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Global COVID-19 pandemic and reporting behavior - An analysis of the Food and Drug Administration adverse events reporting system

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Abstract

Purpose: To describe the characteristics of adverse event reporting in the United States (US) Food and Drug Administration Adverse Event Reporting System (FAERS) before and after the outbreak of the COVID-19 pandemic.

Methods: We included all FAERS reports from the US and Canada from November 7, 2019 to July 15, 2020 and divided the study period into three equal time intervals (pre-pandemic, first pandemic, second pandemic). We focused on methotrexate, a broadly used drug unrelated to COVID-19, and (hydroxy)chloroquine, another broadly used drug implicated in COVID-19 treatment. Using descriptive statistics, we compared reporting characteristics before and after the COVID-19 outbreak.

Results: During the study period, 366 998 cases (60% female, median age: 59 years) were submitted to FAERS. The daily median number of reports (1796 in the pre-pandemic, 1810 in the second pandemic time interval) and other characteristics remained stable. The daily median number of reports for methotrexate decreased from 28 in the pre-pandemic to 15 in the second pandemic time interval, with no considerable differences in other characteristics. The daily median number of reports for (hydroxy) chloroquine increased slightly from 1 in the pre-pandemic to 3 in the second pandemic time interval, while there were also changes in the demographics of cases and an increase in the proportion of cases reported by health professionals.

Conclusions: The overall reporting to FAERS did not change after the outbreak of the COVID-19 pandemic. However, some stimulated reporting was observed for (hydroxy)chloroquine, highlighting the need for caution when conducting pharmacovigilance analyses with substances related to COVID-19.

KEYWORDS

adverse drug reactions reporting systems, chloroquine, COVID-19 pandemic, hydroxychloroquine, methotrexate, pharmacovigilance

1 | INTRODUCTION

Spontaneous reporting systems (SRS) were established more than 50 years ago to collect post-approval safety information that would enable the early detection of new or rare adverse drug events.[1,2] SRS contain adverse drug event reports that are submitted by health professionals such as physicians or pharmacists but also by drug consumers,[3,4] and they have the advantage of covering a large number of patients and a wide range of drugs. Therefore, SRS constitute a relatively cost-effective data source that allows the identification of safety signals regarding the use of both newly marketed and long-established drugs.[4-7]

Despite their usefulness, SRS also have a number of limitations. The two most important limitations are closely related to reporting behavior and include stimulated reporting and under-reporting.[5] Stimulated reporting refers to the potential increase in adverse event reporting rates following safety warnings issued by regulatory agencies or the publication of relevant study findings.[5,6] Further, stimulated reporting can also appear as clustering of adverse event reports triggered by the activities of consumer-based support groups or reporting activity related to litigation.[4,5,7] On the other hand, under-reporting refers to the well-established fact that less than 10% of all adverse events are reported.[8] Of note, under-reporting does not only affect older drugs and mild adverse events but also newer drugs and serious adverse events.[9] Given this link between reporting behavior and data characteristics in SRS databases, major events that could affect reporting behavior are of major interest for pharmacovigilance.

On January 20, 2020, the first case of COVID-19, that is an infection with the new SARS-CoV-2 virus, was recorded in the Unites States (US). Ten days later, the COVID-19 outbreak was declared a public health emergency of international concern by the World Health Organization (WHO), a major event with potential influence on the reporting behavior of adverse events. We hypothesized that these events may have influenced individual reporting behavior. On the one hand, stimulated reporting could become apparent for drugs potentially related to COVID-19. On the other hand, under-reporting could emerge in the case of adverse events for drugs unrelated to COVID-19. Further, the reporting behavior of specific groups such as health professionals or consumers could be affected. To this end, we described the characteristics of adverse events reporting in one of the largest SRS, the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), before and after the outbreak of the COVID-19 pandemic.

2 | METHODS

2.1 | Data source and study period

For this study, we used the FAERS database, which is based on voluntary reporting by health professionals and patients as well as mandatory reporting by pharmaceutical companies.[4,10,11] We included all FAERS reports from the US and Canada filed from November 7, 2019 to July 15, 2020. We chose not to include reports from all countries, since only a fraction of non-US adverse events is reported to FAERS.[12] We did include reports from Canada additionally to those from the US, though, given the similar time courses of the first wave of the COVID-19 pandemic in the two countries.

2.2 | Assessment of adverse drug events

Case information was assessed from the different FAERS datasets containing (i) patient demographic and administrative information, (ii) drug/biologic information, (iii) outcomes, (iv) reactions, and (v) indications for use (diagnoses) for the reported drugs. Demographic variables included age and sex. Reporters' types of occupation were classified as physician, pharmacist, other health professional, lawyer, or consumer. Only cases with a drug considered as primary suspect were included, assuming that such cases can better depict individual reporting behaviors, especially when it comes to physicians and other health professionals. Periodic (i.e., non-expedited) reports by the pharmaceutical companies were excluded to avoid 'artificial' peaks in reporting related to regulatory obligations of drug manufacturers.

We also assessed reports related to specific medications to further explore the potential impact of the pandemic on adverse event reporting. First, we focused on methotrexate, which is an old, broadly used immunosuppressive agent unrelated to COVID-19. Second, we focused on (hydroxy)chloroquine, a drug used in the treatment of autoimmune disorders and in malaria, which was granted an emergency use authorization (EUA) by the FDA on March 28, 2020.[13] The EUA allowed treatment of certain hospitalized patients with COVID-19 when a clinical trial was unavailable, but was revoked on June 15, 2020.[13]

Outcomes were classified hierarchically (i.e., death, life-threatening, hospitalization - initial or prolonged, disability, congenital anomaly, required intervention to prevent permanent impairment/damage and other serious [important medical event]). The most common reactions and indications were displayed by the reported preferred terms (i.e., the distinct descriptors for a symptom, sign, diagnosis of disease, therapeutic indication, investigation, surgical or medical procedure, and medical, social, or family history characteristic) according to the "Medical Dictionary for Regulatory Activities". Further, these terms were grouped into their respective system organ classes, that is groupings by etiology, manifestation site, or purpose.[14]

2.3 | Statistical analysis

We displayed the number of reports by week (using only full calendar weeks, starting November 11, 2019 and ending July 12, 2020) and by day to examine a continuous reporting behavior. We did that for drugs included in FAERS overall and for methotrexate and (hydroxy) chloroquine separately. Moreover, we divided the study period into three equal time intervals of 84 days (=12 weeks) each ('pre-pandemic interval' from November 7, 2019 to January 29, 2020; 'first pandemic

interval' from January 30, 2020 to April 22, 2020; 'second pandemic interval' from April 23, 2020 to July 15, 2020) to characterize the time course of reporting before and in the beginning of the pandemic. The cut-off between pre-pandemic and first pandemic time interval was January 30, 2020, the date when the outbreak was declared a public health emergency of international concern.[15] We then assessed case characteristics in the three intervals using descriptive statistics (median, interquartile range [IQR], percentages). Reported characteristics were based on the respective non-missing values, which resulted in different denominators. All analyses were performed using SAS, Version 9.4 (SAS Institute Inc).

3 | RESULTS

3.1 | All cases - entire study period

During the study period, 366 998 cases were submitted to FAERS, with a median [IQR] of 1778 [286.5 to 2031.5] reports per day. The highest numbers were observed on March 5, 2020 (n = 3988, Supplementary Figure 1) and in the 28th calendar week of 2020 (n = 13 434, Figure 1). Most cases were reported by consumers, followed by non-physician health professionals and physicians (Table 1). More than half of all reports referred to female patients and median age was 59 years. One of three cases had an initial or prolonged hospitalization and 19% had a fatal outcome. The most common indications for pharmacotherapy among all reported cases were rheumatoid arthritis (8.5%) and multiple sclerosis (4.0%). The most frequently reported adverse events were death (8.6%), drug ineffectiveness (7.3%), and off-label use (5.6%). In terms of system organ classes, general disorders and administration site conditions were most often reported (39.7%), followed by injury, poisoning, and procedural complications (24.9%). The most frequently involved primary suspect drugs were adalimumab (3.7%), ranitidine (3.1%), and methotrexate (1.8%, Table 2).

3.2 | All cases - pre-pandemic versus pandemic time intervals

The median daily number of reports remained stable during the study period. Moreover, the results were comparable between the pre-pandemic and pandemic time intervals regarding most case characteristics (i.e., demographics, outcomes, indications for treatment, commonly reported adverse events). However, the proportion of reports submitted by lawyers increased almost 8-fold from the pre-pandemic to the second pandemic time interval (Table 1). Moreover, whereas ranitidine and tenofovir were with 8.1% and 3.8% the most commonly reported drugs in the second pandemic time interval, they were not among the top 10 in both other time intervals.

3.3 | Methotrexate cases - entire study period

For methotrexate, 6717 cases were reported with a median [IQR] of 20 [3.5 to 42] reports per day and a maximum on December 4, 2019 (n = 140, Table 3 and Figure S2) and in the 49th calendar week of 2019 (n = 449, Figure 2). Nearly three quarters of cases referred to female patients and median age was 58 years (Table 3). About half of the cases were reported by other health professionals, followed by physicians (27.8%), and consumers (22.8%). Regarding the reported outcomes, 3% were fatal. As expected, the most commonly reported

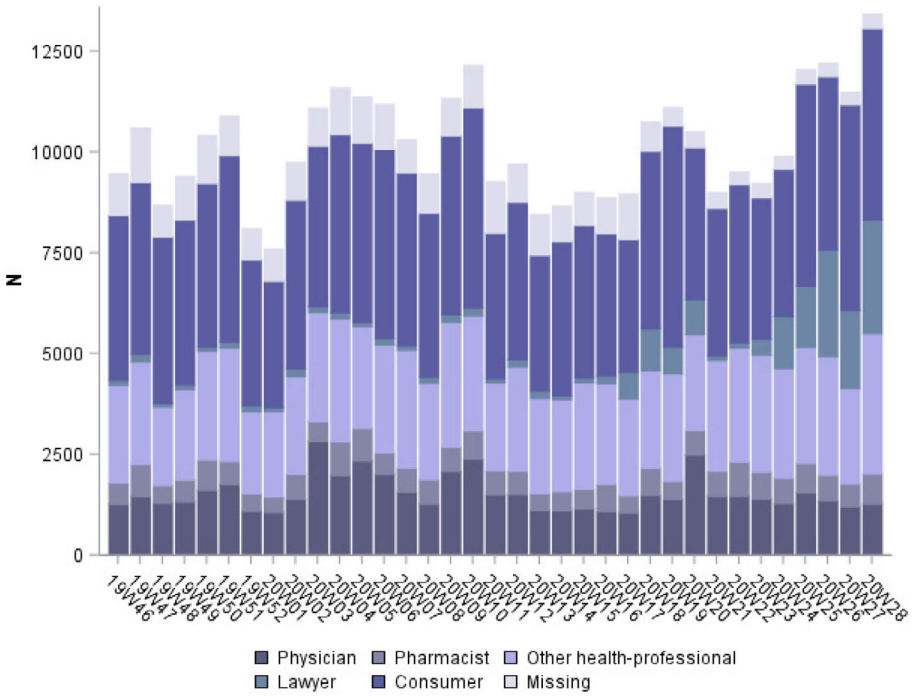

FIGURE 1 Number of reported cases per calendar week by reporter [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of spontaneous reports

	Total (*N* = 366 998)	Pre-pandemic time interval[a](*N* = 118 772)	First pandemic time interval[b](*N* = 117 941)	Second pandemic time interval[c](*N* = 130 285)
Median number of reports per day (IQR)	1778 (286.5–2031.5)	1795.5 (236–2037)	1736.5 (273–1907)	1810 (363.5–2135)
Sex	*N* = 314 941	*N* = 107 354	*N* = 106 661	*N* = 100 926
Female	59.7%	59.9%	59.4%	60.0%
Male	40.3%	40.1%	40.6%	40.0%
Age	*N* = 221 540	*N* = 74 815	*N* = 72 641	N = 74 084
Median (IQR)	59 (45–70)	59 (44–70)	59 (44–70)	60 (46–70)
0–17	5.3%	5.3%	5.6%	5.0%
18–39	14.4%	15.4%	14.6%	13.3%
40–59	30.9%	31.3%	30.8%	30.6%
60–79	41.0%	39.8%	40.6%	42.7%
80+	8.4%	8.2%	8.4%	8.5%
Reporter	*N* = 338 070	*N* = 106 631	*N* = 106 144	*N* = 125 295
Physician	16.3%	18.0%	17.3%	14.1%
Pharmacist	6.5%	6.7%	6.5%	6.3%
Other health professional	27.6%	27.7%	29.1%	26.2%
Lawyer	5.5%	1.5%	1.9%	11.8%
Consumer	44.2%	46.1%	45.2%	41.6%
Outcome	*N* = 307 060	*N* = 95 371	*N* = 97 536	*N* = 114 153
Death	18.9%	20.7%	17.9%	18.2%
Life-threatening	2.9%	3.3%	2.9%	2.6%
Hospitalization - initial or prolonged	29.8%	31.7%	31.9%	26.4%
Disability	1.5%	1.6%	1.6%	1.4%
Congenital anomaly	0.2%	0.2%	0.2%	0.2%
Required intervention to prevent permanent impairment/damage	0.1%	0.1%	0.1%	0.1%
Other serious (important medical event)	46.6%	42.4%	45.4%	51.1%
Commonly reported indications (PT)±	*N* = 316 577	*N* = 102 780	*N* = 102 675	*N* = 111 122
Product used for unknown indication	*N* = 77 727	*N* = 26 531	*N* = 24 510	*N* = 26 686
Specific indications	*N* = 238 850	*N* = 76 249	*N* = 78 165	*N* = 84 436
	Rheumatoid arthritis (8.5%)	Rheumatoid arthritis (8.2%)	Rheumatoid arthritis 7.5%	Rheumatoid arthritis (9.7%)
	Multiple sclerosis (4.0%)	Multiple sclerosis (4.6%)	Crohn's disease 4.5%	HIV infection (7.3%)
Commonly reported reactions (PT)±	*N* = 366 998	*N* = 118 772	*N* = 117 941	*N* = 130 285
	Death (8.6%)	Death (9.5%)	Death (8.6%)	Death (7.8%)
	Drug ineffective (7.3%)	Drug ineffective (6.8%)	Drug ineffective (7.2%)	Drug ineffective (7.7%)
	Off label use (5.6%)	Off label use (5.2%)	Off label use (6.0%)	Off label use (5.7%)
	Fatigue (5.2%)	Fatigue (4.8%)	Fatigue (5.4%)	Fatigue (5.3%)
	Nausea (4.6%)	Nausea (4.2%)	Nausea (4.7%)	Pain (4.9%)
Commonly reported reactions (SOC)±	*N* = 366 998	*N* = 118 772	*N* = 117 941	*N* = 130 285

TABLE 1 (Continued)

	Total (*N* = 366 998)	Pre-pandemic time interval[a](*N* = 118 772)	First pandemic time interval[b](*N* = 117 941)	Second pandemic time interval[c](*N* = 130 285)
	General disorders and administration site conditions (39.7%)	General disorders and administration site conditions (39.8%)	General disorders and administration site conditions (40.6%)	General disorders and administration site conditions (38.8%)
	Injury, poisoning and procedural complications (24.9%)	Injury, poisoning and procedural complications (23.9%)	Injury, poisoning and procedural complications (23.8%)	Injury, poisoning and procedural complications (27.0%)
	Gastrointestinal disorders (18.5%)	Nervous system disorders (18.1%)	Gastrointestinal disorders (19.5%)	Gastrointestinal disorders (18.8%)
	Nervous system disorders (18.2%)	Gastrointestinal disorders (17.1%)	Nervous system disorders (19.0%)	Nervous system disorders (17.7%)
	Infections and infestations (16.9%)	Infections and infestations (15.9%)	Infections and infestations (18.3%)	Investigations (16.7%)

Abbreviations: IQR, interquartile range; PT, preferred term; SOC, system organ class.
Note: ± Multiple PT or SOC per case possible.
[a]November 7, 2019 to January 29, 2020.
[b]January 30, 2020 to April 22, 2020.
[c]April 23, 2020 to July 15, 2020.

TABLE 2 Most commonly reported drugs

Total (*N* = 366 998)	Pre-pandemic time interval[a](*N* = 118 772)	First pandemic time interval[b](*N* = 117 941)	Second pandemic time interval[c](*N* = 130 285)
Adalimumab (3.7%)	Adalimumab (3.8%)	Adalimumab (4.0%)	Ranitidine (8.1%)
Ranitidine (3.1%)	Methotrexate (2.3%)	Omalizumab (2.4%)	Tenofovir (3.8%)
Methotrexate (1.8%)	Apixaban (1.6%)	Secukinumab (1.7%)	Adalimumab (3.5%)
Apixaban (1.7%)	Certolizumab (1.5%)	Methotrexate (1.6%)	Tocilizumab (2.6%)
Tocilizumab (1.5%)	Ibrutinib (1.4%)	Apixaban (1.6%)	Pirfenidone (2.0%)
Tenofovir (1.5%)	Ocrelizumab (1.3%)	Infliximab (1.4%)	Apixaban (1.8%)
Ibrutinib (1.2%)	Lenalidomide (1.3%)	Ustekinumab (1.4%)	Methotrexate (1.5%)
Lenalidomide (1.2%)	Esomeprazole (1.2%)	Ibrutinib (1.3%)	Ocrelizumab (1.3%)
Secukinumab (1.2%)	Rituximab (1.2%)	Lenalidomide (1.2%)	Oxycodone (1.2%)
Tofacitinib (1.2%)	Tofacitinib (1.2%)	Esomeprazole (1.2%)	Capecitabine (1.2%)

[a]November 7, 2019 to January 29, 2020.
[b]January 30, 2020 to April 22, 2020.
[c]April 23, 2020 to July 15, 2020.

indication was rheumatoid arthritis (69.8%, Table S1). The most common reactions referred to the drug's ineffectiveness (42.9%) and rheumatoid arthritis (20.5%) and, in terms of system organ classes, to general disorders and administration site conditions (74.9%) and musculoskeletal and connective tissue disorders (50.6%).

3.4 | Methotrexate cases - pre-pandemic versus pandemic time intervals

The median daily number of reports referring to methotrexate decreased during the study period (from 28 in the pre-pandemic time interval to 14.5 in the second pandemic time interval; Table 3). Case characteristics with respect to demographics, type of reporter, outcome, indication for treatment, and commonly reported adverse events remained largely unchanged (Table 3, Table S1).

3.5 | (Hydroxy)chloroquine cases - entire study period

Overall, (hydroxy)chloroquine was reported 620 times with a median [IQR] of 1 [0 to 4] report per day and a maximum of 19 cases on March 10, 2020 (Table 3 and Figure S2) and of 38 cases in the 22nd calendar week of 2020 (Figure 2). About 67% of cases were about female patients, and median age was 53 years (Table 3). The (hydroxy) chloroquine related adverse events were most commonly filed by consumers (41.9%), followed by other health professionals (27.0%) and

TABLE 3 Characteristics for reported cases with methotrexate or (hydroxy)chloroquine as primary suspect drugs

	Methotrexate				(Hydroxy)chloroquine			
	Total (*N* = 6717)	**Pre-pandemic time interval[a] (*N* = 2782)**	**First pandemic tine interval[b] (*N* = 1934)**	**Second pandemic time interval[c] (*N* = 2001)**	**Total (*N* = 620)**	**Pre-pandemic time interval[a] (*N* = 84)**	**First pandemic tine interval[b] (*N* = 215)**	**Second pandemic time interval[c] (*N* = 321)**
Median number of reports per day (IQR)	20 (3.5–42)	28 (3.5–51)	20.5 (2–37.5)	14.5 (4.5–38.5)	1 (0–4)	1 (0–2)	1.5 (0–4)	3 (1–5)
Sex	*N* = 6557	*N* = 2734	*N* = 1870	*N* = 1953	*N* = 269	*N* = 38	*N* = 88	*N* = 143
Female	73.9%	74.5%	72.8%	74.1%	67.3%	94.7%	71.6%	57.3%
Male	26.1%	25.5%	27.2%	25.9%	32.7%	5.3%	28.4%	42.7%
Age	*N* = 4597	*N* = 1975	*N* = 1315	*N* = 1307	*N* = 235	*N* = 34	*N* = 74	*N* = 127
Median (IQR)	58 (47–66)	58 (48–65)	58 (45–67)	57 (45–67)	53 (32–65)	40.5 (20–53)	53 (37–64)	55 (35–67)
0–17	6.2%	3.4%	8.3%	8.2%	9.4%	17.6%	9.5%	7.1%
18–39	10.7%	10.4%	10.9%	10.9%	24.7%	29.4%	18.9%	26.8%
40–59	38.5%	41.2%	36.0%	37.0%	27.7%	35.3%	27.0%	26.0%
60–79	41.7%	42.1%	41.5%	41.3%	32.3%	17.6%	39.2%	32.3%
80+	3.0%	2.9%	3.3%	2.7%	6.0%		5.4%	7.9%
Reporter	*N* = 6608	*N* = 2730	*N* = 1896	*N* = 1982	*N* = 599	*N* = 81	*N* = 211	*N* = 307
Physician	27.8%	25.6%	29.4%	29.1%	20.7%	9.9%	33.2%	15.0%
Pharmacist	1.3%	1.0%	1.9%	1.3%	10.4%	4.9%	10.0%	12.1%
Other health professional	48.0%	48.0%	46.0%	50.1%	27.0%	27.2%	22.3%	30.3%
Lawyer	-	-	-	-	-	-	-	-
Consumer	22.8%	25.3%	22.7%	19.5%	41.9%	58.0%	34.6%	42.7%
Outcome	*N* = 6540	*N* = 2705	*N* = 1870	*N* = 1965	*N* = 539	*N* = 69	*N* = 200	*N* = 270
Death	3.0%	2.9%	3.0%	3.0%	10.8%	7.2%	9.0%	13.0%
Life-threatening	2.9%	1.6%	2.7%	4.9%	8.0%	8.7%	3.5%	11.1%
Hospitalization - initial or prolonged	14.1%	13.9%	16.9%	11.9%	17.6%	20.3%	14.0%	19.6%
Disability	2.4%	2.3%	1.8%	2.9%	3.9%	1.4%	6.5%	2.6%
Congenital anomaly	0.2%	0.2%	0.1%	0.2%	0.6%	-	0.5%	0.7%
Required intervention to prevent permanent impairment/damage					0.2%	1.4%		
Other serious (important medical event)	77.5%	79.1%	75.5%	77.2%	59.0%	60.9%	66.5%	53.0%

Abbreviations: IQR, interquartile range.
[a]November 7, 2019 to January 29, 2020.
[b]January 30, 2020 to April 22, 2020.
[c]April 23, 2020 to July 15, 2020.

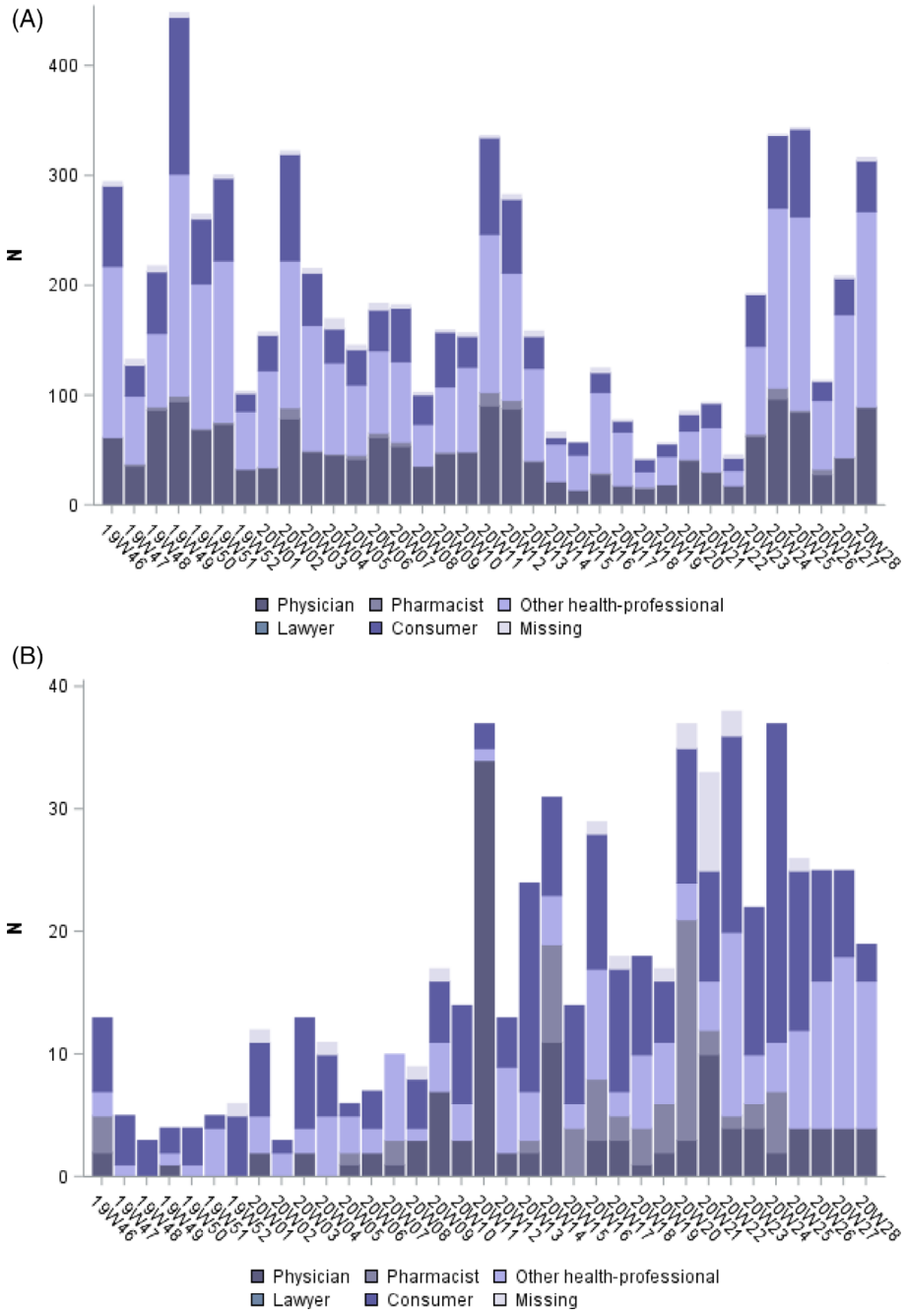

FIGURE 2 Number of reported cases for (A) methotrexate and (B) (hydroxy) chloroquine per calendar week by reporter [Colour figure can be viewed at wileyonlinelibrary.com]

physicians (20.7%). The most often reported indications for (hydroxy) chloroquine were COVID-19 (24.4%) and systemic lupus erythematosus (21.4%, Table S1). The most frequent reactions were drug ineffectiveness (15.5%) and, in terms of system organ classes, general disorders and administration site conditions (41.8%).

3.6 | (Hydroxy)chloroquine cases - Pre-pandemic versus pandemic time intervals

The median daily number of reports with (hydroxy)chloroquine increased numerically but remained low during the study period (from 1 in the pre-pandemic time interval to 3 in the second pandemic time interval; Table 3). The demographics of cases changed, with the proportion of cases referring to male patients increasing from 5.3% to 42.7% and the median age increasing from 40.5 years to 55 years from the pre-pandemic to the second pandemic time interval. Comparing the same intervals, we also observed an increase in the proportion of cases reported by health professionals (from 42.0% to 57.4%) with an accompanying decrease in the proportion of cases reported by consumers (from 58.0% to 42.7%), as well as an increase in the proportion of cases with fatal or life-threatening events (from 15.9% to 24.1%). As expected, a major change between the pre-pandemic and the pandemic time intervals was the emergence of COVID-19

(44.9%) under indications for treatment and 'off-label use' (19.3%) under commonly reported reactions in the second pandemic time interval (Table S1). Other noticeable changes were the increased reporting of 'maternal exposure during pregnancy' (14.0%) and 'premature baby' (8.8%) during the first pandemic time interval and of 'electrocardiogram QT prolonged' (14.3%) during the second pandemic time interval.

4 | CONCLUSIONS

Our study showed that the overall reporting of adverse events to FAERS and most characteristics of reporting such as demographics of cases, reported adverse events and outcomes did not noticeably change after the outbreak of the pandemic. Reporting of adverse events involving methotrexate, a long-established medication unrelated to COVID-19, decreased, though. In contrast, we observed potential signs of stimulated reporting for adverse events involving (hydroxy)chloroquine.

SRS are an invaluable tool in post-marketing pharmacovigilance, but they depend on the reporting of adverse events by health professionals, drug consumers, and others. Thus, it is crucial to consider the potential impact of major events on this reporting behavior. We hypothesized that the ongoing global pandemic could have affected adverse event reporting and thus data characteristics in SRS. Reassuringly, our study findings do not fully support this hypothesis. Indeed, we observed that the daily number of reports and the characteristics of reported cases did not noticeably change before and after the outbreak of the ongoing COVID-19 pandemic. Moreover, although the daily number of reports did decrease for methotrexate, a commonly used drug unrelated to COVID-19, the characteristics of reported cases remained largely unaffected. Of note, the decrease in the reporting of methotrexate related adverse events could be seen as a sign of reporting fatigue during the pandemic. However, it could also be part of longer-term time trend, which our study was not designed to assess.

We also looked specifically at (hydroxy)chloroquine, a drug that has been discussed as part of the management of COVID-19, although several randomized controlled trials and well-conducted observational studies failed to show any beneficial effects in the prevention or treatment of the disease.[16-18] We observed a small elevation in the daily number of reports for adverse events with (hydroxy)chloroquine, which could reflect the potentially wider use of this substance and the amplified media attention during the global pandemic. In concordance, we also observed an increased reporting after the outbreak with tenofovir and tocilizumab, two other drugs related to COVID-19.[19]

We observed an increase in the proportion of cases with (hydroxy)chloroquine) referring to male patients and to fatal or life-threatening outcomes as well as an increase in the age of cases after the outbreak, which is congruent with the demographics of COVID-19 patients and the potentially severe course of the disease. Moreover, there was an increased proportion of health professional initiated adverse event reporting for (hydroxy)chloroquine after the outbreak of the pandemic. This could be due to an increased awareness among physicians, pharmacists and other health professionals regarding the toxicity of the drug. There was also an increase in COVID-19 as indication and in off label use as reported reaction, which could be both related to the EUA announced by the FDA in March 2020 and its revocation in June 2020. Finally, the increased number of reports of QT prolongation underlines the importance of carefully considering potential drug–drug interactions and cardiac comorbidities during treatment with (hydroxy)chloroquine.[20]

Our results also showed reports involving (hydroxy)chloroquine use during pregnancy in the first pandemic time interval with a peak in March 2020. Indeed, this could be related to the overall increased awareness of (hydroxy)chloroquine safety. However, besides its use for the management of disease activity in systemic lupus erythematosus during pregnancy,[21] beneficial effects of (hydroxy) chloroquine in the treatment of pre-eclampsia have recently been described in the literature.[22,23] Thus, the change in the reporting behavior for adverse events with (hydroxy)chloroquine in this case could also reflect this novel indication rather than pandemic related effects. In a similar fashion, the increased number of reports filed for ranitidine is most probably unrelated to the pandemic and a result of the agent's recent market withdrawal due to safety concerns.[24]

The main strength of our study is the large sample size of the US FAERS, the underlying database. This enabled us not only to assess overall characteristics of adverse event reporting before and after the outbreak of the COVID-19 pandemic, but to further look into specific reporting characteristics such as the type of reporter and also to focus on specific medications. The main limitations of our study are the reporting biases inherent to the utilized data source mentioned earlier.[1,5] Another limitation of our study is the absence of the 'denominator', that is the number of exposed patients, which limits the interpretability of the data. Indeed, we were not able to examine whether an increase in adverse event reporting for a specific drug was also accompanied by a more frequent use. However, this should not affect our analyses of the overall reporting behavior. Moreover, our analyses were not designed to incorporate longer-term trends related to reporting in FAERS. In addition, the descriptive methodology precluded causal inferences. Finally, using another cut-off date other than January 30, 2020 or different time intervals could lead to slightly different results.

The overall adverse event reporting to FAERS did not seem to change after the outbreak of the global COVID-19 pandemic, at least in the first 6 months of this unprecedented situation. This provides some reassurance regarding the continuation of use of SRS as a pharmacovigilance tool. That being said, we did observe a potential shift in the reporting behavior of (hydroxy)chloroquine related adverse events. Given that such shifts can lead to a misinterpretation of pharmacovigilance signals, further studies are needed to assess the impact of the pandemic on adverse event reporting for other substances with a potential relation to COVID-19.

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CONFLICTS OF INTEREST

The authors have nothing to declare.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Kathrin Jobski. The first draft of the manuscript was written by Michael Dörks, and all authors commented on the manuscript and revised it critically for important intellectual content. All authors read and approved the final manuscript. Antonios Douros supervised the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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