQL to produce standard 2x2 contingency tables of counts of cases in each category and statistics were computed with R and the R openEBGM package.[6,7,8]

Since some events reported in VAERS are sequelae of the disease itself, and not the vaccine, the analysis omitted records where the patient was diagnosed with the disease intended to be prevented by the vaccine. In addition only events reported within 21 days of vaccine administration were considered. The resulting data was used to create a 2x2 contingency table for each vaccine-event combination with the cells filled with counts of patient cases in each category.

The Empirical Bayes Geometric Mean method (EBGM) was used to compute the relationship between vaccine and the symptoms reported.[9,10] This method is generally accepted as the most robust way to compute therapeutic-adverse event relations, and has been used in other evaluations of vaccine adverse events.[11] FDA guidelines suggest a value of 2.0 as the cutoff for a safety signal.[12] In this study we use the lower boundary of the 90% confidence (0.05 – 0.95 bounds) interval as a conservative estimate of risk, "EBGM .05" In this case the results were stratified by gender and age rounded to 20 year groups. Date stratification was not used because all of the COVID19 reports are grouped together in a limited date range. Therefore date stratification tends to treat date as a confounding variable and substantially lowers the safety signal.

Results

COVID19

Figure 1 shows the most prevalent events adverse events reported in VAERS for all COVID19 vaccines. The EBGM values near 1.0 suggest that the risk of experiencing these is similar to that of any other vaccine in the time period. The number of cases is high because each patient can report several of these events.

Figure 2 shows selected significant cardiovascular events reported for COVID19 vaccine, stratified by age ranges to show age-related differences in risk. The EBGM values reflect the risk above all other vaccines in the time period, and values above 2.0 are considered significant.

One can see from Figure 2 that the age range 60-80 may have a safety signal for these cardiovascular issues, while older and younger age ranges have EGBM values below the cutoff level of 2.0. With all ages combined the EBGM values also suggest signs of safety issues even with stratification by age, however these can be attributed mostly to the results from the 60-80 age group.

Figure 3 shows the counts used in the 2x2 tables that relate COVID19 vaccine to pulmonary embolism and acute myocardial infarction in the 60-80 age group, the figures reflecting the number of patients in each category.

Influenza

As a comparative control the same process was applied to the influenza FLU3 (trivalent) vaccine type, which has the most vaccine event reports in VAERS in the time period studied. The most common events associated with FLU3 vaccines are shown in Figure 4. As with COVID19 vaccines, these are common but not specifically more so for FLU3 than for other vaccines, as indicated by EBGM values close to 1.0.

Figure 5 shows the 2x2 table for pulmonary embolism associated with FLU3 vaccine for the 60-80 year age range for comparison with the COVID19 data in Figure 3. The EBGM .05 value for this association is

far below the threshold for significance at 0.23. (EBGM 0.5 is 0.56) The comparison with all other vaccines administered to patients in this age range suggests that it is less likely than other vaccines to be associated with this issue. The median age for all FLU3 recipients is older than COVID19 recipients at 69 years, vs 48 years for COVID19. Thus the difference cannot be attributed solely to the difference in age distributions of the patient populations.

Discussion

Conclusion of causality for cardiac events from vaccine administration is difficult. Various medical events may happen to occur fortuitously after vaccine administration, and even without vaccinations. The EGBM values computed from VAERS data represent the increased odds of experiencing the event *above that experienced for other vaccines reported in VAERS – not absolute risk for the population.* The raw rate so far for pulmonary embolism after COVID19 vaccination for example is 130 cases out of 101 million doses – roughly 1 in 1 million – which is close to the general population incidence worldwide.[13]

Nonetheless, the statistics show that cardiovascular events have been reported more often after COVID19 vaccine administration than for the other adverse event cases of administration of other vaccines. While this is not determinative for a connection it is concerning. The statistically significant effects at this time to be focused in the age group of 60-80 years.

There are several factors that may contribute to this. The medically infirm have been a priority for early COVID19 vaccination. In addition publicity may have created a reporting bias that did not exist for FLU3 vaccines, especially after publicly announced pauses related to cardiovascular effects. COVID19 is singular in having a specific smartphone app provided to recipients to ease reporting of adverse events.[14] On the other hand the FLU3 influenza vaccine is administered annually to a generally older population than COVID19 without similar reporting rates of cardiac issues.

The comparison of the low incidence, 1 in 1 million, with the EBGM computed rates suggests that the methodology for signal detection could be improved by more systematic reporting of adverse events.

Conclusions

Application of accepted signal detection methods for COVID19 vaccine reports in VAERS results in several signals linking them to cardiovascular adverse events in the 60-80 year age group. These signals are above those of other vaccines administered to a similar demographic, such as the trivalent influenza vaccine. However the incidence rate for these events remains comparable to values for non-vaccinated individuals.

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Figures

Symptom	Cases	EBGM 0.05
Headache	9,168	1.2
Pyrexia	7,381	1.0
Chills	7,375	1.2
Fatigue	6,599	1.2
Pain	6,347	0.9

Figure 1

Cases and EBGM05 for the Most prevalent events reported for COVID19 vaccine. Multiple Adverse Events can be Reported for each Case.

	Pulmonary Embolism		Acute Myocardial Infarction		Cerebrovascular Accident	
Age range	*Cases*	*EBGM .05*	*Cases*	*EBGM .05*	*Cases*	*EBGM .05*
0-20	1	0.5	1	0.5	0	-
20-40	16	1.4	5	1.0	8	1.0
40-60	31	1.3	10	0.9	28	1.3
60-80	60	**2.9**	35	**2.7**	103	**3.0**
80-100	22	1.3	20	1.3	109	1.8
All	130	2.1	71	2.0	251	2.1

Figure 2

Count of reports and EBGM05 for Significant Cardiovascular Events Reported for COVID19 by Age Range, and for all ages combined

	Pulmonary embolism	Other Events	Acute myocardial infarction	Other Events
COVID19	60	8615	35	8,640
Other Vaccines	10	31,791	2	31,799

Figure 3

2x2 Tables for COVID91 Vaccine and Pulmonary Embolism and Acute Myocardial Infarction for patients 60-80 years old for VAERS reports from 2017-2021.

Symptom	Cases	EBGM .05
Pain in extremity	771	1.1
Injection site pain	657	0.9
Pain	649	0.9
Injection site erythema	644	0.9
Pyrexia	586	0.7

Figure 4

Cases and EBGM05 for the Most prevalent adverse events reported for FLU3 vaccine. Multiple Adverse Events can be Reported for each Case.

	Pulmonary embolism	All other adverse events
FLU3	2	3,415
All other vaccines	68	36,991

Figure 5

2x2 Table for FLU3 Vaccine and Pulmonary embolism for patients 60-80 years old for VAERS reports from 2017-2021.