Title: Comparative safety of mRNA COVID-19 vaccines to influenza vaccines: a pharmacovigilance analysis of WHO international database

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Abstract

Background: Two mRNA vaccines developed by Pfizer-BioNTech and Moderna are being roll-out. Despite the high volume of emerging evidence regarding adverse events (AEs) associated with the COVID-19 mRNA vaccines, the previous studies have thus far been largely based on the comparison between vaccinated and unvaccinated control, possibly standing out the AE risks with COVID-19 mRNA vaccination. Comparing the safety profile of mRNA vaccinated individuals with otherwise vaccinated individuals would enable more relevant assessment for the safety of mRNA vaccination.

Methods: We designed a comparative safety study between 18,755 and 27,895 individuals reported to VigiBase for adverse events following immunization (AEFI) with mRNA COVID-19 and influenza vaccines, respectively, from January 1, 2020, to January 17, 2021. We employed disproportionality analysis to rapidly detect relevant safety signals and compared comparative risks of diverse span of AEFIs for the vaccines.

Results: The safety profile of novel mRNA vaccines was divergent from that of influenza vaccines. The overall pattern suggested that systematic reactions like chill, myalgia, fatigue were more noticeable with the mRNA COVID-19 vaccine, while injection site reactogenicity events were more prevalent with the influenza vaccine. Compared to the influenza vaccine, mRNA COVID-19 vaccines demonstrated a significantly higher risk for a few manageable cardiovascular complications such as hypertensive crisis (adjusted reporting odds ratio [ROR], 12.72; 95% confidence interval [CI], 2.47–65.54) and supraventricular tachycardia (adjusted ROR, 7.94; 95% CI, 2.62–24.00), but lower risk of neurological complications such as syncope, neuralgia, loss of consciousness, Guillain-Barre syndrome, gait disturbance, visual impairment, and dyskinesia.

Conclusions: This study has not identified significant safety concerns regarding mRNA vaccination in real-world settings. The overall safety profile patterned a lower risk of serious AEFI following mRNA vaccines compared to influenza vaccines.

Introduction

In May 2020, the 42nd Global Advisory Committee on Vaccine Safety (GACVS) addressed pharmacovigilance preparedness for the launch of the future COVID-19 vaccines;[1] experts have voiced that achieving herd immunity at the population level through mass vaccination is a potential strategy to control coronavirus disease (COVID-19).[2] Two vaccines, the Pfizer-BioNTech mRNA and the Moderna mRNA vaccine, have completed phase 3 trials,[2-5] and are being actively roll-out. These mRNA vaccines are based on new technologies that have not been deployed to the general population, and as such, concerns about their safety in real-world settings intersect with optimism for their extraordinarily encouraging efficacy in clinical trials.[2, 3, 6]

Although the safety profiles of mRNA vaccines have been evaluated in serial clinical trials,[4, 5, 7] concerns remain as the safety evaluations in clinical trials were limited to relatively healthy people, excluding vulnerable populations such as children, pregnant women, and individuals with severe underlying illnesses.[2, 3, 7] However, due to vaccine shortages,[3, 8, 9] vulnerable patients at high risk for severe courses of COVID-19 are prioritized for vaccination.[10] Therefore, the safety results from these trials may be unrepresentative of the populations that are prioritized to receive them.[11] This discrepancy between the trial settings and real-world roll-out strategy warrants urgent interim post-implementation surveillance.[3]

Despite the high volume of emerging evidence regarding adverse events (AEs) associated with the COVID-19 mRNA vaccines, the previous studies have thus far been largely based on the comparison between vaccinated and unvaccinated control, possibly standing out the AE risks with COVID-19 mRNA vaccination. Comparing the safety profile of mRNA vaccinated individuals with otherwise vaccinated individuals would enable more relevant assessment for the safety of mRNA vaccination.

This study aimed to conduct post-implementation pharmacovigilance analysis for the Pfizer-BioNTech and Moderna mRNA vaccines by investigating vaccinated individuals who were reported for AEFIs to VigiBase, the global database of individual case safety reports (ICSRs) provided by the WHO. To the best of our knowledge, this study is the first to report the comparative safety of the mRNA COVID-19 vaccine against conventional influenza vaccines.

Methods

Study design and data source

The large post-implementation pharmacovigilance study was conducted using VigiBase, a WHO global deduplicated individual case safety reports (ICSR) database,[12] which has collected adverse event (AE) reports from over 130 countries and 23 million ICSRs since inception in 1967. VigiBase is managed by the Uppsala Monitoring Center (UMC, Sweden). For the database, reported adverse reactions were coded into the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs).[13]

AE following immunization (AEFI) is defined as any untoward medical event that follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine.[14] AEFIs were reported from various sources, including healthcare professionals, pharmaceutical companies, and patients, and the sources are generally provided with post-market notifications. We extracted AEFI cases from VigiBase reported with two novel mRNA COVID-19 vaccines, Pfizer-BioNTech and Moderna mRNA vaccines, and influenza vaccines from the beginning of 2020 to January 17, 2021. AEFI were reported from America, Europe, and Asia with COVID-19 vaccines and America, Europe, Asia, Africa, and Australia with influenza vaccines. The Ethics Committee of Yonsei University Severance Hospital, Seoul, Republic of Korea, approved this study and granted a waiver of review from the formal Institutional Review Board (no. 4-2020-1379) for the use of de-identified data.

Baseline characteristics

The baseline characteristics of individuals reported to VigiBase for any AEFI after mRNA COVID-19 and influenza vaccination are described in Table 1. The VigiBase provides data on demographics (age, sex, and regions), drug history (components, dosage, regimen, indications, and duration of administration), AEs (MedDRA PT classification terms, time to onset, seriousness of AEs, fetal outcomes, and death), and general administrative information (date of report, reports from clinical trials, and reporter type).

Common AEFI was defined as AEFI with a frequency ≥ 1% of all COVID-19 vaccinated individuals reported for any adverse reaction to VigiBase. A serious AEFI is defined as an AEFI that is associated with death, is life-threatening, involves hospitalization or its prolongation, results in chronic damage/disability, and requires interventions to prevent permanent impairment.[14] The selection process of common and serious AEFI is presented in Figure S1-2.

Removal of potentially false reports

Potentially false reports are partially prevented at an early data collection stage as most national centers review case reports before they are sent to UMC, and incoming reports to the VigiBase are systematically checked according to pre-defined quality criteria; unmet reports are flagged and subsequently inspected by UMC for reprocessing.[12] Despite the effort, the noise safety signals may still exist, and we triaged to select validated safety signals using two approaches. First, we incorporated information component (IC), an indicator value for disproportionate reporting, that has been proven to be effective in avoiding false positive[15] and thus suitable for conducting pharmacovigilance studies using spontaneous adverse reaction reporting databases.[16-18] Second, we triaged to remove potentially

false reports of adverse drug reactions (ADRs) using disproportionality analysis and clinical appraisal. Given that false reports by chance are less likely to survive in stringent association tests, we ran disproportionality analyses for 1980 ADRs and excluded non-significant ADRs that were deemed clinically irrelevant with vaccines or potentially containing false reports, leaving 49 ADRs subjected to comparative analysis of mRNA COVID-19 and influenza vaccines. We further excluded ADRs that were unlikely to be associated with vaccination (i.e., chronic diseases) by manual review. Death, anaphylactic reactions, and selected 49 reported ADRs out of 1980 MedDRA PTs were summarized in Table 2 and analyzed for the comparative safety between the vaccines (Figure 1). Our careful approach of using those reports deemed genuine and clinically meaningful for our comparative analyses minimized the risk of false reports driving the misleading results. The detailed triage process for AEFI is demonstrated in Figure S1-2.

Comparative safety between COVID-19 and influenza vaccines

We have set influenza vaccines as a control given that they have endured iterative and thorough safety evaluations in the form of continued population-based post-market surveillance,[19] which have deemed them acceptably safe.[19, 20] The most frequently reported AEFIs and death after COVID-19 and influenza vaccination were compared in overall individuals reported to the database for AEFI. For uncommon but serious AEFIs that were identified to be potentially associated with the COVID-19 and influenza vaccine ($IC_{0.25} > 0$), the variable adjusted reporting odds ratio (ROR) between mRNA COVID-19 and influenza vaccines for specific AEFI was calculated as described in a previous study[18] to identify comparative safety. The adjusted ROR was used to quantify the degree of difference in odds of specific AEFI between the COVID-19 and influenza vaccine; since the odds of specific AEFI in the influenza vaccine was used as a control, ROR >1 indicates the higher risk of the AEFI in COVID-19 vaccines compared to influenza vaccines.

Statistical analysis

Given that VigiBase is composed of an extensive sample size (23,880,736 reports from inception), the data are eligible for disproportionality analysis (also known as case–non-case analysis), for which a large sample size is essential to guarantee applicable power and resolution.[21] When individuals exposed to a particular drug or vaccine (cases) have higher odds of reporting for certain adverse reaction than those not exposed to the drug or vaccine (non-cases), the association between the intervention and the adverse reaction suggests a possible safety signal. The IC and ROR are indicator parameters used to detect signals from the disproportionate analysis developed by the UMC; > 0 for lower 95% credibility interval endpoint of information component ($IC_{0.25}$) and > 1 for lower confidence interval (CI) of ROR are deemed significant, respectively. The formula for the calculation of the IC is presented in Table S3.

The IC was calculated by comparing observed and expected adverse reaction values using the Bayesian neural network method developed by the UMC,[15] and AEFIs associated with vaccines were detected. Probabilistic logic in intelligent systems (information theory) has been proven to be useful in controlling both big data and missing data.[15] This sensitive algorithm allowed the detection of early signals of mRNA vaccines and identified any potential risks. Of note, VigiBase were not designed to verify the causal relationship between the vaccine and health problems; instead, they were established to detect uncommon or unexpected patterns of AEFIs that imply possible safety concerns with vaccines.

We used a multivariable logistic regression model to produce age and sex adjusted ROR to compare ADR reporting between mRNA COVID-19 and influenza vaccines. Categorical variables are described as number count (%), and continuous variables are reported as median and interquartile range (IQR). The cases reported from COVID-19 and influenza vaccination and full database reports were compared using the $\chi 2$ test or Fisher's exact test. Statistical significance was defined as two-tailed $p < 0.05$. Comparative analyses were conducted using the IBM statistical package for the social sciences (SPSS) version 25.0 (SPSS Inc.).

Results

From January 1, 2020 to January 17, 2021, 18,755 and 27,895 AEFIs for the COVID-19 and influenza vaccines were reported to VigiBase. The AEFIs were most frequently reported from individuals under 64 years of age for COVID-19 and influenza vaccine (Table 1). Ninety-four individuals out of 18755 (0.5%) and 1326 individuals out of 28750 (4.8%) were reported from clinical trials for COVID-19 and influenza vaccines, respectively; the remaining reports were collected from spontaneous, non-clinical trial settings. A total of 23,880,736 and 2,720,221 ICSRs have been reported to VigiBase since the inception of the database (1967) and since 2020, respectively; and these reports were used as non-case. We identified safety signals associated with the vaccines, which are statistically significant (defined as $IC_{0.25} > 0$) compared to non-cases. (Table 2, Table S1).

Common adverse events

COVID-19 and influenza vaccines showed numerous statistically significant AEFIs, of which many were related to systemic reaction and injection site reactogenicity (Table 2). The ten most common AEFIs and deaths for the entire population are shown in Figure 1. A more detailed list of total AEFIs after COVID-19 vaccination and the selection process of common AEFIs are presented in the Supplementary material. In Figure 1, the cross-over pattern suggested that COVID-19-vaccinated individuals are more likely to experience systemic symptoms such as headache, myalgia, pyrexia, and fatigue, while influenza-vaccinated individuals were more likely to experience injection site reactogenicity events.

Uncommon but serious adverse events

Our analysis detected uncommon but serious AEFIs that were significantly associated with COVID–19 vaccines (Table 2).We assessed the comparative safety between COVID-19 and influenza vaccines for serious AEFIs by calculating the adjusted reporting odds ratio (ROR); cardiovascular AEFIs were more prevalent with COVID-19 vaccines: hypertensive crisis (adjusted ROR, 12.72; 95% CI, 2.47–65.54) and supraventricular tachycardia (adjusted ROR, 7.94; 95% CI, 2.62–24.00). In contrast, neurologic AEFIs, such as syncope, neuralgia, loss of consciousness, Guillain-Barre syndrome, gait disturbance, visual impairment, and dyskinesia were more prevalent with influenza vaccines (Fig. 2).

Death

COVID-19-vaccinated individuals experienced fewer deaths compared to those not exposed to the vaccines, possibly indicating a protective effect of the vaccine ($IC_{0.25}$, −1.66; ROR, 0.38; 95% CI, 0.31–0.46, Table 2). Influenza vaccinated individuals also experienced fewer deaths compared to those not exposed to the vaccines ($IC_{0.25}$, −2.22; ROR, 0.26; 95% CI, 0.21–0.31, Table 2).

Discussion

To the best of our knowledge, this is the first post-implementation pharmacovigilance study to investigate a diverse range of adverse reactions and provide comparative views for COVID-19 mRNA vaccine and influenza vaccine. This study has not identified significant safety concerns regarding mRNA vaccination in real-world settings. We have set influenza vaccines as a control given that they have undergone iterative and thorough safety evaluations in the form of continued population-based post-market surveillance,[19] which have deemed them acceptably safe.[19, 20] This interim safety surveillance data revealed that the safety profiles of novel mRNA vaccines may be divergent from those of influenza vaccines; the overall pattern suggested that systematic reactions like chill, myalgia, fatigue were more noticeable with the mRNA COVID-19 vaccine, while injection site reactogenicity events were more prevalent with the influenza vaccine (Fig. 1). The overall safety profile patterned a lower risk of serious AEFI following mRNA vaccines compared to influenza vaccines (Fig. 2).

The two novel vaccines contain mRNAs that encode spike proteins of SARS-CoV-2 formulated in a lipid nanoparticle. In principle, mRNA vaccines have a unique mechanism compared to conventional vaccines in terms of immunogenicity. Exogenously administered mRNA can strongly stimulate the innate immune system through RNA-sensing pattern recognition receptors.[22] Although mRNA has been structurally modified to reduce innate immune responses in current mRNA vaccines,[23] the safety of mRNA vaccines needs to be carefully evaluated. Further safety concerns were raised from the fact that the safety evaluations in clinical trials were limited to relatively healthy people while vulnerable patients at high risk for severe courses of COVID-19 were prioritized to the vaccination in real-world settings.[3, 8, 9] This study was designed to investigate this gap and promptly detect safety signals undiscovered at the trial level, but could snowball as vaccine coverage spans across the billions of people worldwide. Of note, this analysis aims to raise hypotheses for further, more definitive studies, not to test hypotheses and inform recommendations.

Our data revealed that COVID-19-vaccinated individuals experienced significantly fewer deaths compared to those not exposed to the vaccines, possibly indicating a protective effect of the vaccine (Table 2). When stratifying death risk by age group, the proportion of death among all AEFI-reported vaccinated individuals at the age group was higher in the > 65 years age groups, and the tendency was more prominent for those ≥ 75 years old (Table S2). This observation could be explained, in part, by the selective roll-out of mRNA vaccines to particularly vulnerable elderly populations, such as those receiving care in long-term care facilities (LTCF), who are frail and at a higher risk of severe courses. Therefore, it is difficult to attribute the higher odds of death in the elderly, especially those > 75 years, to mRNA vaccination per se without more data that may help extricate a causal relationship. Further studies should be conducted to elucidate the causal relationship and underlying mechanisms for this association.

It is noteworthy that mRNA vaccines demonstrated a significantly higher risk for a few cardiovascular complications, such as hypertensive crisis and supraventricular tachycardia (SVT) compared with influenza vaccines; however, risks for most other cardiovascular adverse events such as atrial fibrillation, myocardial infarction, cardiogenic shock, and cardiac failure were not increased with mRNA vaccination (Supplementary data). Considering hypertensive crisis and SVT are mostly manageable and rarely causing permanent or chronic damages, these cardiovascular signals are less likely to pose a

burden to a large population. Moreover, lower risks of other serious complications, especially neurological complications (i.e., neuralgia, Guillain-Barre syndrome, dyskinesia, and gait disturbance), with mRNA vaccines compared to influenza vaccines may further support the comparative safety of mRNA vaccines in real-world settings (Fig. 2). The findings and hypotheses raised from this first post-implementation surveillance data may support evidence-based discussions and risk-benefit assessments for ongoing mass vaccination.

The results of this study should be interpreted in the context of known limitations. First, VigiBase relies on spontaneous reports, and therefore the data are subject to reporting biases. To address, we triaged to remove potentially false reports using disproportionality analysis and clinical appraisal as demonstrated in the methods. Second, VigiBase was primarily designed to identify unusual or unexpected safety signals that might be associated with vaccines rather than to determine a causal relationship. Therefore, our analysis should be interpreted as confined to the associations, and beware that this analysis is intended to raise hypotheses for further, more definitive studies. Lastly, we employed disproportionality analyses between the AEFIs reported with mRNA COVID-19/influenza vaccines and the total number of individual case safety reports for the entire VigiBase database. However, the advantages of VigiBase and the methods used in this study (disproportionate analysis) have been well established through numerous studies[16, 24-26] and may provide sufficient evidence to bring the potential safety signals to the attention of public health professionals and decision-makers.

Conclusion

This pharmacovigilance study has not identified significant safety concerns regarding mRNA vaccination in real-world settings. The overall safety profile patterned a lower risk of serious AEFI following mRNA vaccines compared to influenza vaccines.

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Disclaimer

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Contributors

MS Kim, SY Jung, and JI Shin contributed to the study concept and design. SY Jung and JI Shin aquisited data. MS Kim and SY Jung analyzed the data. MS Kim and SY Jung wrote the first draft of the manuscript. MS Kim finalized the manuscript. H Kim supported organizing influenza vaccine data and supplementary materials. JE Salem, Jerome Kim, JL Excler, F Marks, JD Clemens supervised the interpretation of vaccine pharmacovigilance results. Jong Gyun Ahn, Se Jin Park, Yehuda Shoenfeld,

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Figures

A Common AEFIs

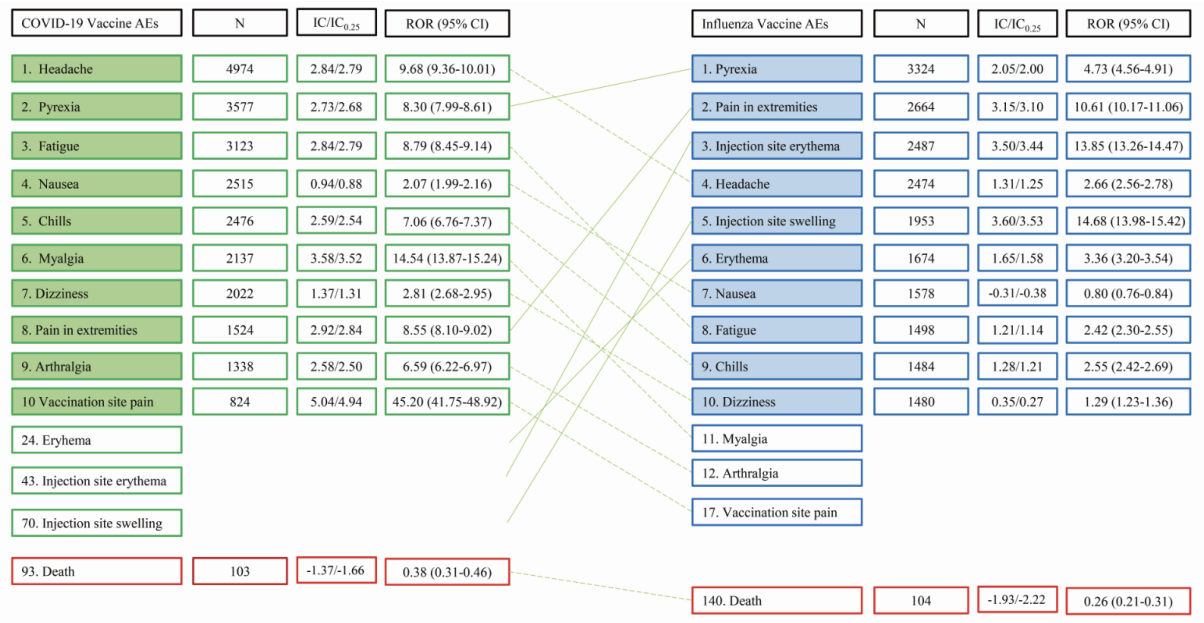

Figure 1. Comparative safety of mRNA vaccines to conventional influenza vaccines: Common adverse events following immunization (AEFIs)

The numbers in the first column represent the ranking of AEFIs. Values > 0 for the lower 95% credibility interval endpoint of the information component ($IC_{0.25}$) and > 1 for the lower confidence interval (CI) of ROR indicate statistical significance. AEFI: Adverse event following immunization, N: Number, IC: Information component, ROR: Reporting odds ratio.

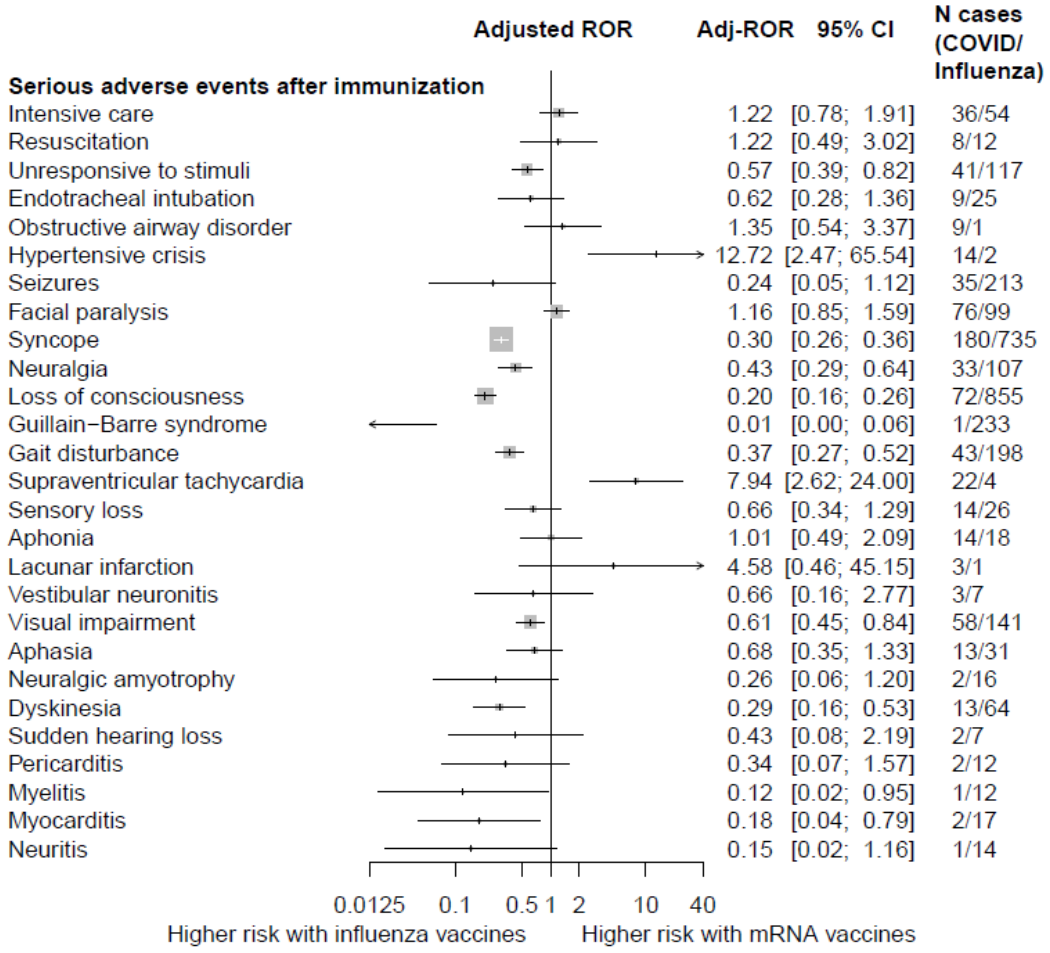

Figure 2. Comparative safety of mRNA COVID-19 vaccines versus influenza vaccines with respect to serious adverse events after immunization (AEFIs). Adj-ROR: Adjusted Reported odd ratios, 95%-CI: 95% confidential interval.

Tables

Table 1. Baseline characteristics of participants vaccinated against COVID-19 and influenza reported to VigiBase for any adverse event following immunization (AEFI)

	COVID-19 Vaccine (n =18755)	Influenza Vaccine (n = 27895)
Regions reporting		
Americas	6947/18755 (37.0)	17730/27895 (63.6)
Europe	11787/18755 (62.9)	8380/27895 (30.0)
Australia	0/18755 (0.0)	1377/27895 (4.8)
Asia	21/18755 (0.1)	327/27895 (1.2)
Africa	0/18755 (0.0)	81/27895 (0.4)
Report from clinical trials	94/18755 (0.5)	1326/28750 (4.8)
Reporting months		
2020.01-2020.10	0/18755 (0.0)	16338/27895 (58.6)
2020.11	1/18755 (0.0)	2302/27895 (8.2)
2020.12	2087/18755 (11.1)	9217/27895 (32.0)
2021.01	16667/18755 (88.9)	898/27895 (3.2)
Reporter		
Health care professional	8459/18755 (45.1)	4054 /27895 (14.5)
Non-health care professional	3364/18755 (17.9)	6009/27895 (21.5)
Unreported	6942/18755 (37.0)	17832/27895 (64.0)
Age groups		
< 45 years	9389/18755 (50.1)	10703/27895 (38.3)
45 - 64 years	6422/18755 (34.2)	6504/27895 (23.3)
65 – 74 years	449/18755 (2.4)	5132/27895 (18.4)
≥ 75 years	1282/18755 (6.8)	2777/27895 (10.0)
Unreported	1213/18755 (6.5)	2779 /27895 (10.0)
Sex		
Male	3838/18755 (20.5)	9263/27895 (33.2)
Female	14514/18755 (77.4)	18262/27895 (65.5)
Unreported	403/18755 (2.1)	370/27895 (1.3)
Serious AEFIs	3737/18755 (19.9)	3343/27573 (12.1)
Outcomes	**n =13058**	**n = 14317**
Deaths*	119/13058	113/14371
Time to AEFIs Onset	**n = 10876**	**n = 14925**
Median days (IQR)	1.0 (0.0-1.0)	0.0 (0.0-0.0)

*As denominator, all vaccinated participants with AEFIs reported rather than all vaccinated persons were used; we did not present percentile estimations given that they must be larger than those observed in real-world settings. The AEFIs for the COVID-19 and influenza vaccine were extracted from January 2020 to January 17, 2021. Values are presented as n (%) or n/N (%), unless otherwise indicated. Severe AEFI was defined as AEFI that is life-threatening, causes persistent or significant disability, requires hospitalization (first or prolonged), or results in death. AEFIs: Adverse events following immunization, IQR: Interquartile range.

Table 2. Adverse events following immunization (AEFIs) associated with the COVID-19 and the influenza vaccine in the full database of the VigiBase from January, 2020.

	COVID-19 vaccine*	$IC/IC_{0.25}$	ROR (95% CI)	Influenza vaccine*	$IC/IC_{0.25}$	ROR (95% CI)	Full database* (since 2020.01)
Total individuals with AEFIs	18,755			27,895			2,720,221
Common AEFIs							
Vaccination site pain	824	**5.04/4.94**	45.20 (41.75-48.92)	868	**4.55/4.45**	31.99 (29.61-34.57)	3,568
Lymphadenopathy	685	**4.66/4.55**	32.27 (29.67-35.09)	287	**2.84/2.67**	7.83 (6.94-8.84)	3,855
Oral paraesthesia	472	**4.68/4.54**	32.62 (29.50-36.08)	150	**2.47/2.23**	5.92 (5.02-6.98)	2,608
Myalgia	2,137	**3.58/3.52**	14.54 (13.87-15.24)	1,443	**2.44/2.37**	5.97 (5.65-6.30)	25,821
Heart rate increased	357	**3.00/2.85**	8.67 (7.78-9.65)	175	**1.41/1.19**	2.73 (2.35-3.17)	6,393
Pain in extremities	1,524	**2.92/2.84**	8.55 (8.10-9.02)	2,664	**3.15/3.10**	10.61 (10.17-11.06)	29,187
Headache	4,974	**2.84/2.79**	9.68 (9.36-10.01)	2474	**1.31/1.25**	2.66 (2.56-2.78)	97,345
Fatigue	3,123	**2.84/2.79**	8.79 (8.45-9.14)	1,498	**1.21/1.14**	2.42 (2.30-2.55)	63,151
Lethargy	242	**2.95/2.76**	8.30 (7.28-9.45)	292	**2.65/2.48**	6.77 (6.01-7.63)	4,491
Pyrexia	3577	**2.73/2.68**	8.30 (7.99-8.61)	3,324	**2.05/2.00**	4.73 (4.56-4.91)	78,189
Chills	2,476	**2.59/2.54**	7.06 (6.76-7.37)	1,484	**1.28/1.21**	2,.55 (2.42-2.69)	59,451
Arthralgia	1,338	**2.58/2.50**	6.59 (6.22-6.97)	1190	**1.84/1.75**	3.79 (3.57-4.02)	32,482
Influenza like illness	359	**2.30/2.15**	5.19 (4.66-5.77)	494	**2.19/2.06**	4.84 (4.42-5.30)	10,486
Chest discomfort	398	**2.01/1.87**	4.21 (3.80-4.65)	231	**0.66/0.47**	1.60 (1.40-1.82)	14,247
Dizziness	2,022	**1.37/1.31**	2.81 (2.68-2.95)	1,480	**0.35/0.27**	1.29 (1.23-1.36)	113,320
Flushing	543	**1.43/1.30**	2.77 (2.55-3.02)	192	-0.64/-0.85	0.63 (0.55-0.73)	29,262
Blood pressure increased	240	**1.37/1.18**	2.64 (2.30-3.00)	100	-0.46/-0.76	0.72 (0.59-0.88)	13,442
Cough	546	**1.14/1.02**	2.27 (2.08-2.47)	702	0.93/0.83	1.96 (1.81-2.11)	35,788
Palpitations	511	**1.04/0.92**	2.10 (1.92-2.30)	183	-1.01/-1.23	0.49 (0.42-0.57)	36,033
Nausea	2,515	**0.94/0.88**	2.07 (1.99-2.16)	1,578	-0.31/-0.38	0.80 (0.76-0.84)	190,359
Diarrhea	748	**0.43/0.32**	1.36 (1.27-1.47)	671	-0.30/-0.41	0.80 (0.75-0.87)	80,681

Dyspnea	774	**0.38/0.27**	1.31 (1.22-1.41)	791	-0.16/-0.27	0.89 (0.83-0.95)	86,465
Death, anaphylactic reaction, and uncommon but serious AEFI†							
Death	103	-1.37/-1.66	0.38 (0.31-0.46)	104	-1.93/-2.22	0.26 (0.21-0.31)	38,799
Anaphylactic reaction	149	-0.12/-0.36	0.92 (0.78-1.08)	147	-0.71/-0.95	0.61 (0.52-0.71)	23,415
Intensive care	36	**3.71/3.20**	17.49 (12.37-24.73)	54	**3.80/3.39**	18.71 (13.98-25.05)	333
Facial paralysis	76	**3.27/2.92**	10.93 (8.66-13.81)	99	**3.10/2.80**	9.76 (7.94-12.01)	1,081
Resuscitation	8	**2.82/1.65**	12.26 (5.96-25.24)	12	**3.02/2.09**	12.87 (7.05-23.52)	102
Syncope	180	**1.64/1.42**	3.20 (2.76-3.71)	735	**3.10/2.99**	9.55 (8.85-10.31)	8,341
Unresponsive to stimuli	41	**1.88/1.41**	3.89 (2.85-5.31)	117	**2.83/2.56**	7.85 (6.50-9.49)	1,560
Endotracheal intubation	9	**2.41/1.32**	7.33 (3.75-14.32)	25	**3.40/2.78**	15.00 (9.84-22.86)	186
Hypertensive crisis	14	**1.95/1.10**	4.42 (2.59-7.52)	2	-1.09/-3.68	0.41 (0.10-1.65)	471
Obstructive airway disorder	10	**2.13/1.10**	5.42 (2.88-10.19)	9	**1.51/0.42**	3.25 (1.67-6.32)	276
Supraventricular tachycardia	22	**2.66/2.00**	7.53 (4.91-11.57)	4	-0.16/-1.90	0.88 (0.33-2.35)	443
Sensory loss	14	**1.89/1.04**	4.19 (2.47-7.14)	26	**2.25/1.64**	5.35 (3.61-7.95)	495
Neuralgia	33	**1.16/0.63**	2.30 (1.63-3.25)	107	**2.29/2.00**	5.20 (4.28-6.31)	2,101
Aphonia	14	**1.17/0.32**	2.38 (1.41-4.04)	18	**0.99/0.25**	2.06 (1.29-3.29)	860
Lacunar infarction	3	**2.31/0.26**	16.01 (4.86-52.77)	1	0.89/-2.90	3.33 (0.45-24.43)	30
Vestibular neuronitis	3	**2.17/0.12**	11.68 (3.60-37.89)	7	**3.04/1.78**	20.48 (9.06-46.30)	40
Loss of consciousness	72	**0.46/0.11**	1.39 (1.10-1.75)	488	**2.65/2.51**	6.76 (6.16-7.41)	7,565
Visual impairment	58	-0.37/-0.77	0.77 (0.59-1.00)	141	**0.33/0.09**	1.27 (1.07-1.50)	10,905
Aphasia	13	0.01/-0.88	1.01 (0.58-1.74)	31	**0.68/0.13**	1.63 (1.14-2.32)	1,869
Neuralgic amyotrophy	2	1.46/-1.13	5.05 (1.23-20.71)	16	**3.90/3.11**	35.93 (20.24-63.80)	59
Gait disturbance	43	-0.77/-1.23	0.58 (0.43-0.78)	198	**0.85/0.64**	1.83 (1.59-2.11)	10,681
Seizure	35	-0.94/-1.46	0.52 (0.37-0.72)	213	**1.08/0.88**	2.15 (1.88-2.47)	9,795
Dyskinesia	13	-0.87/-1.76	0.54 (0.31-0.92)	64	**0.82/0.45**	1.80 (1.40-2.30)	3,506
Sudden hearing loss	2	0.53/-2.06	1.63 (0.40-6.56)	7	**1.68/0.42**	3.93 (1.85-8.37)	179
Pericarditis	2	-0.19/-2.78	0.85 (0.21-3.41)	12	**1.64/0.71**	3.52 (1.98-6.27)	341
Myelitis	1	0.28/-3.52	1.36 (0.19-9.74)	12	**2.97/2.04**	12.20 (6.69-22.24)	107
Myocarditis	2	-1.19/-3.78	0.38 (0.10-1.54)	17	**1.09/0.32**	2.23 (1.38-3.61)	753

Neuritis	1	-0.11/-3.91	0.89 (0.12-6.35)	14	**2.74/1.89**	9.07 (5.24-15.69)	163
Guillain-Barre syndrome	1	-1.84/-5.63	0.20 (0.03-1.46)	233	**4.92/4.73**	48.14 (41.13-56.35)	704

* As denominator, all vaccinated participants with AEFIs reported rather than all vaccinated persons were used; we did not present percentile estimations given that they must be larger than those observed in real-world settings. †Due to the volume, only serious AEFIs that are significantly associated with either COVID-19 or influenza vaccine are listed in this table, while serious AEFIs that were not associated with the vaccines are presented in the supplementary material. The first AEFI associated with the COVID-19 vaccine was reported on December 15, 2020. The IC/IC0.25 and ROR of AEFIs associated with COVID-19 and influenza vaccines were compared with the entire database of VigiBase from January 01, 2020, to January 17, 2021. A positive IC0.25 value (> 0) in bold is the traditional threshold used for statistical signal detection.
AEFI: Adverse event following immunization, IC: Information component, ROR: reporting odds ratio, NA: Not applicable

Supplementary Materials

Table S1. Adverse events following immunization (AEFIs) associated with the COVID-19 vaccine and the influenza vaccine in the full database of the VigiBase since the inception.

	COVID-19 vaccine*	IC/$IC_{0.25}$	ROR (95% CI)	Influenza vaccine* (since inception)	IC/$IC_{0.25}$	ROR (95% CI)	Full database* (since inception)
Total individuals with AEFIs	**18,755**			**259, 281**			**23,880,736**
Common AEFIs							
Vaccination site pain	824	**5.83/5.73**	64.67 (60.21-69.46)	4,002	**2.84/2.82**	8.51 (8.40-8.62)	373.126
Oral paraesthesia	472	**4.96/4.83**	33.79 (30.80-37.06)	1,070	**2.40/2.31**	5.55 (5.22-5.90)	18.691
Lymphadenopathy	685	**4.66/4.55**	32.27 (29.67-35.09)	3,009	**2.45/2.40**	5.80 (5.50-6.01)	50.767
Chills	2,476	**3.37/3.31**	11.84 (11.35-12.36)	13,591	**2.04/2.01**	4.43 (4.35-4.51)	259.281
Myalgia	2,137	**3.29/3.23**	11.01 (10.52-11.51)	15,462	**2.36/2.34**	5.65 (5.55-5.74)	277,724
Heart rate increased	357	**3.00/2.85**	8.67 (7.78-9.65)	1,646	**1.06/0.99**	2.13 (2.02-2.23)	72,444
Headache	4,974	**2.84/2.79**	9.68 (9.36-10.01)	21,657	**1.21/1.19**	2.47 (2.44-2.51)	861,949
Lethargy	242	**2.95/2.76**	8.30 (7.28-9.45)	2,324	**1.87/1.82**	3.80 (3.65-3.97)	58,596
Pain in extremity	1524	**2.79/2.72**	9.22 (8.92-9.52)	16,809	**2.47/2.44**	6.15 (6.05-6.25)	280,304
Pyrexia	3577	**2.73/2.68**	8.30 (7.99-8.61)	36,845	**2.19/2.17**	5.36 (5.30-5.42)	744,496
Fatigue	3,123	**2.64/2.59**	7.33 (7.05-7.62)	11,816	**0.78/0.75**	1.77 (1.73-1.80)	636,092
Arthralgia	1,338	**2.58/2.50**	6.59 (6.22-6.97)	9,001	**1.24/1.21**	2.44 (2.39-2.49)	352,086
Influenza like illness	359	**2.30/2.15**	5.19 (4.66-5.77)	5,057	**2.08/2.04**	4.44 (4.32-4.57)	259,281
Chest discomfort	398	**2.01/1.87**	4.21 (3.80-4.65)	2.405	**0.93/0.88**	1.94 (1.86-2.02)	115,973
Dizziness	2,022	**1.58/1.52**	3.25 (3.10-3.40)	12,991	**0.48/0.46**	1.42 (1.40-1.45)	857,833
Flushing	543	**1.43/1.30**	2.77 (2.55-3.02)	2,210	0.01/-0.05	1.01 (0.96-1.05)	202,377
Blood pressure increased	240	**1.37/1.18**	2.64 (2.30-3.00)	1,012	-0.33/-0.42	0.79 (0.75-0.84)	117,131
Cough	546	**1.14/1.02**	2.27 (2.08-2.47)	10,489	**1.60/1.57**	3.19 (3.13-3.26)	318,259
Palpitations	511	**1.04/0.92**	2.10 (1.92-2.30)	1,502	0.61/-0.77	0.58 (0.55-0.61)	235,840
Nausea	2.515	**0.94/0.88**	2.07 (1.99-2.16)	13,696	-0.09/-0.12	0.93 (0.92-0.95)	1,343,721
Diarrhea	748	**0.43/0.32**	1.36 (1.27-1.47)	5,988	-0.35/-	0.78 (0.76-0.80)	703,359

Dyspnea	774	**0.38/0.27**	1.31 (1.22-1.41)	10,532	**0.50/0.39**	1.44 (1.41-1.47)	686,275
Death, anaphylactic reaction, and uncommon but serious AEFI†							
Death	103	0.34/-1.82	0.28 (0.23-0.34)	986	-2.35/-2.44	0.19 (0.18-0.20)	463,985
Anaphylactic reaction	149	**0.63/0.39**	1.56 (1.32-1.83)	1,214	-0.13/-0.21	0.91 (0.86-0.97)	122,318
Intensive care	36	**3.81/3.30**	17.36 (12.49-24.13)	473	**4.00/3.87**	19.57 (17.72-21.61)	2.679
Facial paralysis	76	**2.69/2.35**	6.74 (5.38-8.45)	1,475	**3.23/3.15**	6.74 (5.38-8.45)	14,463
Supraventricular tachycardia	22	**1.62/0.95**	3.24 (2.13-4.93)	63	-0.57/-0.95	0.67 (0.52-0.86)	8.658
Resuscitation	8	**2.24/1.07**	6.19 (3.09-12.41)	93	**2.34/2.03**	5.44 (4.41-6.70)	1,652
Unresponsive to stimuli	41	**1.37/0.89**	2.63 (1.94-3.58)	780	**1.85/1.75**	3.73 (3.47-4.01)	19,867
Endotracheal intubation	9	**1.88/0.79**	4.34 (2.26-8.36)	240	**3.04/2.85**	9.09 (7.96-10.38)	2,647
Syncope	180	**0.83/0.61**	1.79 (1.55-2.08)	4,129	**1.57/1.52**	3.06 (2.97-3.16)	128,354
Sensory loss	14	**1.47/0.61**	2.95 (1.75-4.99)	305	**2.21/2.04**	4.84 (4.32-5.44)	6,046
Neuralgia	33	**1.11/0.58**	2.20 (1.56-3.10)	740	**1.83/1.72**	3.67 (3.41-3.95)	19,132
Hypertensive crisis	14	**1.43/0.58**	2.88 (1.71-4.87)	47	-0.51/-0.96	0.70 (0.52-0.93)	6,197
Obstructive airway disorder	10	**1.40/0.37**	2.89 (1.55-5.38)	77	**0.68/0.34**	1.62 (1.29-2.03)	4,413
Aphonia	14	**0.92/0.07**	1.96 (1.16-3.32)	150	**0.60/0.36**	1.53 (1.30-1.80)	9,088
Vestibular neuritis	3	**2.10/0.05**	9.50 (3.05-29.57)	50	**3.37/2.94**	12.83 (9.54-17.26)	405
Loss of consciousness	72	-0.09/-0.44	0.94 (0.75-1.19)	2,467	**1.22/1.16**	2.38 (2.29-2.48)	97,354
Lacunar infarction	3	1.03/-1.02	2.47 (0.79-7.66)	4	-1.95/-3.68	0.24 (0.09-0.63)	1,551
Neuralgic amyotrophy	2	1.43/-1.16	4.69 (1.17-18.79)	166	**4.70/4.47**	39.93 (33.27-47.92)	545
Visual impairment	58	-0.82/-1.21	0.56 (0.44-0.73)	1,213	-0.22/-0.31	0.85 (0.81-0.90)	130,577
Aphasia	13	-0.51/-1.40	0.69 (0.40-1.19)	333	**0.36/0.20**	1.29 (1.15-1.43)	23,918
Gait disturbance	43	-1.39/-1.86	0.38 (0.28-0.51)	2.212	**0.49/0.43**	1.41 (1.36-1.48)	145,009
Sudden hearing loss	2	0.37/-2.22	1.39 (0.35-5.58)	63	**1.64/1.26**	3.25 (2.53-4.18)	1,827
Dyskinesia	13	-1.41/-2.30	0.37 (0.21-0.63)	578	**0.24/0.12**	1.18 (1.09-1.29)	45,043

Seizure	35	-2.02/-2.54	0.24 (0.17-0.34)	2,592	**0.38/0.33**	1.31 (1.26-1.36)	183,014
Pericarditis	2	-1.14/-3.73	0.40 (0.10-1.60)	231	**1.73/1.54**	3.43 (3.00-3.91)	6,379
Myocarditis	2	-1.38/-3.97	0.33 (0.08-1.33)	198	**1.25/1.04**	2.43 (2.11-2.80)	7,629
Myelitis	1	-0.42/-4.22	0.66 (0.09-4.71)	264	**3.63/3.45**	14.53 (12.76-16.54)	1,921
Neuritis	1	-1.71/-5.51	0.23 (0.03-1.60)	383	**2.64/2.49**	6.66 (6.00-7.39)	5,629

*The denominator indicates all vaccinated participants with AEFIs reported rather than all vaccinated persons; we did not present percentile estimations given that they must be larger than those observed in real-world settings. †Due to the volume, only serious AEFIs that are significantly associated with either COVID-19 or influenza vaccine are listed in this table, while serious AEFIs that were not associated with the vaccines are presented in the supplementary material. The first AEFI associated with the COVID-19 vaccine was reported on December 15, 2020. The IC/IC0.25 and ROR of AEFIs associated with COVID-19 and influenza vaccines were compared with the entire database of VigiBase from January 01, 2020, to January 17, 2021. A positive IC0.25 value (> 0) in bold is the traditional threshold used for statistical signal detection. AEFI: Adverse event following immunization, IC: Information component, ROR: reporting odds ratio, NA: Not applicable.

Table S2. Proportion of deaths and anaphylactic reactions relative to all COVID-19-vaccinated participants with AEFIs reported for each age group

	Death		Anaphylactic reaction		
	Death*(%)	Non-death	AR (%)	Non-AR	Total†
≥75 years	88 (6.9%)	1194	4 (0.3%)	1278	1282
65-74 years	9 (2.0%)	440	1 (0.2%)	448	449
45-64 years	10 (0.2%)	6412	61 (1.0%)	6361	6422
18-44 years	2 (0.0%)	9252	65 (0.7%)	9189	9254
0-17 years	0 (0.0%)	134	0 (0%)	134	134

*Those reported with preferred terms (PT) of death, sudden death, and cardiac death. †Participants reported to the VigiBase for any adverse events after vaccination. As the percentages were drawn from all vaccinated participants with AEFIs reported rather than all vaccinated populations, the percentile estimations must be larger than those observed in real-world settings. Therefore, they should be cautiously read to avoid exaggerating the estimations. AR: Anaphylactic reaction.

Table S3. Calculation of information component

The following statistical formula was used: IC = log2 ([Nobserved + 0.5]/[Nexpected + 0.5]) where Nexpected = [Ndrug × Nreaction]/Ntotal Nexpected represents the number of case reports expected for the drug-effect combination, and Nobserved indicates the actual number of case reports for the drug-effect combination. Ndrug and Nreaction specify the number of case reports for the drug irrespective of AEs, and for the effect irrespective of the drug respectively. Ntotal corresponds to the total number of case reports in the full database.

Figure S1. The selection process of common adverse events following immunization (AEFIs). *In case there are multiple MedDRA PTs coded for a medical condition, a more comprehensive MedDRA PT or MedDRA PT with the largest case record was selected.

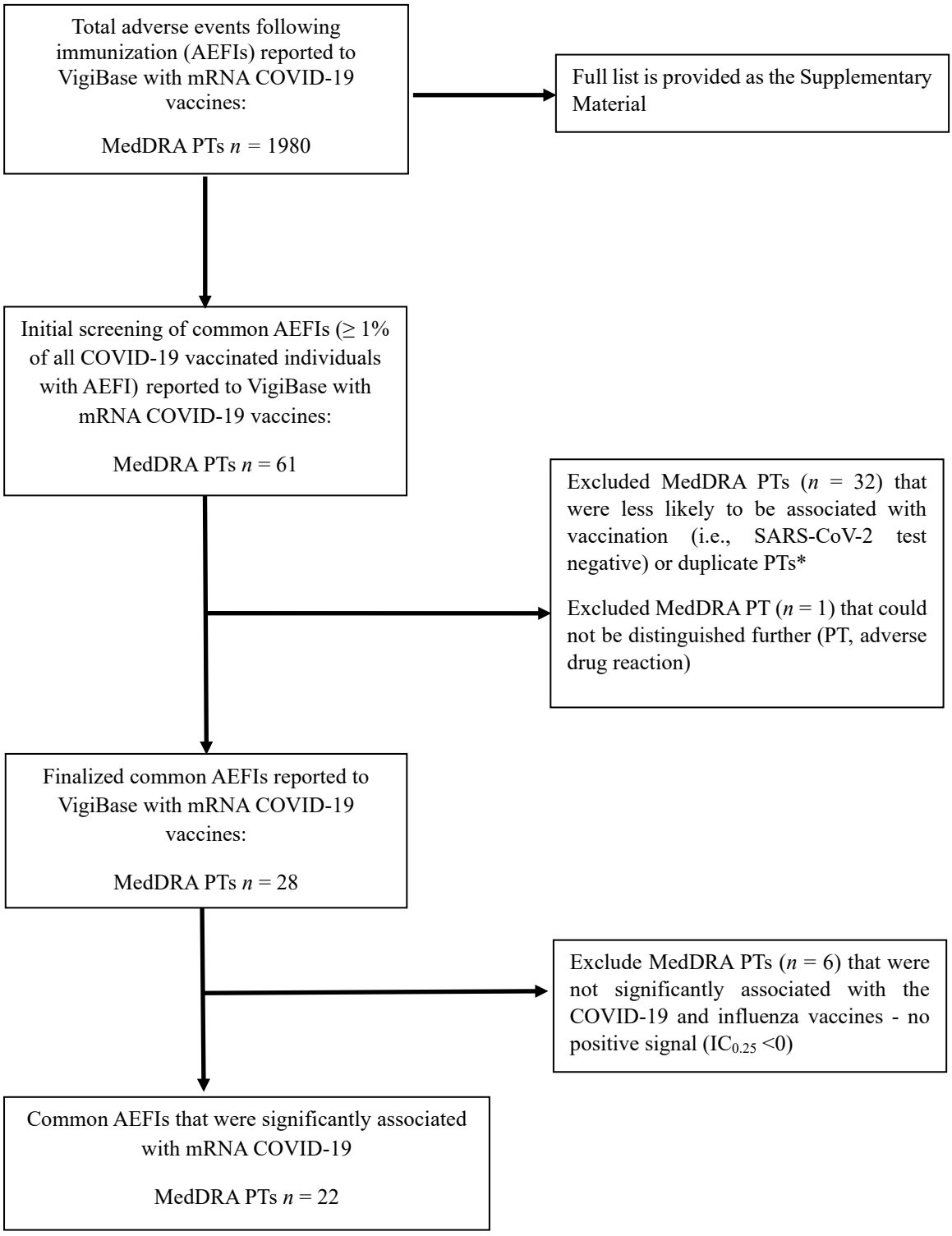

Figure S2. The selection process of serious adverse events following immunization (AEFIs) that are subject to comparative analysis. *In case there are multiple MedDRA PTs coded for a medical condition, a more comprehensive MedDRA PT or MedDRA PT with the largest case record was selected.