OSE-OND: HCQ and CQ in setting of COVID-19 Safety Surveillance
Agenda
Meeting Date: April 14, 2020, 12:30 PM – 2PM

Purpose of meeting:

- OSE OND meeting to discuss safety signals or summary data regarding AEs associated with hydroxychloroquine/chloroquine in the setting of COVID-19.
- To discuss public safety communication and consideration for content.

OSE Participants	OND Participants	Other Participants
OPE	OID	OCOMM
Mike Blum (Deputy Director)	John Farley (Acting Director)	Sarah Kim
Neha Gada (CDSL)	Barbara Styrt (Associate Director for Medical Countermeasures)	Kristen Booze
		Elissa Fuchs
DPV		Adam Ghering
Ida-Lina Diak (DD/OSE Core Team Lead)	DAV	
	Deb Birnkrant (Director)	OCD/PASES
Rachna Kapoor (TL)	Jeff Murray (DD)	Christopher Melton
Kim Swank	Poonam Mishra (DDS)	Sadhna Khatri
Kate McCartan	Mary Singer	
Miriam Chehab	Andreas Pikis	DARS
Drug Utilization	Charu Mullick	Keith Burkhart
Grace Chai	Aimee Hodowanec	
Rajdeep Gill	Kyong Hyon	OMP
Corinne Woods		Jacqueline Corrigan-Curay
Modupe Adereti	DAI	
Patty Greene	Sumathi Nambiar (Director)	OCC
DEPI	Elizabeth O'Shaughnessy	Donald Beers
Monique Falconer	Yuliya Yasinskaya	
Natasha Pratt	Dimitri Iarikov	OEA
DMEPA	Fariba Izadi	Sarah Peddicord
Jo Wyeth		Michael Felberbaum
Celeste Karpow	DRTM	Alison Hunt
RSS	Ozlem Belen (DDS)	Nathan Arnold
Michael Nguyen	Jane Filie	Jeremy Kahn
Catherine Corey	June Germain	Beth Fritsch
Sarah Dutcher		Steve Morin
Danijela Stojanovic	ORO	
	Maureen Dillon Parker	
Dave Graham	Carmen DeBellas	
	Nikia Morris- DST Program Manager	
Saharat Patanavanich (PM)	Emily Riehl-Bedford- Eagle Hill Consultant	
	Lauren Choi	
	Marilyn Pitts	

Agenda Items:

1. **Introduction and General Housekeeping** (Saharat) **– 2 minutes**
2. **Discuss meeting goals** (Neha) **- 3 minutes**
3. **DPV** (Ida-Lina, Rachna, Kim, and Kate) **– 20 minutes**
    I. Literature and FAERS- 10 minutes
    II. National Poison Data System (NPDS) – 5 minutes
        i. Methemoglobinemia cases (Keith Burkhart)
    III. Questions – 5 minutes
4. **Drug Utilization – 20 minutes**
    I. Concurrency data
        i. Sentinel and TriNetX (Danijela Stojanovic) – 10 minutes
        ii. CMS/VA (Dave Graham) – 5 minutes
    II. Questions – 5 minutes
5. **IND Safety Reporting** (Poonam Mishra and Elizabeth O'Shaughnessy) – **10 minutes**
    I. Questions
6. **DMEPA** (Jo Wyeth, Celeste Karpow, Rapid Response Team) - **5 minutes**
    I. ISMP and FAERS reports
    II. Potential for compounded HCQ
    III. Questions
7. **DEPI** (Natasha Pratt) **– brief update – 5 minutes**
    I. Observational data screening
    II. Questions
8. **DSC** (All) **– 20 minutes**
    I. What content is "in" for DSC?
9. **Administrative** (Saharat and Neha) - **5 minutes**
    I. OSE RCM # 2020-701
    II. TSI # 2150 – opened 4/14/2020 (DAI)
    III. Meeting frequency

Action Item(s)	Responsible Parties	Status

DPV summary of adverse event cases from all sources (FAERS, literature, NPDS, ISMP, IND safety reports) -data through 4/12/20

HCQ or CQ FATAL CASES (n=16)

- 15 death cases for HCQ (7 HCQ alone, 1 HCQ+LPV/r, 6 HCQ+azithro, 1 HCQ+azithro+LPV/r), 1 for CQ

HCQ alone (7 cases):

FAERS 17611030 – HCQ only (but also on other QT prolonging meds amiodarone and sertraline) – SOC cardiac disorders, AE **QT prolongation (prelim cause of death viral pneumonia from COVID19)**: From **US**, 61 yo M received two doses of hydroxychloroquine and died the next day. Pharmacist reporter stated "COVID patient QTc of 624 from 541" (dates of EKGs not known). Prelim cause of death viral pneumonia from COVID19.

FAERS 17605416 – HCQ only – SOC cardiac disorders, renal and urinary disorders, metabolism and nutrition disorders, AE **cardiac arrest, ventricular tachycardia, hyperkalemia, hypermagnesemia, renal failure**: From **US**, 41 yo M with no PMH admitted with COVID19 and intubated, in ARDS and renal failure. Received 5 days of hydroxychloroquine (200 mg TID), ceftriaxone and doxycycline for 7 days. Baseline EKG before hydroxychloroquine with 472 (?QTc); on the day after his last dose of hydroxychloroquine he went into VTach, PEA arrest and was unable to be resuscitated. K on last day of hydroxychloroquine was 5.6, magnesium 3.2.

FAERS 17653880 – HCQ only – SOC cardiac disorders, AE **cardiac arrest**: From **France**, 70 y/o male receiving HCQ, ceftriaxone and oseltamivir for coronavirus experienced cardiac arrest/death on day 2 of HCQ, and day 3 of ceftriaxone and oseltamivir.

NPDS 240373362020 – HCQ only – SOC Blood and lymphatic system disorders, AE **methemoglobinemia (died after being placed on comfort measures)**: From **US**, 54 yo M with h/o DM2, intubated for hypoxia, given Plaquenil 400 mg x 2, MetHb 11.9% the next day, HCQ was held, no noticeable change in blood pressure or oxygenation after methylene blue. Met hemoglobin fell to 9%. Patient did not receive additional methylene blue or HCQ. Developed renal failure, decision was made for comfort measures, patient died.

NPDS 23961183222020 – HCQ only – SOC Blood and lymphatic system disorders, AE **methemoglobinemia (cause of death COVID-19 respiratory failure with multisystem organ failure, including septic shock, refractory metabolic acidosis, acute renal failure, anemia, cholecystitis)**: From **US**, 67 yo M with COVID-19, intubated x 5 days, given hydroxychloroquine 200 mg TID x 5 doses, MetHb (9%). On follow up, did not get methylene blue (level did not warrant this). EKG with QTc 480. Patient died.

IND 149141 – HCQ only – (b) (4) .

IND 149141 – HCQ only – (b) (4) .

HCQ + LPV/r (1 case):

FAERS 17581834 – HCQ + LPV/r – SOC respiratory disorders, AE **respiratory failure**: From **Spain**, 80 yo M admitted with fever, chills, general discomfort and progressive dyspnea that began 4 days ago on vacation. Patient started on lopinavir/ritonavir, hydroxychloroquine, and interferon beta-1b and developed respiratory failure and death on 6th day of admission.

HCQ+azithro (6 cases):

FAERS Cases 17644417, 17646286, 17646292 - SOC cardiac disorders, AE **ventricular fibrillation, sudden death**: From **US**, 3 cases of ventricular fibrillation and sudden death (awaiting additional information)

FAERS Case 17605425 - SOC cardiac disorders, AE ***QT prolongation*** **(cause of death not specified to be a cardiac cause, died 4 days after reported prolonged QTc)**: From **US**, 87 yo M with h/o CAD, HTN, CKD stage III (CrCl 12 mL/min) c/o urinary symptoms and mild cough, COVID test was positive. He was given vancomycin, meropenem and started on hydroxychloroquine. QTc prior to HQ was normal (397) then increased to 468 four days after starting HQ. He did not receive HQ on the day of the QTc 468 but received a dose the next day before it was stopped. He received one dose of azithromycin, this was on the day of the QTc 468. No treatment of prolonged QT in the chart. No further discussion of clinical course until report that patient expired seven days after starting HQ and three days after the last dose was given.

FAERS 17649456 - AE **death**: From **US**, 65 y/o female tested positive for COVID-19 and was treated with Hydroxychloroquine, azithromycin, oseltamivir, piperacillin/tazobactam, ceftriaxone and expired the following day.

IND Case 149141 - (b) (4)

HCQ+azithro+LPV/r (1 case):

FAERS 17653955 - AE **death**: 75 y/o male with coronavirus started on azithromycin, levofloxacin, HCQ, and lopinavir/ritonavir. Pt received five days of azithromycin, one day of LPV/r, 3 days of HCQ, and 4 days of Levaquin. Patient died on day 7.

CQ alone (1 case):

NPDS-21586793322020 – SOC Cardiac disorders, metabolism and nutrition disorders, Respiratory disorder, Nervous system disorders, AE **QT prolongation, QRS complex widened, seizure, dyspnea, diarrhea, wide complex bradycardia, V tachycardia, cardiac arrest** - 68 y/o male ingested aquarium product containing chloroquine phosphate in attempt to prevent COVID-19. He developed diarrhea, decreased responsiveness and dyspnea 90 min after ingesting CQ. He developed a widened QRS complex, V, tachycardia, QT prolongation, wide complex bradycardia, seizure, and cardiac arrest

HCQ or CQ + AZITHROMYCIN NONFATAL CARDIAC TOXICITIES

- 9 cases with non-fatal AEs in SOC Cardiac Disorders (8 HCQ, 1 CQ)

QT Prolongation (7 nonfatal cases: 6 HCQ, 1 CQ) [Labeled]

HCQ:

FAERS 17618200 (HCQ+azithro+LPV/r): From **Italy**, 57 y/o male on lopinavir/ritonavir, hydroxychloroquine, and azithromycin for coronavirus. Patient experienced QT prolongation on day 2 of hydroxychloroquine. No other information provided.

FAERS 17611066 (HCQ+azithro, also on tacrolimus): From **US**, 76 yo F, COVID 19 patient, received HQ/azithromycin as part of COVID tx, QTc prolonged to 577 "a few days" after last doses; tacrolimus level also went to >60; CrCl 24.7 ml/min. Outcome unknown.

FAERS 17623040 (HCQ+azithro): From **US**, 78 yo M 1 day after stopping HQ/azithromycin and 5 days after starting these meds, QTc increased from 422 to 479. No treatment or follow up EKG reported.

FAERS 17656876, ISMP Article (HCQ+azithro – azithro dc'd before starting HCQ): From **US**, 70 y/o female initially started on azithromycin and ceftriaxone for CAP, tested positive for COVID-19. One day after azithromycin and ceftriaxone were discontinued, the patient was started on HCQ (400 mg orally BID on day 1, followed by 400 mg orally QD for 4 days). On admission to hospital, the patient's ECG showed QTcB interval of 460 ms. The day HCQ was started, the patient's ECG showed a QTcB of 490 ms. Three days later, the QTcB was 515 ms. On the fifth and last day of HCQ, the patient experienced ventricular fibrillation and coded. After two cycles of CPR, a return of spontaneous circulation was achieved. An ECG performed afterwards showed a QTcB of 605 ms, and all QTc prolonging medications were discontinued. Initially the patient was not responding neurologically. However, after undergoing targeted temperature management post-arrest, the patient now appears to be responding and is expected to recover with good neurological function. *This case also reported ventricular fibrillation.*

NPDS 256993362020 (HCQ+azithro): 83 yo F husband critically ill COVID-19. Pt with lung infiltrates started on HQ and AZ. Pt with SIADH (Na110, K2.0). QTc 550 ms. K repletion (Mg low NML unknown if given) and QTc corrected to 387 ms. Not sure what etiology of SIADH was but low K major contribution to prolonged QTc.

FAERS 17651582 (HCQ+azithro, also on amiodarone): From **US**, 79 y/o male treated with HCQ and azithromycin for COVID-19. Patient was also on amiodarone prior to admission and continued on admission. Drug-Drug interaction occurred leading to QTc prolongation. Baseline QTc was 480 msec. On Day 3 of treatment, QTc was 510 ms and HCQ and azithromycin were discontinued.

CQ:

FAERS 17620078 (CQ+azithro+LPV/r): From **Spain**, patient hospitalized with pneumonia, was given ceftriaxone, azithromycin with chloroquine and LPV/r, withdrawn due to QT distance, recovered from flu-like symptoms, was discharged. Updated version on 4/10 clarifies QT prolongation.

Ventricular fibrillation, Ventricular tachycardia, Wide complex tachycardia (2 nonfatal cases, 2 HCQ) [Labeled]

HCQ:

FAERS 17605439 (HCQ+azithro): From **US**, 85 yo M with wide complex tachycardia after starting Plaquenil and azithromycin for COVID, both meds listed as dc'd but no outcome listed. Report mentions another patient with same AE with this medication combination but no age listed for this patient.

FAERS 17655678 (HCQ+azithro): From **France**, 80 y/o female with coronavirus started on azithromycin, HCQ, and Zosyn and developed ventricular tachycardia and hypokalemia on day 7 of treatment. Azithromycin and HCQ were discontinued and AEs resolved.

OTHER CONCERNING AEs FOR HCQ+AZITHRO

- Metabolism and nutrition disorders
  - SIADH (hypokalemia/hyponatremia) [unlabeled]
    - NPDS 256993362020 (see above)
- Immune system disorders
  - Oropharyngeal edema [unlabeled]
    - NPDS 10424073092020 – From **US**, 51 yo F given HCQ and azithromycin for COVID-19, developed nausea, HA, oropharyngeal edema, stopped meds and this resolved
- Vascular disorders
  - DVT, possible PE [unlabeled]
    - FAERS 17647345 - Phase 2/3 study of efficacy and safety of sarilumab for hospitalized patients with COVID-19. 57 yo M with h/o preDM2, obesity, EtOH use, treated with HCQ and azithromycin, sarilumab. 4 days after sarilumab, 9 days after HCQ, 10 days after azithromycin (not still taking any of these medications at the time of occurrence), had DVT and possible PE, was started on Lovenox, patient had not recovered.

HCQ + azithromycin

29 cases of HCQ+azithro from FAERS, INDs, NPDS, Literature

- 4 with HCQ+azithro+LPV/r, 25 with HCQ+azithro
- 20 from US
- 21 involve an AE

Methemoglobinemia in 2 NPDS fatality cases

- 67 yo 70 kg M COVID-19 positive PMH HTN, Asthma (Hydroxychloroquine 200 mg TID for 5 doses)
- MetHgb level 9% with pO2 of 300 on norepinephrine, vasopressin Developed Renal Failure. Hematocrit 21.3
- Methylene Blue not given
- 54 yo 54 kg M COVID-19 PMH: Diabetes HQ dose 400 mg X 2
- MetHgb 11.9% Intubated ABG pH 6.85 PCO2 56 pO2 427 O2 Sat 88% given 100 mg (2 mg/kg) methylene blue. Hgb 9.3 BP was 87/55 and increased to 94/59.
- BP fell back 80s/50s MetHgb at 18% Hgb 8.3 (Concern for hemolysis)
- Developed Renal Failure given Palliative Care and expired

Hydroxychloroquine and Methemoglobinemia

- Well recognized and labeled adverse event: quinine antimalarial class effect
- Methemoglobin levels < 25% are usually well tolerated
- Glucose-6-Phosphate Dehydrogenase (G6PD) deficient patients are susceptible to developing MetHgb from oxidant stress including infections.
- Mediterranean descent is risk factor for deficiency (Protective vs malaria)
- Methylene Blue may cause oxidant stress and hemolysis in G6PD deficient patients. Patient testing not documented (Concern: Both significant anemia)
- Methylene Blue possible pressor benefit: Inhibits nitric oxide production
- **Action:** (b) (5)

U.S. FOOD & DRUG ADMINISTRATION

COVID-19 Response: Assessment of Hydroxychloroquine and Azithromycin within the TriNetX Network

Initial Findings

April 14, 2020

Study Motivation and Regulatory Setting

- Three fatal FAERS cases with ventricular fibrillation and sudden death after treatment with hydroxychloroquine (HCQ) and azithromycin (AZM)
- Drug Use + Sentinel team contacted on Friday, 4/11 to assess co-administration/co-prescribing of HCQ and AZM in available data sources
  - TriNetX
- Research question: Among all COVID-19 patients, how many are co-prescribed/administered HCQ-AZM (+/- 1 day is primary definition)?

Overview of TriNetX Data

115M+
PATIENTS (EMR DATA)

- **86M+** U.S.
- **45M+** DOWN-LOADABLE

105
HEALTHCARE ORGANIZATIONS

- **60** U.S.
- **250+** U.S. INPATIENT SITES

25
COUNTRIES

- **75%** U.S.
- **17%** EMEA
- **5%** APAC
- **3%** S. AMERICA

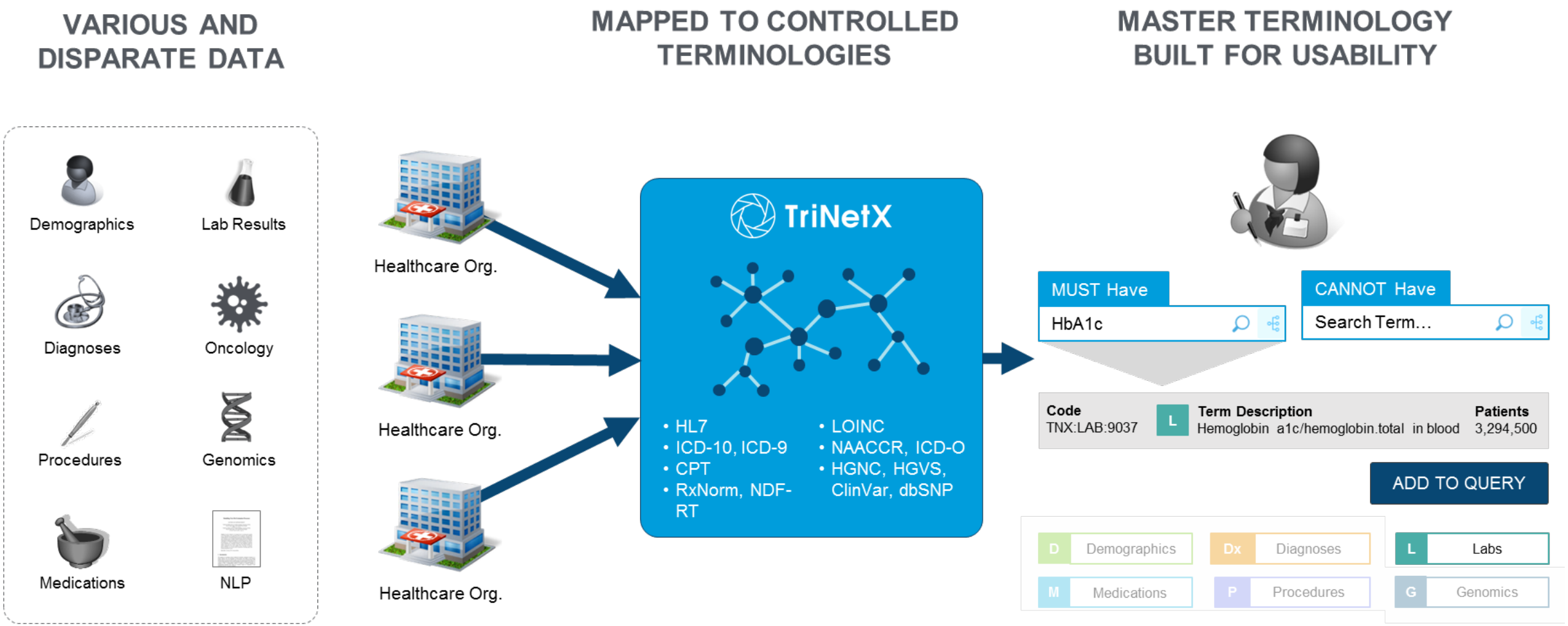
20%
YOY PATIENT LIVES & HCO GROWTH

85%
OF SITES REFRESH DATA AT LEAST MONTHLY

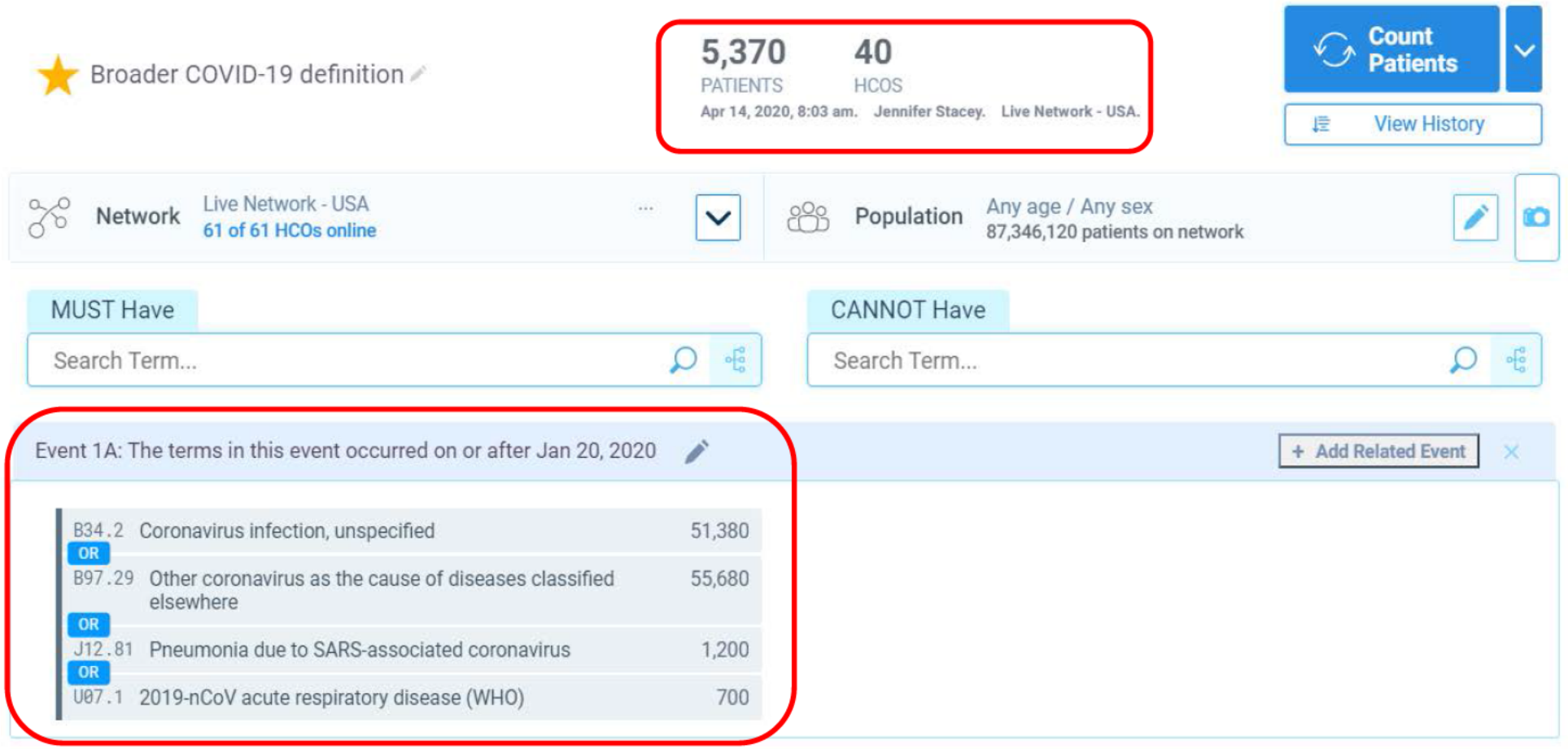
16
TOP 20 PHARMA CUSTOMERS

Statistics as of April 2020.

How It Works

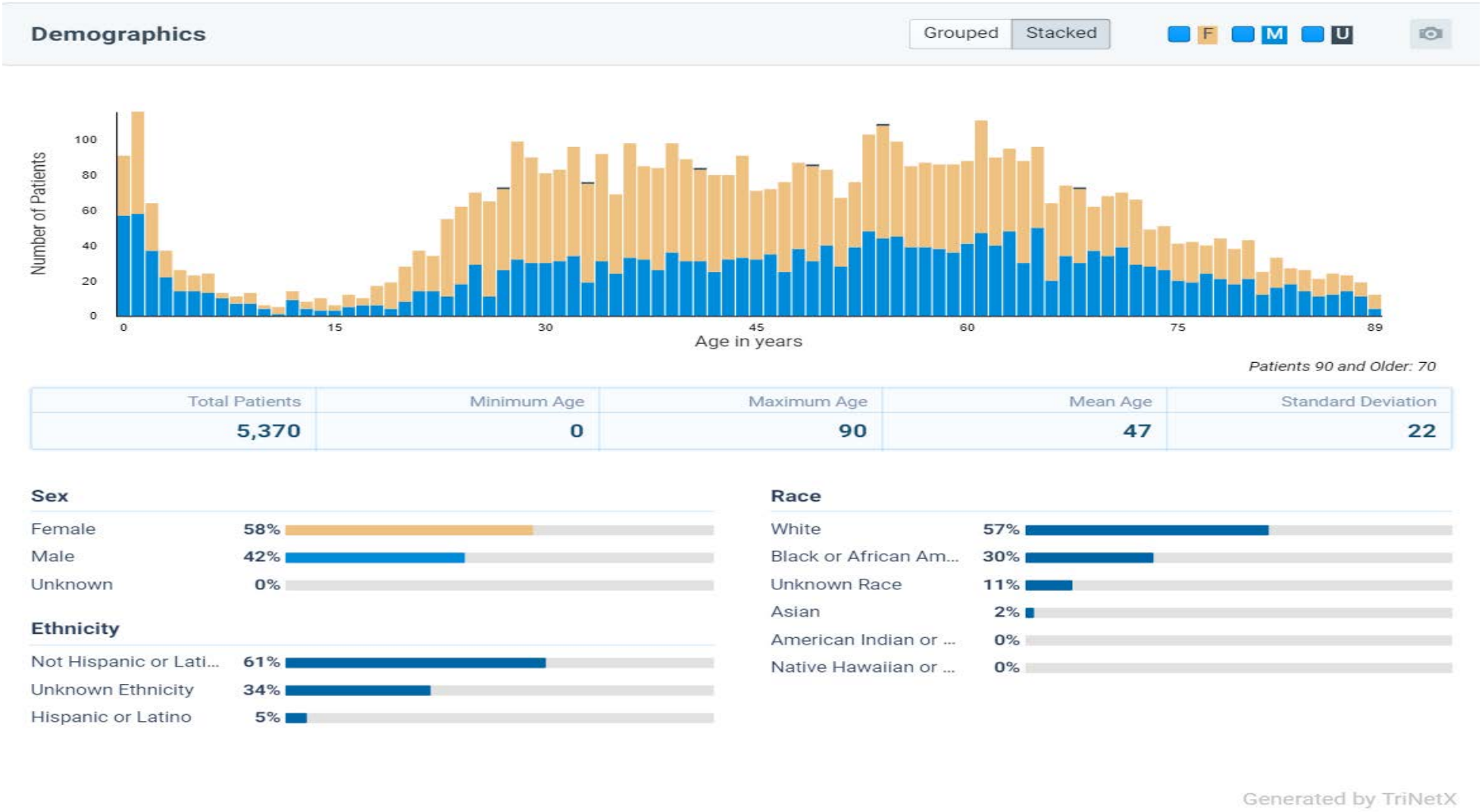

VARIOUS AND DISPARATE DATA
Demographics
Lab Results
Diagnoses
Oncology
Procedures
Genomics
Medications
NLP
MAPPED TO CONTROLLED TERMINOLOGIES
Healthcare Org.
Healthcare Org.
Healthcare Org.
TriNetX
• HL7
• ICD-10, ICD-9
• CPT
• RxNorm, NDF-RT
• LOINC
• NAACCR, ICD-O
• HGNC, HGVS, ClinVar, dbSNP
MASTER TERMINOLOGY BUILT FOR USABILITY
MUST Have
HbA1c
CANNOT Have
Search Term...
Code
TNX:LAB:9037
L
Term Description
Hemoglobin a1c/hemoglobin.total in blood
Patients
3,294,500
ADD TO QUERY
D Demographics
Dx Diagnoses
L Labs
M Medications
P Procedures
G Genomics

COVID-19 Cohort Definition

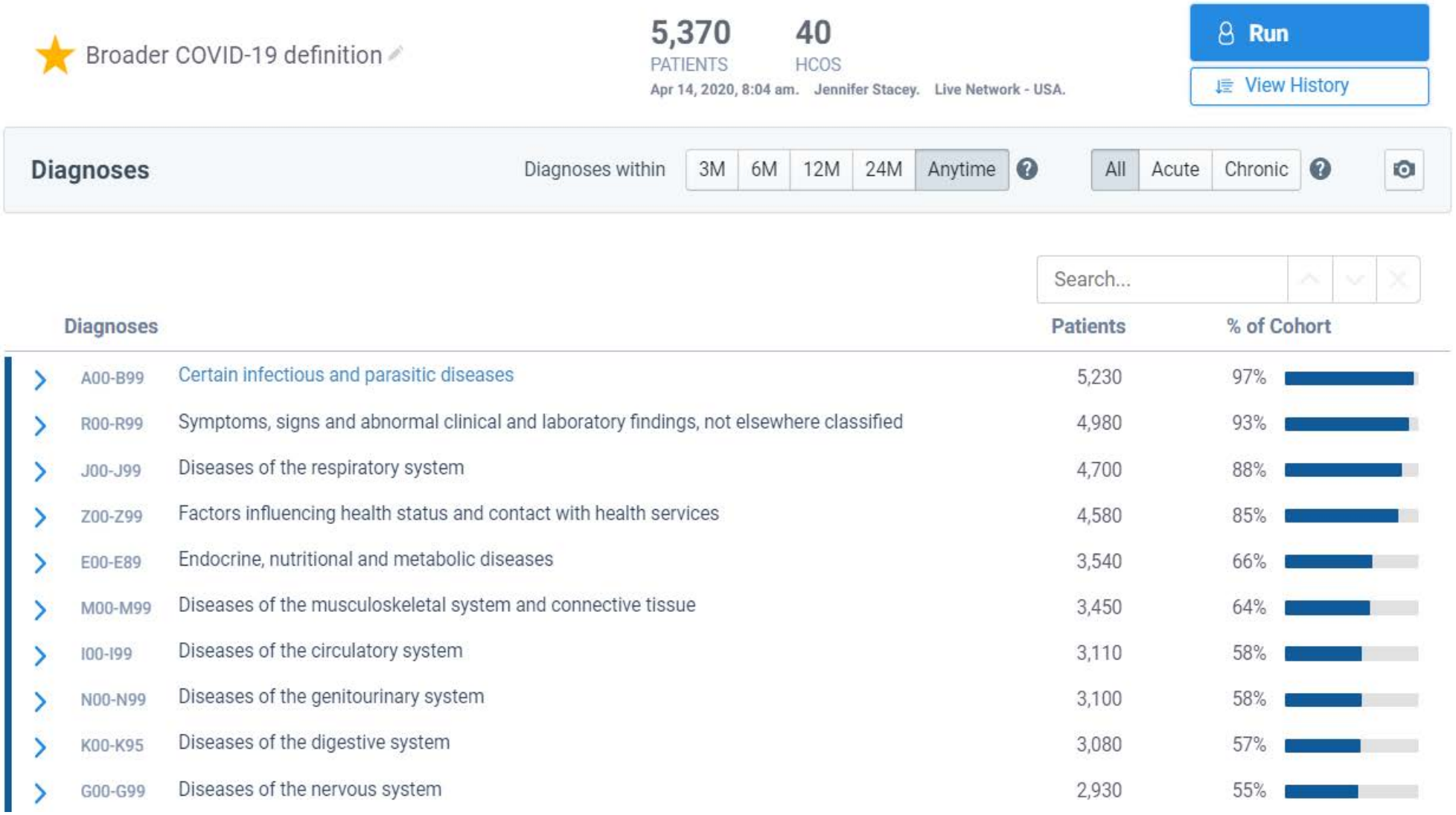


- Based on a set of diagnosis terms that are “ORed”; selected based on evidence from real-world coding practices
- Query period on or after January 20, 2020.

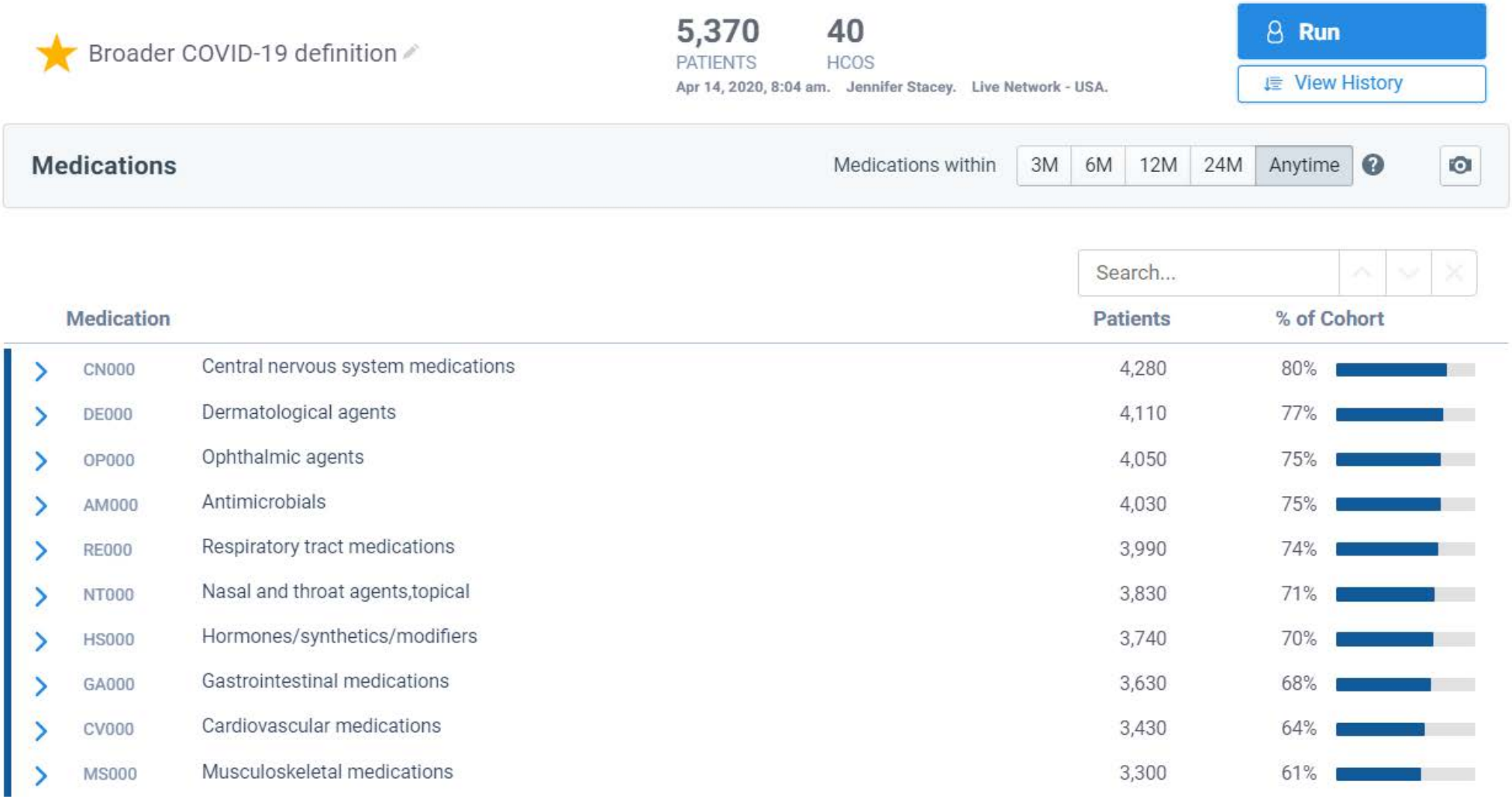
COVID-19 Cohort Demographics: Age, Sex, Race, and Ethnicity



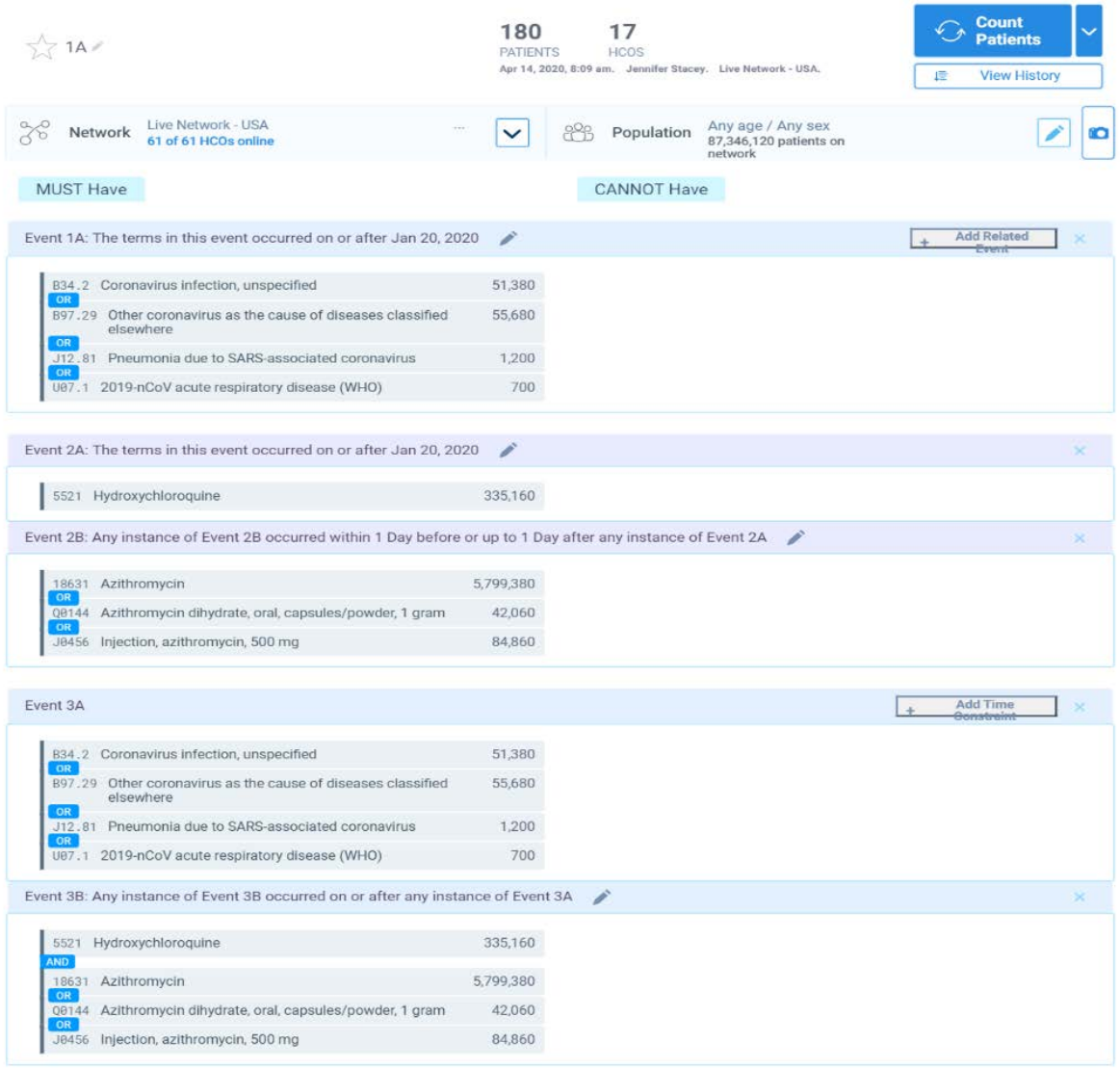
COVID-19 Cohort Demographics: Top Prior Diagnoses



COVID-19 Cohort Demographics: Top Prior Medications



COVID-19 + HCQ/AZM Query Logic

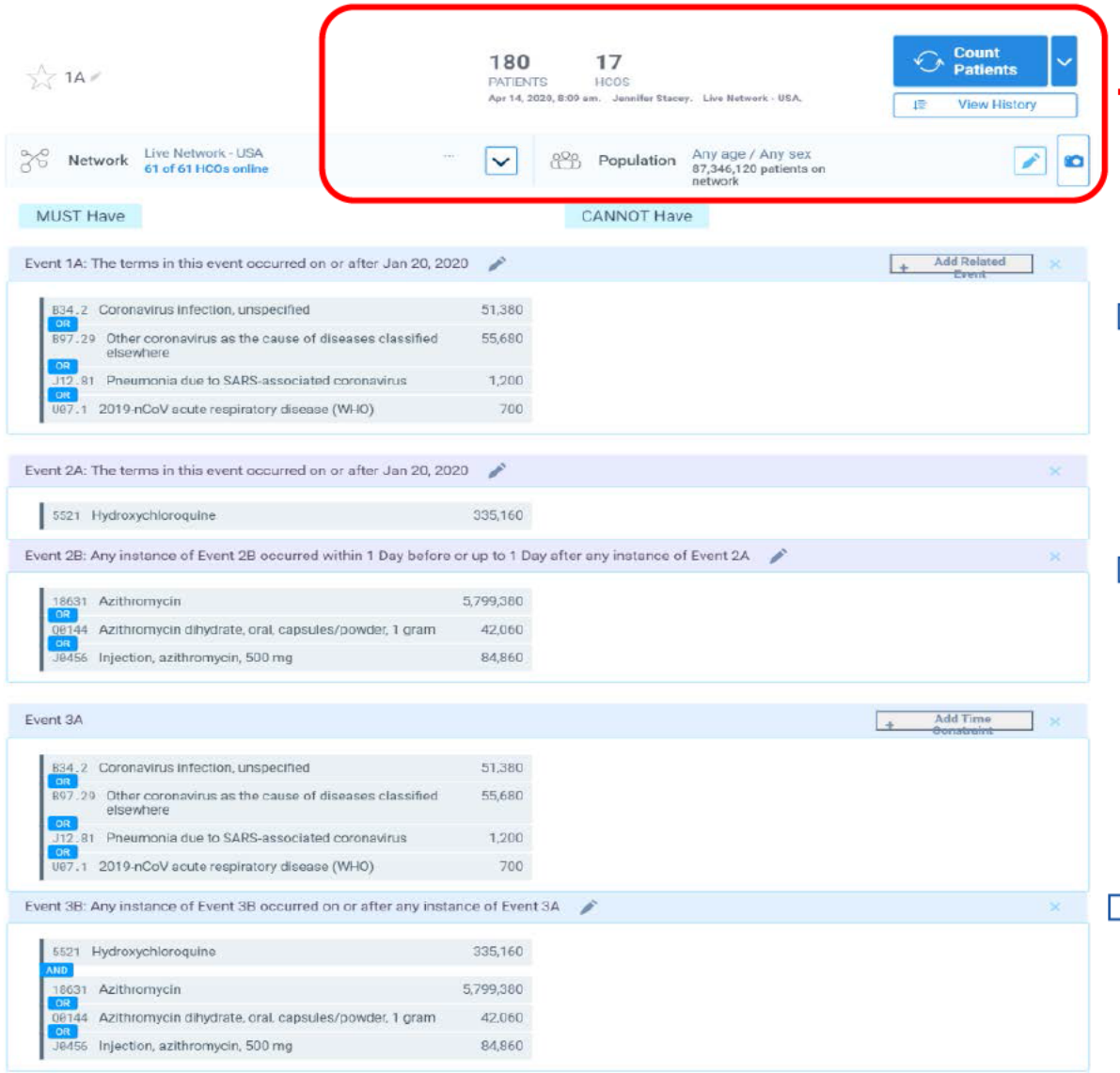


Identify all COVID-19 patients on or after January 20, 2020

Require evidence of HCQ on or after January 20, 2020 AND evidence of AZM us with 1 day (+/-) of HCQ

Require the HCQ/AZM exposure to be AFTER the COVID-19 diagnosis date

COVID-19 + HCQ/AZM Query Logic



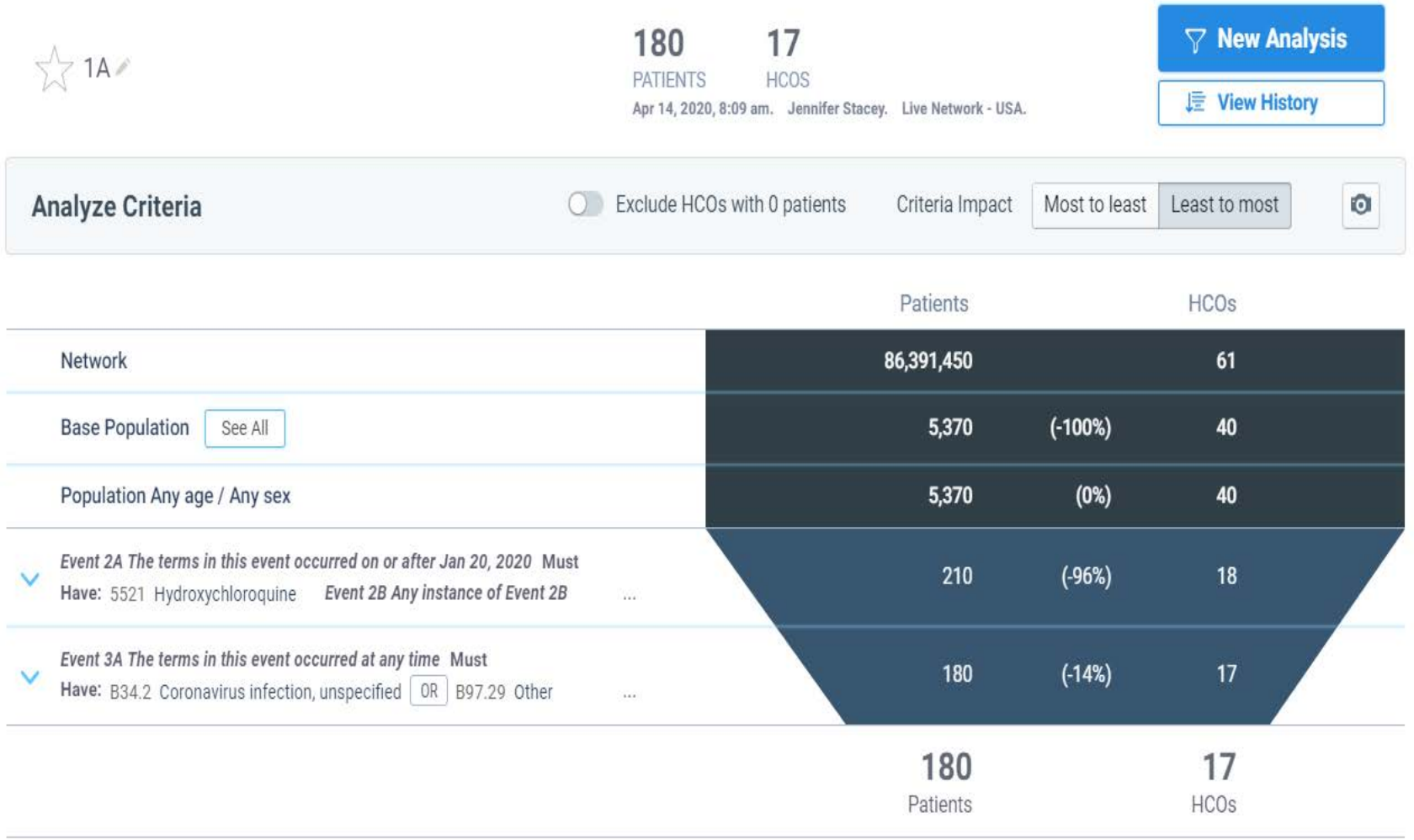
As of 8am this morning, 180 COVID-19 + HCQ/AZM patient identified at 17 health care organizations

Identify all COVID-19 patients on or after January 20, 2020

Require evidence of HCQ on or after January 20, 2020 AND evidence of AZM us with 1 day (+/-) of HCQ

Require the HCQ/AZM exposure to be AFTER the COVID-19 diagnosis date

COVID-19 + HCQ/AZM Attrition Tables



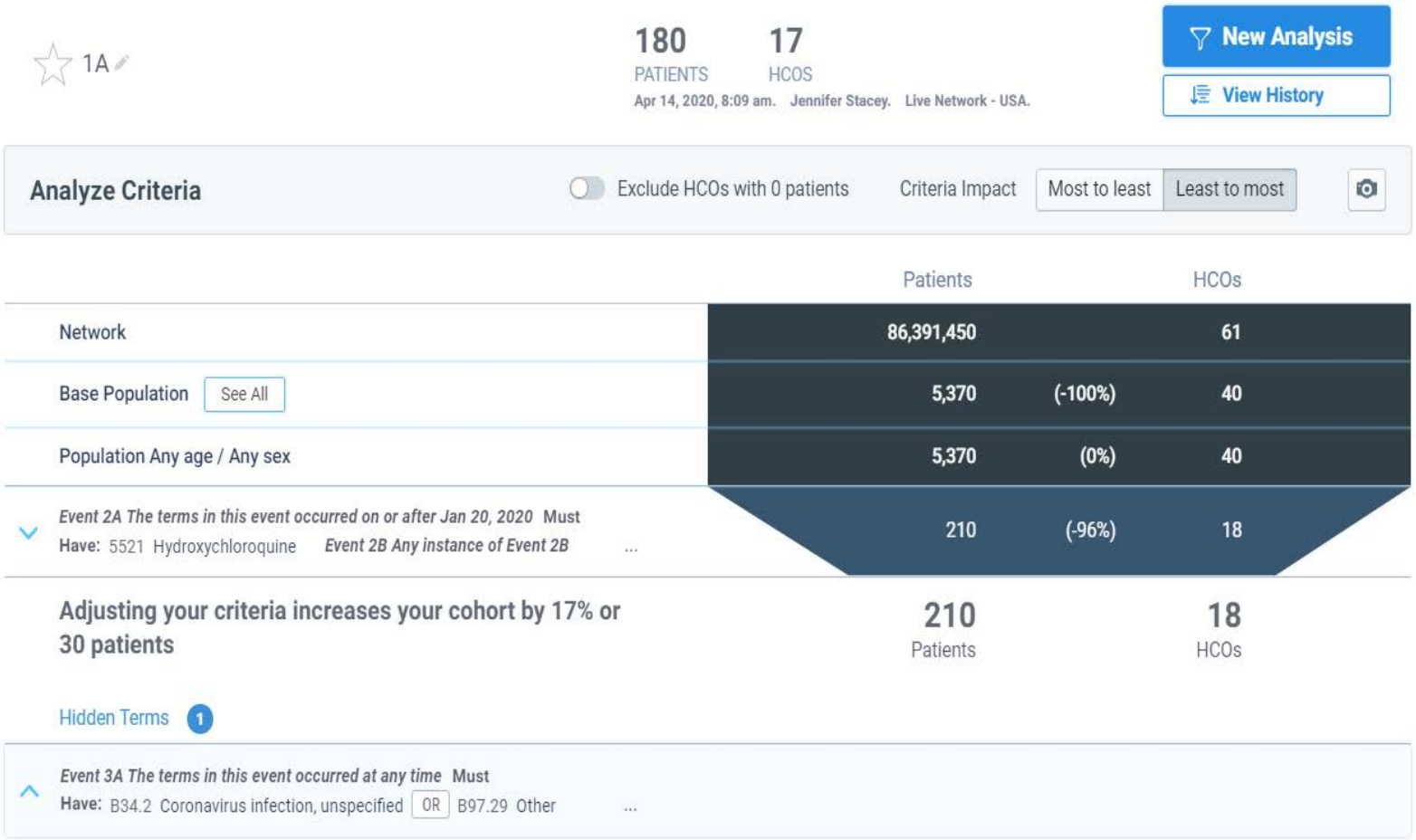
Start with 86 million patients at 61 HCOS

5,370 meet COVID-19 criteria at 40 HCOs

210 meet HCQ/AZM use criteria at 18 HCOs

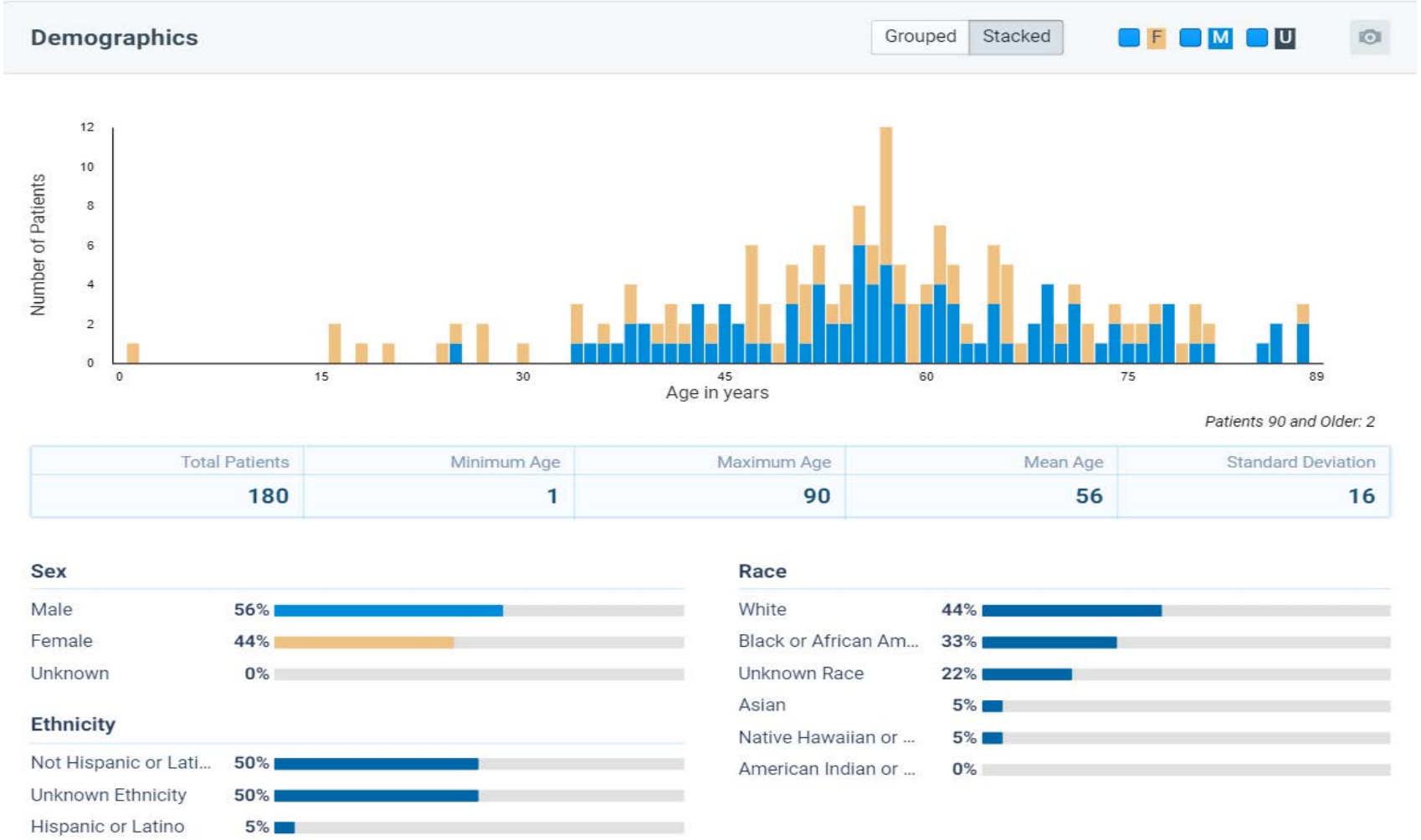
180 have HCQ/AZM after COVID-19 index date at 17 HCOs

COVID-19 + HCQ/AZM Attrition Tables



Removing the requirement that HCQ/AZM must occur <u>after</u> the COVID-19 index date increases sample by 17% to 210 patients

COVID-19 + HCQ/AZM Demographics: Age, Sex, Race, and Ethnicity



COVID-19 + HCQ/AZM Demographics: Top Prior Diagnoses

1A

180 PATIENTS 17 HCOS

Apr 14, 2020, 8:08 am. Jennifer Stacey. Live Network - USA.

Run

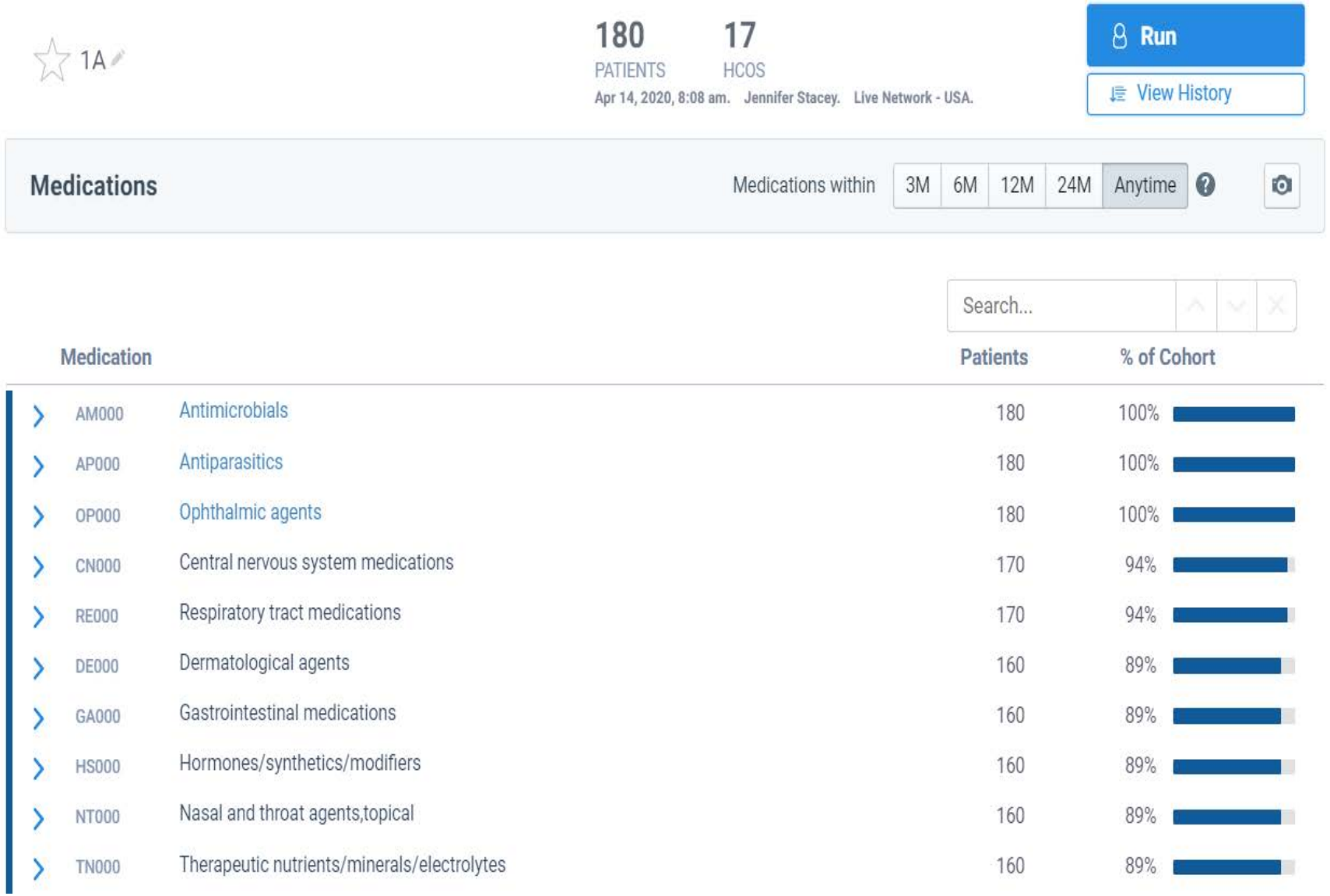
View History

Diagnoses Diagnoses within 3M 6M 12M 24M Anytime All Acute Chronic

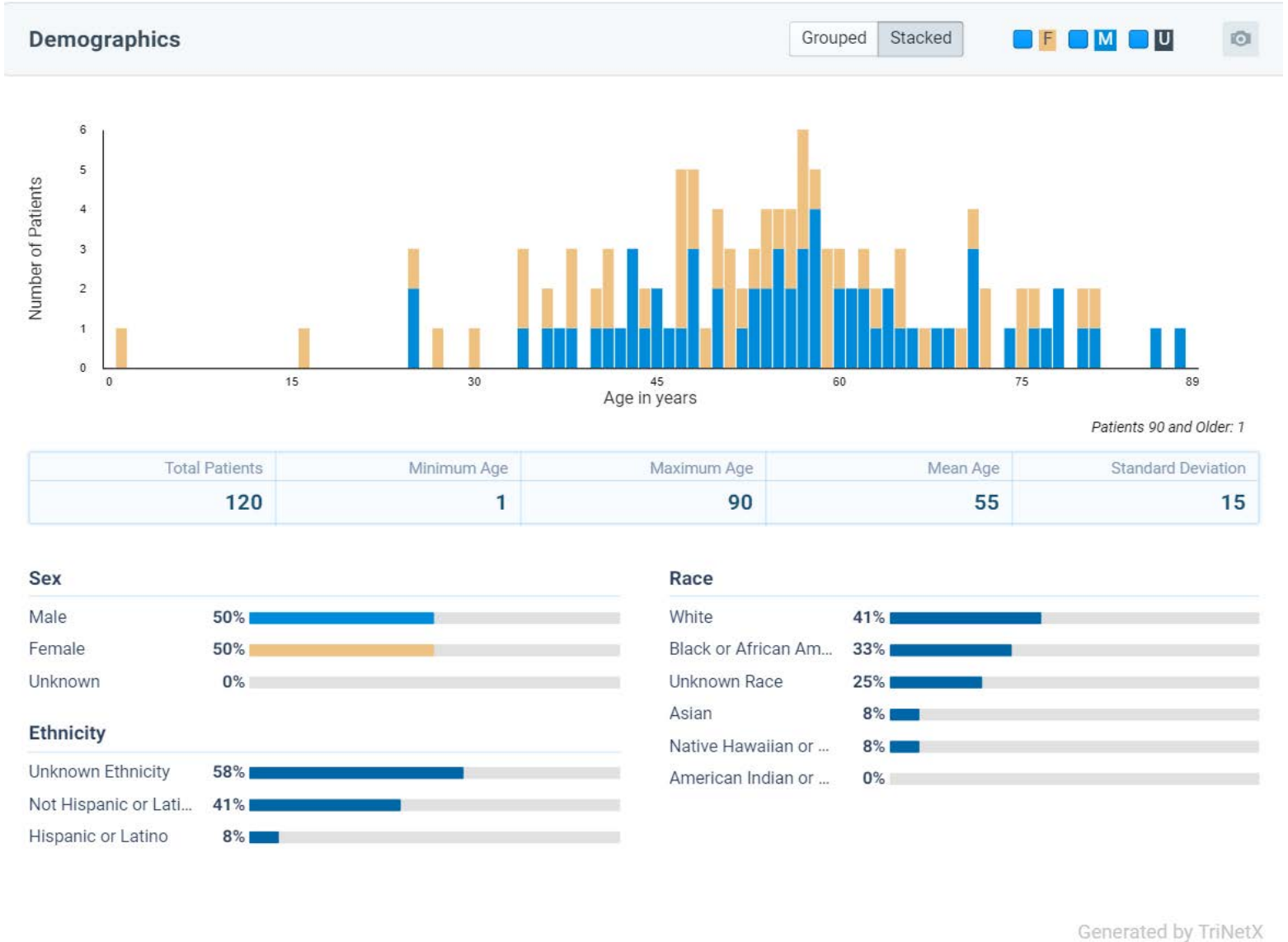
Search...

Diagnoses		Patients	% of Cohort
A00-B99	Certain infectious and parasitic diseases	180	100%
J00-J99	Diseases of the respiratory system	170	94%
R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	170	94%
E00-E89	Endocrine, nutritional and metabolic diseases	130	72%
Z00-Z99	Factors influencing health status and contact with health services	130	72%
I00-I99	Diseases of the circulatory system	110	61%
M00-M99	Diseases of the musculoskeletal system and connective tissue	110	61%
N00-N99	Diseases of the genitourinary system	100	56%
K00-K95	Diseases of the digestive system	90	50%
G00-G99	Diseases of the nervous system	80	44%

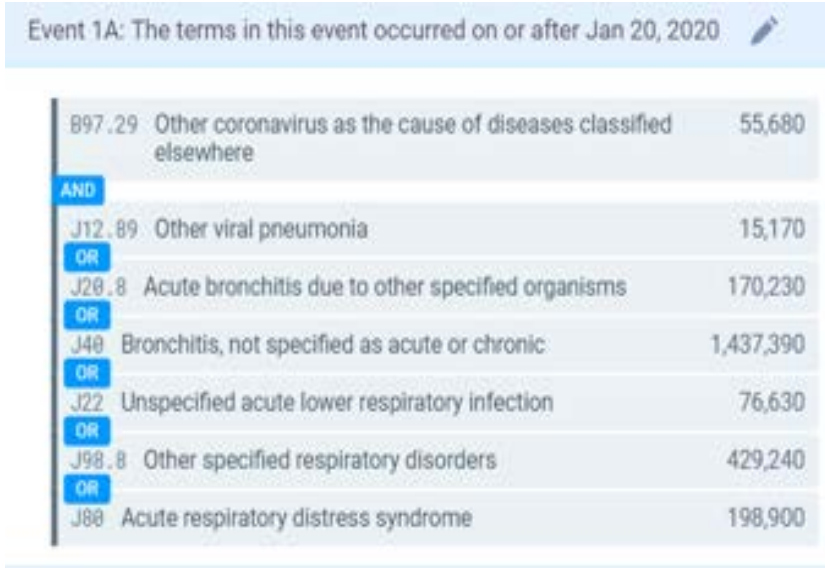
COVID-19 + HCQ/AZM Demographics: Top Prior Medications



COVID-19 + HCQ/AZM Demographics: CDC Definition



Using the more stringent CDC COVID-19 definition identified **120 COVID-19 + HCQ/AZM** patient out of **1,970 total COVID-19 patients**



Summary and Next Steps

- Among 5,370 COVID-19 patients in TriNetX, 180 patients were co-prescribed/co-administered HCQ-AZM (broad definition)
  - Majority of these patients were captured in March
  - Counts will increase as HCOs refresh their data
  - Data doesn't include all 50 states

- Next steps
  - Inpatient vs. outpatient setting
  - Co-administration/co-prescribing (not limited to COVID-19 cohort)


FDA
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ADMINISTRATION

Hydroxychloroquine and azithromycin use in fee-for-service Medicare plus preliminary data from the VA

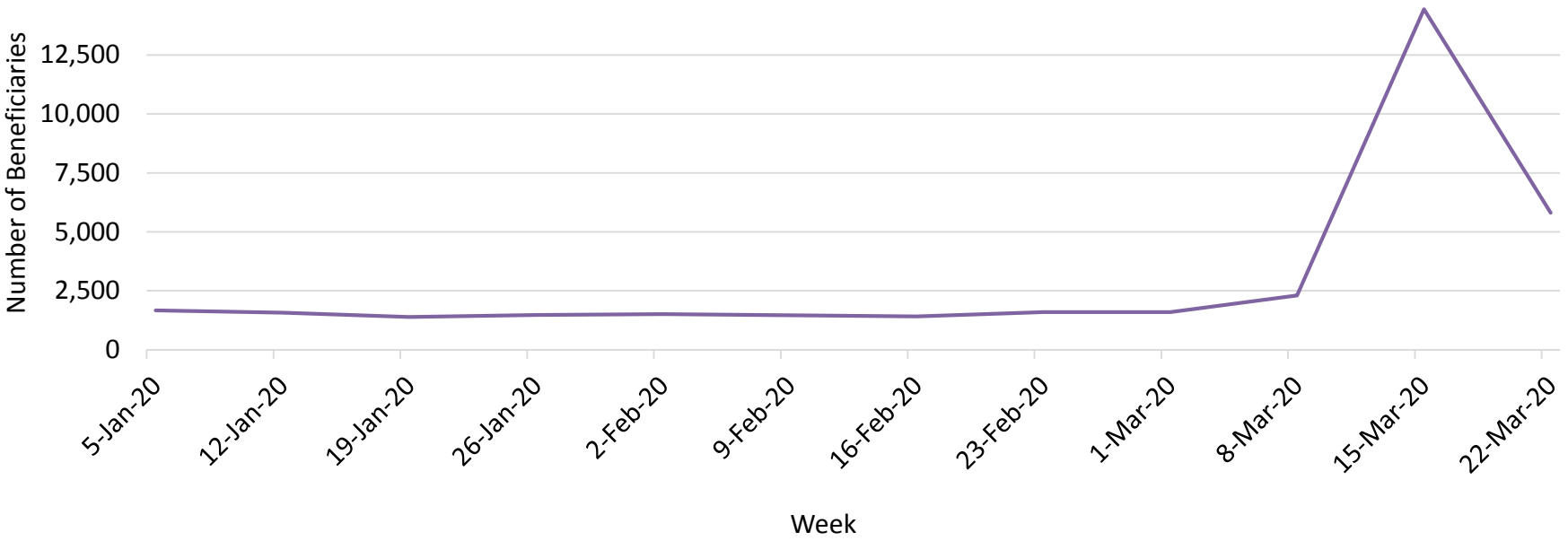
Office of Surveillance and Epidemiology

April 14, 2020

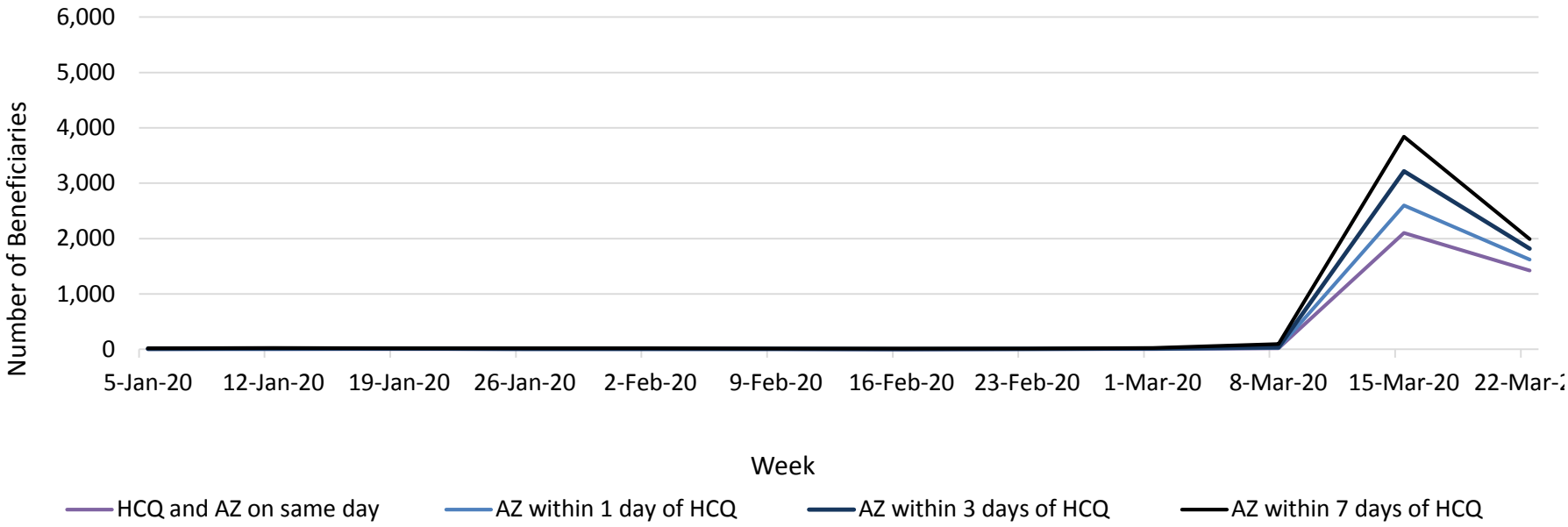
Methods

- Medicare beneficiaries enrolled in Parts A, B, D
- Rx claims through April 2, 2020
  - New users (incidence) required to have 183 days prior enrollment as an unexposed look-back period
  - All users (prevalence) required to be enrolled on the Rx date
- Concurrent use of HCQ and AZ defined as same-day Rxs, or AZ within ± 1, 3, or 7 days of HCQ
- Data from Mar 22-April 2 incomplete due to claims lag

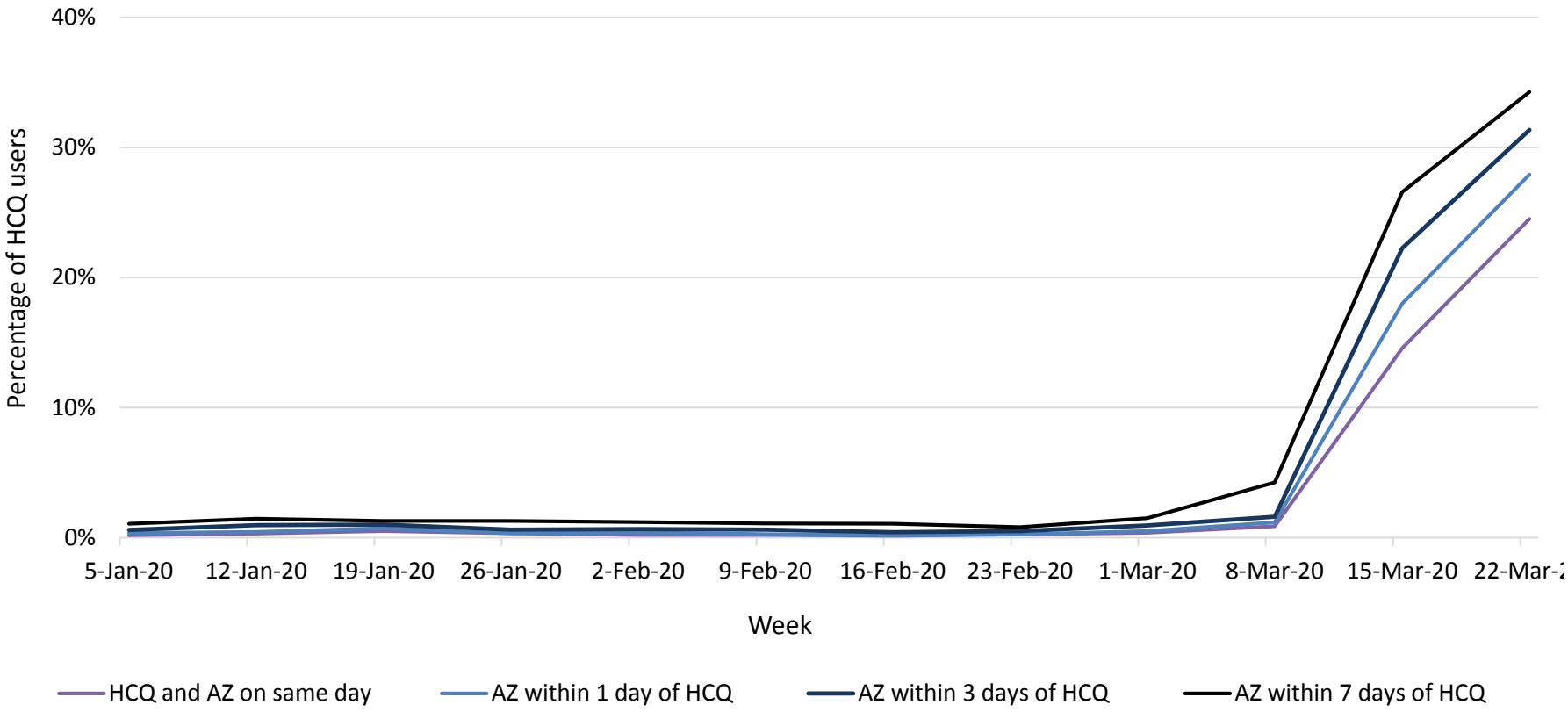
Number of new hydroxychloroquine users, by week, through April 2, 2020



Weekly number of new (incident) hydroxychloroquine and concurrent azithromycin users, through April 2, 2020



Percentage of new users of hydroxychloroquine with concurrent prescription for azithromycin, by week, through April 2, 2020



Azithromycin use in new users of hydroxychloroquine by week, using "same day" and "± 7 days" definitions for concurrent use

Week beginning:	Same day	± 7 days
15-Mar-20	15%	27%
22-Mar-20	24%	34%
29-Mar-20*	21%	31%

* Subject to substantial claims lag

Summary

- Low background use of HCQ in 2019 through early March 2020 (most with diagnosis of RA or SLE)
- Concurrent AZ use generally < 2% among new HCQ users in 2019 through early March 2020
- New HCQ use spiked during the week beginning March 15, 2020 as did use of concurrent AZ, with slight uptick in both during week beginning March 8
- From the week beginning March 15, 2020, the percentage of new users of HCQ with concurrent AZ ranged from 15%-24% using a “same-day” definition, to 27%-34% using a “within 7 days” definition of concurrency
- Absolute counts will increase once claims lag is accounted for

Hydroxychloroquine and azithromycin use within the VA, March 1 to April 10, 2020

	Inpatient	Outpatient
Total HCQ users	1414	5091
Covid-19 proxy*	1184 (84%)	1588 (31%)
HCQ alone	516 (44%)	1539 (97%)
HCQ + AZ ± 5 days	650 (55%)	27 (2%)
HCQ + AZ same day	601 (51%)	23 (1.5%)

* No diagnosis for RA, SLE, malaria from FY19-10Apr2020


FDA
U.S. FOOD & DRUG
ADMINISTRATION

ISMP (Institute for Safe Medication Practice)

- ISMP is issuing weekly special edition newsletters related to COVID-19 to highlight what's going on in the front line and provide links to FDA & CDC information. ISMP is well networked, with readership in the millions.
- Last week, ISMP wrote about a 70-year old female who experienced cardiac arrest on day 5 of taking hydroxychloroquine. The patient was previously on ceftriaxone and azithromycin, which were discontinued before starting hydroxychloroquine. Even though the patient did not receive azithromycin and hydroxychloroquine concomitantly, it was suspected that azithromycin was still at or near a therapeutic concentration when the patient started receiving hydroxychloroquine. The patient is expected to recover (addressed in attached ISMP Acute Care Newsletter, *Safety Alert*.)

FAERS Cases

- No hydroxychloroquine or chloroquine medication error reports received last week
- Our COVID-19 surveillance identified medication errors related to stay at home orders, including:
    - Missed doses and delayed therapy related to clinic closures
    - Pediatric exposures with kids staying at home (addressed in attached ISMP Consumer Newsletter, *Safe Medicine*.)
    - Extra dose or doses greater than recommended (e.g., Combivent 8 puffs daily)
    - Incorrect route (Flolan administered via nebulizer)

Potential for compounded hydroxychloroquine and chloroquine

- Compliance's Compounding Branch anticipate 503B outsourcing facilities may market tablets, oral solutions, and injections.

March/April 2020 ■ Volume 18 Issue 2

SPECIAL EDITION COVID-19

ISMP An ECRI Affiliate

SAFEMedicine®

Protect Yourself from Medication Errors

Advice from FDA

Do NOT take chloroquine phosphate intended for fish to treat COVID-19

The coronavirus (COVID-19) has overwhelmed the world at an alarming rate. Currently, there are no vaccines or medicines approved by the US Food and Drug Administration (FDA) that are proven effective against COVID-19. Recently, there have been some reports of medicines potentially having positive results against COVID-19. Two of these medicines are hydroxychloroquine and chloroquine, which are used to treat malaria, rheumatoid arthritis, and sometimes lupus. In any case, these medicines are not approved by FDA to treat COVID-19, and no one knows for sure if they are safe and effective against COVID-19. More research is needed before that can happen. However, hydroxychloroquine or chloroquine may be given to a person who has a diagnosis of COVID-19 only if a doctor orders it.

Unfortunately, there have been reports of people taking chloroquine phosphate, a chemical used to treat disease in aquarium fish. Some people mistakenly think chloroquine phosphate is the same as the medicine chloroquine that is used for humans. It is NOT. In fact, in one case, a man died after he and his wife took chloroquine phosphate used to treat their aquarium fish. His wife became critically ill.

Chemicals and drugs that are used to treat fish and other animals are not exactly the same as medicines that can be used for humans. Products marketed for veterinary use, or that are otherwise not for human consumption, have not been evaluated for safety and should never be used by humans. Specifically, chloroquine products sold for aquarium use have not been tested by FDA to show they are safe and effective for people. Bottom line—people should not take any chloroquine product unless it has been ordered by a doctor and is obtained through a pharmacy. Also, do not give chloroquine products to pets or livestock to prevent COVID-19. If you are concerned about the health of your animals, please contact your veterinarian.

Beware of fraudulent coronavirus tests, vaccines, and treatments

As many Americans "shelter at home" to try to slow the spread of the coronavirus (COVID-19), some may wonder if there are products they can use to diagnose, treat, cure, or prevent the virus from affecting them or their loved ones. Searching the internet for information about COVID-19 may lead to some accurate and helpful information (www.ismp.org/ext/411). But some sites advertise fraudulent products, including products claiming to be tests, medicines, vaccines, or supplements for COVID-19. Don't be fooled by these products!

continued on page 2 — **FDA:** Fraudulent tests, vaccines, treatments >

60 seconds SAFETY TIPS

■ **Use hand sanitizers safely.** Hand hygiene is the most important way to prevent the spread of germs. It is best to wash your hands with soap and lukewarm water for at least 20 seconds, especially after going to the bathroom, before preparing meals and eating, and after coughing, sneezing, or blowing your nose. Now, it is even more critical to wash your hands after being out in public (e.g., grocery shopping). But soap and water are not always readily available. So, what should you do?

During the COVID-19 crisis, the Centers for Disease Control and Prevention (CDC) recommends using an alcohol-based hand sanitizer when soap and water are not available. The hand sanitizer should contain at least 60% ethanol alcohol or 70% isopropyl alcohol. You can tell if the sanitizer contains at least 60% ethanol alcohol or 70% isopropyl alcohol by looking at the product label. But don't be fooled—we recently found on the internet one hand sanitizer advertised as "anti-bacterial disinfectant 75% alcohol portable gel" that actually contained only 20% of a 75% alcohol base. The other 80% was primarily water. This means the alcohol is even further "watered down" and will not be very effective.

According to CDC, laboratory data shows that 60% ethanol alcohol or 70% isopropyl alcohol, the ingredients in CDC-recommended hand sanitizers, inactivates viruses that are genetically and physically similar to the COVID-19 virus (www.ismp.org/ext/415). But adding alcohol to non-alcohol-based hand sanitizers is not effective. Consumers should not attempt to make their own hand sanitizer, as it may

continued on page 2 — **SAFETY TIPS** >

*Brand medicines appear in **green**; Generic medicines appear in **red***

Advice from FDA

> **FDA:** Fraudulent tests, vaccines, treatments — continued from page 1

First, the US Food and Drug Administration (FDA) is reporting that unauthorized fraudulent test kits are being marketed to test for COVID-19 in the home. At this time, FDA has not authorized any test kits for use in the home. However, FDA clearly sees the value in making safe and accurate test kits available, which may include home collection. The FDA is actively working with test developers on this.

Next, there are no current vaccines or medicines approved by FDA to prevent or treat COVID-19. In fact, COVID-19 has never been seen in humans before, which is why there are no FDA-approved medicines to treat the virus. FDA is working with vaccine and drug companies to develop these products as quickly as possible, but it takes time.

Fraudulent health claims, tests, and products can pose serious health risks by keeping people from seeking appropriate care or can delay necessary medical treatment. Unfortunately, some people and companies illegally market fraudulent products to try to profit from them during a crisis. In fact, FDA and the Federal Trade Commission recently issued warnings to 7 companies that were selling fraudulent COVID-19 products such as teas, essential oils, and tinctures to consumers.

Here's what you can do: First and foremost, if you can, stay home! Frequently wash your hands for at least 20 seconds with soap and lukewarm water. Hand sanitizer can also be used when necessary (see ***SAFETY TIP*** in right column, page 1). If you must go out, maintain social distancing by staying 6 feet away from others, and wear a cloth facemask covering your nose and mouth in public settings where social distancing is difficult (e.g., grocery store, pharmacy).

If you or a loved one have COVID-19 symptoms (e.g., fever, cough, shortness of breath), contact your doctor or healthcare provider. Your doctor or healthcare provider will advise you about whether you should get tested and the process for being tested with an appropriate test. If you or a loved one have symptoms, visit the Centers for Disease Control and Prevention (CDC) website for more information (www.ismp.org/ext/421).

Only visit reputable websites (see ***Worth visiting...*** on page 3) for the most accurate information about COVID-19. Be cautious of websites and stores selling products that claim to test, prevent, treat, or cure COVID-19. While false and misleading claims can seem especially appealing during a national crisis:

- You cannot test yourself in the home for COVID-19 at this time.
- "Miracle cures" that claim scientific breakthroughs are likely a hoax.
- Personal testimonials about products do not replace scientific evidence.

If you have a question about a treatment or test found online, talk to your healthcare provider or doctor. If you have a question about a medicine, call your pharmacist or the FDA. The FDA's Division of Drug Information (DDI) is available to answer almost any drug question by email (druginfo@fda.hhs.gov) and by phone (1-855-543-DRUG [3784] and 301-796-3400).

FDA You can find these articles (www.ismp.org/ext/410, www.ismp.org/ext/412, www.ismp.org/ext/413) and more on FDA's Consumer Health Information website at: www.ismp.org/ext/422. This website features the latest updates on medicines and products regulated by FDA. Sign up for a free email subscription at: www.ismp.org/ext/262.

60 SECONDS SAFETY TIPS — continued from page 1

not be effective. Some homemade products have also resulted in skin burns.

When using a hand sanitizer, it is important to read and follow the ***Drug Facts*** panel on the product label. To be most effective, the hand sanitizer should be rubbed all over your hands. Make sure to get it between your fingers and on the back of your hands. It is also important not to wipe or rinse off the hand sanitizer before it dries. Hand sanitizer is not effective if your hands are visibly dirty or greasy—wash dirty or greasy hands with soap and water instead. Children should use hand sanitizer only under adult supervision.

■ **Poisoning alert!** During the COVID-19 outbreak, hand sanitizers may be readily available in the home. Be sure to keep hand sanitizers up and away, and out of reach and sight of children. The pleasant smell and brightly colored bottles may be appealing to children. If a child drinks even a small amount of hand sanitizer, it can cause alcohol poisoning. Between 2011 and 2015, US poison control centers received nearly 85,000 calls about hand sanitizer poisonings among children.

Also, since many children are home from school during the COVID-19 outbreak, remember to store ALL medicines up and away and out of reach and sight of children. The US Food and Drug Administration (FDA), recently received a report about a child home from school who took two doses of his mother's medicine after finding it in a drawer. If a child takes unauthorized medicine or drinks hand sanitizer, call the **Poison Help** hotline at 1-800-222-1222.

■ **Keep up with childhood vaccinations when possible.** The COVID-19 outbreak continues to affect communities across the US differently. Some of the strategies used to slow the spread of disease include using telemedicine instead of face-to-face visits for routine medical care. The American Academy of Pediatrics (AAP) strongly supports well-child care and

continued on page 3 — ***SAFETY TIPS*** >

Worth visiting...

Many consumers have already bookmarked certain internet sites to help guide them to reliable information during the COVID-19 outbreak. The following websites should be included as primary resources because they provide the most accurate information about how to protect yourself and what to do if you become sick.

The Centers for Disease Control and Prevention (CDC)—COVID-19 (www.ismp.org/ext/411)

The CDC offers reliable information about the disease, symptoms, treatment, and slowing the spread of COVID-19. Highlights of the site include:

- An interactive self-checker to help consumers make decisions and seek appropriate medical care
- What to do if you are sick, including guidance on testing
- Precautions for all consumers to take to slow the spread of COVID-19
- Special precautions for older adults and people with underlying medical conditions
- Tips for daily life
- Guidance for keeping communities safe

The World Health Organization (WHO)—COVID-19 (www.ismp.org/ext/372)

The WHO offers a broad range of information about how COVID-19 is affecting the world. It has a section called *Public Advice,* which highlights two important topics:

- When and how to use masks
- Mythbusters: False information about how COVID-19 is spread and how it can be prevented

The state and federal US Department of Health & Human Services (HHS)—Coronavirus 2019 (COVID-19) Updates (www.ismp.org/ext/375)

HHS is the lead federal agency for the COVID-19 outbreak response in the US. This website is updated daily and includes news and tips for consumers to follow.

US Food and Drug Administration (FDA)—Coronavirus Disease 2019 (COVID-19) Frequently Asked Questions (FAQs) (www.ismp.org/ext/420)

This site includes FAQs on topics such as general information, vaccines, medicines, tests for COVID-19, food products, and pets. Examples include:

- What do I do if I get a rash or other reaction to hand sanitizer?
- Why aren't blood centers testing donors for SARS-CoV-2?
- I recently recovered from COVID-19, can I donate convalescent plasma?
- Is the US food supply safe?
- If my pet has been exposed to someone who has COVID-19, do they need to be quarantined?

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Report medication and vaccine errors to ISMP: Call 1-800-FAIL-SAF(E), or visit www.ismp.org/ext/87. ISMP guarantees the confidentiality of information received and respects the reporters' wishes regarding the level of detail included in publications.

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60 SECONDS SAFETY TIPS continued from page 2

keeping up with childhood vaccinations during the outbreak (www.ismp.org/ext/417). It is critical to maintain vaccination levels to prevent a resurgence of vaccine-preventable diseases in the future. However, AAP warns that the benefits of vaccinations and well-child care should be carefully balanced with the risk of exposure to COVID-19 in each community. Thus, some pediatricians may not be able to provide well-child visits and vaccinations for ALL patients in their practices.

Newborn care and vaccination of infants and young children through 24 months of age should continue when possible (www.ismp.org/ext/418). Vaccines can prevent certain diseases such as pneumonia, influenza (flu), pertussis, and measles (www.ismp.org/ext/419). Well visits and vaccinations may need to be rescheduled for older children and adolescents, unless they are being seen for another reason.

If you have an infant or child 24 months or younger who needs a well-child check-up and childhood vaccinations, call your pediatrician to see how this can be accomplished safely. For example, your pediatrician may:

- Schedule well-child visits in the morning and sick-child visits in the afternoon to keep sick children away from healthy children
- Separate well children and sick children in different areas of the clinic or office, or use different treatment rooms for the check-up
- Use one office location for only well-child visits, and another for sick-child visits (if multiple office sites)
- Use separate locations in the community for holding well-child visits

In some cases, parents may be able to conduct most of the well visit check-up via telemedicine (audio/video), and just bring the child into the office for a quick weight, height, brief physical, and vaccinations. This allows parents to minimize the time they spend in the pediatrician's office.

April 9, 2020 ■ Volume 25 Issue 7

SPECIAL EDITION COVID-19

ISMP An ECRI Affiliate

Acute Care ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

Planning for anticipated shortage of smart infusion pumps and dedicated administration sets

With the significant increase in the number of critically ill patients admitted to hospitals due to the coronavirus (COVID-19) pandemic, some organizations are already experiencing unprecedented shortages of smart infusion pumps and dedicated administration sets, while others are still anticipating such shortages. The following information is intended to support organizations that are considering various alternatives, including gravity flow of infusions, and careful allocation of smart infusion pumps for intravenous (IV) drug delivery for the patients most in need. Many of these alternatives might be unfamiliar to current staff, so the availability of just-in-time education and instruction manuals is key to avoid misuse.

Identify medications requiring smart pumps. The first step to smart infusion pump and administration set conservation is for hospitals to develop a list of medications that absolutely require delivery via smart infusion pumps, with an understanding that those not on the list may be administered using alternative means, if necessary, as described below. Medications to include on the list should be identified carefully by considering those on the *ISMP List of High-Alert Medications in Acute Care Settings* (www.ismp.org/node/103), and those on the organization's list of high-alert medications. The list will likely include at least IV infusions of vasopressors, antiarrhythmic agents, opioids, sedation and anesthetic agents, neuromuscular blocking agents, antithrombotics, and insulin. When developing the list of infusions that require administration via a smart infusion pump, also consider patient criteria, such as age, severity of illness, and comorbidities; infusion rate criteria, such as very low infusion rates; and vascular access criteria (e.g., central lines).

Take inventory of all available pumps. In addition to smart infusion pumps used in typical patient care units, some pumps may be located "off the beaten path," both on- and off-site, in settings such as interventional radiology, perioperative areas, ambulatory care/procedural areas, and surgery centers. Don't forget to take inventory of syringe pumps, including those unused in anesthesia supplies due to postponement of elective procedures. Syringe pumps might be used to administer small volume medications; however, clinical staff may require training if unfamiliar with syringe pumps, some of

continued on page 2 — Shortage of smart pumps >

Patient taking hydroxychloroquine right after discontinuing azithromycin develops QTc prolongation and cardiac arrest

Problem: A 70-year-old woman with a history of non-Hodgkin lymphoma, chronic obstructive pulmonary disease (COPD), adrenal insufficiency, and hypertension was hospitalized with a cough and shortness of breath. She was initially treated for community-acquired pneumonia with oral azithromycin, 500 mg on day 1, followed by 250 mg daily for 4 days, along with cef**TRIAX**one 1 g intravenous (IV) every 24 hours. She was tested for COVID-19 and confirmed to be positive. One day after azithromycin and cef**TRIAX**one were discontinued, the patient was started on oral hydroxychloroquine 400 mg twice daily on day 1, followed by 400 mg daily for 4 days.

continued on bottom of page 3— QTc prolongation >

HEALTHCARE WORKERS ARE OUR HEROES

Our hearts, thoughts, and prayers continue to go out to the courageous healthcare workers who are selflessly serving on the frontlines of the COVID-19 public health emergency, risking their own safety in the service of others. We are truly grateful for your unyielding compassion for patients and their families, and for the power and grace you display daily despite coping with unspeakable tragedies and unimaginable exhaustion in this battle against COVID-19. From all of us at ISMP, we sincerely thank every one of you for all that you do.

"You treat a disease, you win, you lose. You treat a person, I guarantee you, you'll win, no matter what the outcome."
Patch Adams

COVID-19 *Collaboration*

Suspending independent double checks

A need to conserve personal protective equipment (PPE) has led to consideration of suspending or modifying independent double checks at the bedside prior to administration of high-alert medications to COVID-19 positive or presumptive positive patients. Abandoning independent double checks and making sweeping changes to the requirements to document the check in electronic health records (EHRs) compromises patient safety and can lead to unsafe practice habits in the future. Most organizations contributing to dialogue about this challenge are not abandoning all independent double checks but are establishing ways to conduct critical parts of independent double checks without entering a patient's room. Thus, the hard stop in EHRs requiring dual documentation of verification before proceeding now reflects only the components of the check that can be accomplished outside the patient's room. In a

continued on page 2 — *Collaboration* >

> Shortage of smart pumps — continued from page 1

which require the use of validated syringes and volumes, as well as specific processes for priming administration sets. Some facilities may still have older, general purpose pumps without a drug library, particularly in outpatient locations, that may be considered for use. If it is necessary to obtain additional pumps, it is best to buy or rent the same models currently used; however, pumps from other manufacturers might need to be considered, along with plans to limit the locations where the different pumps are used. Biomedical staff should be consulted if introducing pumps that are not already in mainstream use (e.g., for calibration prior to use), and instruction manuals should be available for all pumps in use on a shared online site for easy access by staff.

IV to oral (or IM) conversion. Organizations should switch patients from IV to oral therapies as soon as possible. This should be considered for all appropriate patients who can swallow and meet other facility-defined criteria (e.g., no fever), including patients in the emergency department (ED) and long-term care facilities associated with the health system. If oral administration is not possible, another option might be intramuscular (IM) injections instead of IV administration for certain medications.

Use IV push instead of infusions. Administering medications via IV push instead of as a secondary infusion should also be considered when appropriate. Hospital-specific IV push guidelines, along with the *ISMP Safe Practice Guidelines for Adult IV Push Medications* (www.ismp.org/node/97), should be consulted before considering this alternative. To support IV push administration, prefilled and/or ready-to-administer syringes of medications should be dispensed whenever possible; nurses should dilute the syringe contents only when necessary according to hospital policy or the product labeling. Also, it would be helpful for pharmacy staff to indicate how fast to administer the drug (e.g., "give over 3 minutes") on the pharmacy label (if space permits) and on the medication administration record (MAR). Those administering IV push medications should also be cautioned about inadvertent bolus injections when flushing the line, particularly with extension sets or when the port closest to the patient cannot be used for IV push administration. The timing of actual medication administration to the patient must be considered when administering IV push medications through extension sets.

Administration set change policy. Another item that should be reviewed is the hospital's current administration set change policy. The Infusion Nurses Society (INS) *Frequently Asked Questions Related to COVID-19 Health Care Challenges* notes that, primary and secondary administration sets used for continuous infusions (other than lipids, blood, or blood products) should be changed no more frequently than every 96 hours (www.ismp.org/ext/405). According to the Centers for Disease Control and Prevention (CDC), this may be extended, as long as the administration set is changed at least every 7 days (www.ismp.org/ext/406). However, tubing used to administer propofol infusions should be replaced every 6 or 12 hours, when the vial is changed, per the manufacturer's recommendation. Extension sets are "add-on devices," so precautions must be taken to limit the potential for contamination and misconnection.

Potential role for gravity infusions. Readers may recall a time when IV medications and solutions were administered by gravity infusion. With an anticipated infusion pump shortage, it is now time to again consider gravity administration of certain infusions. Examples may include IV hydration, some IV antibiotics, medications that are not high-alert, and others that might be appropriate for gravity infusion upon assessment during the ordering and dispensing process. To gauge the rate of flow in mL/hour for gravity infusions, it is necessary to know how many drops per mL the administration set delivers (e.g., 10, 15, 20, 60 drops per mL). The number of drops delivered is controlled by the roller clamp (gravity flow control clamp). In last week's newsletter (www.ismp.org/node/15321), a **Table** from B. Braun was included to help nurses count the number of drops of fluid needed for the required flow rate (mL/hour) using sets delivering varying drops per mL. This same **Table** is included on **page 5**.

continued on page 3 — Shortage of smart pumps >

COVID-19 *Collaboration* cont'd from pg 1

hospital where infusion pumps remain in the patient's room, the nurse who enters the room takes a picture of the pump screen using a mobile phone device left in the room, and sends the picture to a nurse outside the room via a secure messaging system. This allows most components of the independent double check to occur.

Independent double checks should be used judiciously for only the most vulnerable high-alert medications—not for all high-alert medications (www.ismp.org/node/12490). ISMP recommends first evaluating your requirements for independent double checks to see if you can narrow their use to just a few of the most vulnerable high-alert medications. Fewer independent double checks strategically placed at the most vulnerable points of the medication use process will be more effective than an overabundance of independent double checks. For example, one hospital reported that independent double checks for subcutaneous insulin have been suspended for all except U-500 insulin, and the dual signoff in the EHR for subcutaneous insulin has been disabled. For any independent double checks suspended during the pandemic, ensure you are also using other higher leverage strategies (e.g., use of barriers, computer alerts with hard stops, standardization, barcode scanning) to prevent or detect errors.

Keep in mind that video conferencing technologies may allow independent double checks to be conducted virtually, particularly in the pharmacy. For example, a pharmacist verifying orders at home and a pharmacist working at the hospital may be able to provide independent double checks for each other. Video conferencing or the use of digital images in intravenous (IV) workflow systems may also be useful for pharmacy technicians during sterile production. If this technology reduces the number of people in the cleanroom, it will also reduce the need for PPE. Before initiating video conferencing, check with information technology staff to see if your organization requires a secure system for such activities.

Capturing COVID-19 adverse events

One health system shared that it has added a question to its online event reporting system, "Is this event related to COVID-19 (coro-

continued on page 3 — *Collaboration* >

> Shortage of smart pumps — continued from page 2

Tubing with integrated dial-calibrated IV flow rate regulators (e.g., **RATE FLOW** regulator, **DIAL-A-FLOW**) can be used to regulate the flow rate instead of the roller clamp. Add-on regulators are also available (www.ismp.org/ext/407). Although these devices make it easier to set the flow rate by dialing the mL/hour, they are only marginally more accurate, providing just an estimate of the flow rate based on compression of the tubing. Even when these flow regulators are used, staff still need to count the number of drops and adjust the flow rate as necessary.

A time tape should be affixed along the vertical edge of the infusion bag (**page 5**) to assist in visual checking of the total volume infused at a given time. Practitioners should be reminded that gravity flow rates may be influenced by a number of factors, including the bag height, type of IV access, position of the patient's arm, and length of the tubing.

Subcutaneous infusions. Subcutaneous gravity infusions may be an option for parenteral delivery of medications and solutions for some patients. This is mainly appropriate for hydration in locations such as the ED, urgent care, long-term care, and other non-acute care settings where patients do not require rapid fluid administration in large amounts. Subcutaneous infusions may be considered for certain drug infusions, such as potassium chloride replacement administered in hydration fluids. Up to 3,000 mL per day (1 mL per minute via two administration sites) has been given using this technique, also known as hypodermoclysis (Humphrey P. Hypodermoclysis: an alternative to i.v. infusion therapy. *Nursing 2011*. 2011;41[11]:16-7; www.ismp.org/ext/408). The upper arms, chest, abdomen, and thighs have been used as sites. Hyaluronidase can be used in conjunction with this method, given locally or via a Y-connector, to increase the rate of absorption from subcutaneous tissue. Subcutaneous infusions are contraindicated in patients at increased risk of pulmonary congestion or edema, and in patients with clotting disorders.

Other alternatives. Other alternative types of infusion devices should be considered during infusion pump shortages, such as volumetric burette tubing (e.g., **BURETROL**, **SOLUSET**), elastomeric devices, and other non-electronic rate controllers.

ISMP greatly appreciates the support of Shawn O'Connell, RN, MS, Director, Medical Affairs, from the B. Braun Corporation, for outlining and assisting in the development of this article.

> QTc prolongation — continued from page 1

In our March 26, 2020, Special Edition newsletter (www.ismp.org/node/14917), we warned about the risk of QTc prolongation and ventricular arrhythmias in patients who take hydroxychloroquine (or chloroquine) and azithromycin together. At that time, we noted that electrocardiogram (ECG) monitoring was imperative.

On admission to the hospital, this patient's ECG showed a QTcB interval (a heart rate-corrected QT interval using Bazett's formula) of 460 milliseconds (ms). A prolonged QTc increases the risk of developing ventricular arrhythmias, including torsades de pointes and fatal ventricular fibrillation. A borderline QTc for women is between 451-470 ms, and an abnormally long QTc is above 470 ms. The day oral hydroxychloroquine was started, the patient's ECG showed a QTcB of 490 ms. Three days later, the patient's QTcB was 515 ms. On the fifth and last day of taking hydroxychloroquine, the patient experienced ventricular fibrillation and coded. After two cycles of cardiopulmonary resuscitation, a return of spontaneous circulation was achieved. An ECG performed afterwards showed a QTcB of 605 ms, and all QTc-prolonging medications (www.ismp.org/ext/428) were discontinued. Initially, the patient was not responding neurologically. However, after undergoing targeted temperature management (therapeutic hypothermia) post-arrest, the patient now appears to be responding and is expected to recover with good neurological function.

continued on page 4 — QTc prolongation >

COVID-19 Collaboration cont'd from pg 2

navirus)?" to help centralize these events, allow rapid analysis of quickly emerging risks, and reduce leadership's reaction time with knowing about and addressing these issues. A weekly summary is being provided to the leadership command center. Several Patient Safety Organizations (PSOs) have also noted that their reporting systems include a mechanism to indicate if an incident is related to COVID-19. Although the number of reported COVID-19 events to PSOs is low, most are associated with communication breakdowns, largely in emergency departments and during transitions of care, or pressure injuries from positioning COVID-19 patients in the prone position.

Flagging adverse events associated with COVID-19 also makes it easier to pass on relevant information, in confidence, to ISMP and the US Food and Drug Administration (FDA). **Please remember to report COVID-19-related challenges, ideas, and preventable adverse events to ISMP** via email (ismpinfo@ismp.org), phone (215-947-7797), or online at: www.ismp.org/MERP, so we can share these risks and strategies in our newsletters as well as with FDA.

Code team and carts

When a patient has a cardio-respiratory arrest, the typical scenario is to bring the entire code team and code cart to the patient's bedside. However, to minimize practitioner exposure to COVID-19, conserve PPE, and reduce the risk of code cart surface contamination, code carts and some code team members, including pharmacists, are now remaining outside the room when a presumptive or confirmed COVID-19 patient suffers a cardio-respiratory arrest. One hospital reported that pharmacists pass medications from the code cart into the patient's room as needed. Several other hospitals created a "grab bag" or "starter kit" to bring into the room with enough medications (e.g., EPINEPHrine, calcium chloride, sodium bicarbonate, 10% dextrose and water, prefilled saline flush solutions) and equipment to begin resuscitation. Some practitioners reported that a mobile work phone, typically left in COVID-19 isolation rooms for communication, is used during codes to communicate with code team members (e.g., pharmacists) who remain outside the patient's room. "Grab bags" and "starter kits" used for suspected or con-

continued on page 4 — Collaboration >

> QTc prolongation — continued from page 3

The hospital determined that the patient suffered ventricular fibrillation and cardiac arrest due to QTc prolongation from the combination of hydroxychloroquine and azithromycin. Even though the patient did not receive azithromycin and hydroxychloroquine concomitantly, given the long half-life of azithromycin (68 to 72 hours in adults), it was suspected that azithromycin was still at or near a therapeutic concentration when the patient started receiving hydroxychloroquine.

Safe Practice Recommendations: This adverse event reinforces our recent newsletter reminder for ECG monitoring of all patients who receive these medications in combination (or close together). The hospital where this event occurred now requires monitoring of all patients taking these medications via continuous telemetry and a daily 12-lead ECG at baseline and while therapy continues. The hospital also noted that the event clearly showed the need to act on increasingly prolonged QTc intervals. In fact, hospitals should consider whether azithromycin and hydroxychloroquine should be administered, either separately or concurrently, to patients with a baseline QTc elevated above 450 ms (men) or 470 ms (women), as both drugs (also chloroquine) may prolong the QT interval.

Keep in mind that azithromycin has a half-life up to 72 hours, hydroxychloroquine up to 40 days, and chloroquine up to 5 days. So, discontinuing one drug and starting another too soon may result in a similar adverse event. Also, remember that elderly patients with other serious underlying conditions, who are already vulnerable to complications from COVID-19, may be at higher risk for cardiac and hepatic side effects from these agents.

Worth visiting...

IBM Micromedex and DynaMed COVID-19 Resource Catalog (www.ismp.org/ext/389)

IBM Micromedex and DynaMed are providing FREE public access to their referential database for medication information as well as their peer reviewed clinical content, including systematic literature reviews in 28 specialties for comprehensive disease topics, health conditions, and abnormal findings. Users will be able to access drug monographs, drug consults, disease monographs, and patient education materials.

National Institutes of Health (NIH) (www.ismp.org/ext/423)

Get the latest information about research underway to study and address the COVID-19 viral threat, including more than 300 clinical trials studying symptoms, testing, possible vaccines, and possible treatments (e.g., remdesivir, chloroquine, hydroxychloroquine).

The Society of Infectious Diseases Pharmacists (SIDP) (www.ismp.org/ext/398)

SIDP has developed a series of YouTube videos on medications considered for treating patients with COVID-19, including remdesivir, chloroquine and hydroxychloroquine; lopinavir and ritonavir; ribavirin; tocilizumab; and angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs).

National Association of Boards of Pharmacy (NABP)—NABP Passport (www.ismp.org/ext/425)

NABP Passport is a temporary authorization that facilitates pharmacists and pharmacy technicians practicing in another state. The program, developed in response to COVID-19, allows states to efficiently grant temporary or emergency licensure. License verifications for NABP Passport are conducted at no cost to the applicant or the boards of pharmacy. NABP monitors emergency declarations and updates the status of each COVID-19 authorization accordingly. To date, 18 states recognize NABP Passport.

COVID-19 *Collaboration* cont'd from pg 3

firmed COVID-19 patients are then cleaned according to facility-established guidelines.

Remember that masks and other PPE often make communication more difficult. During all codes, always use repeat back to confirm all drug and dose choices.

Announcements

Healthcare worker memorial

As frontline healthcare workers care for patients with COVID-19, they commit themselves to difficult, draining work, and put themselves at risk of infection. Tragically, hundreds of healthcare workers throughout the world have died. *Medscape*, an online global destination for medical news and expert perspectives, has started a list of our fallen colleagues (www.ismp.org/ext/403) to make sure they are not forgotten. The publication is asking for help in, sadly, updating the list as needed. Please submit the names of healthcare workers who have died after contracting COVID-19 by visiting: www.ismp.org/ext/404.

FREE access to IHI Open School courses

The Institute for Healthcare Improvement (IHI) is providing FREE access through May 31 to numerous Open School courses associated with improvement capability, patient safety, leadership and teamwork, person- and family-centered care, and the design of educational experiences (educator's toolkit). These modules also offer a total of 9.75 continuing education credits. For details, visit: www.ismp.org/ext/409.

To subscribe: www.ismp.org/node/10

ISMP An ECRI Affiliate

ISMP Medication *Safety Alert!* Acute Care (ISSN 1550-6312)

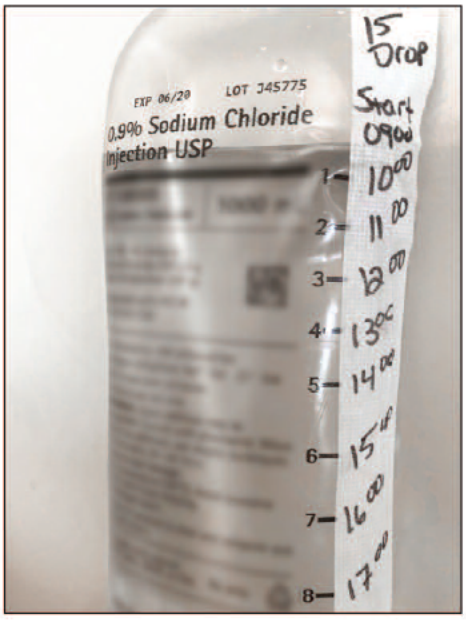
Report medication and vaccine errors to ISMP: Call 1-800-FAIL-SAF(E), or visit: www.ismp.org/MERP or www.ismp.org/VERP. ISMP guarantees the confidentiality of information received and respects the reporters' wishes regarding the level of detail included in publications.

B BRAUN
SHARING EXPERTISE

GRAVITY FLOW RATE DRIP CHART

Flow Rate (mL/hr)	**10** drops =1 mL (drops/min)	**15** drops =1 mL (drops/min)	**20** drops =1 mL (drops/min)	**60** drops =1 mL (drops/min)
10	2	2	3	10
25	4	6	8	25
50	8	12	17	50
75	12	19	25	75
100	17	25	33	100
125	21	31	42	125
150	25	37	50	150
200	33	50	67	200
250	42	62	83	250
500	83	125	167	500
1,000	167	250	333	1,000

- Confirm tubing set drip rate on set package, i.e., 10, 15, 20, or 60 drops/mL
- Recommended that all gravity infusion bags be time taped for additional flow confirmation
- Alterations of bag height distance to patient will affect flow rate



TSI Classification Memo

Memorandum: TSI Classification
Division of Anti-Infective Products
Office of Infectious Diseases

Date of Memorandum: 04/10/2020
Safety Issue Name: Risk of cardiac toxicity with hydroxychloroquine (or chloroquine) with or without azithromycin when used for the treatment of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.
Tracked Safety Issue Number: 2150
Responsible Organization: Division of Anti-infectives
Safety Cross Discipline Team Leader: Elizabeth O'Shaughnessy, MD **(Safety CDTL)**

Initial classification category	Emergency □	Priority X	Standard □
(Category identified when TSI was created)			
Most recent classification category	Emergency □	Priority □	Standard □
New classification category	Emergency □	Priority □	Standard □

Relevant classification factors (check all that apply):

Hazard assessment:

X Relative seriousness of the safety issue
□ Estimated size of the population exposed to the risk of the drug
□ Suspected frequency of harm to patients exposed to risk from the drug

Modulating factors:

□ Context of use – availability and risk profiles of therapeutic alternatives
X Context of use – Risks posed to vulnerable populations
X Context of use – Clinical setting in which the drug is used
□ Quality of the data suggesting the risk
X Biologic plausibility

Briefly describe the basis for the new TSI classification category, specifying how the classification factors were applied:

The safety issue is the potential risk of cardiac toxicity, i.e., QTc prolongation or other cardiac conduction disorders, cardiomyopathy, and cardiac death, associated with the combination of hydroxychloroquine (or chloroquine) plus azithromycin or hydroxychloroquine (or chloroquine) monotherapy for the investigational treatment of patients with COVID-19 caused by SARS-CoV-2 infection.

Signatory Authority: OND SRPM

Hydroxychloroquine plus azithromycin or hydroxychloroquine monotherapy are being used worldwide among many investigational treatments for COVID-19. The magnitude of the effect of the combination of these drugs on QT interval or arrhythmia risk has not been well studied and the optimal dosing and duration of treatment for COVID-19 is unknown. Hydroxychloroquine and chloroquine appear to be relatively safe when used as monotherapy at the recommended doses for labeled indications in autoimmune disorders (lupus erythematosus and rheumatoid arthritis) and malaria; however, in those studies of COVID-19 that have reported more detailed results, hydroxychloroquine was proposed at higher doses than used in the treatment of autoimmune disorders and with azithromycin.[1]

In a large meta-analysis of users of hydroxychloroquine, short-term hydroxychloroquine treatment was considered relatively safe, but an increased risk of 30-day cardiovascular mortality was observed when azithromycin was added to hydroxychloroquine.[2]

QTc prolongation and other cardiac adverse effects in patients with COVID-19 treated with hydroxychloroquine plus azithromycin have been recently reported in the medical literature. Increases in the QT interval was reported in 84 patients with COVID-19 treated with hydroxychloroquine plus azithromycin at a single center in the US.[3] In 11% of these patients, the QTc increased to >500ms which is a known risk for arrhythmia and sudden cardiac death. There were no episodes of torsades de pointes or cardiac arrest. The development of acute renal failure, not baseline QTc, was reported as a strong predictor of QTc prolongation in the patients in the study.

A French pharmacovigilance database reported 43 cases of cardiac adverse effects in patients treated with hydroxychloroquine alone or in combination (in particular with azithromycin) for COVID-19.[4]

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[1] Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and Azithromycin as a treatment of COVID-19: preliminary results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020 Mar 20:105949. doi: 10.1016/j.ijantimicag.2020.105949.

[2] Jennifer C.E. Lane, James Weaver, Kristin Kostka, et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study. medRxiv (preprint, not peer reviewed), April 10, 2020; https://doi.org/10.1101/2020.04.08.20054551

[3] Chorin E, Dai M, Shulman E, et al. The QT Interval in Patients with SARS-CoV-2 Infection Treated with Hydroxychloroquine/Azithromycin. medRxiv (preprint, not peer reviewed), April 3, 2020; https://doi.org/10.1101/2020.04.02.20047050

[4] Agence Nationale de Sécurité du Médicament et des Produits de Santé. Medicines used in patients with COVID-19: enhanced surveillance for adverse effects – Information Point. Press Release April 10, 2020

Signatory Authority: OND SRPM

Ventricular fibrillation and non-fatal cardiac arrest associated with QTc prolongation was reported in an elderly patient with multiple comorbidities who received hydroxychloroquine and azithromycin for COVID-19.[5]

The number of patients being treated with hydroxychloroquine plus azithromycin or hydroxychloroquine monotherapy is likely to increase as COVID-19 cases increase worldwide. Patients with comorbidities such cardiac disease and renal insufficiency are likely to be at increased risk of cardiac adverse effects of hydroxychloroquine (or chloroquine) plus azithromycin or hydroxychloroquine (or chloroquine) alone.

There is biological plausibility for a cardiac safety risk as hydroxychloroquine (or chloroquine) and azithromycin are independently associated with QT interval prolongation, torsades de pointes, and sudden cardiac death. Life-threatening and fatal cardiomyopathy are associated with hydroxychloroquine (or chloroquine). Cardiac adverse effects, including QT prolongation and cardiomyopathy is in the Warnings section of the labeling for hydroxycholoroquine (and chloroquine), and QT prolongation is in the Warnings and Precautions of the labeling for azithromycin.

The cardiac safety of hydroxychloroquine (or chloroquine) plus azithromycin or hydroxychloroquine (or chloroquine) monotherapy in patients with COVID-19 warrants ongoing monitoring and will be evaluated in collaboration with the Office of Surveillance and Epidemiology (OSE). The Division of Anti-Virals (DAV) and the Division of Rheumatology and Transplant Medicine (DRTM) collaborated with the Division of Anti-Infectives (DAI) in opening this TSI.

[5] ISMP Medication Safety Alert. April 9, 2020, Volume 25, Issue 7.

Signatory Authority: OND SRPM

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FARIBA IZADI
04/14/2020 09:45:48 AM

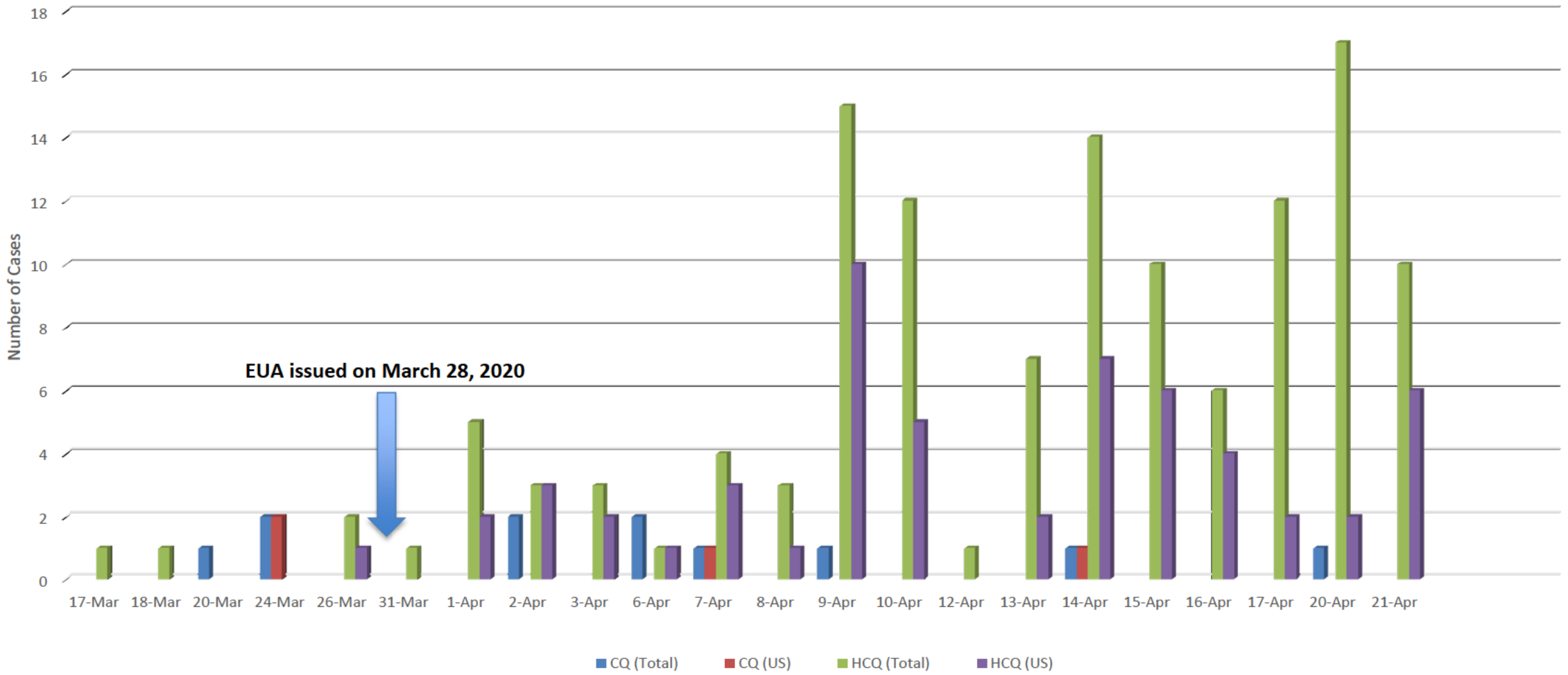
Hydroxychloroquine (HCQ) and Chloroquine (CQ) Safety Overview in the Setting of COVID-19

April 24, 2020

DPV Surveillance Activities

- FAERS: Daily monitoring for cases of adverse events associated with any product reportedly used for the prevention or treatment of COVID-19
  - Additional daily query specifically for HCQ and CQ
- Literature: Daily review of Embase Alerts for specific products and weekly review of PubMed Early alerts for COVID-19 and safety related (non-case report) articles
- NPDS: Daily surveillance query for any exposure calls related to HCQ and CQ
- CureID: Daily monitoring for relevant COVID-19 related case reports or literature

Reporting Trend of HCQ and CQ cases (all data sources)



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Most Frequently Reported PTs in FAERS

Event-Preferred Terms(PTs)	Percent of Total
OFF LABEL USE	30.0
ELECTROCARDIOGRAM QT PROLONGED	14.7
HEPATITIS	10.7
CORONA VIRUS INFECTION	7.3
CONDITION AGGRAVATED	6.7
HEPATOCELLULAR INJURY	5.3
SUDDEN DEATH	5.3
ACUTE KIDNEY INJURY	4.7
ACUTE RESPIRATORY DISTRESS SYNDROME	4.7
DRUG INTERACTION	4.0
RESPIRATORY FAILURE	4.0
TRANSAMINASES INCREASED	4.0
CARDIAC ARREST	3.3
DIARRHOEA	3.3
HAEMOGLOBIN DECREASED	3.3
HEPATITIS ACUTE	3.3
MALAISE	3.3
PNEUMONIA	3.3
VENTRICULAR TACHYCARDIA	3.3
ACUTE RESPIRATORY FAILURE	2.7
ALANINE AMINOTRANSFERASE INCREASED	2.7
CORONAVIRUS TEST POSITIVE	2.7
DYSPNOEA	2.7
MULTIPLE ORGAN DYSFUNCTION SYNDROME	2.7
OXYGEN SATURATION DECREASED	2.7
PRODUCT USE IN UNAPPROVED INDICATION	2.7
PULMONARY EMBOLISM	2.7
VENTRICULAR FIBRILLATION	2.7

- Majority of PTs are either:
  - Known and labeled events for HCQ/CQ and/or primary concomitant medications (azithromycin, lopinavir/ritonavir)
    - Cardiac-related terms
    - Hepatic-related terms
  - Known effects of COVID-19
    - Respiratory-related terms
    - Hepatic-related terms
    - Pulmonary embolism
- PTs are consistent with the AEs reported in cases from other data sources (literature, NPDS)

Hydroxychloroquine and Chloroquine Cases Reporting Adverse Events in the Setting of COVID-19 (n=161)

	HCQ (n=149) †	CQ (n=12)
Source ‡		
FAERS (December 1, 2019 through April 21, 2020)	130	10
Literature (January 1, 2020 through April 21, 2020)§	7	0
NPDS (March 24, 2020 through April 21, 2020)	8	2
Non IND Study Report	4	0
Sex	(n=141)	(n=12)
Male	97	7
Female	44	5
Age (years)	(n=136)	(n=11)
Range	18-95	38-83
Median	63	64
Mean	60	61
Country of Origin		
US	60	4
Foreign	89	8

† One case referred to "hydrochloroquine." This was likely referring to hydroxychloroquine and was therefore counted in this group.
‡ FAERS – includes any case identified in either FAERS alone or both FAERS and literature or both FAERS and in an IND safety report. Literature – includes cases only identified in the literature. IND safety report – includes only cases identified in an IND safety report.
§ Literature search strategy for identification of case reports involving adverse event(s) and COVID-19 treatment: Embase search for "remdesivir," "favipiravir," "lopinavir/ritonavir," "tocilizumab," "sarilumab," "hydroxychloroquine," and "chloroquine" from January 1, 2020 - April 21, 2020. PubMed Early Alerts for COVID19 have also been reviewed from March 15, 2020 - April 16, 2020.

- Data Sources
  - Predominately from FAERS (n=130)
    - Direct reports (n=27)
    - EUA report (n=1)
  - US Poison Center Control and medical literature add to the totality of the data, methemoglobinemia fatal cases (n=2) identified in National Poison Data System
  - No safety reports directly under the IND for HCQ treatment in setting for COVID-19 as of yet
- US reporting represents ~40% of data
- Reporting in males >> females
- Median and mean age ~60-64 years

HCQ/CQ Dosage in all patients n= 116 (47 US)

Reported Dosage	N=116
400 mg/day	51
600 mg/day	10
800 mg/day x1 day, then 400 mg/day	10
800 mg/day	7
200 mg/day	5
800 mg	3
1 teaspoon of powder	2
400 mg BID x 1 day, 200 mg BID x 4 days	2
Miscellaneous*	26
Unknown	35

*One case each reported doses ranging from 100mg to 2000mg

- Most frequently reported dose 400mg/day
  - ~66% (77/116) report QT prolonging medicine, including ~40% (46/116) with azithromycin
  - COVID-19 use: Treatment (n=87), prophylaxis (n=4), unknown (n=25)
- HCQ maximum doses for FDA approved indications:
  - Rheumatoid Arthritis: 600 mg daily (maintenance in adults)
  - Lupus: 400mg daily
  - Malaria: 400mg weekly (prophylaxis) and 400 mg, at 6 hours, 24 hours and 48 hours after the initial dose (treatment).

Hydroxychloroquine and Chloroquine Cases Reporting Serious Non-Cardiac Adverse Events in the Setting of COVID-19*

	HCQ	CQ
Serious Non-Cardiac AEs of Interest (Labeled for HCQ/CQ)[‖]	**(n=36)**	**(n=5)**
Psychiatric Disorders	(n=1)	(n=0)
Hallucinations/psychosis	1	0
Blood and Lymphatic System Disorders	(n=6)	(n=0)
Hemolytic anemia/G6PD deficiency related issues	0	0
Pancytopenia/thrombocytopenia/anemia/leukopenia	6	0
Hepatobiliary Disorders	(n=28)	(n=4)
Hepatitis/increased liver enzymes/hyperbilirubinemia	28	4
Nervous System Disorders	(n=0)	(n=1)
Seizure	0	1
Endocrine Disorders	(n=1)	(n=0)
Hypoglycemia	1	0
Immune System Disorders	(n=1)	(n=0)
Exacerbation of psoriasis	1	0
Serious Unlabeled Non-Cardiac AEs[‖]	**(n=10)**	**(n=2)**
Methemoglobinemia	2	0
Hypokalemia	3	1
Hyponatremia	1	0
Oropharyngeal edema	1	0
Acute kidney injury	3	1
Hyperglycemia	1	0
Non-Cardiac Fatal Cases	29	0

* Data through April 21, 2020

[‖] A case may have reported more than one AE. The FDA reviewer assessed the reported AEs were probably/possibly associated with HCQ or CQ use.

- Labeled events
  - Majority are in the Hepatobiliary Disorders SOC
  - COVID-19 is associated with hepatobiliary issues
- Unlabeled events
  - Hypokalemia and hyponatremia primarily reported in cases of QT prolongation
  - Acute Kidney Injury has been shown in COVID-19 patients with more severe disease
  - Methemoglobinemia – both cases were fatal and reported in NPDS- actively monitoring

HCQ and CQ Cases Reporting Serious Cardiac Adverse Events

Hydroxychloroquine and Chloroquine Cases Reporting Fatal and Non-Fatal Cardiac Adverse Events in the Setting of COVID-19 (n=48)		
	Hydroxychloroquine (n=44) †	Chloroquine (n=4)
Serious Cardiac AEs (Labeled for HCQ/CQ) †	(n=38)	(n=4)
QT prolongation	24	4
VA, VF, VT	8	0
Tachyarrhythmia (including Wide QRS complex tachycardia)	4	0
QRS prolonged	3	1
Bradycardia	2	0
TdP	1	0
AV block	1	0
Cardiomyopathy	0	0
Indication		
Treatment	42	2
Prophylaxis	2	2
Concomitant Treatments of Interest §	(n=36)	(n=3)
Azithromycin	26	0
LPV/r	3	0
Azithromycin + LPV/r	3	1
Other QT prolonging drugs	10	2
Serious Unlabeled Cardiac AEs †	(n=2)	(n=0)
Atrial fibrillation	2	0
Fatal Cardiac Cases	14	1

* FAERS – includes any case identified in either FAERS alone or both FAERS and literature or both FAERS and in an IND safety report. Literature – includes cases only identified in the literature. IND safety report – includes only cases identified in an IND safety report.
§ A case may have more than one concomitant treatment.
† A case may have more than one AE. The FDA reviewer assessed the reported AEs were probably/possibly associated with HCQ or CQ use.
Abbreviations: AE = adverse event, CQ = chloroquine, HCQ = hydroxychloroquine, LPV/r = lopinavir/ritonavir, NPDS = National Poison Data System, VA = ventricular arrhythmia, VF = ventricular fibrillation, VT = ventricular tachycardia, TdP = Torsades de pointe

- ~81% of the cardiac AE cases report concomitant QT prolonging medicines including ~54% with concomitant azithromycin
- QT prolongation most common cardiac SAE
- 31% (14/48) cases are fatal
- ~91% (44/48) of cases reported use for treatment of COVID-19

HCQ/CQ Case Report Trends in Setting of COVID-19

- Majority of reported SAEs consistent with known safety profile for HCQ/CQ or known effects of COVID-19
- Majority of cases report use for treatment
- HCQ/CQ dosage appears consistent with FDA approved dosing for approved indications
- Cases for both all SAEs and cardiac SAEs report concomitant QT prolonging drugs with high frequency

U.S. FOOD & DRUG ADMINISTRATION

Division of Epidemiology-II
Rapid Review

Hydroxychloroquine (HCQ) ± azithromycin (AZM) observational safety and effectiveness study data

April 24, 2020

Observational data streams: Comparative HCQ treatment outcome results

- Preliminary analyses shared with FDA
  - NY State data
- Publications using observational data
  - NEJM by Ip et al. (Hackensack Meridian Health network)
  - VA study by Magagnoli et al. (*preprint*)

Comparative study of cardiac safety -NY State

- HCQ+AZM (n=299), HCQ (n=65), AZM (n=121), neither drug (n=101)
- Main finding:

  Compared to treatment with HCQ alone, HCQ+AZM is associated with increased risk of:
  - Cardiac arrest, arrhythmia and abnormal EKG (aRRs were not statistically significant)
- Limitations:
  - Potential residual confounding:
    - only adjusted for limited baseline characteristics (abnormal X-ray, respiratory rate>22, age, sex and facility)
    - patients who received combination therapy were more likely to have pre-existing conditions, but pre-existing conditions and co-medications were not adjusted
  - Small sample size

NY State data analysis (main results)

	Hydroxychloroquine + azithromycin		Hydroxychloroquine - azithromycin		Azithromycin only		Neither drug	
	%	(n)	%	(n)	%	(n)	%	(n)
Diarrhea	10.4	(31/299)	3.1	(2/65)	9.1	(11/121)	6.9	(7/101)
Hypoglycemia	2.3	(7/299)	0.0	(0/69)	0.8	(1/121)	5.0	(5/101)
Prolonged QT	10.7	(32/299)	9.2	(6/65)	6.6	(8/121)	4.0	(4/101)
Cardiac arrest*	14.7	(44/299)	7.7	(5/65)	7.4	(9/121)	6.9	(7/101)
Arrhythmia*	24.8	(74/299)	9.2	(6/65)	12.4	(15/121)	7.9	(8/101)
Abnormal EKG[a]*	29.8	(89/299)	15.4	(10/65)	16.5	(20/121)	9.9	(10/101)
Relative Risk								
Cardiac arrest	RR	ARR	RR	ARR	RR	ARR	RR	ARR
vs. Neither drug	2.12*	1.33	1.11	0.68	1.07	0.76	---	---
vs. AZM only	1.98*	1.76	1.03	0.89	---	---	---	---
vs. HQC only	1.91	1.97	---	---	---	---	---	---
Arrhythmia*								
vs. Neither drug	3.12*	1.75	1.17	0.79	1.57	1.38	---	---
vs. AZM only	2.00*	1.27	0.74	0.57	---	---	---	---
vs. HQC only	2.68*	2.21	---	---	---	---	---	---
Abnormal EKG[a]*								
vs. Neither drug	3.01*	1.69	1.55	0.98	1.67	1.37	---	---
vs. AZM only	1.80*	1.23	0.93	0.72	---	---	---	---
vs. HQC only	1.94*	1.72	---	---	---	---	---	---

NY State analysis results (baseline characteristics)

	Hydroxychloroquine + azithromycin		Hydroxychloroquine - azithromycin		Azithromycin only		Neither drug	
	%	(n)	%	(n)	%	(n)	%	(n)
Risk behaviors								
Smoking								
Current	5.1	(12/237)	0.0	(0/46)	1.9	(2/103)	3.8	(3/79)
Former	17.3	(41/237)	17.4	(8/46)	16.5	(17/103)	11.4	(9/79)
No	77.6	(184/237)	82.6	(38/46)	81.6	(84/103)	84.8	(67/79)
Vaping								
Current	0.9	(1/110)	0.0	(0/31)	0.0	(0/59)	2.3	(1/43)
Former	0.9	(1/110)	0.0	(0/31)	0.0	(0/59)	0.0	(0/43)
No	98.2	(108/110)	100	(31/31)	100.0	(59/59)	97.7	(42/43)
Alcohol abuse								
Current	4.7	(10/211)	2.5	(1/40)	2.0	(2/102)	2.6	(2/77)
Former	3.3	(7/211)	5.0	(2/40)	1.0	(1/102)	0.0	(0/77)
No	91.9	(194/211)	92.5	(37/40)	97.0	(99/102)	97.4	(75/77)
Preexisting condition								
Obesity (BMI≥30)	47.9	(120/256)	41.2	(21/51)	40.7	(35/86)	29.2	(21/72)
Cancer	4.0	(4/299)	1.5	(1/65)	5.0	(6/121)	3.0	(3/101)
Gastrointestinal/Liver disease	0.0	(0/299)	0.0	(0/65)	0.0	(0/65)	0.0	(0/65)
Renal disease	8.7	(26/299)	15.4	(10/65)	7.4	(9/121)	11.9	(12/101)
Chronic lung conditions	16.1	(48/299)	24.6	(16/65)	18.2	(22/121)	11.9	(12/101)
Metabolic disorders*	38.8	(116/299)	38.5	(25/65)	27.3	(33/121)	26.7	(27/101)
Diabetes*	34.8	(104/299)	35.4	(23/65)	25.6	(31/121)	20.8	(21/101)
Hypertension	57.9	(173/299)	52.3	(34/65)	49.6	(60/121)	51.5	(52/101)
Coronary Artery Disease (CAD)*	14.7	(44/299)	10.8	(7/65)	5.8	(7/121)	7.9	(8/101)
Congestive Heart Failure (CHF)	7.0	(21/299)	9.2	(6/65)	5.0	(6/121)	5.0	(5/101)
Dementia	5.3	(16/299)	4.6	(3/65)	6.6	(8/121)	11.9	(12/101)

Comparative studies of all-cause mortality (safety/effectiveness) - NY State, NEJM article, VA study

- Reported inconsistent trend of association between HCQ+AZM, HCQ, AZM use with mortality
- Limitations
  - Difficult to interpret the findings without cause of death
  - Indication for channeling bias/confounding by disease severity
    - Trend is inconsistent: some study results showed that HCQ treated patients had lower COVID-19 severity, but other study results showed that treated population in general were “sicker” than non-treated population
  - Concerns for residual confounding
    - Frequently missed potential confounders: co-medications, pre-existing conditions
  - Imprecise effect estimates with wide CIs, due to small sample size
  - Generalizability:
    - Eg. to non-male, younger population (VA), to other regions

Studies of comparative analyses on all-cause mortality

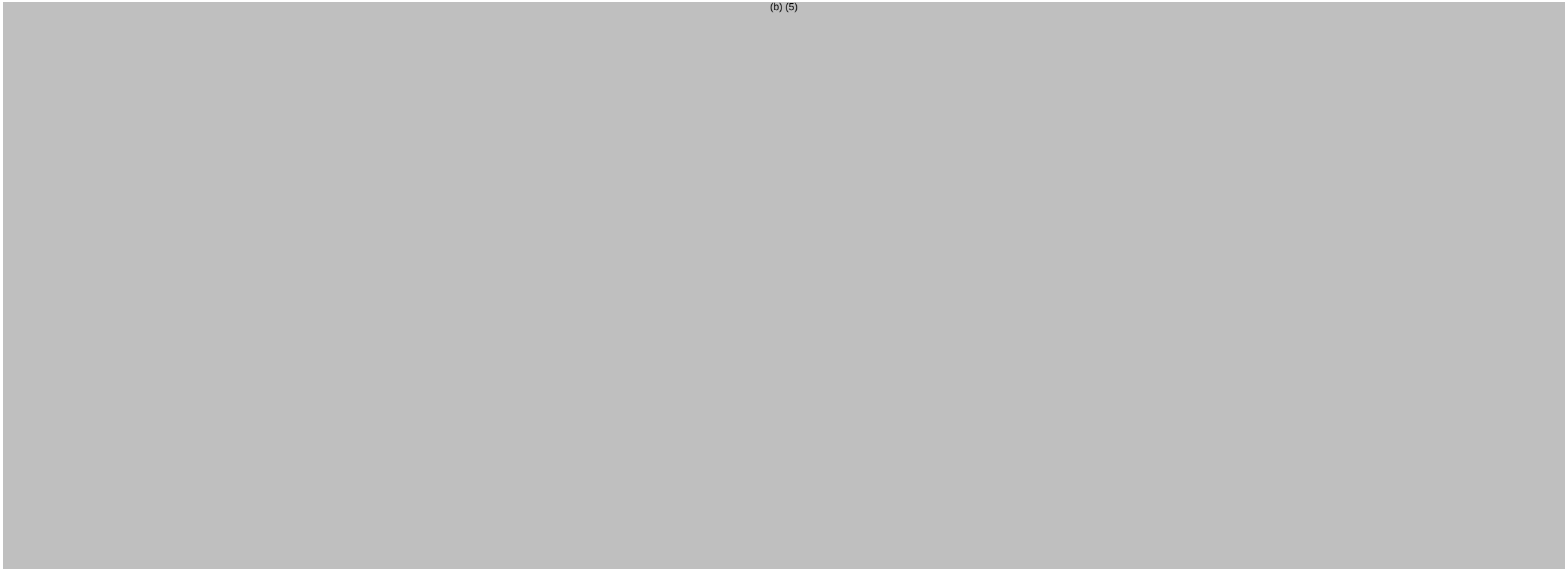
- Main findings

	HCQ+AZM	HCQ	AZM	Reference group
NY State Adjusted HR[1] n	 1.15 (0.57-2.31) n=299	 0.71 (0.28-1.8) n=65	 0.6 (0.27-1.35) n=121	 No HCQ or AZM n=101
NEJM Adjusted HR[2] n	 0.89 (0.42-1.87) n=666	 1.02 (0.59-1.74) n=202	 0.91 (0.48-1.72) n=72	 No HCQ or AZM n=115
VA study Adjusted HR[3] n	 1.14 (0.56-2.32) n=101	 **2.61 (1.10-6.17)** n=90	 - 	 No HCQ n=177

1. Adjusted for respiratory, age, sex, abnormal chest X-ray/MRI
2. Adjusted for risk score calculated by age, sex, ICU admission at index date, Ferritin, Insulin, arrythmia
3. Adjusted for PS calculated by age, sex ,race, BMI, comorbid condition, vital sign, laboratory data during hospitalization

Suggestions for improvement on observational data for safety and effectiveness studies

(b) (5)

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ADMINISTRATION

Comparative cardiac safety study -OHDSI study (RA study population)

- Main findings:
  - No excess risk of cardiotoxicity identified for 30-day HCQ use compared to sulfasalazine use
  - When AZM was added to HCQ, increased risk of 30-day CV mortality, chest pain/angina and heart failure were observed
- Limitations:
  - Heterogeneity of databases (Mixture of claims and ambulatory EHR data)
    - Incomplete capture of outcomes and covariates in ambulatory EHR
    - Validity of outcome events and exposure captured in ambulatory setting is unclear
  - Outcomes that showed significant association might not all be associated with QT-prolongation
    - CV death: 1+ CV-event recorded in 30 days prior to death
  - The design does not support the conclusion
    - HCQ may not have been used concomitantly with as AZM as defined in the study
    - HCQ+ AZM compared to HCQ+ Amoxicillin
  - Generalizability to COVID-19 population

#R00X	
Stakeholder	OHDSI
Date	4/8/2020
Question	What is the safety of hydroxychloroquine, alone and in combination with azithromycin compared to sulfasalazine in rheumatoid arthritis patients?
Patients	956,374 and 310,350 users of hydroxychloroquine (HCQ) or sulfasalazine (SSZ), respectively and 323,122 and 351,956 users of hydroxychloroquine-azithromycin (AZM) or hydroxychloroquine-amoxicillin (AMX). All participants had a history of rheumatoid arthritis (a condition occurrence or observation indicating RA any time before or on the same day as therapy initiation)
Method of Covid dx	Not applicable
Rx of interest	HCQ and HCQ+AZM
Comparator(s)	SSZ and HCQ+AMX
Outcomes – clinical	16 serious adverse events (SAEs) were considered. Hospital-based events included gastrointestinal bleeding, acute renal failure, acute pancreatitis, myocardial infarction, stroke, transient ischemic attack, and cardiovascular events (composite). Events from primary and secondary care data included angina/chest pain, heart failure, cardiac arrhythmia, bradycardia, venous thromboembolism, end stage renal disease, and hepatic failure. Mortality outcomes were obtained only from data sources with reliable information on death date (CPRD, IMRD, IPCI, Optum, SIDIAP, VA) and cardiovascular events preceding death records (CPRD, IMRD, Optum, VA), with the former contributing to informing all-cause mortality, and the latter also used to assess to cardiovascular death.
" " - ascertainment	Based on codes that were previously published in this network of databases.
Data	14 sources of claims data or electronic medical records from Germany, Japan, Netherlands, Spain, UK, and USA. The study period started from 1/09/2020 and ended at the latest available date for all data sources in 2020.
Linkage for analyses (y/n)	n
Study design	Retrospective new user cohort (primary analyses) and self-controlled case series (SCCS)
Analytic method	Analysis code was sent to participating sites and only aggregate summary statistics were returned and pooled using a meta-analytic approach. Cohort: Two active comparator analyses were used: first, incident users of HCQ were compared to new users of SSZ; second, incident use of AZM amongst prevalent users of HCQ was compared to incident use of AMX during ongoing HCQ use. Propensity score stratification was used for adjustment. Negative control outcomes analyses

	and empirical calibration were used to further adjust for unresolved confounding with calibrated HRs (CalHRs) and 95% confidence intervals estimated. SCCS: Exposed and unexposed time periods were compared within the same individuals. A conditional Poisson regression was used to fit the outcome model using the Cyclops package, with a hyperparameter selected through 10-fold cross-validation.
Foci for adjustment	Cohort: Baseline patient characteristics were constructed for inclusion as potentially confounding covariates. From tens of thousands of covariates, key predictors of exposure classification were selected for the propensity score. The predictor variables included were based on all observed patient characteristics and covariates available at each data source, including conditions, procedures, visits, observations and measurements. All covariates that occur in fewer than 0.1% of patients within the target and comparator cohorts were excluded prior to propensity score model fitting for computational efficiency. SCCS: Age, season and other drug exposures were adjusted as time-varying covariates.
Novel approach*	N
Main results	None of the SAEs appeared consistently increased with the short-term use of HCQ (vs. SSZ). Long term treatment of HCQ was associated with increased cardiovascular mortality (meta-analytic calHR = 1.65, 1.12-2.44). Short-term (30-day fixed follow-up) use of HCQ+AZM (vs. HCQ+AMX) was associated with three SAES: chest pain/angina (meta-analytic CalHR 1.15 (1.05-1.26), heart failure (meta-analytic CalHR 1.22 (1.02-1.45), and cardiovascular mortality (meta-analytic CalHR 2.19 (1.22-3.94)
Strengths	Large sample size; confirmation of findings in SCCS which controls for intrinsic confounders (e.g., genetics); use of active comparators limits potential for confounding by indication.

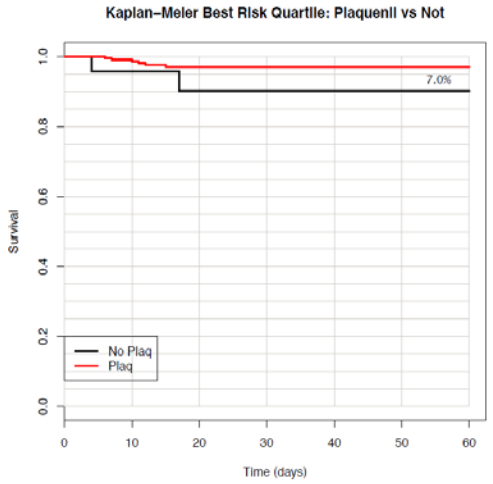
Limitations	• Heterogeneity of databases (Mixture of claims and ambulatory HER data)
	  • Some data sources only have ambulatory EHR→ incomplete capture of outcomes and covariates
	  • Validity of outcome events captured in ambulatory setting is unclear
	  • Validity of exposure status captured by prescription records is unclear
	• The outcomes (cardiac death) that showed significant association with treatment might not all be associated with QT-prolongation
	  • Cardiac death was defined as having 1+ "cardiovascular" events recorded in <u>30 days prior to death</u>
	• The design does not support the conclusion
	  • HCQ may not have been used concomitantly with AZM as defined in the study
	  • HCQ+ AZM compared to HCQ+ Amoxicillin… the finding on this comparison cannot inform the safety of HCQ+AZM, because the treatment and active control group (HCQ+Amoxicillin) had HCQ (i.e., the relative risk they estimated is compared AZM to amoxicillin)
	• Generalizability to COVID-19 population could be limited
	  • RA population may not be representative of COVID-19 patient population

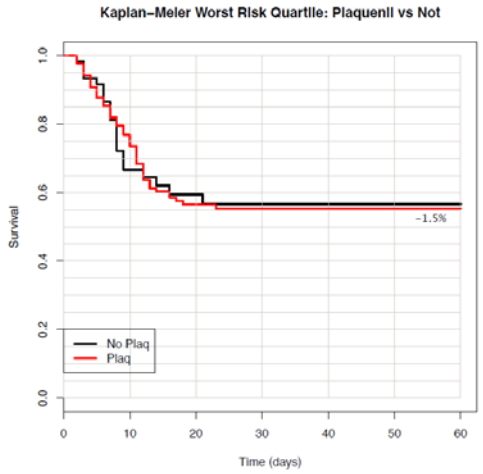
	• HCQ dose prescribed for RA is lower than what is proposed for COVID-19 treatment • The same US subjects may be included in multiple databases.
Comments	This study is not informative regarding potential cardiac risk associated with HCQ or HCQ+AZM use in COVID-19 population
Assessment	Low impact
Action	(b) (5)
*describe novel data or methods compared to sources available through FDA contracts, etc.	

#R00X Hackensack Meridian Network	
Stakeholder name	**Hackensack Meridian Network**
Date	04/23/2020
Question	Efficacy of hydroxychloroquine (HCQ) alone, HCQ + azithromycin (AZM) and tocilizumab in the treatment of SARS-CoV-2 positive patients across 13 Hackensack Meridian hospitals spanning New Jersey.
Patients	1055 hospitalized patients were included in the prospective observational database within the Hackensack Meridian Health Network (Edison, NJ) Inclusion criteria for the database were: • Positive SARS-CoV-2 diagnosis by reverse transcriptase polymerase chain reaction, • Hospitalized within the time frame of March 1, 2020until April 8, 2020, Exclusions included: • Pregnant • Already part of a randomized clinical trial, and • Died on first day of randomization
Method of Covid dx	Positive SARS-CoV-2 diagnosis by reverse transcriptase polymerase chain reaction,
Rx of interest	HCQ +/- AZM and tocilizumab. 868/1055 patients (82%) received at least one dose of hydroxychloroquine during the study timeframe (23% as single agent and 77% in combination with azithromycin). Treatment was started a median of 5 days (Iqr 2-8) after self-reported symptoms. Dosing regimens varied with a 4 day median duration of therapy (Iqr 4-5). No information on dose used was provided.
Comparator(s)	Non users of the drug of interest.
Outcomes - clinical	The primary outcome measurement was overall survival (OS) with follow-up through April 8, 2020.
“ ” - ascertainment	Indicated by in hospital death recorded in the EHR.

Data	Data accrued during hospitalization and recorded in the Hackensack Meridian Network COVID-19 Observational Database including: • Demographics (age, gender, race) • Presenting features and laboratory results on admission • Laboratory results on entry to ICU (if applicable) • Treatments • Survival outcomes
Linkage for analyses (y/n)	None stated
Study design	Retrospective comparative cohort study using electronic health records (EPIC; Verona, WI) from hospitalized COVID patients in the Hackensack Meridian Health network in New Jersey
Analytic method	• Cox regression on the association between treatment and survival stratified by the HMH risk score. • Follow up began on hospital admission date until April 8, 2020 • Both unadjusted and adjusted analyses presented. • Adjusted via stratification into four risk levels (low-high risk) using the Hackensack Meridian Risk Score rather than adjusting for covariates individually in the Cox model.
Foci for adjustment	Adjustment in this analysis was via stratification by the Hackensack Meridian Risk Score. The rationale was that adjustment for multiple covariates can cause collinearity. The patient risk score was derived by including covariates in a Cox regression model. Covariates considered for inclusion in the risk score included: gender, age, whether entered hospital directly to intensive care unit (ICU), body mass index (BMI), diabetes, hemoglobin A1c, insulin use, COPD, asthma, inhaled corticosteroid use, hypertension, cancer, coronary disease, stroke, heart failure, arrhythmia, renal failure, baseline creatinine, rheumatologic disorder, HIV or hepatitis, inflammatory bowel disease, advanced liver disease, serum ferritin, and d-dimer. However, only gender, age, and whether the patient entered the ICU upon admission to the hospital were definitely included others were added pending statistical significance and no further details are given.
Novel approach*	The risk score for COVID 19 appears to be novel

Main results	Those not treated with hydroxychloroquine had a higher median age compared to treated (70 years vs 65 years). Those with a lower risk score were more likely to receive hydroxychloroquine. Among patients with the lowest quartile HMH-RS 91% received hydroxychloroquine compared to 90%, 82% and 78% in HMH-RS 2, 3, and 4. In the hydroxychloroquine cohort as of April 8, 2020, there were 199 deaths (19%), 437 successful hospital discharges (41%) and 419 patients still receiving hospital care (40%). Causes of death were respiratory 63%, cardiac 18% and infectious 8% **Safety** Discontinuation of hydroxychloroquine due to prolongation of QTc or arrhythmias was recorded in the electronic health records in 14 (1.6%) and 2 (0.2%) patients. During hospitalization, arrhythmias were noted in 3.9%, cardiomyopathy 1.1%, neurologic events 1.4% and renal failure 6.3%. **HCQ** • Unadjusted analyses HCQ: HCQ appeared to prolong survival compared to non-use. • Adjustment by risk score stratification HCQ: No statistically significant survival benefit across any of the 4 risk categories HR 0.92;p=0.63). • Similar results were seen when AZM was added to HCQ HR: 0.89; p=0.76 • Kaplan Meier curves illustrating results for the HCQ only analysis among the lowest and highest risk score. patients are shown below and indicate no substantial difference between the treated and non-treated. • In an unplanned, post-hoc analysis, when stratified by race, the death rate among hospitalized African-American patients was less than for Caucasians (14% vs 21%). • A chance finding indicated history of rheumatologic disease was deemed to be protective. 4.2% of patients had rheumatologic diseases. • Authors suggest that although hydroxychloroquine may have anti-viral effects, the agent may not be able to control the cytokine storm and pro-inflammatory response that accompanies acute respiratory failure

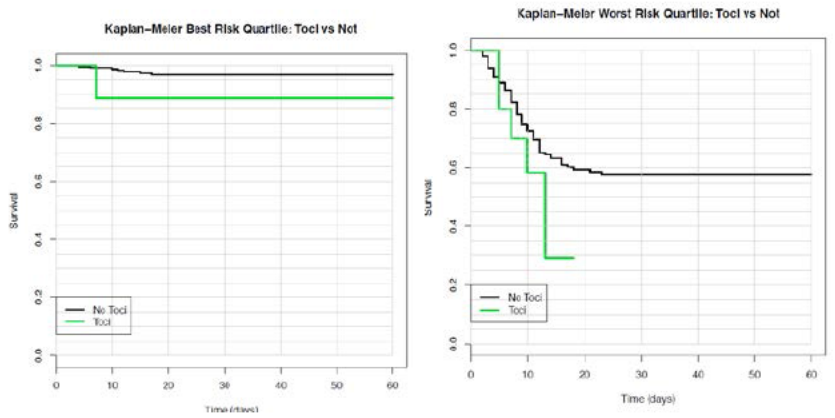




Tocilizumab (not included in NEJM paper submission)

Only 53 patients received tocilizumab. Updated analyses with more tocilizumab treated patients are pending.

Results suggest that tocilizumab use may be detrimental and lead to increased mortality especially among those with higher risk scores.

	
Strengths	Access to hospitalization data and lab results
Limitations	• Sample of hospitalized COVID patients from hospital network in New Jersey limits generalizability. • Small sample size only 1055 patients available in database. No indication of how many patients were included in each analysis • There was no information on how missing information on treatment and other covariates was handled. It is acknowledged as a limitation in the discussion. • Used non-users of treatment as a comparator group. This raises many issues related to confounding by indication and confounding by frailty, especially, in seriously unwell hospitalized patients. The decision to treat some patients with a drug and not others often cannot be accounted for in standard adjustments and so residual confounding is an issue. Indeed, in descriptive analyses the authors show that those with a lower risk score were more likely to receive hydroxychloroquine. • No information was provided on the dose of each study treatment used. • Did not list which covariates were actually used to derive risk score based on their statistical significance to the outcome. Selecting covariates in this way rather than taking account of clinical relevance also may increase residual confounding. There was no indication that concomitant medication (non COVID treatment) was accounted for.

	• Small numbers of tocilizumab treated patients (approx. 50) larger numbers are needed in updated analyses.
Comments	18% of deaths in the hydroxychloroquine study were due to cardiac issues- it is not clear how many of these were in the treated group but raises concerns about side effects of hydroxychloroquine. Overall, there seem to be a number of important limitations listed above that need to be addressed before this data could be useful in making decisions about the efficacy of any of the treatments under investigation.
Assessment	Low impact
Action	(b) (5)
*describe novel data or methods compared to sources available through FDA contracts, etc.	

#R00X VA	
Stakeholder name	US Department of Veterans Affairs (VA)
Date	04/22/2020
Question	Retrospective analysis sought to analyze the associations between hydroxychloroquine and azithromycin use and clinical outcomes.
Patients	368 male patients with laboratory confirmed SARS-CoV-2 infection in an inpatient setting. Index dates ranged from March 9, 2020 to April 11, 2020, and patients were followed from index until hospital discharge or death.
Method of Covid dx	SARS-CoV-2 status was classified by laboratory results that were extracted from VA laboratory data.
Rx of interest	hydroxychloroquine (HC) and azithromycin (AZ): 1) HC-treated; 2) HC- and AZ-treated. Patients were identified as exposed to HC or AZ if they had a dispensed drug from the VA bar code medication administration (BCMA) data file during their hospitalization.
Comparator(s)	HC-untreated
Index time	Index date was defined as the date of a hospitalization with a positive SARS-CoV-2 laboratory test
Censor for follow-up	Patients were followed from index until hospital discharge or death
Outcomes - clinical	Hospitalization (discharge or death), whether ventilation was required, and the result of hospitalization among patients requiring ventilation.
" " - ascertainment	Ventilator usage was coded using HCPCS/CPT codes (31500, 94003, 94002, E0463) and ICD-10-PCS codes (5A0955, 5A0945, 5A0935, 5A1522F, 5A1522G, 5A1522H). The results of the hospitalization were coded from the discharge disposition status on the inpatient record.
Data	Veterans Affairs Informatics and Computing Infrastructure.
Linkage for analyses (y/n)	N
Study design	Retrospective cohort
Analytic method	The Fine and Gray competing risk proportional hazards model was used to assess the association between treatment status and the study outcomes.
Foci for adjustment	Propensity scores for HCQ alone and HC+AZ were created based on all baseline characteristics. Demographic and clinical characteristics included age, sex, race, and body mass index (BMI). For comorbid conditions, the authors utilized ICD-10-CM codes and calculated the Charlson comorbidity index from relevant patient data. Vital sign data include heart rate, pulse oximetry, respirations, temperature, and blood pressure (BP). All vital sign data were

	collected at the first set of vital results during the patient's hospitalization and all were prior to ventilation if applicable. Laboratory data during hospitalization were also evaluated for each patient and consisted of liver function tests, albumin, bilirubin, creatinine, blood urea nitrogen, erythrocytes, hematocrit, platelets, white blood cells, C-reactive protein, procalcitonin, troponin, and erythrocyte sedimentation rate.
Novel approach*	
Main results	Overall mortality: There were 27 deaths (27.8%) in the HC group (n=97), 25 deaths (22.1%) in the HC+AZ group (n=113), and 18 deaths (11.4%) in the no HC group (n=158). Compared to the no HC group, there was a higher risk of death from any cause in the HC group (adjusted HR, 2.61; 95% CI, 1.10 to 6.17; P=0.03) but not in the HC+AZ group (adjusted HR, 1.14; 95% CI, 0.56 to 2.32; P=0.72). Among patients who required mechanical ventilation there was no significant risk of death after ventilation in either the HC group (adjusted HR, 4.08; 95% CI, 0.77 to 21.70; P=0.10) or the HC+AZ group (adjusted HR, 1.20; 95% CI, 0.25 to 5.77; P=0.82). Mechanical ventilation: Mechanical ventilation occurred in 13.3% of the HC group, 6.9% of the HC+AZ group, and 14.1% of the no HC group. Compared to the no HC group there was no risk of difference in the risk of ventilation in the HC group (adjusted HR, 1.43; 95% CI, 0.53 to 3.79; P=0.48) or the HC+AZ group (adjusted HR, 0.43; 95% CI, 0.16 to 1.12; P=0.09).
Strengths	• Rigorously identified cases, covariates and outcomes from an integrated national health care system. • All patients were hospitalized for covid-19 which offers control for disease severity.
Limitations	• This study has limited generalizability to female, outpatient, or younger populations (the median age of this study was over 65. • The "standard of care" that all patients received is not clearly defined, it was also unclear if the standard of care was different between the comparison groups • No information was provided on the dose of each study treatment used. • The index time is hospitalization, which introduced "immortal time" in patients who received HC or HC+AZ • Cause of death was not provided. The authors suggest that mortality in this group might be • attributable to drug effects on or dysfunction in non-respiratory vital organ systems, however this assertion cannot be assessed without information on the cause of death. • Potential for residual confounding, patients treated with HC (with or without AZ) were more likely to have severe disease as assessed by baseline ventilatory status and metabolic and hematologic parameters. Co-medication use was not accounted for in the adjusted model. However, only the association between HC alone and risk of death persisted after propensity score adjustment. • Some covariates (i.e. laboratory data captured throughout hospitalization) may be captured after treatment initiation, which could introduce bias due to adjustment of an intermediate variable between exposure and outcome

	• Study is likely underpowered for most of the analyses because confidence intervals for most of the HRs were wide and crossed 1.0
Comments	• The study is of better quality than other studies in this topic, in that they captured/adjusted for rich baseline characteristics, however, the results still need to be interpreted with cautious given the limitations
Assessment	Informative but does not reach the quality to support regulatory action, because it was unclear if the mortality is due to treatment effectiveness or safety.
Action	(b) (5)
*describe novel data or methods compared to sources available through FDA contracts, etc.	

#R00X BORBA	
Stakeholder name	Borba *et al.*
Date	04/15/2020
Question	Safety (primary) and efficacy (secondary) of two chloroquine (CQ) doses for treatment of severe hospitalized pts due to SARS-CoV2
Patients	81 adult patients admitted to a Brazilian hospital between March 23 and April 5, randomized to high-does (n=41) and low-dose (n=40) CQ arms
Method of Covid dx	Clinical-epidemiological suspected cases or cases confirmed by RT-PCR
Rx of interest	CQ (High dose: 600mg b.i.d. for 10 days vs Low dose: 450mg for 5 days; b.i.d only for Day 1)
Comparator(s)	None (with reference to historical mortality data in pts w/o CQ)
Outcomes - clinical	Mortality by D6 (follow-up ongoing until D28), viral clearance, progression status (i.e. oxygen support need, ICU need), QTc, ventricular tachycardia, etc.
" " - ascertainment	
Data	Primary data from a Phase IIb clinical trial (CloroCovid-19; NCT04323527)
Linkage for analyses (y/n)	n
Study design	Phase IIb, randomized, double-blinded clinical trial
Analytic method	ITT analysis; Chi-square, Fisher's exact test; Kaplan-Meier survival curves
Foci for adjustment	None
Novel approach*	n
Main results	High-dose CQ arm showed toxicity signals (i.e. longer QT) as well as higher mortality by Day 6 (17%), compared to low-dose arm (10%) and historic data in pts w/o CQ (13.5%)
Strengths	Primary data from clinical trial; double-blinded
Limitations	Imbalanced baseline characteristics (i.e. older pts >75 yrs and pts with baseline heart diseases only in high-dose arm); ITT only, no PT analysis; short and incomplete follow-up; small sample size; confounding by comedication (i.e.

	ceftriaxone, azithromycin and oseltamivir, which might also increase QT); data errors in Table 3 (numbers inconsistent with those in main text)
Comments	Baseline imbalance between high-dose vs low-dose CQ arms disqualified this study from concluding on the safety and efficacy differences between these two arms
Assessment	Low impact
Action	(b) (5)
*describe novel data or methods compared to sources available through FDA contracts, etc.	

Connecting hydroxychloroquine in vitro antiviral activity to in vivo concentration for prediction of antiviral effect: a critical step in treating COVID-19 patients

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Abstract:

Translation of in vitro antiviral activity to the in vivo setting is crucial to identify potentially effective dosing regimens of hydroxychloroquine. In vitro EC50/EC90 values for hydroxychloroquine should be compared to the in vivo free extracellular tissue concentration, which is similar to the free plasma hydroxychloroquine concentration.

Keywords: Hydroxychloroquine, SARS-CoV-2, COVID-19, antiviral activity

Introduction

The recently published article by Yao et al. aimed to derive optimized dosing regimens of hydroxychloroquine (HCQ) for the treatment of SARS-CoV-2 based on in vitro antiviral pharmacology experiments and physiologically-based pharmacokinetic (PBPK) modeling and simulation (M&S) [1]. The unprecedented global COVID pandemic necessitates expeditious, pharmacologically-anchored development of therapeutic agents to both treat and prevent the adverse clinical sequelae of SARS-CoV-2. Mechanistically-informed approaches including, but not limited to, PBPK and other M&S strategies may be helpful in 1) deriving dosing regimens of therapeutic agents likely to have acceptable risk/benefit profiles; 2) identifying where in the course of disease treatment should be initiated; and 3) providing mechanistic insights into data derived from clinical trials. To the extent that translational research similar to that conducted by Yao et al. may be used to inform future drug development programs and clinical management strategies, herein, we wish to share our perspectives on how to link in vitro antiviral activity and drug exposure at the putative target site of action in predicting the in vivo antiviral effect of HCQ.

A key goal in PBPK modeling, as illustrated by Yao et al., is to derive appropriate dosing regimens by integrating in vitro experimental pharmacological data with understanding of physiological process and drug properties in order to simulate which regimens would achieve adequate concentrations in target tissues of relevance. To estimate in vivo antiviral activity, the ratio of free extracellular drug concentration in tissue in vivo to the in vitro EC50 or EC90 value is generally calculated. The higher this ratio, the greater the confidence in achieving in vivo antiviral efficacy.

Yao et al. recommended dosing regimens based on the ratios of free lung trough concentration to the in vitro EC50 value (R_{LTEC}=Ctrough,lung/EC50), where the free lung trough concentration was calculated as the PBPK model-simulated lung trough concentration adjusted with the chloroquine (CQ)/HCQ unbound fraction (fu,plasma) in plasma, and the EC50 values were the initial CQ/HCQ concentrations in the cell culture media that led to 50% of the maximum antiviral activity. The PBPK model-simulated lung trough concentration was based on the lung-to-plasma partition coefficient obtained from rats and assumed to be the same in both rats and humans as no human data are available. The authors indicated that the free lung trough HCQ concentrations would be approximately 21- to 169-fold of the EC50 value under different dosing regimens resulting in high HCQ R_{LTEC} values; this would suggest high likelihood for in vivo antiviral activity and thus provide a rationale to support HCQ as a potentially efficacious regimen inhibiting SARS-CoV-2 assuming an antiviral mechanism of action/benefit.

In this brief report, we summarize HCQ's potential mechanism of action against SARS-CoV-2, in vitro anti-SARS-CoV-2 studies, pharmacokinetic (PK) properties for HCQ, and provide a high-level assessment regarding how to link in vitro antiviral activity and in vivo drug concentration to assess the antiviral effect of HCQ for SARS-CoV-2.

HCQ/CQ's potential mechanism of action against SARS-CoV-2

HCQ and CQ are known to accumulate highly in acidic organelles, such as endosomes, the Golgi apparatus, and lysosomes. The intracellular concentrations can be up to 1000-fold higher than the extracellular drug concentrations (e.g., the concentrations in the cell culture media in the reported in vitro studies) [2, 3] (Figure 1). The proposed mechanism of CQ's anti-coronavirus activity is related to its intracellular pH modulation effect. The increased endosomal pH was believed to block virus/cell fusion. The impairment of terminal glycosylation of angiotensin converting enzyme 2 (ACE2) caused by pH elevated Golgi apparatus may result in reduced binding affinities between ACE2 and SARS-CoV spike protein [4]. A more recent study confirmed the endosomal pH-related mechanism for CQ and explored the antiviral mechanism for HCQ [5]. Both CQ and HCQ affected the number and/or size/morphology of early endosomes and endolysosomes, and the authors hypothesized that this could result in failure of further transport of virions to the ultimate release site.

In vitro antiviral activity against SARS-CoV-2

In two papers, the in vitro antiviral activity of CQ and HCQ against SARS-CoV-2 for both treatment and prophylaxis was reported using EC50 values that represent the drug concentrations initially added to the cell culture media instead of the intracellular drug concentration [1, 5]. It was reported that the initial drug concentration could decrease significantly due to intracellular accumulation during the incubation [6]. This could lead to a much lower estimated EC50 value if the measured steady state drug concentration had been used to estimate EC50. However, after examining the experimental conditions reported by both studies [1, 5], we consider the impact of extracellular drug concentration drop during the in vitro study on EC50 estimate is insignificant.

In vivo drug exposure

CQ and HCQ are known to have significantly higher tissue concentrations compared to those in plasma. The CQ product label reports tissue concentrations 200-700 fold higher than plasma in animals [7] while MacIntyre et al. [6] suggests HCQ may have similarly high tissue/plasma ratio in the rat (Figure 1). The mechanism for the high tissue/plasma ratio is due to the accumulation of CQ/HCQ in acidic organelles such as endosome, Golgi apparatus, and lysosomes inside tissue cells [6]. Therefore, despite the high tissue intracellular concentrations, the free tissue extracellular concentration should be similar to the free plasma concentration [8] (Figure 1). It should be noted that various types of concentrations have been reported, such as blood, serum, and plasma concentrations with different units. A study investigated the distribution of CQ in blood and showed an average blood-to-plasma concentration ratio of 7.6 and serum-to-plasma concentration ratio of 2 [9]. The higher concentrations of CQ in serum might be due to the release of CQ from leucocytes and thrombocytes during the clotting process. Therefore, at least 1000 g centrifugal force was recommended to process the blood samples and obtain reliable plasma concentration of CQ. HCQ showed a similar mean blood-to-plasma concentration ratio of 7.2 [10]. A similarly high centrifugal force (1200 g) had to be applied to obtain reliable plasma concentration of HCQ[10, 11]. Given the similar intracellular accumulation between CQ and HCQ, the serum-to-plasma concentration ratio for HCQ is expected to be approximately 2 as well for the same reason. When linking in vitro antiviral activity and in vivo exposure, the HCQ concentrations in different matrices (whole blood, serum or plasma) need to be converted to the unbound concentration in plasma. PK models developed from improperly processed plasma

samples can lead to a "plasma" concentration prediction as high as the whole blood concentration [12]. Any application of such PK models to support HCQ dosing regimen is questionable [13, 14].

Results:

Linking in vitro antiviral activity and in vivo hydroxychloroquine concentrations

Based on the above considerations, we re-calculated the R_{LTEC} values using free lung extracellular trough concentrations which should be similar to the free plasma concentrations (Cplasma*fu,plasma) extracted from figure 3 in Yao et al.[1] instead of the predicted "free lung trough concentrations" (Cplasma*Kp*fu,plasma) reported by Yao et al which included the highly accumulated intracellular concentration as discussed previously. These results are listed in Table 1B and showed lower R_{LTEC} values (0.11-0.34) compared to those reported by Yao et al (21-169). When a higher EC50 value as reported by Liu et al. [5] was used, even lower R_{LTEC} values (0.017-0.054) were obtained, suggesting the possibility that in vivo concentrations of HCQ that would be achieved with the highest proposed dosing regimen (D1 800 mg + 400 mg, D2-D10 400 mg QD) may not result in adequate clinical antiviral activity against SARS-CoV-2, as the R_{LTEC} values ranged from 0.005 to 0.34, depending on the values of EC50/EC90 . Similar R_{LTEC} range (0.03-0.89 when compared to EC50, and 0.007 to 0.064 when compared to EC90) was obtained for CQ (D1-D10 500 mg BID) (data not shown). The in vivo HCQ concentration range is added to the concentration-inhibition (%) plots from both Yao et al. and Liu et al. to visualize the magnitude of in vivo concentration range relative to the in vitro concentration ranges (Figure 2).
It should be noted that our calculation assumed similar in vivo cellular accumulation as those seen in in vitro studies. Even though we used model-predicted HCQ plasma concentration from Yao et al. for comparison purposes, observed concentrations from various clinical trials can be used for similar calculations. When using reported PK parameters, blood and serum concentrations should be properly converted to free plasma concentration before comparison with EC50/EC90 values.

Discussion

Multiple other reports [5, 15-19] also cited the significantly higher lung concentration relative to the in vitro EC50 as the rationale to support CQ/HCQ as a potentially efficacious regimen against SARS-CoV-2. However, as stated earlier, the in vitro EC50 values used in these reports were based on the drug concentrations in the cell culture media (extracellular concentration). In order to use the significantly higher lung (intracellular) concentration to predict the potential in vivo antiviral efficacy, we believe the in vitro corresponding antiviral potency parameter, e.g. EC50_intracellular, should be calculated based on the intracellular concentrations in the antiviral experiments. EC50_intracellular will be significantly greater than the currently reported EC50 values. As a result, the ratio between in vivo intracellular concentration and EC50_intracellular would still be low, suggesting low potential for in vivo antiviral activity at doses that would not be rate-limiting from the standpoint of toxicity.

Our assessment should be put in proper context. It should be noted that much is unknown about both the pathogenesis of SARS-CoV-2-induced COVID-19 as well as the relevant mechanism of action for treatments that ultimately prove to be safe and effective for COVID-19 prophylaxis and treatment. We only considered viral inhibition activity in the calculation, while HCQ may have additional relevant pharmacological properties (e.g., anti-inflammatory/immunomodulatory effects). It has been hypothesized that the immunomodulatory effect of HCQ may be beneficial during the moderate/late stage of COVID-19 disease progression [20]. Adequate and well-controlled clinical trials will ultimately be critical in determining which treatment modalities will be safe and effective, at what stages of infection and disease, and at what dose regimens. As in vitro studies showed antiviral activities for CQ and HCQ, in vivo antiviral efficacy may be possible only if the in vivo concentration is sufficiently high. However, CQ and HCQ have potential QT prolongation risk, especially when being used in combination with another QT prolonger, such as azithromycin [21, 22]. Therefore, a strategy to increase the drug exposure at the site of action (e.g., through targeted delivery) while minimizing the systemic exposure may be desirable.

In conclusion, the translation of in vitro antiviral activity to appropriate clinical dosing regimens is complex and multifactorial. For the case of CQ/HCQ, the in vitro antiviral EC50 values reported in the literature [1, 5] were extracellular drug concentrations present in cell culture media, and should be compared with in vivo free drug concentration in the plasma (likely to be equal to free extracellular tissue concentration). Under the assumption that in vivo cellular accumulation is similar to that from the in vitro studies, the calculated free lung concentrations that would result from proposed dosing regimens are well below the in vitro EC50/EC90 values, making the antiviral effect against SARS-CoV-2 not likely achievable with a safe oral dosing regimen. Well-designed clinical trials that leverage full understanding of drug pharmacology and disposition, as well as disease pathogenesis, will be necessary to definitively determine whether the risk/benefit balance is favorable for a given treatment.

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Disclaimer:
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Figure Legends:

Figure 1 Mechanism of pH-driven intracellular accumulation of HCQ in the in vitro cell culture system and in vivo lung tissue. HCQ has a high logP (3.84) and pKa (9.67, 8.27) and can freely diffuse across the cell membrane in its unionized from to enter the cell and the lysosome. Once inside the lysosome, HCQ becomes protonated in the acidic environment, preventing it from crossing the lysosomal membrane back to the cytoplasm.

Figure 2 Predicted HCQ free lung extracellular concentration (equal to free plasma concentration) range (0.077-0.305 μM, red double-end arrows) with different dosing regimens (Table 1) and HCQ SARS-CoV-2 inhibition concentration-response curves at MOI of 0.01. The blue double-end arrows (15.1-121.7 μM) represent the "free lung trough concentration" obtained from Yao et al.[1]. The HCQ SARS-CoV-2 inhibition concentration-response curves were adapted from Liu et al.(left) [5], and Yao et al.(right) [1].

Table 1. **A:** Model predicted HCQ free trough concentration (Ctrough,u) and free maximal concentration (Cmax,u) in plasma on days 1, 3, 5 and 10 following different proposed dosing regimens in healthy subjects (data were digitized from Figure 3 in Yao et al. article[1].). **B**: Re-calculated ratios of free lung extracellular (or free plasma) trough concentration to in vitro extracellular EC50 or EC90 (R_{LTEC}) with different dosing regimens of HCQ.

A

Dosing Regimen[a]	**Ctrough,u (μM)**				**Cmax,u (μM)**			
	Day 1	Day 3	Day 5	Day 10	Day 1	Day 3	Day 5	Day 10
D1 800 mg + 400 mg D2-D10 400 mg QD	0.108	0.118	0.155	0.228	0.165	0.186	0.223	0.305
D1 600 mg BID D2-D10 400 mg QD	0.115	0.118	0.155	0.228	0.185	0.185	0.221	0.302
D1 600 mg BID D2-D10 200 mg BID	0.115	0.131	0.164	0.244	0.182	0.159	0.192	0.271
D1 400 mg BID D2-D10 200 mg BID	0.077	0.109	0.145	0.225	0.122	0.134	0.174	0.259
D1 400 mg BID D2-D5 200 mg BID	0.077	0.109	0.145	0.101	0.122	0.134	0.173	0.102

B

	R_{LTEC} (Ctrough,u/EC50)							
Dosing Regimen[a]	**EC50 = 0.72 μM[1][b]**				**EC50 = 4.51 μM[5][b]**			
	Day 1	Day 3	Day 5	Day 10	Day 1	Day 3	Day 5	Day 10
D1 800 mg + 400 mg D2-D10 400 mg QD	0.15	0.16	0.22	0.32	0.024	0.026	0.034	0.051
D1 600 mg BID D2-D10 400 mg QD	0.16	0.16	0.22	0.32	0.026	0.026	0.034	0.051
D1 600 mg BID D2-D10 200 mg BID	0.16	0.18	0.23	0.34	0.026	0.029	0.036	0.054
D1 400 mg BID D2-D10 200 mg BID	0.11	0.15	0.20	0.31	0.017	0.024	0.032	0.050
D1 400 mg BID D2-D5 200 mg BID	0.11	0.15	0.20	0.14	0.017	0.024	0.032	0.022
	R_{LTEC} (Ctrough,u/EC90)							
Dosing Regimen [a]	**EC90 = 10 μM[1] [b]**				**EC90 = 16.9 μM[5] [b]**			
	Day 1	Day 3	Day 5	Day 10	Day 1	Day 3	Day 5	Day 10
D1 800 mg + 400 mg D2-D10 400 mg QD	0.011	0.012	0.015	0.023	0.006	0.007	0.009	0.013
D1 600 mg BID D2-D10 400 mg QD	0.012	0.012	0.015	0.023	0.007	0.007	0.009	0.013
D1 600 mg BID D2-D10 200 mg BID	0.012	0.013	0.016	0.024	0.007	0.008	0.010	0.014
D1 400 mg BID D2-D10 200 mg BID	0.008	0.011	0.014	0.023	0.005	0.006	0.009	0.013
D1 400 mg BID D2-D5 200 mg BID	0.008	0.011	0.014	0.010	0.005	0.006	0.009	0.006

Notes:

[a] Dosing regimen information was obtained from Table 1 in Yao et al. article[1]. The Ctrough concentrations were digitized from Figure 3 in Yao et al. article[1]. The fraction unbound in plasma (fu,plasma) is 0.5. The model performance regarding the HCQ plasma concentration prediction has been independently verified by the authors of this report.

[b] The EC50 values for HCQ against SARS-CoV-2 infection in vitro at different multiplicity of infection (MOI, the ratio between the number of viruses and the number of host cells) reported by Liu et al were 4.51 µM (MOI=0.01), 4.06 µM (MOI = 0.02), 17.31 µM (MOI = 0.2), and 12.96 µM (MOI = 0.8) at 48 hours post-infection[5]. The EC50 values reported by Yao et al. were 6.14 µM (MOI = 0.01 for at 24 hours post-infection), and 0.72 µM (MOI = 0.01 at 48 hours post-infection)[1]. The EC90 values for HCQ reported by Liu et al were 16.9 µM (MOI=0.01), 22.3 µM (MOI = 0.02), and >50 µM (MOI = 0.2 and 0.8)[5]. The EC90 values reported by Yao et al. were 16.5 µM (MOI = 0.01 at 24 hours post-infection), and 10 µM (MOI = 0.01 at 48 hours post-infection)[1]. Only EC50 and EC90 values representing MOI of 0.01 were used in the calculation above.

Figure 1

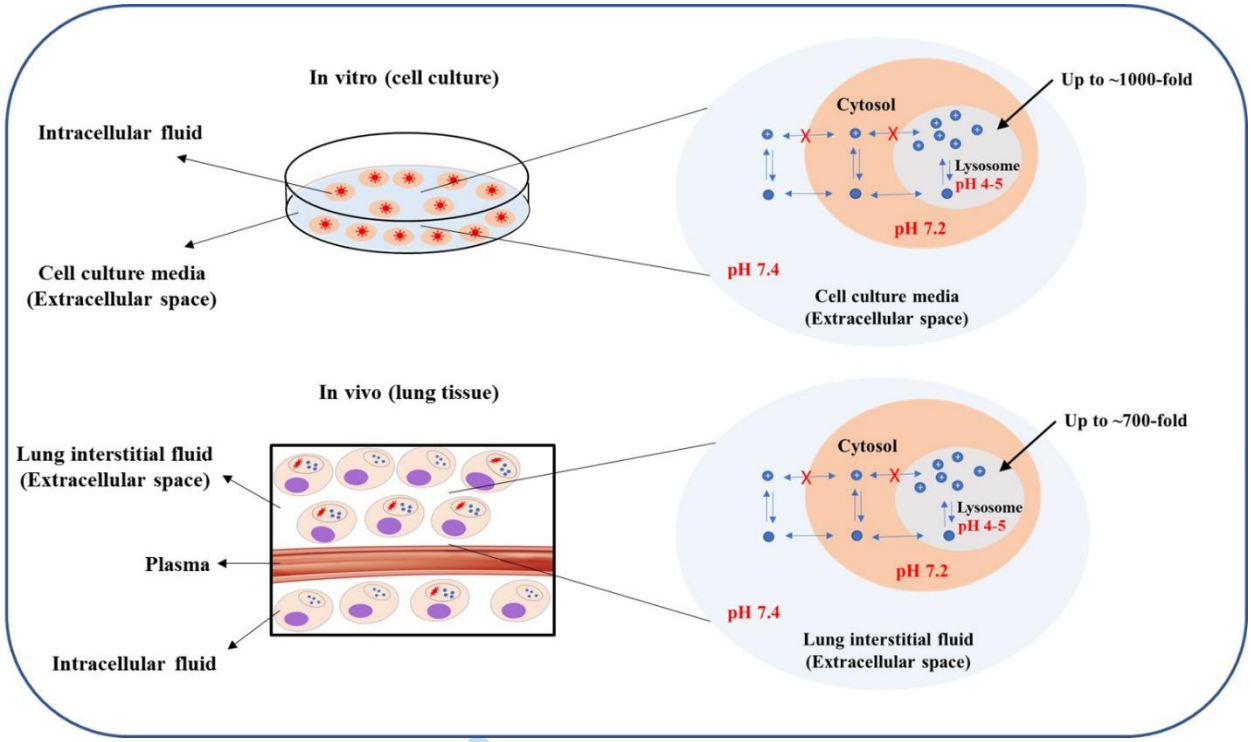

Figure 2