Journal of International Technology and Information Management

Volume 30 | Issue 3 Article 5

2021

A Data Driven Approach to Profile Potential SARS-CoV-2 Drug Interactions Using TylerADE

Robert P. Schumaker
University of Texas at Tyler, rob.schumaker@gmail.com

Michael A. Veronin
University of Texas at Tyler, mveronin@uttyler.edu

Trevor Rohm
Hereford Regional Medical Center, trevor.rohm@dschd.org

Matthew Boyett
University of Texas at Tyler, mboyett2@patriots.uttyler.edu

Rohit R. Dixit
Siemens Digital Industries Software, dixit.rohit@siemens.com

Recommended Citation

Schumaker, Robert P.; Veronin, Michael A.; Rohm, Trevor; Boyett, Matthew; and Dixit, Rohit R. (2021) "A Data Driven Approach to Profile Potential SARS-CoV-2 Drug Interactions Using TylerADE," *Journal of International Technology and Information Management*: Vol. 30: Iss. 3, Article 5.
DOI: https://doi.org/10.58729/1941-6679.1504
Available at: https://scholarworks.lib.csusb.edu/jitim/vol30/iss3/5

A Data Driven Approach to Profile Potential SARS-CoV-2 Drug Interactions Using TylerADE

Robert P. Schumaker
(*University of Texas at Tyler*)

Michael A. Veronin
(*University of Texas at Tyler*)

Trevor Rohm
(Hereford Regional Medical Center)

Matthew Boyett
(*University of Texas at Tyler*)

Rohit R. Dixit
(*Siemens Digital Industries Software*)

ABSTRACT

We use a data driven approach on a cleaned adverse drug reaction database to determine the reaction severity of several covid-19 drug combinations currently under investigation. We further examine their safety for vulnerable populations such as individuals 65 years and older. Our key findings include 1. hydroxychloroquine/chloroquine are associated with increased adverse drug event severity versus other drug combinations already not recommended by NIH treatment guidelines, 2. hydroxychloroquine/azithromycin are associated with lower adverse drug event severity among older populations, 3. lopinavir/ritonavir had lower adverse reaction severity among toddlers and 4. the combination of azithromycin, hydroxychloroquine and tocilizumab is safer than its component drugs. While our approach does not consider drug efficacy, it can help prioritize clinical trials for drug combinations by focusing on those with the lowest reaction severity and thus increase potential treatment options for covid-19 patients.

Keywords: SARS-CoV-2, Adverse Drug Events, FDA FAERS, TylerADE

ISSN: 1941-6679-On-line Copy

INTRODUCTION

While the SARS-CoV-2 global pandemic brought much attention to the discovery of a vaccine, the use of existing medication to reduce respiratory infection and alleviate patient symptoms is equally important. So far there has been no safe and effective treatment for the virus. Several medicines have received high-profile attention such as the anti-malarial drugs hydroxychloroquine/chloroquine which shown early evidence of effective prevention (Liu et al., 2020), and further clinical studies finding hydroxychloroquine more effective than chloroquine (Fantini et al., 2020). Hydroxychloroquine has been found useful for suppressing the cytokine storm in late stages of infection, but not effective in inhibiting the early onset stages (Yao et al., 2020). Interest has also increased for the drug combination of hydroxychloroquine/azithromycin after US President Donald Trump tweeted that the combination was one of "the biggest game changers in the history of medicine" (Trump, 2020). His tweet cited a small French study of 36 patients that had encouraging results (Gautret et al., 2020). However, treatment guidelines from the National Institutes of Health (NIH) recommended against their use because of potential toxicity (National Institutes of Health, 2020).

NIH further recommended against the use of lopinavir/ritonavir because of negative clinical trial data and has recommended against the use of interferons and janus kinase inhibitors. Besides insufficient clinical data to either recommend for or against hydroxychloroquine/chloroquine, the NIH also lacks clinical data to provide a recommendation for or against the use of interleukin inhibitors such as anakinra, sarilumab, siltuximab and tocilizumab.

As of this writing, these four drugs are just entering worldwide clinical trials.

While it is vitally important to find effective drugs or combinations in the treatment of coronavirus, it is also important to do so quickly by filtering out drug combinations with the potential for toxicity or harm.

Adverse Drug Events (ADEs) are a medical problem that can cause a wide variety of symptoms including discomfort, pain, permanent injury or even death.

These reactions could be an allergy, overdose, a medication error, an unexpected interaction between drugs or a reaction that exacerbates an existing disease (health.gov, 2017).

In 1969 the US Food and Drug Administration (FDA) created a reporting system to collect and disseminate adverse drug event data.

.

This system, the FDA's Adverse Event Reporting System (FAERS) was created with the mission to become a centralized repository for pharmaceutical manufacturers to monitor their post-marketed products for evidence of adverse medical device and drug-related events. This voluntary system collects reports from drug manufacturers, medical professionals and the general public through MedWatch Forms FDA 3500A, 3500 and 3500B respectively. MedWatch collects patient demographic information, current medications, the disease or diseases being treated, symptoms, patient outcome and information about the reporter.

This information is publicly available[1] and between 2004 Quarter 1 and 2018 Quarter 2, this reporting system contained nearly 135 million records across 11 million adverse drug events. However, the FDA FAERS system lacks controls in terms of data entry. This has led to a dirty data problem for FAERS that prevents it from reaching its potential as a pharmacovigilance tool (Veronon et al., 2020). Example problems include non-standardized data such as misspelled drug names, use of multiple brand names for the same drug, abbreviations, extraneous information, excessive punctuation/formatting, mixed capitalizations and non-descriptive data such as "unknown purposes." Further, some records contain nonsense data such as patient age of 7,200 years, 168,000lbs weight or symptoms such as acupuncture, adolescence or adoption. Fortunately these are a minority of records, however, even as a minority they pose certain problems if left untreated (Veronin et al., 2020). As a result there are several commercial and open-source tools that provide cleaning and simple search capabilities of FAERS data.

However, these systems have drawbacks with respect to the amount of cleaning performed and/or the ability to form complex queries. Our motivation is to create a pharmacovigilance system, the Tyler Adverse Drug Event System (TylerADE), to perform data cleaning and standardization of FAERS data that can be used to identify adverse reaction severity scores based on complex SQL queries such as combinations of medication, demographic partitioning by age and gender as well as adverse reaction symptoms. This system will allow researchers a finer-grained analysis of adverse drug event data to uncover potentially unknown drug interactions. This research has the potential to improve the efficiency of pharmacological research by identifying potentially unknown drug interactions that merit further clinical study and improve patient safety.

The focus of this paper is to use TylerADE on current SARS-CoV-2 drugs under consideration by the NIH as a potential tool to identify those drug combinations with significant adverse reactions. While this system is not meant to be a replacement to existing drug interaction knowledge or clinical studies, we envision it as a complimentary tool that researchers can use to fulfill the promise of FAERS.

[1] https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm

.

The rest of this paper is structured as follows. Section 2 is the literature review and examines the FDA drug approval process, assessing adverse drug event causality, FAERS data and research gaps. Section 3 presents our research questions. Section 4 is the system design and introduces the TylerADE System. Section 5 is the experimental design. Section 6 delivers the experimental results and discussion. Finally Section 7 provides the study conclusions, limitations and future directions.

LITERATURE REVIEW

To better understand the impacts of adverse drug events on society, we will explain the drug approval process in the United States, examine several pharmacovigilance systems that identify post-approval problems, investigate current systems that use FAERS data, describe the current state of SARSCoV-2 drugs under investigation and finish with a discourse on the research gaps found within the literature.

FDA Drug Approval Process

In the United States, the Center for Drug Evaluation and Research (CDER), a division of the FDA, is responsible for ensuring the safety of all prescription and over-the-counter (OTC) drugs. Although CDER does not test the drugs themselves, they rely on testing data from both the manufacturers and the Office of Testing and Research to determine if the drug's health benefits outweigh the risks.

Before a new drug comes to the market, pharmaceutical manufacturers will submit a new drug application along with evidence that it is safe and effective. CDER then reviews the data and if the benefits outweigh the risks, the manufacturer will then be invited to submit an investigational new drug application. After a typical 30 day review period, the pharmaceutical company may begin Phase 1 clinical trials using human subjects. At this stage, a several month study of 20-100 volunteers will test dosing rates and patient side effects. If the clinical trial proves successful, the data is sent to CDER for analysis and approval (US Dept of Health and Human Services, 2017). Approximately 70% of drugs will successfully complete this phase (US Food & Drug Administration, 2020). Drugs will then move to Phase 2 clinical trials where several hundred volunteers will be tested for up to two years to determine drug efficacy and patient side effects. The results will then be forwarded to CDER and approximately 33% of drugs will successfully complete this phase (US Food & Drug Administration, 2020). If approved, drugs will then move to Phase 3 clinical trials where up to several thousand volunteers will be tested for 1-4 years on efficacy and adverse reactions with approximately 25%-30% of drugs moving to Phase 4. At this stage only 17% of drugs are approved for use (Harper, 2020).

.

This process can take an average of 15 years and cost upwards of $2 billion (Divon, 2015).
Following approval, drugs enter a post-marketing phase meaning that they are available for use. These drugs are monitored and can either be administratively or voluntarily withdrawn from the market. An administrative withdrawal is typically made within a 1-6 year period following its entrance into the market (Onakpoya et al., 2016). Drugs can also be voluntarily withdrawn from the market by the manufacturer. One such example was Merck and Co.'s anti-inflammatory drug Vioxx which was later found to increase the risk of heart attack and stroke (Sibbald, 2004).
This post-marketing review of adverse drug reactions is then collected via MedWatch and made available to manufacturers and researchers alike.

Identifying Drug Interactions

When clinical healthcare professionals are confronted with identifying interactions from multiple medications, they will generally consult drug interaction references to look for any known interaction potential. *The Nursing Drug Handbook* or online references such as *Micromedex* and *LexiComp* can provide useful information for known drug interactions. However, no reference can account for all interactions nor estimate the likelihood of an adverse event occurring (Kheshti et al., 2016).

Adverse Drug Event Severity Assessment

In order to assess the impact severity of adverse drug events on patient health, several scales have been developed. The first is a categorization section in MedWatch where reporters can document patient outcome by selecting predetermined boxes as shown in Figure 1.

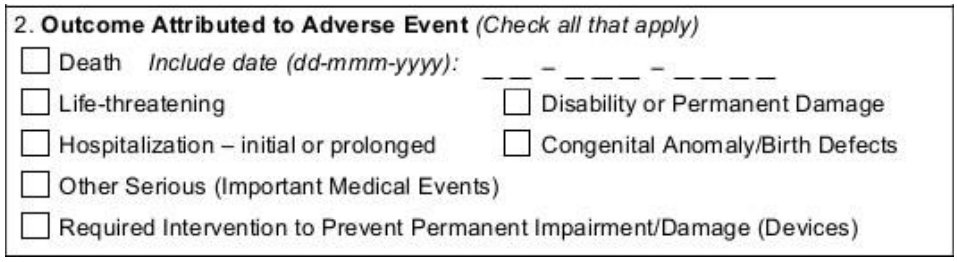
2. **Outcome Attributed to Adverse Event** *(Check all that apply)*
☐ Death *Include date (dd-mmm-yyyy):* _ _ – _ _ _ – _ _ _ _
☐ Life-threatening ☐ Disability or Permanent Damage
☐ Hospitalization – initial or prolonged ☐ Congenital Anomaly/Birth Defects
☐ Other Serious (Important Medical Events)
☐ Required Intervention to Prevent Permanent Impairment/Damage (Devices)

Figure 1: MedWatch FDA Form 3500 Patient Outcomes

.

While useful for reporting ADEs, it is important to note that these categories lack explanatory descriptions and must be interpreted by the reporter whom may not be a medical professional. This could lead to some confusion especially with how to interpret *other serious* or what constitutes *life-threatening*.

Modified Hartwig-Siegel

The scale used in FAERS reporting is a derivative of the Modified HartwigSiegel severity scale that categorizes adverse drug reactions into seven levels (Hartwig et al., 1992).

- Level 1: An ADE occurred but required no change in treatment with the suspected drug.
- Level 2: The ADE required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment required. No increase in LOS (Length of Stay).
- Level 3:The ADE required that treatment with the suspected drug be held, discontinued, or otherwise changed, and/or an antidote or other treatment was required. No increase in LOS.
- Level 4: (A) Any level 3 ADE which increases LOS by at least 1 day, or (B) The ADE was the reason for admission.
- Level 5: Any level 4 ADE which requires intensive medical care.
- Level 6: The adverse reaction caused permanent harm to the patient.
- Level 7: The adverse reaction either directly or indirectly led to the death of the patient.

The primary differences between the Modified Hartwig-Siegel and FDA Form 3500 is the latter de-emphasis of *length of stay* as a criteria and the absence of an option for *no change in treatment*.

Hartwig Severity Assessment

One of the first attempts at quantifying severity is the Hartwig scale that examines adverse reactions in five areas with yes/no categories. This tool calculates severity as the sum of all yes answers (Hartwig et al., 1991).

.

- A. Increased monitoring needed? YES NO
- B. Vital signs change? YES NO
- C. Additional lab work ordered? YES NO
- D. Treatment needed? YES NO
- E. Increase in LOS? YES NO

While the Hartwig scale is useful to categorize drug reaction severity, it lacks the granularity found in the either the Modified Hartwig-Siegel or MedWatch.

Sources of ADE Data

There are several sources of ADE data including medical literature review, the Internet and observational reports (Ventola, 2018). Medical literature review typically involves text mining of abstracts from sources such as PubMed to identify potential interaction signals. Pharmacovigilance systems that use the Internet will typically monitor social media or chat forums to mine discussions for relevant drug interactions. Observational systems rely on mining reports generated from sources such as EHRs or adverse reports submitted to appropriate government agencies. Of the later there are three major data sources where adverse event data can be found; DAWN, NEDS and FAERS. All are voluntary repositories of data collected within the United States.

The Drug Abuse Warning Network (DAWN) is a large-scale survey of medical records used to monitor drug abuse trends nationwide (Joranson et al., 2000). DAWN is a type of public health surveillance system to monitor drug-related visits to hospital emergency rooms and identify trends. The eligibility criteria to enter data in this source is any non-federal US shortstay hospital with at least one 24-hour emergency department (Substance Abuse and Mental Health Services Administration, 2019). While useful for monitoring drug abuse, the DAWN network was discontinued in 2011 and its counterpart NEDS contains similar data. Both DAWN and NEDS were found to be statistically similar in data composition (Sivigny & Caces, 2018).

NEDS, the National Emergency Department Sample, is a data service from the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ), a division of the US Department of Health and Human Services. This repository collects data from nearly 31 million US emergency room visits annually across 953 hospitals and provides diagnostic ICD coding, patient demographics, insurance and patient outcome.

Although extensive in scope, data records can be sparse.

.

A third major data source of ADE data is FAERS. Since its creation in 1969, this repository has undergone several transformations over the years, however, its mission remains the same; to voluntarily collect adverse reaction reports for drugs, medication errors and medical devices from manufacturers, medical professionals and the general public (Toki & Ono, 2018). This massive database is publicly available and the ADE component contains nearly 135,000,000 records spread over seven tables from 2004 to 2018 Quarter 2 on adverse events, product complaints, and medication error reports. Manufacturers, consumers, and health care professionals submit voluntary reports of adverse drug interactions to the FDA. MedWatch then collects patient demographic data, the adverse event's impact on patient health (e.g., disability, hospitalization, life-threatening condition or death), product availability, suspected products or devices and information about the reporter. Because of the lack of training and the variety of reporters contributing to FAERS, many database fields contain a non-trivial amount of non-standardized data (Veronon et al., 2020).

Using FAERS Data

There are several studies that use FAERS data to identify adverse reactions from the combination of two drugs. One such study focused on data mining FAERS to detect a statistical association between two drugs and found that reporting odds ratio provided better signal detection of an adverse event than proportional reporting ratio, information component and empirical Bayes geometric mean (Sakaeda et al., 2013). A second study mined interactions between two drugs using logistic regression and found 85% precision and 80% accuracy in predicting that an adverse event would not occur (Ibrahim et al., 2016).

In a bid to apply pharmacovigilance to FAERS data, several notable systems have been developed. One system manually curated the adverse effects of cardiovascular medicines using FAERS and MEDLINE (Xu & Wang, 2014). In this study drug-disease pairs were identified by semantic markers such as <drug> CAUSE <side effect> or <drug> TREAT <disease> from MEDLINE and compared to adverse effects data in FAERS. This combined method found marginally better precision and recall than FAERS alone, however, nearly 90% of the data was sacrificed to achieve the higher accuracy.

The largest obstacle to using FAERS data is data integrity, requiring cleaning. Some of the common problems involve drug misspellings/abbreviations (Xu & Wang, 2014), duplicate, missing and non-standardized data (Banda et al., 2016), drug trade names vs generics (Sakaeda et al., 2013), making the use of FAERS particularly difficult (Saragdhar et al., 2016).

ISSN: 1941-6679-On-line Copy

.

Because of the dirty data problem in FAERS, there are companies that offer paid services for curated ADE data such as Advera Health Analytics[2], DrugLogic[3] and FDAble[4]. In addition to paid services there are also several freely available tools: AERSMine, AEOLUS and OpenVigil FDA.

AERSMine

AERSMine is an ontological tool that normalizes FAERS data and aggregates drugs and indications (Saragdhar et al., 2016). It allows researchers to search and categorize patients based on demographics, indications, drugs and drug classes as well as use exclusion filters. While a useful graphical tool to identify patient groups based on apriori knowledge, the drawback is that it does not consider multiple drug interactions. Further, the system is limited in the scope of drugs to search. For example, the antiviral drug lopinavir only exists in conjunction with ritonavir and cannot be queried separately.

AEOLUS

AEOLUS (Adverse Event Open Learning through Universal Standardization) is another open-source FAERS data source that cleans raw FAERS by imputing missing values, removing duplicate records, standardizing drug names against OHDSI and reactions/indications against MedDRA for a standard vocabulary (Banda et al., 2016). AEOLUS also does not evaluate multiple drug interactions. This system reports 95% cleaning of drug-related data.

OpenVigil FDA

OpenVigil FDA is an online pharmacovigilance tool that interfaces with the OpenFDA website and allows for easier navigation and analysis (Böhm et al., 2016). This tool also allows for the analysis of adverse effects between two drugs. While not entirely clear on the data cleaning aspects, OpenVigil FDA reports 88.1% cleaning of drug-related data. Like AERSMine, OpenVigil FDA also relies on preset drug names and does not query lopinavir by itself.

[2] http://www.adverahealth.com

[3] http://www.druglogic.com

[4] http://www.fdable.com

.

The drawbacks to AERSMine, AEOLUS, OpenVigil FDA and other systems are that they either limit themselves to curated drugs or at most the interaction between two drugs. A more powerful system that can investigate multiple drug combinations as well as data related to patient demographics could be a useful tool to researchers.

SARS-CoV-2 Drugs Under Investigation

To find safe and effective treatments for SARS-CoV-2, the FDA has streamlined the clinical investigation process to speed drug research and test for possible treatment options. Drugs with antiviral properties as well as immunotherapy drugs are currently under investigation. As of this writing, the NIH is currently providing the following covid-19 treatment guidelines (National Institutes of Health, 2020). They are not FDA approved at this time.

Antimalarials

- Hydroxychloroquine/chloroquine: Insufficient clinical data to recommend for or against

Antiviral Nucleotide Analog

- Remdesivir: Insufficient clinical data to recommend for or against

Combination Treatment Antimalarial/Antibiotic

- Hydroxychloroquine/azithromycin: Recommends Against

Combination Treatment Antivirals HIV Drugs

- Lopinavir/ritonavir: Recommends Against

Host Modifiers/Immune-Based Therapy

- Interleukin-6 Inhibitors (sarilumab, siltuximab, tocilizumab): Insufficient clinical data to recommend for or against
- Interleukin-1 Inhibitors (anakinra): Insufficient clinical data to recommend for or against
- Interferons: Recommends Against
- Janus Kinase Inhibitors: Recommends Against

.

Some combinations such as hydroxychloroquine/azithromycin are recommended against because of drug safety issues rather than efficacy. If combinations of drugs could be investigated to determine historical adverse reaction severity, clinical trials could then focus on testing efficacy for those with lesser adverse drug reactions. This will hopefully lead to effective treatment sooner.

Research Gaps

From our analysis of the literature, the following gaps in research emerge. First, the process of identifying multiple drug interactions either relies on known interactions that are documented in interaction handbooks, or rely on datasets that require a significant investment in cleaning. Our first challenge is to develop such a system that can produce meaningful, clean data.
Second, we didn't find any system that focused on the patient severity risk from multiple drug interactions. Our second challenge is to incorporate historical data of adverse reaction severity for drugs.
Third, we did not find any systems that examined the interactions of covid-19 drugs under investigation by the NIH.
Our aim is to build a system to produce clean data, that incorporates historical patient severity measures from adverse drug interactions, and to study those interactions for specific covid-19 drug combinations. Our focus is to address patient safety and in turn prioritize clinical research to determine efficacy.

RESEARCH QUESTIONS

To address these gaps in the literature we plan to answer the following research questions.

1. What is the adverse drug reaction safety for antiviral drug combinations?

We plan to investigate covid-19 drug combinations such as hydroxychloroquine/chloroquine, hydroxychloroquine/azithromycin and lopinavir/ritonavir with a focus on patient demographics and symptom frequency. Answering this question will help address whether certain patient demographics respond to antiviral combinations better than others.

.

2 What is the adverse drug reaction safety for interleukin drug combinations?

Applying the same framework to interleukin inhibitors of anakinra, sarilumab, siltuximab and tocilizumab; what drug combinations are safer than others?

3 What is the adverse drug reaction safety for drug combinations of three covid-19 drugs?

Exploring different combinations might yield interesting results not previously explored.

SYSTEM DESIGN

To answer these research questions we constructed the Tyler Adverse Drug Event System (TylerADE) as shown in Figure 2.

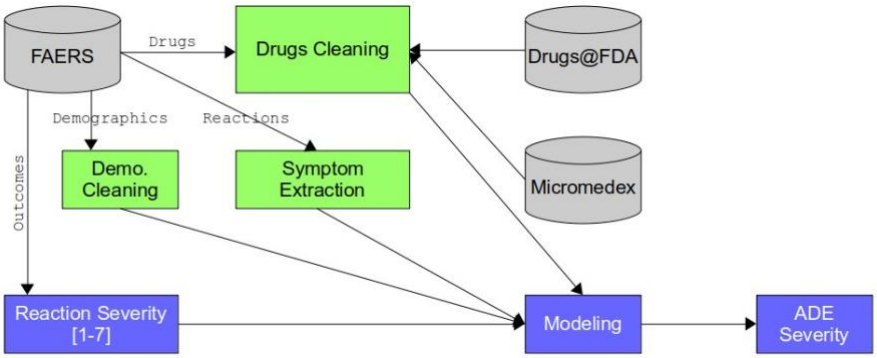

Figure 2: TylerADE System

The TylerADE System is composed of several important areas that crossreference multiple external data sources. The first step is to download and ETL the FAERS data including legacy AERS data, to TylerADE.

.

Drugs → Drugs Cleaning

Once the ETL process has completed, the drug data needs to pass through a series of automated cleaning steps before it is ready for use.

This stage standardizes the data by converting all drug names to uppercase, removing punctuation/spaces, acronym expansion, correlating drug name information against Drugs@FDA and Micromedex Solutions (databases of current drug names), and then removing drugs that are vague or lightly used in the corpus. The steps are listed below.

1. Capitalize all drug names

2. Remove all leading and trailing whitespace, newline and tab characters, leading numbers, special characters and null values

3. Expand all drug name abbreviations (e.g.; VIT B12 → VITAMIN B12)

4. Partition individual records with multiple drug names into separate records

5. Cross-reference each drug name against Drugs@FDA

6. For drugs not found in (5) convert the drug name to its generic form using Micromedex Solutions (Truven Health Analytics, 2017)

7. Remove records with vague drug names (e.g.; painkiller, multivitamin)

8. Remove records of any drug that appears less than 30 times

Performing these steps resulted in a cleaning of 98.3% of the drugs data which exceeds the published results of other open-source systems.

Reactions → Symptom Extraction

Patient symptom data from the Reactions table is cleaned in a similar manner. Symptoms are made uniform through capitalization, removal of whitespace/extraneous characters, spellchecked, and aggregated for similar symptoms (e.g.; respiratory arrest and respiratory failure).

ISSN: 1941-6679-On-line Copy

.

Demographics → Demo. Cleaning

Demographic cleaning involves data conversions and omitting values for a minority of data from FAERS.

1. Convert age to years

2. Omit age data for ages less than 0 or greater than 120

3. Convert gender codes other than Male or Female to Other

Outcomes → Reaction Severity

Reaction severity scores are recorded in the Outcomes table as 7 - death, 6 - life-threatening, 5 - hospitalization, 4 - other serious, 3 - required intervention, 2 - disability or permanent damage, and 1 - congenital anomaly.

EXPERIMENTAL DESIGN

For our experiment we used FAERS data from 2004 Quarter 1 through 2018 Quarter 2. This data encompasses a total of 135,276,263 records across 7 tables. A breakdown of FAERS data is shown in Table 1.

Table 1: FAERS Data by Table (2004Q1 - 2018Q2)

Table Name	Num Records
Demographics	11,094,567
Drugs	39,367,610
Indications	23,159,273
Outcomes	8,646,482
Reactions	35,555,800
Report Sources	2,232,896
Therapies	15,219,635

ISSN: 1941-6679-On-line Copy

.

Indications are the diagnoses such as rheumatoid arthritis, multiple sclerosis and hypertension. Reactions are the observed symptoms such as nausea, death or fatigue. Drugs are the drug names and other vital information linked to the ADE. As shown by the number of records in the table, ADEs typically involve multiple drugs, from a minimum of 1 to a maximum of 152. In looking further at ADEs with the potential of multiple drug events, there are 8,552,410 records in which two or more drugs were reported.

In terms of cleaned demographic data and gender, 6,129,171 ADE records were female (55.2%), 3,891,117 males (35.1%) and 1,074,279 were other (9.7%).

In terms of ADEs by age ranges, Table 2 shows that most ADEs occurred for patients between 50 and 64 years and that the elderly had the highest proportion of reported death from ADEs.

From this data we plan to test those drug combinations under investigation for covid-19 treatment. In particular, how safe are these various drug combinations for differing patient demographics. Using the cleaned data from the TylerADE system, we will perform a data-driven analysis to evaluate patient reaction severity.

EXPERIMENTAL RESULTS AND DISCUSSION

To evaluate the benefits of a data-driven approach to determine drug combination safety, we will examine several antiviral covid-19 treatments in cluding hydroxychloroquine/azithromycin, hydroxychloroquine/chloroquine and lopinavir/ritonavir before using our technique on interleukin inhibitors anakinra, sarilumab, siltuximab and tocilizumab, to identify the most promising combinations for further clinical study from a drug safety perspective.

Table 2: ADEs by Age Groups

Age Group	Number ADEs	%Death
Toddlers [0-4]	577,800	15.8%
Children [5-12]	96,920	7.3%
Teens [13-19]	163,223	8.3%
Early Adults [20-34]	557,838	8.8%
Mid-Adults [35-49]	930,981	9.8%
Late Adults [50-64]	1,608,995	11.1%
Retired Adults [65-79]	1,526,699	14.2%
Elderly [80+]	546,757	19.6%

.

Research Question 1: What is the adverse drug reaction safety for antiviral drug combinations

To answer this we investigate the antiviral drug combinations of hydroxychloriquine/azithromycin, hydroxychloriquine/chloriquine, and lopinavir/ritonavir.

Hydroxychloroquine and Azithromycin

Using the cleaned data in TylerADE, we analyzed the reaction severity of hydroxychloroquine/azithromycin by performing a count of adverse reaction outcome categories as shown in Table 3.

Table 3: Hydroxychloroquine and Azithromycin Reaction Severity

	Reaction Outcome Severity Categories						
Drug	1	2	3	4	5	6	7
Hydroxychloroquine	284	1,831	231	26,964	15,424	1,536	2,747
Azithromycin	659	1,787	387	18,809	17,901	2,436	3,960
Together	0	21	1	257	169	9	29

Hydroxychloroquine and azithromycin both had a similar number of adverse drug events, 49,017 and 45,939 respectively, whereas their combination only occurred 486 times. Examining their distributions, hydroxychloroquine versus the combination showed statistical difference in reaction severity (χ^2 =43.2, *df* =6, $p-value$ = $1.06E-07$). Azithromycin versus the combination showed statistical equivalence (χ^2 =8.7, *df* =6, $p - value$ = 0.192), meaning that azithromycin had a similar reaction severity profile as the combination. This is notable because azithromycin has 45,939 adverse drug event records and 45,453 records without hydroxychloroquine. Whereas hydroxychloroquine has similar numbers of records and does not share the same reaction severity profile as the combination. This likely indicates that azithromycin is the primary driver of adverse reactions in the combination.

Focusing further, hydroxychloroquine had an average reaction severity of 4.45, azithromycin 4.63 and taken together 4.48. Recall that a reaction severity of 4 represents *other serious* and 5 is *hospitalization*. From a drug safety perspective, hydroxychloroquine is involved in less severe adverse drug reactions than either

.

azithromycin or the combination which lends support to NIH guidelines to not recommend this combination for covid-19 treatment.
However, other patient-related characteristics could be a factor to explore. To do this we partitioned reaction severity outcomes of the combination of hydroxychloroquine and azithromycin by patient age and gender as shown in Table 4.

Table 4: Hydroxychloroquine and Azithromycin by Demographic

Demographic	n	$\bar{x}$
Toddlers [0-4]	21	4.52
Children [5-12]	2	4.50
Teens [13-19]	3	4.00
Early Adults [20-34]	34	4.62
Mid-Adults [35-49]	84	4.40
Late Adults [50-64]	158	4.46
Retired Adults [65-79]	75	4.60
Elderly [80+]	4	4.50
Male	106	4.62
Female	369	4.44
Other	11	4.09

From this data we noticed reaction severity was fairly uniform across age. It was interesting to note the average reaction severity for retired adults and elderly was 4.60 and 4.50 respectively, indicating that patients receiving hydroxychloroquine/azithromycin and had an adverse reaction required more extensive medical care. This finding is also remarkable because it is absent the influence of covid-19 which is also known to lengthen hospital stays. Given what we know about covid-19 and its increased fatality rates for the elderly, the combination hydroxychloroquine/azithromycin marginally increases risk for older populations.
Examining differences of gender, we found that males had a higher reaction severity to the drug combination (4.62) versus females (4.44) with differences that were statistically different (χ^2 =13.5, df = 6, $p{-}value$ = 0.0362). This result is also in line with observations that covid-19 infections disproportionately affect male patients. Recommending a drug combination with known higher adverse reaction severity

.

for males already disproportionately affected by covid-19 would only exacerbate the problem.

We further examined the top ten patient symptoms by reaction severity for hydroxychloroquine/azithromycin as shown in Table 5. Only symptoms with ten or more cases are shown to reduce noise from seldom seen symptoms.

Table 5: Hydroxychloroquine and Azithromycin by Symptoms

Symptom	n	$\bar{x}$
Respiratory Failure	17	5.71
Cardiac Arrest	18	5.61
Septic Shock	14	5.57
Fluid Overload	14	5.36
Hypotension	19	5.32
Tachycardia	16	5.25
Type 2 Diabetes Mellitus	12	5.25
Gastric Bypass	11	5.18
Sepsis	12	5.08
Retching	11	5.00

From this data we found that respiratory failure, cardiac arrest and septic shock were the three most severe adverse reactions (5.71, 5.61 and 5.57 respectively). Recall that 5 represents *hospitalization* and 6 is *life-threatening*. Symptoms also appear to cluster around cardiopulmonary, toxicity or gastrointestinal.

Looking at the symptom data for patients 65 years and older, the most severe (5 or higher) and frequent ($n \geq 3$) adverse reaction outcomes were associated with abasia, abdominal pain upper, anaemia, atrial fibrillation, blood glucose increased, bone pain, chest discomfort, coagulopathy, constipation, gastrointestinal haemorrhage, haemoptysis, haemorrhagic anaemia, heart rate increased, hyperhidrosis, malaise, melaena, renal failure and shock haemorrhagic. Given the NIH's recommendation against using the combination of hydroxychloroquine/azithromycin because of toxicity and negative clinical results, the adverse symptom data would concur with the toxicity assessment.

.

Hydroxychloroquine and Chloroquine

We further examine the reaction severity outcomes of the drug combination hydroxychloroquine/chloroquine as shown in Table 6.

Table 6: Hydroxychloroquine and Chloroquine Reaction Severity

	Reaction Outcome Severity Categories						
Drug	1	2	3	4	5	6	7
Hydroxychloroquine	284	1,831	231	26,964	15,424	1,536	2,747
Chloroquine	4	72	22	1,238	1,089	108	330
Together	0	7	3	122	92	7	30

We also examined patient-related characteristics of age and gender as shown in Table 7.

Table 7: Hydroxychloroquine and Chloroquine by Demographic

Demographic	n	$\bar{x}$
Toddlers [0-4]	16	4.81
Children [5-12]	0	–
Teens [13-19]	0	–
Early Adults [20-34]	19	4.37
Mid-Adults [35-49]	60	4.63
Late Adults [50-64]	99	4.81
Retired Adults [65-79]	19	4.39
Elderly [80+]	6	5.33
Male	54	4.61
Female	204	4.67
Other	5	5.80

.

From the age data there were zero reported adverse events for children [5-12] and teens [13-19]. The data did exhibit increasing reaction severity as it relates to age. The reaction severity for elderly was much higher (5.33) indicating that patients with adverse reactions generally required more extensive medical care.
Examining differences in gender, we found that females had a higher reaction severity to the drug combination (4.67) versus males (4.61), however the differences were found to be statistically equivalent ($\chi^2 = 10.2$, $df = 6$, $p - value = 0.118$). Unlike the prior combination, hydroxychloroquine with chloroquine showed no reaction severity differences by gender.

Looking at patient symptoms, we listed the top ten by reaction severity as shown in Table 8. Only symptoms with ten or more cases are shown to reduce noise from seldom seen symptoms.

Table 8: Hydroxychloroquine and Chloroquine by Symptoms

Symptom	n	$\bar{x}$
Overdose	13	5.92
Cardiac Arrest	20	5.85
Hypokalaemia	11	5.82
Respiratory Failure	14	5.43
Myocardial Infarction	10	5.00
Cardiomyopathy	14	4.86
Cardiac Failure Congestive	12	4.75
Pneumonia	33	4.70
Muscular Weakness	11	4.64
Atrioventricular Block Complete	10	4.60

From this table we found that overdose, cardiac arrest and hypokalaemia were the three most severe adverse reactions from the drug combination (5.92, 5.85 and 5.82 respectively). Symptoms appear to be mostly cardiopulmonary.
Given the NIH's neutral stance on the combination of hydroxychloroquine/chloroquine, the adverse event data would suggest that this combination poses an increased risk versus hydroxychloroquine/azithromycin. This risk is observed in a higher incidence of drug interaction severity among elderly populations and symptoms of mostly a cardiac nature. We would recommend a review of clinical study data to verify these results.

.

Lopinavir and Ritonavir

Performing the same analysis for the drug combination lopinavir/ritonavir we performed a count of adverse reaction outcome categories as shown in Table 9.

Table 9: Lopinavir and Ritonavir Reaction Severity

	Reaction Outcome Severity Categories						
Drug	1	2	3	4	5	6	7
Lopinavir	1,919	674	232	7,678	6,689	1,205	2,272
Ritonavir	3,996	1,872	455	26,059	21,964	3,506	6,372
Together	1,910	665	230	7,521	6,587	1,198	2,233

Lopinavir had 20,669 adverse reaction events, ritonavir 64,224 and their combination occurred 20,344 times. Examining their distributions, lopinavir versus the combination showed statistical equivalence in reaction severity ($\chi^2 = 0.3$, $df = 6$, $p - value = 0.999$) and showed significant overlap indicating that lopinavir and ritonavir are commonly seen together in the data. Ritonavir versus the combination showed statistical difference in reaction severity ($\chi^2 = 350.1$, $df = 6$, $p - value = 1.505E-72$). Focusing further, lopinavir had an average reaction severity of 4.42, ritonavir 4.50 and taken together 4.41. Extracting adverse drug events for lopinavir that does not include ritonavir, lopinavir's adverse severity was 4.57, considerably higher than the combination 4.41. Ritonavir exclusive of lopinavir was 4.54. This was an interesting finding as both drugs taken together had a lower adverse reaction severity than exclusive of each other.

We further examine other patient-related characteristics of age and gender as shown in Table 10.

From the data, the drug combination disproportionately affects children [5-12] and those 35 and older. However, the elderly were most impacted (5.15).

.

Table 10: Lopinavir and Ritonavir by Demographic

Demographic	n	$\bar{x}$
Toddlers [0-4]	2,365	3.71
Children [5-12]	164	4.64
Teens [13-19]	249	4.44
Early Adults [20-34]	2,898	4.36
Mid-Adults [35-49]	4,647	4.74
Late Adults [50-64]	2,306	4.77
Retired Adults [65-79]	478	4.87
Elderly [80+]	13	5.15
Male	11,264	4.59
Female	6,918	4.33
Other	2,214	3.78

Examining differences of gender, we found that males had a higher reaction severity to the drug combination (4.59) versus females (4.33) with differences that were statistically significant (χ^2 =2,680.0, df = 6, $p - value \approx 0$).
We further examined the top ten patient symptoms by reaction severity for lopinavir/ritonavir as shown in Table 11. Only symptoms with ten or more cases are shown to reduce noise from seldom seen symptoms.

.

Table 11: Lopinavir and Ritonavir by Symptoms

Symptom	n	$\bar{x}$
Suicide	20	6.85
Death Neonatal	72	6.19
Vomiting Projectile	10	6.10
Oxygen Consumption Decreased	14	6.00
Enterococcal Infection	12	6.00
Bladder Distension	10	6.00
Metastatic Neoplasm	10	6.00
Aspiration	17	5.94
Cardiac Arrest	10	5.90
Sudden Cardiac Death	18	5.89

From this data we found that suicide, neonatal death and projectile vomit were the three most severe adverse reactions (6.85, 6.19 and 6.10 respectively). Recall that 6 represents *life-threatening* and 7 is *death*. Symptoms appear to vary and are not restricted to limited groupings.

Looking at symptom data for patients 65 years and older, the most severe (5.5 or higher) and frequent (n≥25) adverse reaction outcomes were associated with bone marrow failure, circulatory collapse, hepatic failure, hepatotoxicity, multiple organ dysfunction syndrome, pneumonia, pneumonia bacterial and sepsis. It is important to note that no symptom was associated with an average adverse reaction severity of 6 or higher. This would imply that in spite of the NIH recommendation against the combination of lopinavir/ritonavir, from a patient safety perspective (and not drug efficacy), perhaps a re-evaluation of this combination for patients 65 years and older may be of benefit.

Answering Research Question 1

So to answer our first research question of *what is the adverse drug reaction safety for antiviral drug combinations*, our analysis found hydroxychloriquine to cause lesser adverse reactions than hydroxychloriquine/azithromycin (4.45 and 4.48 respectively). The combination was also adversely affecting retired adults and males (4.60 and 4.62 respectively).

For hydroxychloriquine/chloriquine, the combination was more severe at 4.69. This combination also adversely affected the elderly and females (5.33 and 4.67 respectively).

.

However, for early adults and retired adults the reaction severity was much less (4.37 and 4.39 respectively). For lopinavir/ritonavir the combination had an adverse severity of 4.41. This combination also adversely affected the elderly (5.15) and males (4.59). However, for toddlers the reaction severity is considerably less (3.71). To further investigate, we analyze reaction severity by age grouping for hydroxychloroquine/azithromycin, hydroxychloroquine/chloroquine and lopinavir/ritonavir as shown in Figure 3.
Baseline represents all adverse drug events in the cleaned FAERS database and we use it for comparison to several drug combinations; hydroxychloroquine/azithromycin (H+A), hydroxychloroquine/chloroquine (H+C) and lopinavir/ritonavir
(L+R). From this figure, the elderly [80+] are disproportionately affected more by hydroxychloroquine/chloroquine (5.33) and lopinavir/ritonavir (5.15) versus the baseline of all drugs (5.00). The interesting combination is hydroxychloroquine/azithromycin that has dramatically lower reaction severity for this population (4.50). The other combination to note is lopinavir/ritonavir for Toddlers [0-4] that has a reduced reaction severity of 3.71.

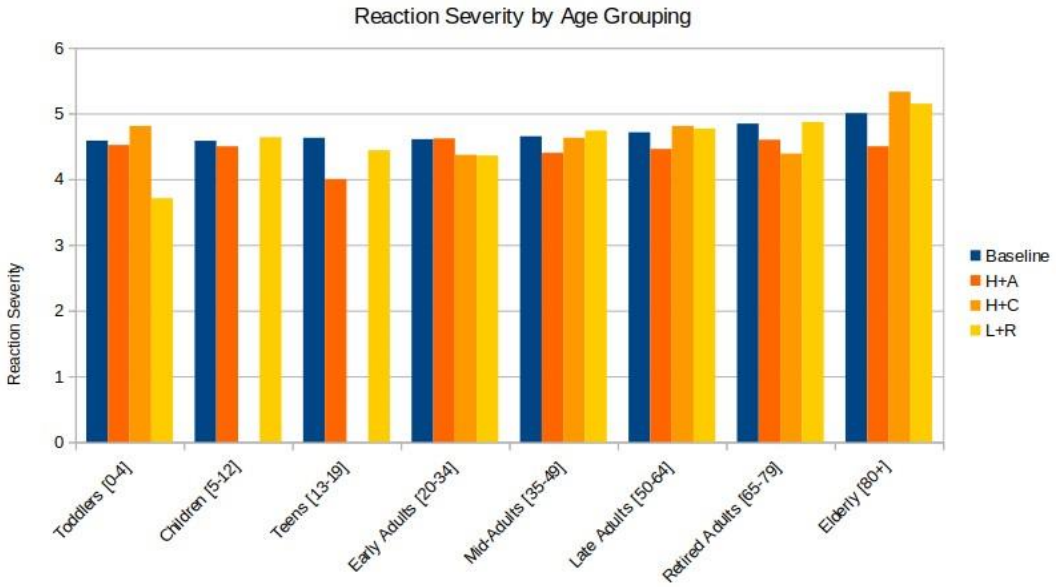

Figure 3: Reaction Severity by Age Grouping

The NIH currently recommends against hydroxychloriquine/azithromycin, is neutral towards hydroxychloriquine/chloriquine, and recommends against

.

lopinavir/ritonavir. From our analysis of patient safety at the macro-level, all three combinations pose risk (4.48, 4.69 and 4.41 respectively). However, from the perspective of different age groups and genders, we observed a variety of reaction severity outcomes with some posing much lower reaction severity. Perhaps further study could determine if the benefits of these combinations can outweigh the risks for specific patient populations.

Research Question 2: What is the adverse drug reaction safety for interleukin drug combinations?

Using the cleaned data from TylerADE, we analyzed the reaction severity of interleukins: anakinra, sarilumab, siltuximab and tocilizumab. We then performed a count of adverse reaction outcome categories as shown in Table 12.
From the data, sarilumab and siltuximab had the fewest adverse reaction records of 18 and 38 respectively, whereas anakinra and tocilizumab had 3,680 and 34,793 respectively. Analyzing each combination for reaction severity is shown in Table 13.

Table 12: Interleukin Reaction Severity Counts

	Reaction Outcome Severity Categories						
Drug	1	2	3	4	5	6	7
Anakinra	21	87	12	1,589	1,314	255	402
Sarilumab	0	3	0	13	2	0	0
Siltuximab	0	0	0	17	10	6	5
Tocilizumab	47	955	15	18,160	11,527	1,667	2,422

.

Table 13: Interleukin Reaction Severity Averages

Drug	n	$\bar{x}$		
Anakinra	3,680	4.76		
Sarilumab	18	3.78		
Siltuximab	38	4.97		
Tocilizumab	34,793	4.58		
Drug	**n**	$\bar{x}$	χ^2	**p-value**
Anakinra and Sarilumab	3	4.00	25.0	0.0003
Anakinra and Siltuximab	0	-	6.57	0.363
Anakinra and Tocilizumab	898	4.56	236.4	3.23E-48
Sarilumab and Siltuximab	0	-	14.6	0.023
Sarilumab and Tocilizumab	7	4.00	18.8	0.004
Siltuximab and Tocilizumab	4	5.00	13.7	0.033

From this data, sarilumab had the lowest reaction severity of 3.78 versus siltuximab at 4.97. There were no observations of anakinra/siltuximab or sarilumab/siltuximab in the data. It was further worth noting that interleukin combinations containing sarilumab had lower reaction severity. For our chisquared analysis we compared the individual drugs against each other. From a drug safety perspective it would appear that sarilumab is the safest of the four, however, we also recognize the limited adverse reaction data and would suggest clinical study to verify these results.

Given the prevalence of the combination of anakinra and tocilizumab, we further examine other patient-related characteristics of age and gender as shown in Table 14.

.

Table 14: Anakinra and Tocilizumab by Demographic

Demographic	n	$\bar{x}$
Toddlers [0-4]	61	4.75
Children [5-12]	76	4.92
Teens [13-19]	17	4.71
Early Adults [20-34]	31	4.65
Mid-Adults [35-49]	97	4.25
Late Adults [50-64]	172	4.48
Retired Adults [65-79]	46	4.24
Elderly [80+]	3	4.67
Male	332	4.85
Female	513	4.35
Other	**53**	**4.85**

From the data, the drug combination disproportionately affects toddlers [0-4], children [5-12] and teens [13-19]. However, early adults [20-34] and elderly [80+] were also observed to be adversely affected. Patients with ages between 35 and 79 appeared the least impacted.

Examining differences of gender, we found that males had a higher reaction severity to the drug combination (4.85) versus females (4.35) with differences that were statistically significant ($\chi^2 = 164.0$, $df = 6$, $p - value = 8.27E-33$).

We further examined the top ten patient symptoms by reaction severity for anakinra/tocilizumab as shown in Table 15. Only symptoms with ten or more cases are shown to reduce noise from seldom seen symptoms.

.

Table 15: Anakinra and Tocilizumab by Symptoms

Symptom	n	$\bar{x}$
Respiratory Failure	12	6.08
Activated Partial Thromboplastin Time Prolonged	11	5.45
Blood Fibrinogen Decreased	11	5.45
Blood Pressure Inadequately Controlled	11	5.45
International Normalised Ratio Increased	11	5.45
Pleural Effusion	12	5.42
Serum Ferritin Increased	13	5.38
Pneumocystis Jirovecii Pneumonia	21	5.29
Lung Infection	12	5.25
Infection	10	5.20

From this data we found that pulmonary-related symptoms were the most severe adverse reactions. Anakinra and tocilizumab are both immunotherapy drugs and are most commonly used for the treatment of rheumatoid arthritis via inflammation reduction.

It is interesting that this drug combination would affect the lungs rather than cause typical immunosuppressant problems such as diabetes, fatigue, neurological impairment and gastrointestinal issues. Regardless of the source of these symptom changes, in the context of a potential therapy for covid-19 patients, using a drug combination with the added potential for pulmonaryrelated adverse reactions might be problematic.

Research Question 3: What is the adverse drug reaction safety for drug combinations of three covid-19 drugs?

To answer Research Question 3 we investigated every 3 drug combination of antivirals and interleukins we previously studied. Many of these combinations, especially between antivirals and interleukins, lack guidance from the NIH for their use as covid-19 treatments. Using a data-driven approach we hope to uncover new potential treatments that are relatively low in adverse reaction severity.

Table 16 demonstrates reaction severity outcomes for three covid-19 drug combinations ($n \geq 10$) of antivirals and interleukins. For many combinations we observed zero entries. This absence of adverse reactions is likely due to sparse prescriptions of the combination rather than a panacea.

.

Table 16: Three Drug Combination Reaction Severity

Drug Combination	n	$\bar{x}$
Azithromycin, Hydroxychloroquine and Tocilizumab	14	4.21
Azithromycin, Lopinavir and Ritonavir	1,066	4.91
Chloroquine, Hydroxychloroquine and Tocilizumab	20	4.95
Hydroxychloroquine, Lopinavir and Ritonavir	17	4.65

We call attention to the combination of azithromycin, hydroxychloroquine and tocilizumab (4.21). This three drug combination has lower adverse reaction severity than any of its components as shown in Table 17. The next lowest adverse reaction severity is that of hydroxychloroquine/tocilizumab (4.24), and interestingly enough, neither this nor the three drug combination has guidance from the NIH as a potential covid-19 treatment.

Table 17: Three Drug Combination Reaction Severity

Drug Combination	n	$\bar{x}$
Azithromycin, Hydroxychloroquine, Tocilizumab	14	4.21
Azithromycin, Hydroxychloroquine	486	4.48
Azithromycin, Tocilizumab	88	4.78
Hydroxychloroquine, Tocilizumab	5,494	4.24
Azithromycin	45,939	4.63
Hydroxychloroquine	49,017	4.45
Tocilizumab	34,793	4.58

We also examined patient-related characteristics of age and gender as shown in Table 18.

ISSN: 1941-6679-On-line Copy

.

Table 18: Azithromycin, Hydroxychloroquine and Tocilizumab by Demographic

Demographic	n	$\bar{x}$
Toddlers [0-4]	0	–
Children [5-12]	0	–
Teens [13-19]	0	–
Early Adults [20-34]	2	4.50
Mid-Adults [35-49]	6	4.17
Late Adults [50-64]	1	4.00
Retired Adults [65-79]	1	4.00
Elderly [80+]	0	–
Male	4	4.25
Female	10	4.20
Other	0	–

From this data, the combination of azithromycin, hydroxychloroquine and tocilizumab had adverse reactions observed in patients between 20 and 79 years of age. Of the 14 adverse reactions observed, 11 were categorized as *other serious* and 3 were *hospitalization*. Males were also observed to have higher adverse reactions (4.25) than females (4.20).

From a drug safety perspective, the three drug combination of azithromycin, hydroxychloroquine and tocilizumab appears to have decreased reaction severity and should be evaluated in a clinical trial as a potential covid-19 treatment.

CONCLUSIONS, LIMITATIONS AND FUTURE DIRECTIONS

We employed a data-driven approach to determine covid-19 drug combination safety using a cleaned version of FDA FAERS data in TylerADE. We found that the combination hydroxychloroquine/azithromycin had an average adverse reaction severity of 4.48 for all populations reporting an adverse drug reaction. We further found males more impacted and drug event severity marginally increased with patient age. When compared against the other drug combinations, hydroxychloroquine/azithromycin has the least adverse reactions severity on elderly [80+] populations (4.50).

ISSN: 1941-6679-On-line Copy

.

The drug combination of hydroxychloroquine/chloroquine had an average adverse reaction severity of 4.69 for all populations and no differences between gender. However, elderly [80+] patients were disproportionately affected with an average adverse reaction severity of 5.33. The drug combination of lopinavir/ritonavir had an average adverse reaction severity of 4.41 for all populations and also disproportionately affected males (4.59) and the elderly [80+] (5.15). It was also interesting to note that lopinavir/ritonavir had the least adverse reaction on toddlers [0-4] (3.71). For the interleukins, sarilumab when used in combination demonstrated lower adverse reaction severity than other interleukin drugs in combination. Finally, we found that the combination of azithromycin, hydroxychloroquine and tocilizumab had low adverse reaction severity (4.21) and from a drug safety perspective shows potential as a covid19 treatment option.

There are several limitations to this study. First, this study relies on adverse drug event reports reported to the FDA. We recognize that not all adverse drug events will be reported or there could be a skew towards reporting only the most severe adverse events. To accommodate this we only made comparisons within the datasets between drugs. Second, we rely on the reported data to be accurate and complete. We employed a painstaking process of data cleaning to ensure the reliability of data and omitted it when necessary. Third, although there are large numbers of adverse drug events on total, some drug combinations have few records and made comparison difficult. We did include the number of records in these situations so that readers can make an informed decision. Fourth, the purpose of this study is to evaluate drug combination safety from historical records. It is meant as a prelude to clinical trial data. Drug efficacy is not considered. Fifth, dosing, manufacturer and route of administered drugs was not considered.

Only the presence/absence of the drug was evaluated. While we recognize their importance, we felt partitioning to this level of detail would dilute the data to be of little comparative value and felt it best for clinical trial data to address those concerns.

Future directions include investigating the safety of other drug combinations that show promise such as other antivirals and interleukins. Further partitioning of data based on patient ethnicity or pre-existing conditions might also prove insightful.

Acknowledgments

We would like to acknowledge the efforts of the following Data Analytics Lab alumni Pooja Dhake, Harshini Elath, Danya Mason, Anthony Scoggins and Johnathon Stone, for helping to clean the FAERS data.

.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

Banda, J. M., Evans, L., Vanguri, R. S., Tatonetti, N. P., Ryan, P. B., & Shah, N. H. (2016). A curated and standardized adverse drug event resource to accelerate drug safety research. *Scientific data*, *3*.

Böhm, R., von Hehn, L., Herdegen, T., Klein, H.-J., Bruhn, O., Petri, H., & Höcker, J. (2016). OpenVigil FDA–inspection of US american adverse drug events pharmacovigilance data and novel clinical applications. *PloS one*, *11*(6), e0157753.

Divon, J. (2015). *Toronto startup has a faster way to discover effective medicines*. Retrieved October 6, 2017, from http://www.theglobeandmail. com/report-on-business/small-business/startups/toronto-startuphas-a-faster-way-to-discover-effective-medicines/article25660419/

Fantini, J., Scala, C. D., Chahinian, H., & Yahi, N. (2020). Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against sars-cov-2 infection. *International Journal of Antimicrobial Agents*.

Gautret, P., Lagier, J., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J., Giordanengo, V., Viera, V., Dupont, H.,

Honore, S., Colson, P., Chabriere, E., Scola, B. L., Rolain, J., Brouqui, P., & Raoult, D. (2020). Hydroxychloroquine and azithromycin as a treatment of covid-19: Results of an open-label non-randomized clinical trial. *International Journal of Antimicrobial Agents*.

Harper, M. (2020). *Why president trump is at odds with his medical experts over using malaria drugs against covid-19*. Retrieved March 22, 2020, from https://www.statnews.com/2020/03/22/why-trump-at-oddswith-medical-experts-over-malaria-drugs-against-covid-19/

.

Hartwig, S., Denger, S., & Schneider, P. (1991). Severity-indexed, incident report-based medication error-reporting program. *American Journal of Hospital Pharmacy*, *4*, 2611–2616.

Hartwig, S., Siegel, J., & Schneider, P. (1992). Preventability and severity assessment in reporting adverse drug reactions. *American Journal of Hospital Pharmacy*, *49*, 2229–2232. health.gov. (2017). *Overview - adverse drug events*. Retrieved February 18, 2017, from https://health.gov/hcq/ade.asp

Ibrahim, H., Saad, A., Abdo, A., & Eldin, A. (2016). Mining association patterns of drug-interactions using post marketing fda's spontaneous reporting system. *Journal of Biomedical Informatics*, *60*, 294–308.

Joranson, D., Ryan, K., Gilson, A., & Dahl, J. (2000). Trends in medical use and abuse of opioid analgesics. *Journal of the American Medical Association*, *283*, 1710–1714.

Kheshti, R., Aslipour, M., & Namazi, S. (2016). A comparison of five common drug-drug interaction software programs regarding accuracy and comprehensiveness. *Journal of Research in Pharmacy Practice*, *5*, 257–263.

Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., Li, Y., Hu, Z., Zhong, W., & Wang, M. (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting sars-cov-2 infection in vitro. *Cell Discovery*, *6*.

National Institutes of Health. (2020). *Therapeutic options for covid-19 currently under investigation*. Retrieved April 22, 2020, from https : //covid19treatmentguidelines.nih.gov/therapeutic-options-underinvestigation
Onakpoya, I., Heneghan, C., & Aronson, J. (2016). Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: A systematic review of the world literature. *BMC Medicine*, *14*.

Sakaeda, T., Tamon, A., Kadoyama, K., & Okuno, Y. (2013). Data mining of the public version of the FDA adverse event reporting system. *Int J Med Sci*, *10*(7), 796–803.

Saragdhar, M., Tabar, S., Schmidt, C., Kushwaha, A., Shah, K., Dahlquist, J., Jegga, A., & Aronow, B. (2016). Data mining differential clinical outcomes associated with drug regimens using adverse event reporting data. *Journal of Nature Biotechnology*, *34*(7), 697–700.

.

Sibbald, B. (2004). Rofecoxib (vioxx) voluntarily withdrawn from market. *Canadian Medical Association Journal*, *171*, 1027–1028.

Sivigny, E., & Caces, M. (2018). When dawn went dark: Can the nationwide emergency department sample (neds) fill the surveillance gap left by the discontinued drug abuse warning network (dawn)? *Drug and Alcohol Dependency*, *192*, 201–207.

Substance Abuse and Mental Health Services Administration. (2019). *Dawn drug abuse warning network*. Retrieved March 25, 2019, from https: //www.samhsa.gov/data/data- we- collect/dawn- drug- abusewarning-network

Toki, T., & Ono, S. (2018). Spontaneous reporting on adverse events by consumers in the united states: An analysis of the food and drug administration adverse event reporting system database. *Drugs - Real World Outcomes*, *5*, 117–128.

Trump, D. (2020). *Donald J. Trump on Twitter*. Retrieved March 21, 2020, from https://twitter.com/realDonaldTrump/status/1241367239900778501

Truven Health Analytics. (2017). *Micromedex(r) 2.0*. Retrieved September 20, 2017, from http://www.mircomedexsolutions.com/

US Dept of Health and Human Services. (2017). *How drugs are developed and approved*. Retrieved October 6, 2017, from https://www.fda.gov/ Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ default.htm

US Food & Drug Administration. (2020). *Step 3: Clinical research*. Retrieved April 28, 2020, from https://www.fda.gov/patients/drugdevelopment-process/step-3-clinical-research

Ventola, C. (2018). Big data and pharmacovigilance: Data mining for adverse drug events and interactions. *Pharmacy and Therapeutics*, *43*, 340– 351.

Veronin, M., Schumaker, R., Dixit, R., Dhake, P., Mason, D., & Ogwo, M. (2020). A systematic approach to cleaning of drug name records in the faers database. *International Journal of Big Data Management*, *Forthcoming*.

Veronon, M., Schumaker, R., Dixit, R., & Ogwo, M. (2020). The irony of medwatch and the faers database: An assessment of data input errors and potential consequences. *The Journal of Pharmacy Technology*, *Forthcoming*.

ISSN: 1941-6679-On-line Copy

.

Xu, R., & Wang, Q. (2014). Large-scale combining signals from both biomedical literature and the FDA adverse event reporting system (FAERS) to improve post-marketing drug safety signal detection. *BMC bioinformatics*, *15*(1), 17.

Yao, X., Ye, F., Zhang, M., Cui, C., Huang, B., Niu, P., Liu, X., Zhao, L., Dong, E., Song, C., Zhan, S., Lu, R., Li, H., Tan, W., & Liu, D. (2020). In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (sars-cov-2). *Clinical Infectious Diseases*.

.