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A pharmacovigilance study to quantify the strength of association between the combination of antimalarial drugs and azithromycin and cardiac arrhythmias: implications for the treatment of COVID-19.

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ABSTRACT

Background: Hydroxychloroquine, an antimalarial drug, combined with azithromycin has been considered a potential treatment for COVID-19. However, these drugs may cause electrocardiogram QT prolongation (QTp) and torsade de Pointes (TdP). We examined potential safety signals for these cardiac arrhythmias.

Methods: Using the OpenVigil 2.1 MedDRA platform, we mined data from the U.S. Food and Drug Administration's Adverse Event Reporting System (FAERS) from December 2019 to June 2020. We extracted individual case safety reports based on exposures of seven antimalarial drugs, azithromycin, and combinations. All other drugs in FAERS served as controls. Events of interest included QTp and TdP, with associations between drug exposures and events expressed as adjusted Reporting-Odds-Ratios (aRORs) and confidence intervals. The lower end of aROR 95% confidence interval >1 was used as the statistically significant signal detection threshold.

Results: QTp safety signals were found for hydroxychloroquine[aROR:11.70 (10.40–13.16)], chloroquine [aROR:18.97 (11.30–31.87)], quinine[aROR:16.66 (10.18–27.25)], atovaquone[aROR:6.91 (4.14–11.56)], azithromycin alone [aROR:28.02 (22.87–34.32)] and hydroxychloroquine + azithromycin [aROR:75.23 (51.15–110.66)]. TdP safety signals were found for hydroxychloroquine [aROR: 5.62 (4.94–6.38)], chloroquine[aROR:49.37 (30.63–79.58)], and hydroxychloroquine + azithromycin[aROR:33.09 (21.22–51.61)].

Conclusion: Hydroxychloroquine/chloroquine and/or azithromycin was associated with QTp/TdP safety signals and their use should be monitored carefully.

1. Introduction

In late December 2019, the coronavirus disease 2019 (COVID-19) has started to spread in Wuhan, the capital city of Hubei province, China [1]. The novel coronavirus, SARS-CoV-2 carries a risk for all the population especially the elderly and patients with preexisting conditions. It can lead to severe acute respiratory syndromes, hospitalizations (including intensive care unit admissions), and death in all patients irrespective of age. On 12 March 2020, the World Health Organization (WHO) has declared the COVID-19 outbreak a pandemic [2]. Global data suggest an important epidemiological burden associated with COVID-19. As of 2 October 2020, 34, 495,176 laboratory-confirmed cases had been documented, and a total of 1,025,729 deaths globally [3]. As of October 06, there are a total of 7,436,278 laboratory-confirmed cases and 209,560 deaths in the USA [4].

Measures to slow the spread of COVID-19 include quarantine, social distancing, and isolation [5]. Measures to prevent include the development of vaccines, which is currently a hot research area. Unfortunately, there is currently no vaccine to protect people against COVID-19 [6]. Currently, therapeutic options for patients with COVID-19 mainly focus on experimental drugs (e.g. Aviptadil (RLF-100), tradipitant) as well as the repurposing of

existing drugs [7,8]. Among the available therapeutic drugs candidates for repurposing, antimalarial drugs chloroquine (CQ)/ hydroxychloroquine (HCQ) have been considered potential 'miracle cures' for patients with COVID-19 in light of promising results from clinical trials [9]. CQ/HCQ are used to prevent or treat malaria infections caused by *plasmodium falciparum* and to treat connective tissue diseases such as rheumatoid arthritis and lupus [10].

The results of the study conducted by Gautret et al. suggest a significant reduction in viral load in COVID-19 patients receiving the combination of HCQ and azithromycin [11]. In the face of these results, the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) followed by the US Food and Drug Administration (FDA) issued an emergency use authorization allowing off-label recommendation use of HCQ for COVID-19 as a treatment on 28 March 2020 [12]. These actions from the regulatory bodies in France and the United States have sparked concerns in the clinical and research community over the fact that these drugs have the potential to cause QTp and torsade de Pointes (TdP). Chatre et al. [13] recommended that clinicians be aware of severe and potentially irreversible cardiac toxicities related to the use of

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CQ or HCQ in the long-term treatment of connective tissue diseases. These recommendations go a step further by requiring treatments to stop as soon as cardiac manifestations occur. A statement guidelines from the Canadian Heart Rhythm Society mentions that the addition of azithromycin to HCQ may lead to QT prolongation [14]. In the same vein, Das et al [15] conducted a systematic review on the efficacy and safety of the use of HCQ along with azithromycin in COVID-19 patients. They concluded that the use of this treatment combination warrants caution. Finally, there was no evidence of QTp or TdP monitoring in the Gautret et al study [11].

Therefore, there is a critical need to examine safety signals for cardiac arrhythmias (QTp and TdP) from a pharmacovigilance perspective to ensure patient safety, especially in anticipation of high demand and use of CQ/HCQ and/or azithromycin in the war against COVID-19. Besides, several studies have investigated the use of other antimalarial drugs as candidates for repurposing, reemphasizing the importance of conducting pharmacovigilance studies [16,17]. Two pharmacovigilance studies assessed the risk of QTp and TdP following the use of HCQ/CQ and or azithromycin using data from the U.S. Food and Drugs Administration Adverse Event Reporting System (FAERS) [18,19]. Although informative, the results of these studies offer limited insights on these safety signals since the data used were obtained in the period pre-COVID-19 (Before December 2019).

The main objective of this study was to determine potential safety signals for QTp and TdP in patients using HCQ/CQ and/or azithromycin as treatment candidates for COVID-19 using data from the FAERS from December 2019 to the second quarter of 2020 (peri-COVID-19 period). We also determined potential safety signals for five additional antimalarial drugs alone or in combination with azithromycin.

2. Material and methods

2.1. Study design and data sources

We conducted a disproportionality analysis of the FAERS. FAERS is a publicly available database that contains domestic and foreign information on adverse events and medication error reports submitted to the FDA in the form of ICSRs [20]. ICSRs in the FAERS database provide general administration information including patient characteristics [age, gender (sex)], reporting country, drugs (indications for the drug, concomitant drugs, dosage information and route of administration), events (suspected adverse drug reactions, and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology, and outcomes [21]. FAERS database follows the international safety reporting guidance issued by the International Conference on Harmonization (ICH E2B) [22].

2.2. Procedures

Using the OpenVigil 2.1 MedDRA platform [23], we mined data from the FAERS from December 2019 to the second quarter of 2020 (551,018 total reports). The OpenVigil 2.1 MedDRA

platform allows for the estimation of disproportionality measures used for signal detection.

We used structured query language to extract ICSRs based on exposures of seven antimalarial drugs alone (CQ/HCQ, amodiaquine, quinine, mefloquine, primaquine, atovaquone) and, azithromycin alone, and combinations (exposed). All other drugs in FAERS served as controls (non-exposed to antimalarial drugs/azithromycin).

Two major events (QTp, TdP), suspected to be induced by the treatments (exposure variables) were identified following the MedDRA hierarchy and extracted through OpenVigil 2.1. Example of query logic processes to retrieve frequency counts for events following exposure to HCQ and to create 2 × 2 contingency tables of drug exposure vs event for disproportionality analyses are presented in Appendix 1 and 2 respectively.

Age (categorized as less than 18, 18–64, 65+, Unknown), gender (categorized as male, female, unknown), country (transformed into 'region' and categorized as Europe, Asia, Africa, North America, South America, Not specified) were identified from ICSRs. Drugs interacting with antimalarial drugs are likely to increase their plasma concentrations through pharmacokinetic interactions. Drug-drug interactions (DDIs) between antimalarial drugs (CQ/HCQ, amodiaquine, quinine, mefloquine, primaquine, atovaquone) and azithromycin were identified from the summary of the product characteristics (SPC) (Appendix 3).

2.3. Statistical analysis

We conducted a disproportionality analysis to calculate reporting odds ratios (RORs) for signal detection. The estimation of RORs was done for each antimalarial drug, azithromycin, and combinations. We compared the odds of QTp or TdP in ICSRs indicating patients treated with antimalarial drugs and antibiotics (cases) with the odds of QTp or TdP in ICSRs indicating patients treated with all other drugs (non-cases). Additionally, we conducted a robustness analysis by adjusting the calculated RORs for potential confounders including age, gender, and the reporting regions. These suspected confounders were confirmed by the subgroup analyses using the covariates (Data available upon request). The adjusted RORs were calculated using the Mantel-Haenszel approach [24]. Since we aimed to control for categorical variables (or simultaneously for more than one categorical variable), each modality of the categorical variable (or each group formed by the combination of the categorical variables) was treated as a stratum.

Let us consider that we are adjusting the OR for two binary confounding variables denoted Z_1 and Z_2. The strata are the following: Stratum 1 = {$Z_1 = 1$ and $Z_2 = 1$}, Stratum 2 = {$Z_1 = 1$ and $Z_2 = 0$}, Stratum 3 = {$Z_1 = 0$ and $Z_2 = 1$} and Stratum 4 = {$Z_1 = 0$ and $Z_2 = 0$}. Then, contingency tables are calculated for each stratum as follows:

	Y = 1	Y = 0
X = 1	a_i	c_i
X = 0	b_i	d_i

Once these contingency tables are calculated, the Mantel-Haenszel OR (adjusted OR) is calculated as (where I denotes

the number of strata, and n_i is the number of observation in the stratum$i$):

$$OR = \frac{\sum_{i=1}^{I} \frac{a_i d_i}{n_i}}{\sum_{i=1}^{I} \frac{c_i d_i}{n_i}}$$

The standard error is calculated as:

$$SE = \sqrt{\frac{V}{Q*R}}$$

Where

$$Q = \sum_{i=1}^{I} \frac{a_i b_i}{n_i}$$

$$R = \sum_{i=1}^{I} \frac{c_i d_i}{n_i}$$

$$V = \sum_{i=1}^{I} \frac{(a_i+b_i)(c_i+d_i)(a_i+c_i)(b_i+d_i)}{n_i^2(n_i-1)}$$

Thus, the lower (LB) and upper (UB) bounds of the 95% confidence interval are given by:

$$LB = exp(\ln(OR) - 1.96 * SE)$$
$$UB = exp(\ln(OR) + 1.96 * SE)$$

The results of the disproportionality analysis were presented using forest plots. All analyses were performed using the statistical software package Stata SE, Release 14 (College Station, TX: StataCorp LP).

3. Results

3.1. Disproportionality analysis: unadjusted analyses

3.1.1. A-electrocardiogram QT prolonged
The crude RORs (cRORs), with their 95% CIs, are presented in Figure 1. When the drugs are used as a single agent, we found safety signals for HCQ [aROR:9.82 (7.79–12.37), p-value: <0.001], CQ [aROR: 18.46 (5.84–58.55), p-value: <0.001], quinine [aROR: 42.95 (20.84–88.53) p-value: <0.001], azithromycin [aROR: 40.10 (28.80–-55.83) p-value: <0.001]. When the drugs are used in combination, we only found safety signals for HCQ + azithromycin [aROR: 243.31 (163.40–362.30), p-value: <0.001].

3.1.2. B-Torsade de pointes
When the drugs are used as a single agent, we found safety signals only for CQ [aROR: 46.21 (6.39–334.14). When the drugs are used in combination, we only found safety signals for HCQ + azithromycin [aROR: 71.05 (17.38–290.46), p-value: <0.001].

3.2. Disproportionality analysis: adjusted analyses

3.2.1. A-electrocardiogram QT prolonged
The adjusted RORs (aRORs), with their 95% CIs, are presented in Figure 2. When the drugs are used as a single agent, we found safety signals for HCQ [aROR:11.70 (10.40–13.16), p-value: <0.001], CQ [aROR: 18.97 (11.30–31.87), p-value: <0.001], quinine [aROR: 16.66 (10.18–27.25) p-value: <0.001],

Figure 1. Disproportionality analysis for QT prolongation and torsade de pointes with six antimalarial drugs and azithromycin, showing the crude reporting odds ratios (cRORs) with 95% confidence intervals and p-values.

cROR: Crude reported odds ratio; 95% CI: 95% Confidence interval. There was no report of torsade de pointes in individual case safety reports in the Food and Drugs Administration Adverse Event Reporting System.
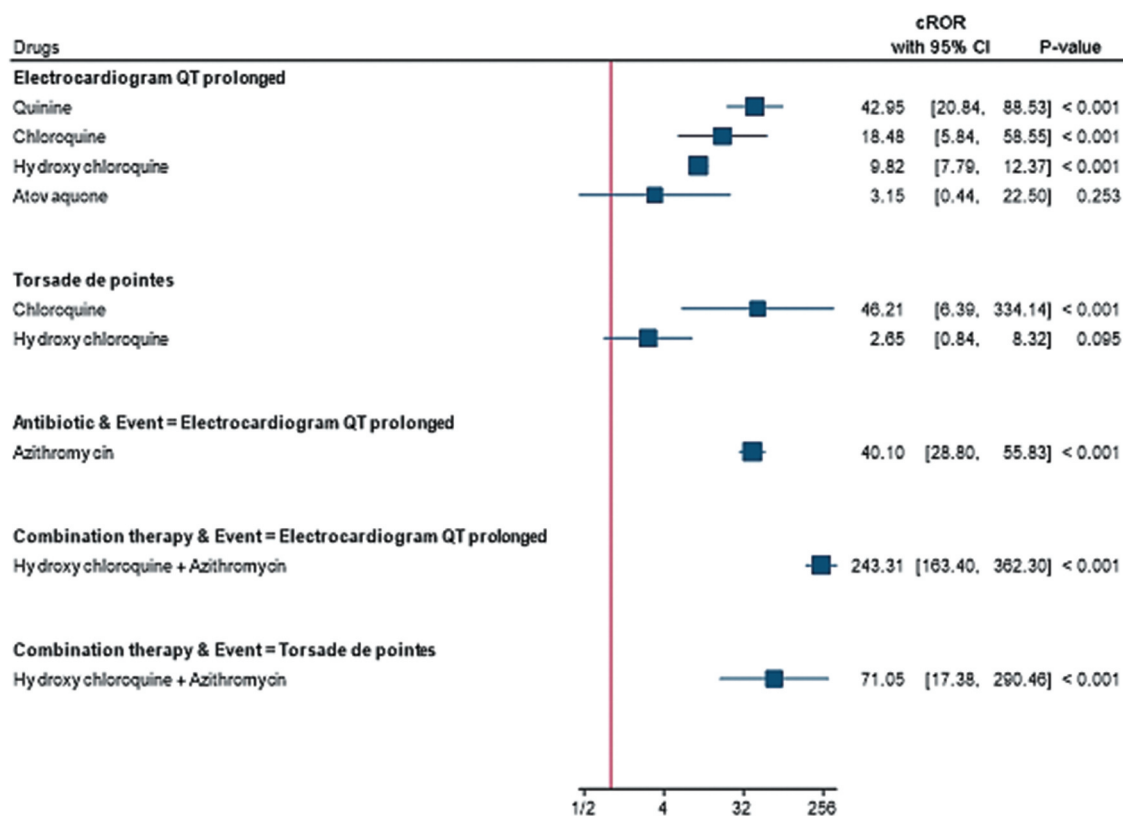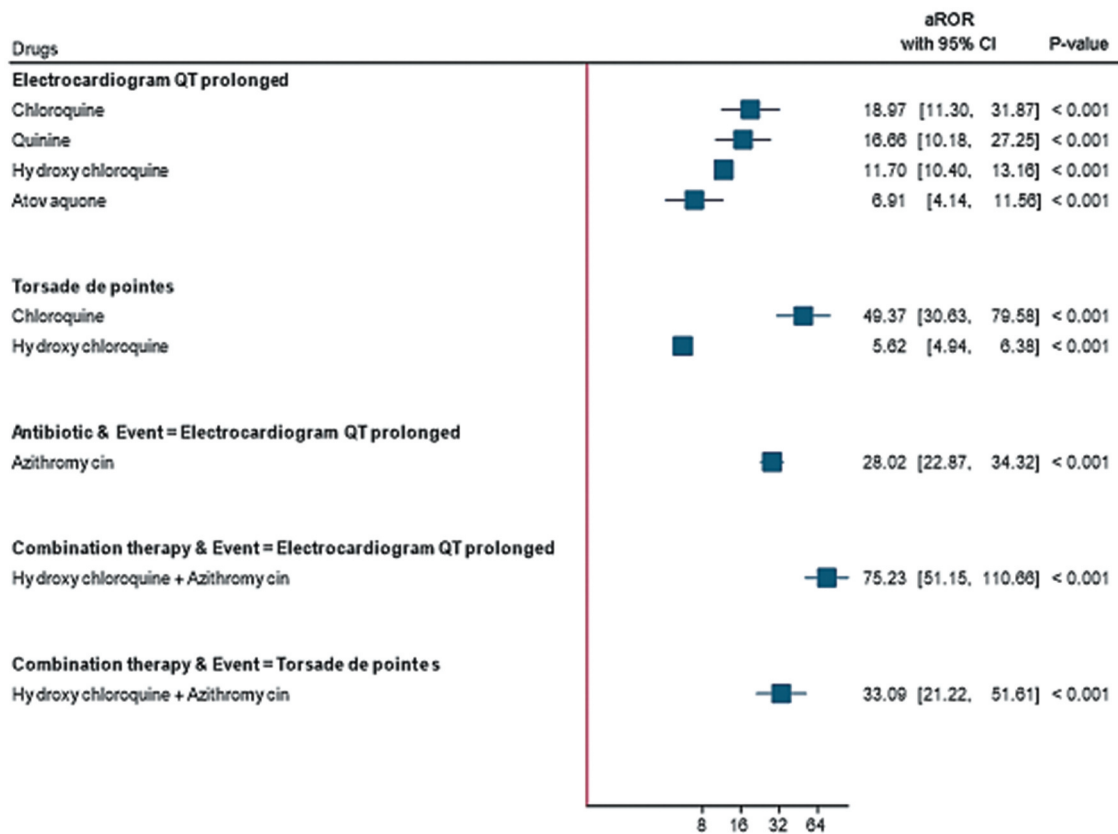
Figure 2. Disproportionality analysis for QT prolongation and torsade de pointes with six antimalarial drugs and azithromycin, showing the adjusted reporting odds ratios (aRORs) with 95% confidence intervals and p-values.

aROR: Adjusted reported odds ratio; 95% CI: 95% Confidence interval. There was no report of torsade de pointes in individual case safety reports in the Food and Drugs Administration Adverse Event Reporting System.

atovaquone [aROR: 6.91 (4.14–11.56), p-value: <0.001], azithromycin alone [aROR: 28.02 (22.87–34.32), p-value: <0.001]. When the drugs are used in combination, we only found safety signals for HCQ + azithromycin [aROR: 75.23 (51.15–110.66), p-value: <0.001].

3.2.2. B-Torsade de pointes

When the drugs are used as a single agent, we found safety signals for HCQ [aROR: 5.62 (4.94–6.38), p-value: <0.001], CQ [aROR: 49.37 (30.63–79.58), p-value: <0.001] (Figure 2). When the drugs are used in combination, we only found safety signals for HCQ + azithromycin [aROR: 33.09 (21.22–51.61), p-value: <0.001].

4. Discussion

In this study, we quantified the risk of QTp and TdP in patients receiving antimalarial drugs (HCQ, amodiaquine, CQ, quinine, mefloquine, primaquine, atovaquone) and azithromycin (individual and combination therapy) from the FAERS December 2019-Second quarter of 2020) through the OpenVigil 2.1 platform. The latter offers an opportunity to generate unbiased pharmacovigilance analyses since it uses cleaned FAERS data [23] (i.e. duplicates and incomplete reports are removed from the original dataset). We found cardiac arrhythmias safety signals associated with several antimalarial drugs, including CQ/HCQ, and/or azithromycin. These results go beyond the already known potential for HCQ and azithromycin to induce cardiac arrhythmias described in the medications' SPC as these suspected associations are quantified in the current study using a large pharmacovigilance database (FAERS) and labeled as safety signals specifically in the context of COVID-19. For azithromycin, evidence from observational studies in regards to the association between macrolides and cardiovascular events is mixed [16].

Recently, several studies assessed the effectiveness and safety of HCQ with or without azithromycin. From a safety point of view, Sarayani et al. [17] conducted a pharmacovigilance study using data from FAERS (1969–3rd quarter 2019) to examine risks of HCQ with or without azithromycin, including QT segment prolongation, TdP, and death. The authors reported that only azithromycin as a monotherapy was associated with TdP/QT prolongation events, which warrants caution in its use. These results are supported by our findings as it relates to the use of azithromycin alone. As for HCQ/CQ alone or in combination with azithromycin, our results conflict. Potential explanations for these discrepancies may include the differences in data mining approaches used to extract and identify cases and non-cases in the FAERS, the comparator, and denominator used for the measure of association (all other drugs in the FAERS in our study versus amoxicillin in Sarayani et al) and the time horizon covered by the data

(1963- December 2019, the period before COVID-19). A similar study by Singh et al. aimed at determining and characterizing HCQ-associated cardiovascular adverse events (CV-AEs) [18]. Our results are in agreement with the findings of the study by Singh et al. as it relates to HCQ. Though, the magnitude of our findings is greater given that the aROR for HCQ is significantly higher than the one reported by Singh et al. This may be due to our study using FAERS data during the COVID-19 period (December 2019–2nd quarter of 2020) while Singh et al. used FAERS data for the period from 29 May 1998, to 31 December 2019. The scope of the current study is broader as it examined seven antimalarial drugs alone or in combination with azithromycin, with ROR adjusted for potential confounders.

Rosenberg et al. [25] conducted a multicentre retrospective cohort study of adverse effects of HCQ among patients with COVID-19. Cardiac arrest was more frequent in patients who received HCQ with azithromycin, compared with patients who received neither drug, even after adjustment. Mercuro et al. [26] conducted a study to characterize the risk and degree of QT prolongation in patients with COVID-19 in association with their use of HCQ with or without concomitant azithromycin. They found that patients who were hospitalized and received HCQ for COVID-19 frequently experienced QTc prolongation and ADEs, including a case of torsades de pointes with the administration of HCQ and azithromycin. Chorin et al. [27] conducted a retrospective study of 251 patients diagnosed with COVID-19 and treated with HCQ + azithromycin to determine the risk for cardiac arrhythmias and death. The authors concluded that HCQ + azithromycin significantly prolongs the QTc interval in patients with COVID-19. These results are consistent with our findings.

With the increasing utilization of spontaneous reporting systems for post-marketing surveillance and pharmacovigilance, several well-recognized limitations of the database should be noted. As the reporting of adverse events is passive, it is subject to inherent limitations that may introduce selection bias to the analysis using the database [28]. The limitations are underreporting, overreporting, and data quality. Underreporting is common due to several reasons. First, it is hard to determine whether a drug is the root cause of an adverse event. Second, physicians only report serious or unexpected adverse events. Third, physicians may be reluctant to report an adverse event due to different reasons such as lack of time. Overreporting is less common than under-reporting. It is believed that the reports are skewed to more extensively used drugs and more serious adverse events. The data quality in spontaneous reporting is not perfect. First, some mistakes could be made due to the manual reporting process. Second, some data elements may be missing or incomplete including dosage, clinical indications, and drug-drug interactions. Third, reports could be duplicated due to multiple reporting sources. Fourth, reports do not follow a strict format. Unlike clinical trials, the spontaneous reporting system that collects information on adverse events relies on passive and opportunistic reporting. This causes a long-standing issue of missing denominators, which indicates the accurate number of patients taking the drug. Thus, it is hard to establish a causal relationship between a drug and an adverse event. Notwithstanding these limitations, this study is the first one to quantify the association between seven antimalarial drugs and/or azithromycin and cardiovascular adverse events. The case/non-case method used is known to be able to detect relatively rare signals for adverse drug reactions (ADRs) such as QTp and TdP [29,30].

5. Conclusion

In the face of COVID-19 and the quest for effective and safe treatments, we recommend that a careful risk-benefit assessment be performed in patients with a previous history of cardiac disorders (and especially cardiac arrhythmia) requiring CQ, HCQ, quinine, atovaquone alone or in combination with azithromycin. In these at-risk patients, periodic and close cardiac monitoring with clinical evaluation and electrocardiograms are warranted.

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Appendix 1. Example: Query processing logic to estimate the frequency of adverse drug reactions for Hydroxychloroquine

```
SELECT
  pt AS event,
  COUNT(pt) AS Count_ISRs,
  COUNT(Distinct Case_id) AS Count_independent_cases
FROM
  public.rep_event,
  public.report
WHERE
  report.isr= rep_event.isr
  AND rep_event.isr = ANY(
    (
        (
          SELECT
            report.isr
          FROM
            public.report
WHERE
  (
    (
      EXISTS(
        SELECT
          *
        FROM
         public.drugusage
        WHERE
          (
            drugusage.brandname IS NULL
            AND EXISTS(
              SELECT
                *
              FROM
                d_appl
              WHERE
                d_appl.drug_seq = drugusage.drug_seq
                AND lower(d_appl.drugname) = lower('hydroxychloroquine')
            )
          )
          AND drugusage.isr = report.isr
        )
      )
    )
  )
UNION
  (
    SELECT
      report.isr
    FROM
      public.report
    WHERE
      (
        (
          EXISTS(
            SELECT
              *
            FROM
              public.drugusage
            WHERE
              (
                drugusage.brandname IS NOT NULL
                AND EXISTS(
                  SELECT
                    *
                  FROM
                    product
```

```
                  WHERE
                    lower(product.brandname) = lower(drugusage.brandname)
                    AND lower(product.drugname) = lower
('hydroxychloroquine')
                )
              )
              AND drugusage.isr = report.isr)
            )
          )
        )
      )
    )
GROUP BY
  pt
ORDER BY
  Count_ISRs DESC
```

Appendix 2. Example: Query processing logic used to generate a 2 × 2 contingency table for the disproportionality analysis for hydroxychloroquine and QT prolongation

```
SELECT
  COUNT(DISTINCT isr) AS count
FROM
  public.report
WHERE
  isr = ANY(
    (
      (
        (
          SELECT
            report.isr
          FROM
           public.report
          WHERE
            (
              (
                EXISTS(
                  SELECT
                    *
                  FROM
                    public.drugusage
                  WHERE
                    (
                      drugusage.brandname IS NULL
                      AND EXISTS(
                        SELECT
                          *
                        FROM
                          d_appl
                        WHERE
                          d_appl.drug_seq = drugusage.drug_seq
                          AND lower(d_appl.drugname) = lower
('hydroxychloroquine')
                      )
                    )
                    AND drugusage.isr = report.isr
                  )
                )
              )
            )
```

```
UNION
  (
    SELECT
      report.isr
    FROM
      public.report
    WHERE
      (
        (EXISTS(
          SELECT
            *
          FROM
            public.drugusage
          WHERE
            (
              drugusage.brandname IS NOT NULL
              AND EXISTS(
                SELECT
                  *
                FROM
                  product
                WHERE
                  lower(product.brandname) = lower(drugusage.brandname)
                  AND lower(product.drugname) = lower('hydroxychloroquine')
              )
            )
            AND drugusage.isr = report.isr)
        )
      )
  )
  INTERSECT(SELECT
  report.isr
FROM
  public.report
WHERE
  (EXISTS(SELECT
      *
FROM
  public.rep_event
WHERE
  report.isr = rep_event.isr
  AND rep_event.pt = 'electrocardiogram qt prolonged')
  )
)
Query Sum Drug:
  SELECT
    COUNT(DISTINCT isr) AS count
  FROM
    public.report
  WHERE
    isr = ANY(
      (
        (SELECT
          report.isr
        FROM
          public.report            WHERE
          (
            (
              EXISTS(
                SELECT
                  *
                FROM
                  public.drugusage
                WHERE
                  (
                    drugusage.brandname IS NULL
                    AND EXISTS(
                      SELECT
                        *
                      FROM
                        d_appl
                      WHERE
```

```
                  d_appl.drug_seq = drugusage.drug_seq
                  AND lower(d_appl.drugname) = lower('hydroxychloroquine')
                )
              )
              AND drugusage.isr = report.isr
              )
          )
        )
      )
      UNION
        (
          SELECT
            report.isr
          FROM
            public.report
          WHERE
            (
              (
                EXISTS(
                  SELECT
                    *
                  FROM
                    public.drugusage
                  WHERE
                    (
                      drugusage.brandname IS NOT NULL
                      AND EXISTS(
                        SELECT
                          *
                        FROM
                          product
                        WHERE
                          lower(product.brandname) = lower(drugusage.brandname)
                          AND lower(product.drugname) = lower('hydroxychloroquine')
                      )
                  )
                AND drugusage.isr = report.isr)
              )
            )
          )
        )
      )
  )
  Query Sum Adverse Event:
    SELECT
      COUNT(DISTINCT isr) AS count
    FROM
      public.report
    WHERE
      isr = ANY(
        (
          SELECT
            report.isr
          FROM
            public.report
          WHERE
            (
              EXISTS(
                SELECT
                  *
                FROM
                  public.rep_event
                WHERE
                  report.isr = rep_event.isr
                  AND rep_event.pt = 'electrocardiogram qt prolonged'
              )
            )
          )
        )
      )
  Query Sum Drug/Adverse Event:
    SELECT
      COUNT(DISTINCT isr) AS count
    FROM
      public.report
    WHERE
      1=1
```

Appendix 3.

Table 1. Common chloroquine drug-drug interactions.

Drug Interactions	Effect	Recommendation
Digoxin	Concomitant use of hydroxychloroquine and digoxin therapy may result in increased serum digoxin levels:	Serum digoxin levels should be closely monitored in patients receiving combined therapy
Insulin or antidiabetic drugs	As hydroxychloroquine may enhance the effects of a hypoglycemic treatment	A decrease in doses of insulin or antidiabetic drugs may be required
Drugs that prolong QT interval and other arrhythmogenic drugs	Hydroxychloroquine prolongs the QT interval	should not be administered with other drugs that have the potential to induce cardiac arrhythmias. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs.
Mefloquine and other drugs that are known to lower the convulsive threshold	Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g., mefloquine) may increase the risk of convulsions.	..
Antiepileptics	The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.	..
Methotrexate	The combined use of methotrexate with hydroxychloroquine has not been studied and may increase the incidence of adverse effects.	..
Cyclosporin	An increased plasma cyclosporine level was reported when cyclosporine and hydroxychloroquine were co-administered	..
Praziquantel	Chloroquine has been reported to reduce the bioavailability of praziquantel.	..
Antacids and kaolin	Antacids and kaolin can reduce the absorption of chloroquine;	an interval of at least 4 hours between intake of these agents and chloroquine should be observed.
Cimetidine	Cimetidine can inhibit the metabolism of chloroquine, increasing its plasma level.	Concomitant use of cimetidine should be avoided.
Ampicillin	chloroquine significantly reduced the bioavailability of ampicillin.	..

Sources: US Food and Drug Administration(FDA) website