Sentinel

Strategies for the Use of Real-World Data to Conduct COVID-19-Related Pharmacoepidemiology Studies

ICPE 2021 All Access

August 25, 2021

Disclosures, Funding, and Disclaimers

Work discussed was funded by the U.S. Food and Drug Administration's Sentinel Initiative (Master Agreement 75F40119D10037) and supported in part by HCA Healthcare.

The views expressed represent those of the authors and do not necessarily represent the official views of the U.S. Food and Drug Administration or HCA Healthcare or any of its affiliated entities.

The authors have no relevant disclosures.

https://www.sentinelinitiative.org/
https://hcahealthcare.com/

Introduction

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RWD and COVID-19

The pandemic has demanded the rapid conduct of assessments of COVID-19 natural history and treatment utilization, safety, and effectiveness

There are important considerations for studying COVID-19 in general, and with RWD:

- Near real-time data – challenges and opportunities
- Study-specific fit-for-purpose data assessment must be done
- COVID-related laboratory tests, diagnoses, severity, complications
- Collaboration, transparency, and replication of key studies

Objectives

Describe key considerations, challenges to implementing pharmacoepi studies of COVID-19 with observational data
Explain how use of a Master Protocol can facilitate harmonization and evaluation of RWD across data partners
Review approaches to defining key variables of interest for COVID-19 studies (infection status, severity, complications, treatments)
Discuss the importance of promoting collaborations to enhance the validity and generalizability of pharmacoepidemiologic results

Agenda

01 **Use of Master Protocols**

Vincent Lo Re, MD, MSCE - Univ. of Pennsylvania

Wei Hua, MD, PhD - US FDA

02 **Studying COVID-19 using inpatient EHR data**

Candace Fuller, PhD, MPH

Harvard Pilgrim Health Care Institute

03 **Studying COVID-19 using claims data**

Noelle Cocoros, DSC, MPH

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04 **Collaborations - researchers, data providers, regulatory agencies**

Silvia Perez-Vilar, PhD, PharmD

US FDA

05 **Discussion**

Sentinel

A Master Protocol to Identify COVID-19 and Relevant Data in the US FDA Sentinel System

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CENTER FOR CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS

FDA U.S. FOOD & DRUG ADMINISTRATION

Pandemic Response – Infrastructure Development to Facilitate Drug Safety and Effectiveness Evaluation Using RWD

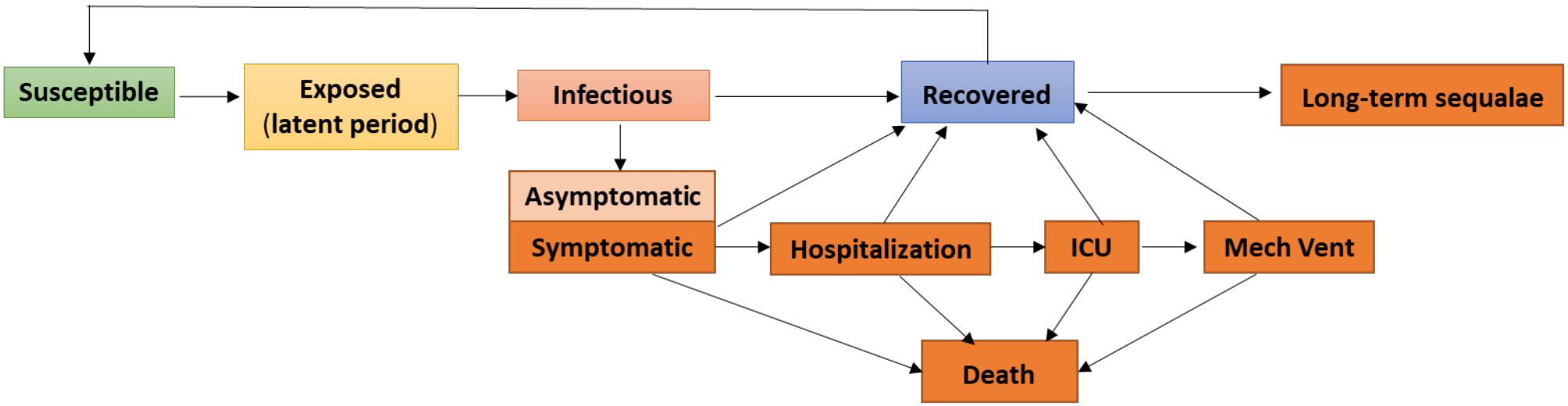
- FDA formed a multidisciplinary team in March 2020 to establish COVID-19 cohorts for understanding of natural history of disease, drug safety/effectiveness using RWD

- Forward looking given:
  - Limited data on COVID-19 disease and treatments
  - Unclear how pandemic would evolve
  - Uncertainty how the federal/local policies would impact transmission dynamics

Establishing COVID-19 Cohorts to Address Needs

- Describe course and outcomes of COVID-19 illness in various demographic groups and examine changes overtime
- Determine prognostic factors for COVID-19 based on data early in course of illness
- Determine incidence, determinants of COVID-19-related complications
- Study effectiveness, safety of intervention to treat COVID-19 and its complications
- Provide a benchmark, or serve as an external control, for single-arm trials of COVID-19 treatments in relevant patient populations

Inclusive Cohort to Provide Integrated View of COVID-19 Progression



Parameters impacted by the timing, duration, and strength of behavioral intervention and healthcare resources, and vary by time and region

- Not restricted by age, sex, medical setting, pregnancy status, or any other feature
- Capture patient transitions, allow for open-ended follow-up
- Create sub-cohorts to address specific questions

Identify Key Variables in Clinical Trials and Reported Real-World Data

- Identify variables to identify patients, inclusion/exclusion criteria, exposures, outcomes, risk factors, confounders, effect modifiers, colliders
- Align variables with clinical trials to facilitate comparison of findings and interpretation of RWE
  - Inclusion/exclusion criteria, endpoints
  - Develop definitions to reflect clinical concepts (baseline COVID-19 severity categories)
- Continue to update as new information becomes available from various sources

Considerations For Alignment Between RCT and RWD

#	Baseline COVID-19 severity categorization (FDA Guidance, May 2020) *	Suggested practical severity definition for RWD **
1	**Asymptomatic** [SARS-CoV-2 testing] Positive testing by standard RT-PCR assay or equivalent test AND [Symptoms] No symptoms in Row 2	**Asymptomatic or very mild** Positive laboratory test for SARS-CoV-2 (consistent with inclusion criteria of specific study) AND No symptoms from the Conceptual Definition, Row 2 list and no pneumonia AND No initiation of any oxygen therapy or hospitalization
2	**Mild illness** [SARS-CoV-2 testing] Positive testing by standard RT-PCR assay or equivalent test AND [Symptoms] Could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea AND [No clinical signs indicative of Moderate, Severe, or Critical Severity]	**Mild illness** Positive laboratory test for SARS-CoV-2 (consistent with inclusion criteria of specific study) AND Any symptom from the Conceptual Definition, Row 2 list (*excluding* new-onset dyspnea) but no pneumonia AND No initiation of any oxygen therapy or hospitalization
3	**Moderate illness** [SARS-CoV-2 testing] Positive testing by standard RT-PCR assay or equivalent test AND [Symptoms] Could include any symptom of Mild illness or shortness of breath with exertion AND [Clinical signs] Such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute AND [No clinical signs indicative of Severe or Critical Severity]	**Moderate illness** *[In contrast with Mild, must have dyspnea or pneumonia or hospitalization (without ICU)]* Positive laboratory test for SARS-CoV-2 (consistent with inclusion criteria of specific study) AND Any symptom from the Conceptual Definition, Row 2 list (*including* new-onset dyspnea) or pneumonia AND No initiation of any oxygen therapy or ICU admission or organ failure
4	**Severe illness** [SARS-CoV-2 testing] Positive testing by standard RT-PCR assay or equivalent test AND [Symptoms] Could include any symptom of Moderate illness or shortness of breath at rest, or respiratory distress AND [Clinical signs] Such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 <300 AND [No criteria for Critical Severity]	**Severe illness** *[In contrast with Moderate, must have initiation of any oxygen therapy (without intubation/IMV or ECMO) or admission to ICU]* Positive laboratory test for SARS-CoV-2 (consistent with inclusion criteria of specific study) AND Any symptom from the Conceptual Definition, Row 2 list (*including* new-onset dyspnea) or pneumonia AND Hospitalization or admission to ICU but no intubation/IMV or ECMO and no organ failure
5	**Critical illness** [SARS-CoV-2 testing] Positive testing by standard RT-PCR assay or equivalent test AND Evidence of critical illness, at least one of the following: [1. Respiratory failure] At least one: endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation) OR [2. Shock] Systolic blood pressure < 90 mmHg, or diastolic blood pressure < 60 mmHg or requiring vasopressors OR [3. Multi-organ dysfunction/failure]	**Critical illness** Positive laboratory test for SARS-CoV-2 (consistent with inclusion criteria of specific study) AND Organ failure recorded during a hospitalization or evidence of intubation/IMV or ECMO

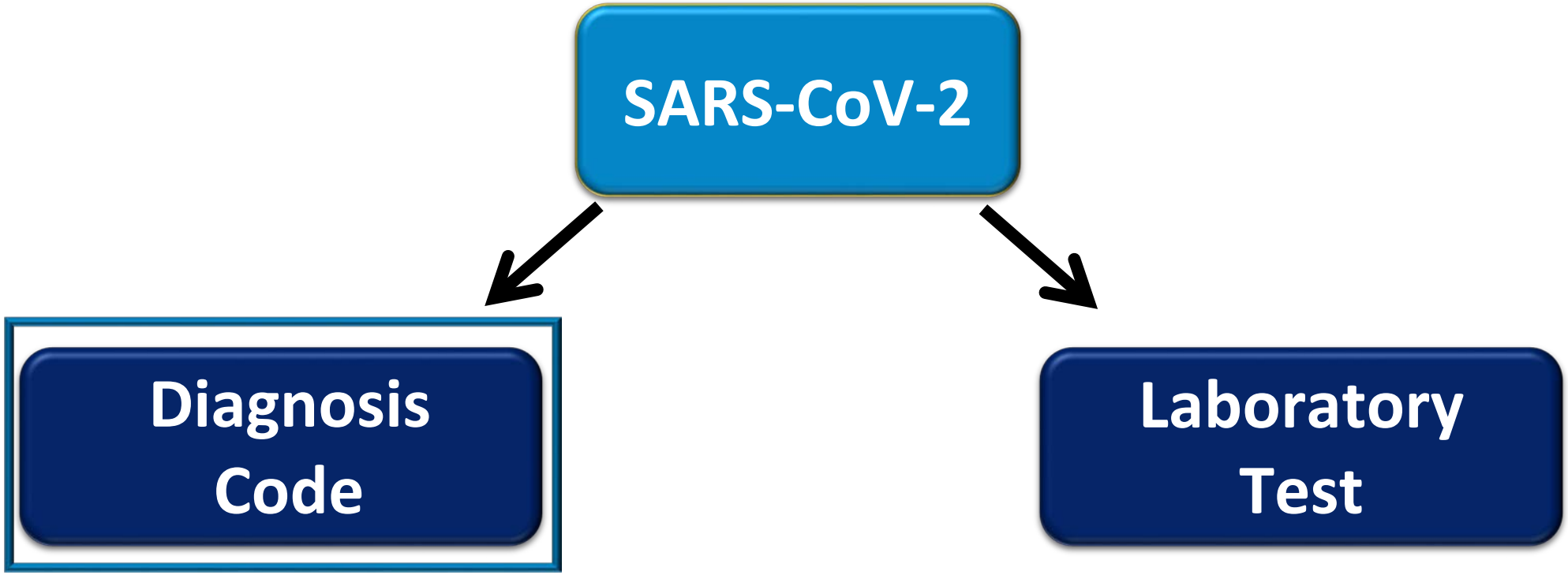
* US Food and Drug Administration. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry, May 2020

** COVID-19 Natural History Master Protocol, October 2020 https://www.sentinelinitiative.org/methods-data-tools/methods/master-protocol-development-covid-19-natural-history

Considerations For Specific Populations

Data Elements Wishlist (Source: clinical trials, individual case reports, observational studies, professional society/group recommendations, federal partners, other stakeholders)	Priority for Specific Population			
	Adults	Pediatrics	Pregnant Women	Patients Receiving COVID-19 Meds
Demographics				
- *Age, sex, race, ethnicity, Smoking, alcohol, height, weight, etc.*				
Pre-existing conditions				
- *Allergy, asthma, COPD, hypertension, diabetes, cardiovascular, cerebrovascular, neurological disease, chronic kidney disease, chronic liver disease, malignancy, HIV, organ transplantation, stem cell transplantation, rheumatic disease, sickle cell disease, G6PD deficiency, congenital malformation, etc.*				
Concomitant medications for comorbidities				
- *Immunosuppressive therapy, immunostimulant therapy, ACEi/ARB, NSAIDS, antiviral therapy, antibiotic therapy, etc.*				
Covid-19 signs and symptoms (Date, Time)				
- *List of symptoms, respiratory rate, heart rate, blood pressure, SaO2, other variables required for defining severity, etc.*				
COVID-19 lab and imaging findings (Date, Time, Results)				
- *PCR or other clinically utilized test, SARS-CoV-2 viral load, WBC differential, hemoglobulin, anemia, platelet count, albumin, ALS, AST, creatinine, lactate dehydrogenase, creatine kinase, cardiac troponin, BNP, NT-proBNP, prothrombin, serum ferritin, CRP, IL-6, procalcitonin, chest XR, CT scan, EKG, echocardiography, etc.*				
COVID-19 Specific treatments and supportive Medications (Date, Time)				
- *COVID-19 specific meds (e.g., remdesivir), non-med therapies (e.g., convalescent plasma), vasopressors, etc.*				
COVID-19 progression, complications, and outcomes (Date, Time, Duration)				
- *Respiratory failure, ARDS, shock, MODS, acute cardiac injury, arrythmia, AKI, hepatic injury, thrombotic events, neurological disorders (e.g., GBS, meningitis, encephalitis), bacterial superinfections, Kawasaki disease, multi-system hyperinflammatory syndrome, hospitalization, ICU, oxygen therapy, death, etc.*				
Pregnancy outcomes				
- *Live birth term, live birth pre-term, SAB, stillbirth, termination, C-section, maternal death, pre-eclampsia, pregnancy-related thrombosis, small for gestational age, major malformations, vertical transmission, etc.*				

Master Protocol Considerations in Identifying Persons with SARS-CoV-2 Infection in Sentinel



Requires Consideration of Type of Data Available:

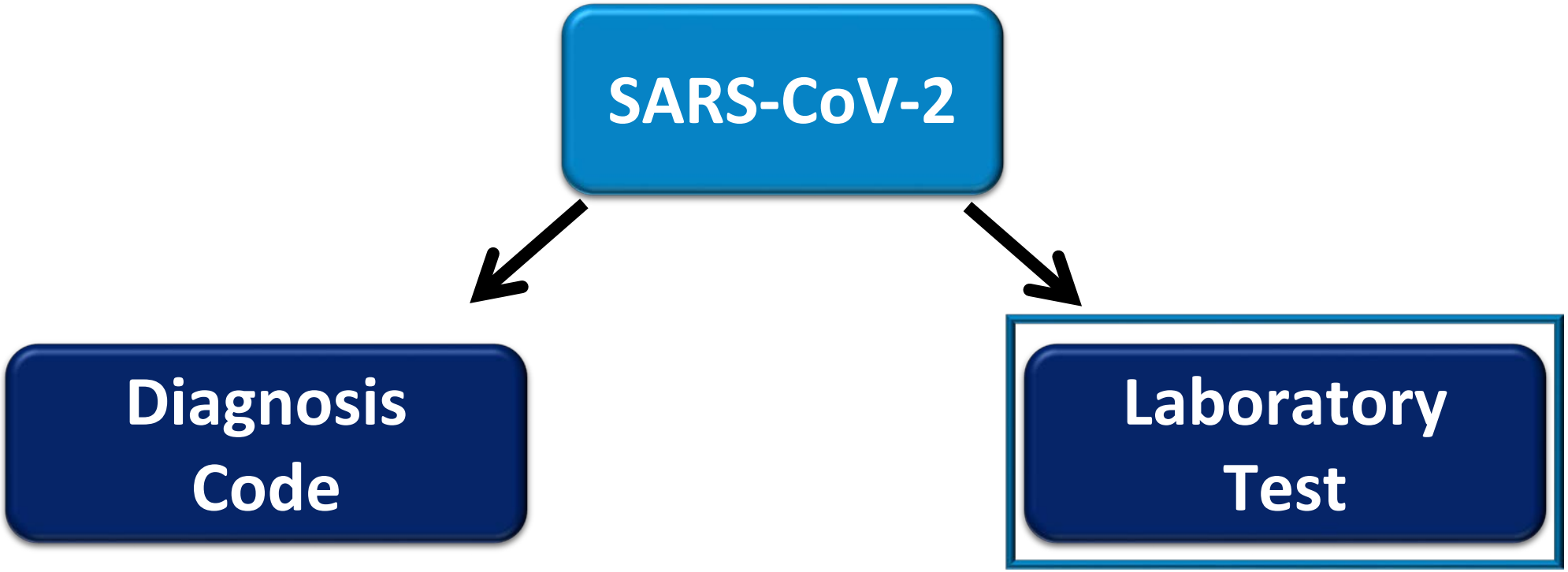
Administrative vs. Electronic Health Records

Considerations in Identifying Persons with SARS-CoV-2 Infection: Diagnosis Codes

ICD-10	Code Description	
U07.1	COVID-19 identified	Specific Widely used
B34.2	Coronavirus infection, unspecified site	Non-specific
B97.21	SARS-associated coronavirus	
B97.29	Other coronavirus as cause of disease	
J12.81	Pneumonia due to SARS-associated coronavirus	

- Validity of U07.1 unknown in Sentinel (established 1 April, 2020)
- Conducted study to assess **accuracy** of U07.1 diagnosis code

Master Protocol Considerations in Identifying Persons with SARS-CoV-2 Infection in Sentinel



Requires Consideration of Type of Data Available:

Administrative vs. Electronic Health Records

Considerations in Identifying Persons with SARS-CoV-2 Infection: Laboratory Tests

Considerations:

- Availability of laboratory test during study period of interest
- How test is used by clinicians caring for persons with COVID-19
- Accuracy of test → potential for misclassification

Considerations in Identifying Persons with SARS-CoV-2 Infection: Laboratory Tests

SARS-CoV-2 Laboratory Test	Test Considerations
Nucleic acid test	• Most widely used to detect SARS-CoV-2 • High sensitivity, specificity • Genetic variants may lead to false-negative results
Antigen test	• High false-negative rate vs. nucleic acid tests • False-positive rate may be high, esp. if asymptomatic
Antibody test	• Determines previous viral exposure or immune status • Not appropriate to identify newly diagnosed COVID-19

Cheng MP. *Ann Intern Med* 2020;172:726-734.

Dinnes J. *Cochrane Database of Systematic Reviews* 2021; Issue 3. Art. No.: CD013705.

Approaches to Identifying Persons with SARS-CoV-2 Infection in Sentinel Master Protocol

Classify health plan members with COVID-19 if they had:

1. Ambulatory or hospital discharge ICD-10 (any position)
   or
   Positive SARS-CoV-2 nucleic acid test (any location)

Index Date (April 2020→)

- 1st COVID-19 ICD-10 date
- Specimen collection date for 1st SARS-CoV-2 lab test

2. Positive SARS-CoV-2 nucleic acid test (any location)

3. Index diagnosis in hospital

4. Index diagnosis in ambulatory setting

Master Protocol Assessment of Severity of COVID-19 at Diagnosis: Scheme #1

COVID-19 Severity	Criteria
Asymptomatic or very mild	No symptoms or pneumonia AND No initiation of oxygen therapy or hospitalization
Mild	Any symptom (*excluding* new-onset dyspnea) but no pneumonia AND No initiation of oxygen therapy or hospitalization
Moderate	Any symptom or pneumonia AND No initiation of oxygen therapy, ICU admission, or organ failure
Severe	Any symptom or pneumonia AND ICU admission, but no mechanical ventilation or organ failure
Critical	Organ failure or mechanical ventilation

Master Protocol Assessment of Severity of COVID-19 at Diagnosis: Scheme #1

Fever, cough, sore throat, malaise, headache, muscle pain, GI symptoms, dyspnea

COVID-19 Severity	
Asymptomatic or very mild	No symptoms or pneumonia AND No initiation of oxygen therapy or hospitalization
Mild	Any symptom (*excluding* new-onset dyspnea) but no pneumonia AND No initiation of oxygen therapy or hospitalization
Moderate	Any symptom or pneumonia AND No initiation of oxygen therapy, ICU admission, or organ failure
Severe	Any symptom or pneumonia AND ICU admission, but no mechanical ventilation or organ failure
Critical	Organ failure or mechanical ventilation

Master Protocol Assessment of Severity of COVID-19 at Diagnosis: Scheme #2

COVID-19 Severity	Criteria
Mild	Not hospitalized
Moderate	Hospitalized, but not admitted to ICU or mechanically ventilated
Severe	Hospitalized *plus* either admitted to ICU or mechanically ventilated

Master Protocol Baseline Data to Collect for Pharmacoepidemiologic Analyses of COVID-19

Data Element(s)	Potential Variables to Collect (Examples)
Demographics	Age at diagnosis, sex, race/ethnicity, geographic location
Pre-Existing Conditions	Pregnancy, cardiovascular disease, diabetes, hypertension, liver disease, kidney disease, COPD, current smoking, alcohol abuse
Pre-Existing Medications	Statins, ACE/ARBs, anticoagulants, anti-platelet drugs
Laboratory Results	Hemoglobin, platelets, serum creatinine, liver function
Vital Signs	Blood pressure, respiratory rate, heart rate, O_2 saturation
Radiographic Reports	Chest X-ray, chest CT, chest MRI

Master Protocol Longitudinal Data to Collect for Pharmacoepidemiologic Analyses of COVID-19

Data Element(s)	Potential Variables to Collect (Examples)
Medications	Statins, ACE/ARBs, anticoagulants, anti-platelet drugs
Laboratory Results	Hemoglobin, platelets, serum creatinine, liver function, D-dimer
Vital Signs	Blood pressure, respiratory rate, heart rate, O_2 saturation
Radiographic Reports	Chest X-ray, chest CT, chest MRI
SARS-CoV-2 Treatments	Remdesivir, dexamethasone, plasma, monoclonal antibodies, baricitinib
COVID-19 Supportive Therapies	Supplemental O_2, high flow nasal cannula, mechanical ventilation, extracorporeal membrane oxygenation
COVID-19 Complications	Acute DVT, acute PE, pneumonia, bacterial infections, fetal demise, death

Sentinel Master Protocol Includes Important Data Considerations for COVID-19 Analyses

- Duration of baseline period → may vary by data source
- Need to explore ascertainment, completeness of variables → SARS-CoV-2 tests, D-dimer, O_2 saturation, inpatient meds
- Missing data → race, symptom onset, over-the-counter meds
- Uncertain validity of variables → supplemental O_2, COVID-19 severity
- Need to review medical records → validations, extract radiographic reports

Sentinel Master Protocol Considers Important Potential Limitations for COVID-19 Analyses

Misclassification bias
- SARS-CoV-2 diagnosis, COVID-19 severity, supplemental O_2
- Validation studies

Selection bias
- Variability in SARS-CoV-2 testing over time, by disease severity and geographic location
- Sensitivity analyses: by time periods, COVID-19 severity, setting of diagnosis, location

Protopathic bias
- Medications may be prescribed for early symptoms of disease not yet diagnosed
- Sensitivity analyses: examine different exposure windows prior to COVID-19 diagnosis

Collider bias
- Likelihood of being sampled relates to risk factor and outcome of interest
- Sensitivity analyses: probability weighting of sample, negative control analyses

Summary: Utility of Master Protocol* for Pharmacoepidemiologic Analyses of COVID-19

- Global need for rapid acquisition of data across different settings, subgroups
- Facilitate harmonization of study designs, methods across data sources
- Assess homogeneity of findings across data sources, regions, countries
- Promote collaboration, communication across regulatory agencies

* Access at: https://www.sentinelinitiative.org/methods-data-tools/methods/master-protocol-development-covid-19-natural-history

Acknowledgements

- **Harvard Pilgrim Health Care Institute**
  - W. Katherine Yih, PhD, MPH
  - Jennifer Lyons, PhD
  - Maria Kempner, BA
  - Christine Draper, BA
  - Dena M. Carbonari, MS
  - Meighan Rogers Driscoll, MPH
  - Darren Toh, ScD
- **US Food and Drug Administration**
  - Yodit Belew, MD
  - Kirk Chan-Tack, MD
  - Leyla Sahin, MD
  - Susan McCune, MD
  - Dionna Green, MD
  - Gerri Baer, MD
  - Ann McMahon, MD
  - Fang Tian, PhD
  - Sarah Dutcher, PhD
  - Brian Kit, MD, MPH

Funding: HHSF223201400030I

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Studying COVID-19 Using Inpatient EHR Data

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HARVARD MEDICAL SCHOOL

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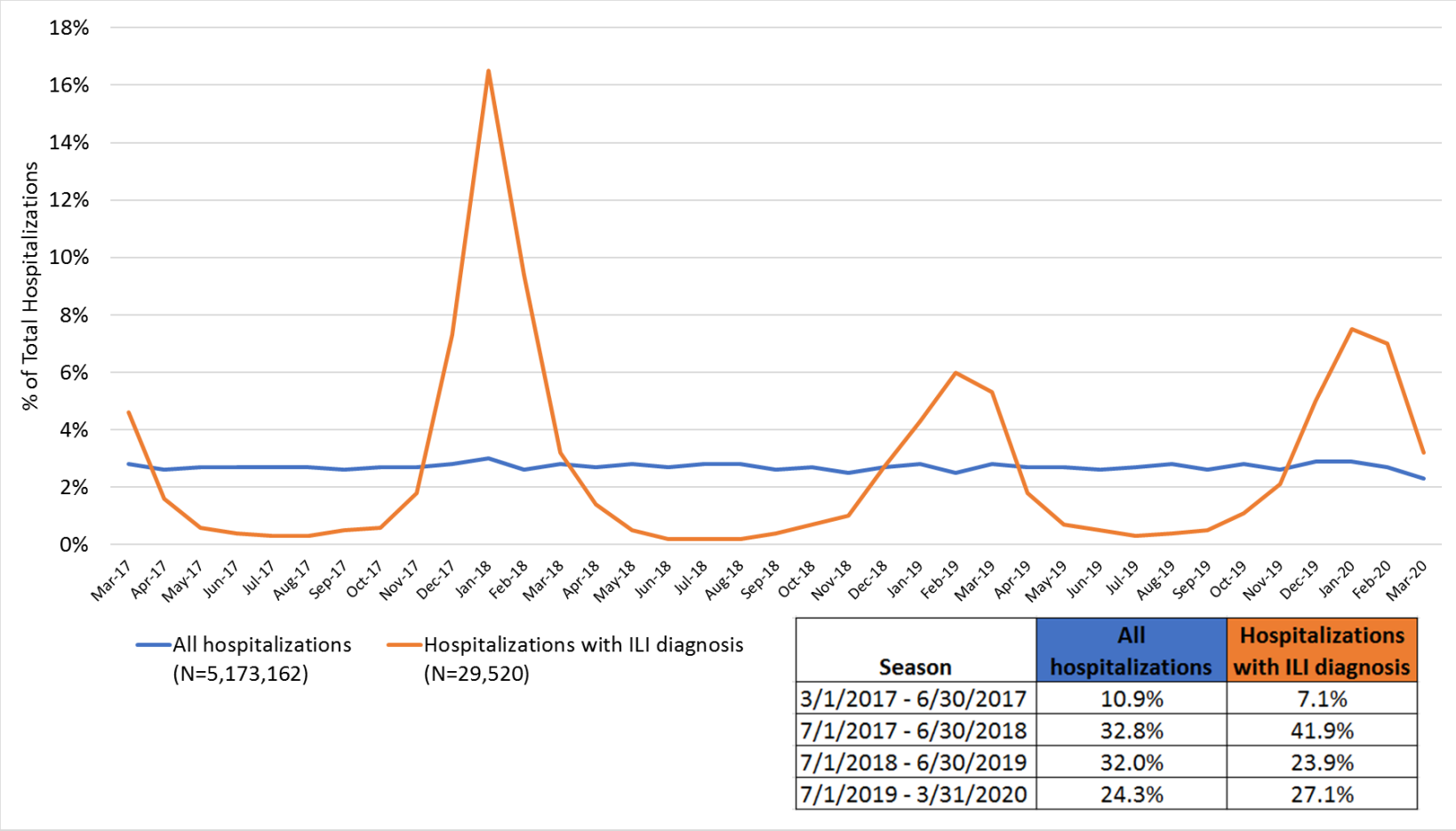
Inpatient EHR Data During the COVID-19 Pandemic

- Pharmacoepidemiologists need to understand the clinical course of COVID-19 to support assessments of the safety and effectiveness of drugs
- Requires detailed inpatient data
  - In the US claims data can be inadequate for this purpose, and EHRs are often not linked to other data sources
- Detailed real-time information on hospitalized patients on a large scale can only come from inpatient EHR
  - Capturing / analyzing data during a public health emergency is a challenge
  - Need for near real-time surveillance for large and diverse patient populations is only growing
- Ongoing monitoring helps respond to on-demand questions regarding clinical characteristics of COVID-19 patients, treatments, and outcomes

Leveraged Sentinel's Pandemic Preparation Activities* at HCA Health Care: Hospitalizations with Influenza, March 2017 - March 2020



Season	All hospitalizations	Hospitalizations with ILI diagnosis
3/1/2017 - 6/30/2017	10.9%	7.1%
7/1/2017 - 6/30/2018	32.8%	41.9%
7/1/2018 - 6/30/2019	32.0%	23.9%
7/1/2019 - 3/31/2020	24.3%	27.1%

- Routine reports on patterns of care and clinical outcomes
- Direct engagement with system experts very helpful

*Assessing Sentinel System Capability to Collect and Analyze Medical Countermeasure Data for the FDA Office of Counterterrorism and Emerging Threats (OCET): https://www.sentinelinitiative.org/methods-data-tools/methods/assessing-sentinel-system-capability-collect-and-analyze-medical

PDS Pharmacoepidemiology & Drug Safety
ispe Official Journal of the International Society for Pharmacoepidemiology

REVIEW | Free Access

A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System

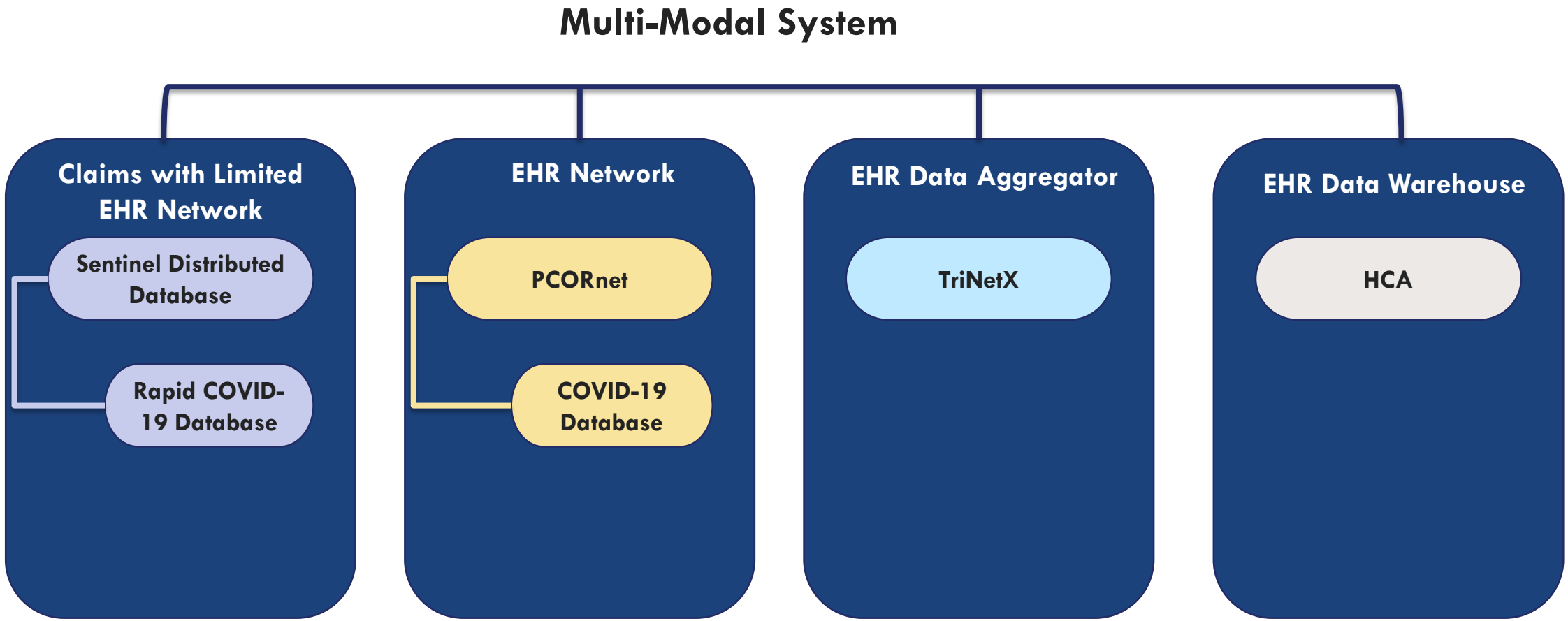
Noelle M. Cocoros, Candace C. Fuller, Sruthi Adimadhyam, Robert Ball, Jeffrey S. Brown, Gerald J. Dal Pan, Sheryl A. Kluberg, Vincent Lo Re 3rd, Judith C. Maro, Michael Nguyen, Robert Orr, Dianne Paraoan, Jonathan Perlin, Russell E. Poland, Meighan Rogers Driscoll, Kenneth Sands, Sengwee Toh, W. Katherine Yih, Richard Platt, And the FDA-Sentinel COVID-19 Working Group ... See fewer authors

First published: 02 April 2021 | https://doi.org/10.1002/pds.5240

Members of the FDA-Sentinel COVID-19 Working Group: Catherine Corey, MSPH; Grace Chai, PharmD; Sarah K. Dutcher, PhD; Wei Hua, MD; Brian Kit, MD; Silvia Perez-Vilar, PhD; Danijela Stojanovic, PhD; Corinne Woods, MPH.

Cocoros NM, et al. A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System. Pharmacoepidemiol Drug Saf. 2021 Jul;30(7):827-837. doi: 10.1002/pds.5240. Epub 2021 Apr 18. PMID: 33797815.

Currently Available Data Sources for Sentinel



Inpatient EHR Data in the Time of COVID-19

Inpatient EHRs provide

- Near real-time data for surveillance
- Detailed clinical information about care received in hospital

Important Challenges and Considerations
Data completeness –real-time data
Identifying persons with COVID-19 – inpatient tests
Patient characteristics – during stay only, self-reported race/ethnicity
High risk conditions- coded during stay
Inpatient treatments, supportive therapies – care received in hospital
Complications and death – inpatient only
Deep understanding of source data – engage with clinicians

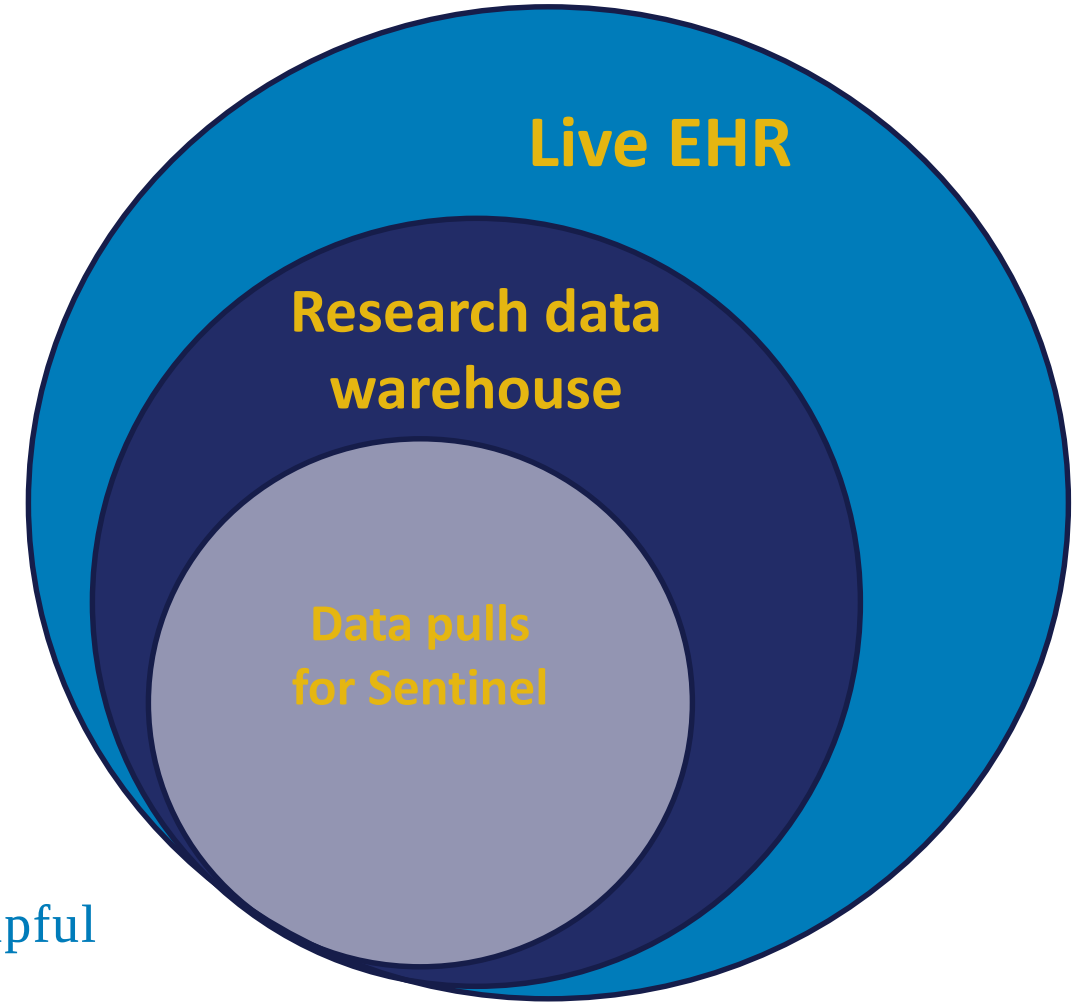
Inpatient EHR Data Analyzed for COVID-19 Studies

When working with "fresh data" – must balance freshness with completeness

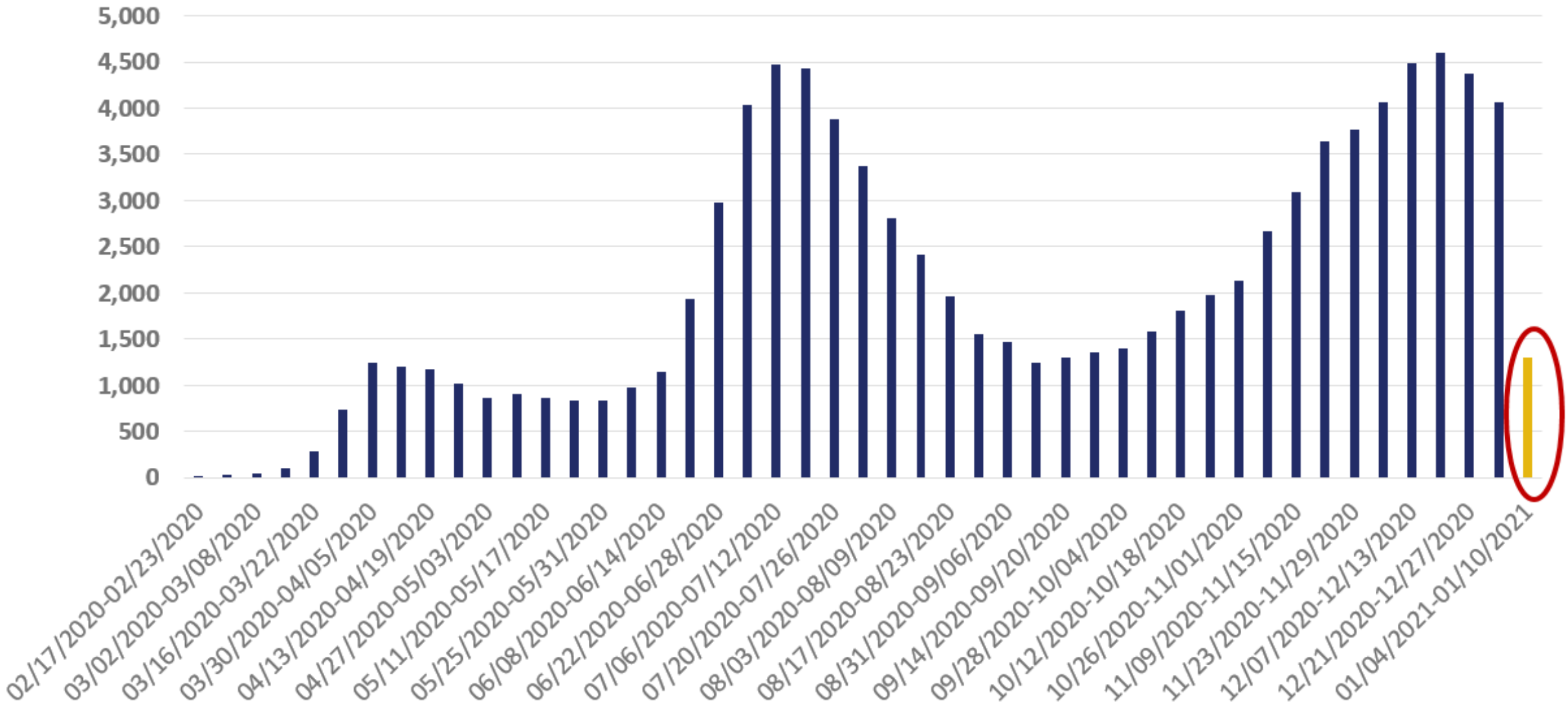
- How frequently to update, and what data streams are needed?
- Interoperability- (e.g., Meditech, Epic)
- What variables need standardization?
  - Coded data (e.g., ICD-10-CM) may not be sufficient

- **To ensure complete: restricting data pulls to discharged patients "completely coded"**

- Direct engagement with system experts very helpful



COVID-19 Hospitalizations by Admission Week, Data Pulled Late January 2020 (n=140 hospitals)



How to Identify Persons with COVID-19?

- COVID-19 diagnosis or laboratory confirmed cases?
  - PPV of inpatient COVID-19 diagnosis compared to SARS-CoV-2 tests during pandemic is expected ↑
    - If **incidence** ↓ may change
  - Inpatient EHR data may only contain detail about laboratory tests conducted **in same** hospital
    - Recent analyses across 140 hospitals- 79% hospitalized adults with record of SARS-CoV-2 test during hospitalization- 97% of these had + result (majority PCR)

ICD Code	Date Established	Description
B34.2	10/1/2015	Coronavirus infection, unspecified
B97.2	10/1/2015	Coronavirus as the cause of diseases classified elsewhere
B97.21	10/1/2015	SARS-associated coronavirus causing diseases classified elsewhere
B97.29	10/1/2015	Other coronavirus as the cause of diseases classified elsewhere
J12.81	10/1/2015	Pneumonia due to SARS-associated coronavirus
U07.1	4/1/2020	COVID-19
J12.82	1/1/2021	Pneumonia due to coronavirus disease 2019

Considerations for Inpatient SARS-CoV-2 Tests

Example SARS-CoV-2 PCR test **LOINC***

Proc_Mnem	Proc_Name	Clinical_Proc_EMR_ID	Code
COVID19CALL	STATE CALL TEST	N/A	
COV19M	SARS-CoV-2 IgM Antibody	SARS-CoV-2 IgM Antibody	
COV19G	SARS-CoV-2 IgG Antibody	SARS-CoV-2 IgG Antibody	
COVIDEVAL	Coronavirus 2019 Evaluation	Miscellaneous Test	
COVID19IH	Novel Coronavirus (2019 nCoV)	Coronavirus (COVID-19)(PCR)	
COVID19	Novel Coronavirus 2019 nCoV	Coronavirus (COVID-19)(PCR)	
COVID19	Novel Coronavirus 2019 nCoV	Coronavirus (PCR)	
COVID19Transfer	COVID19Transfer	Coronavirus (COVID-19)(PCR)	
COVID19CONF	Coronavirus 2019 Confirmation	Coronavirus (PCR)	
COVID19LCA	NOVEL CORONAVIRUS 2019 nCov	Coronavirus 2019 (NAA)	
COVID19IH	NOVEL CORONAVIRUS 2019 nCoV	Coronavirus (COVID-19)(PCR)	94532-9
COVID19IHWH	NOVEL CORONAVIRUS 2019 nCoV	Coronavirus (COVID-19)(PCR)	94532-9

- Requires identifying tests- practices may vary by hospital, LOINCs* may not be available
- Can be challenging to classify test type (PCR, antibody, or antigen)
- May require consultation with individual hospitals

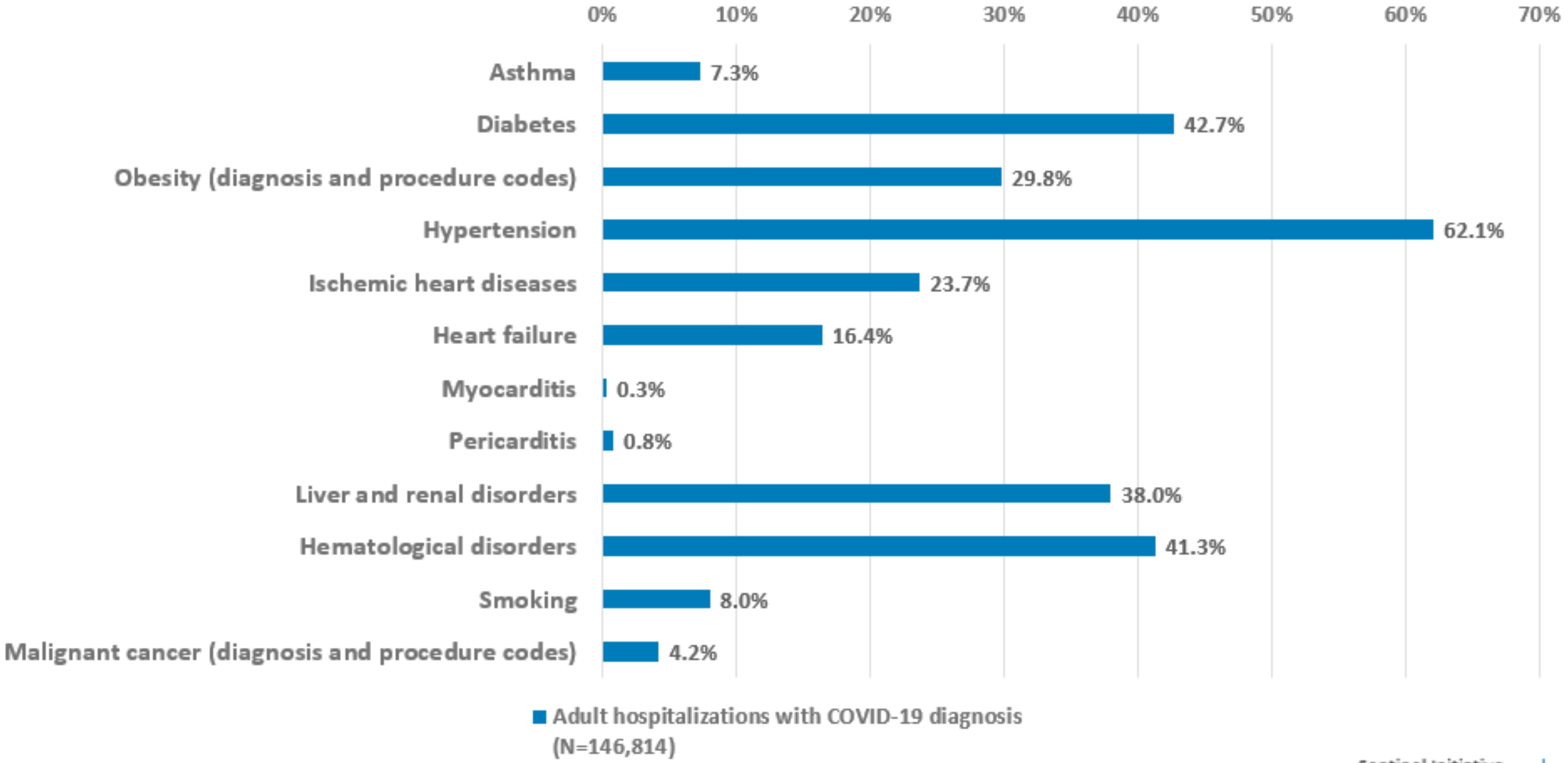
*Logical Observation Identifiers Names and Codes, https://loinc.org/sars-coronavirus-2/

Considerations for Inpatient SARS-CoV-2 Tests

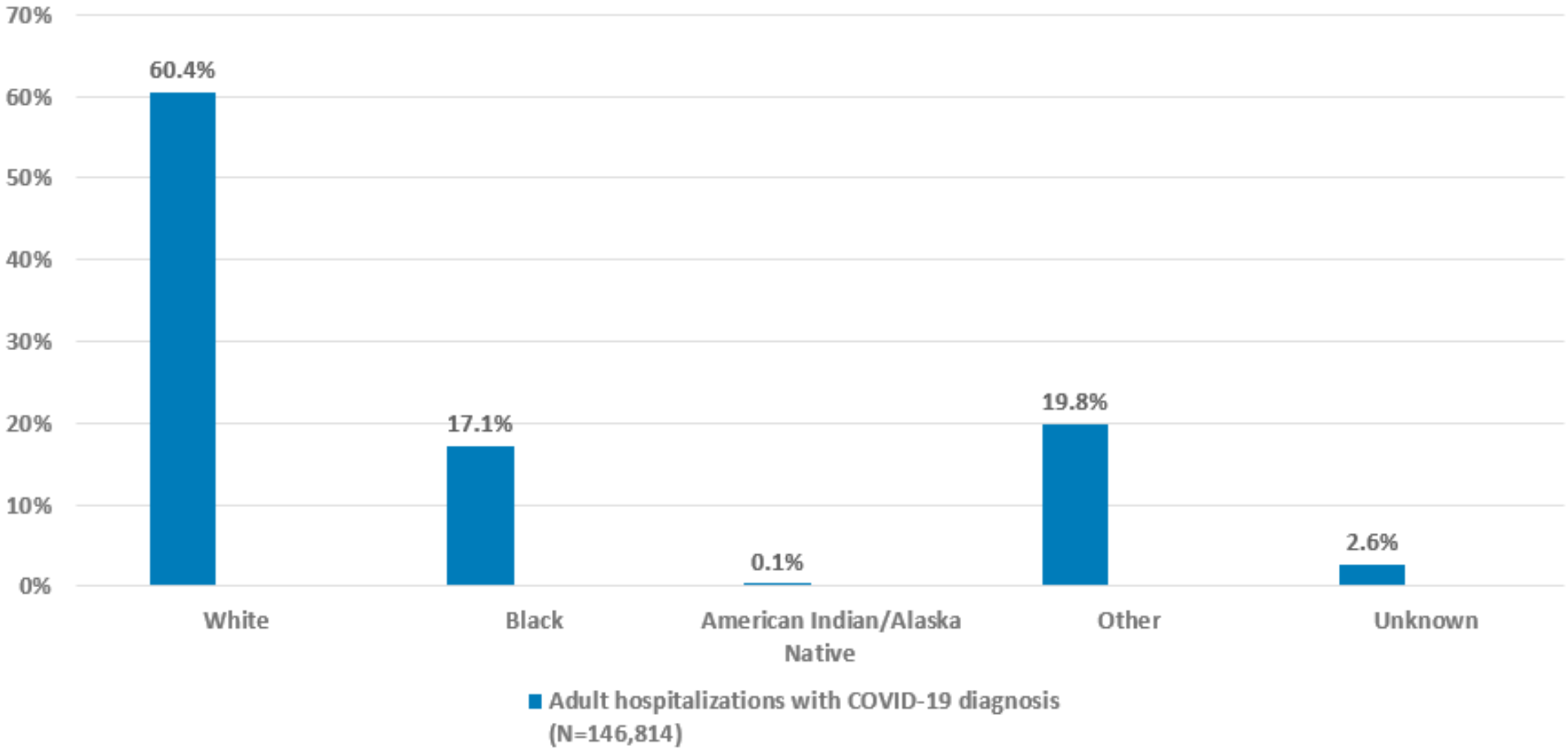
Example results:

Example results
Presum Positive
Presumptive Pos
Negative
Confrimed Positive
Verbal Positive
Antigen POS
Positive retest IP
Negative
Not Detected
Neg
Pos
Negativ
Undet
Undetected
Detected Abnormal
Confirmed Detection
Not DetA
NegativeA
INPATIENT POS
IP NEGATIVE
Comment: Patient Neg
NEGATIVEO

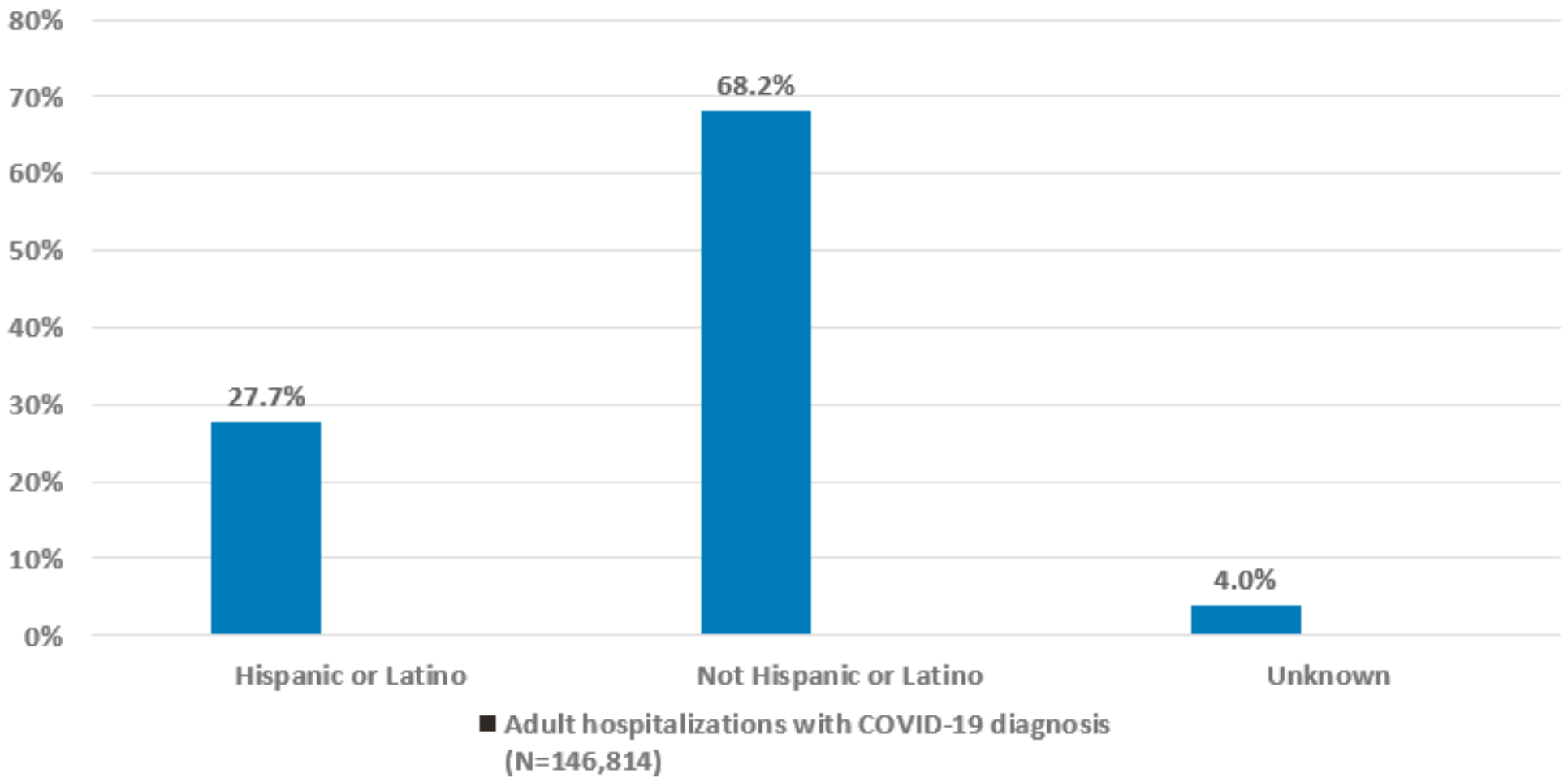
What Covariates to Collect? Example High-Risk Conditions Coded During Hospitalization



What Covariates to Collect? Inpatient EHR - Race Often Well Captured

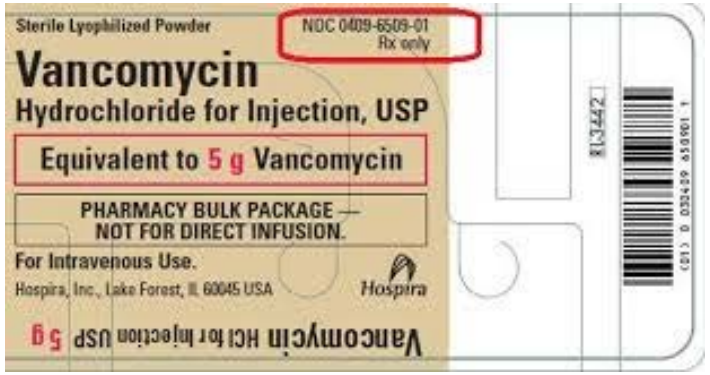


What Covariates to Collect? Inpatient EHR-Ethnicity Often Well Captured



How to Define Exposure? Inpatient Medications

- Administrations often include:
  - Date, Time
  - Dose, Route
- Many systems also have **orders**



What is most useful to your study?

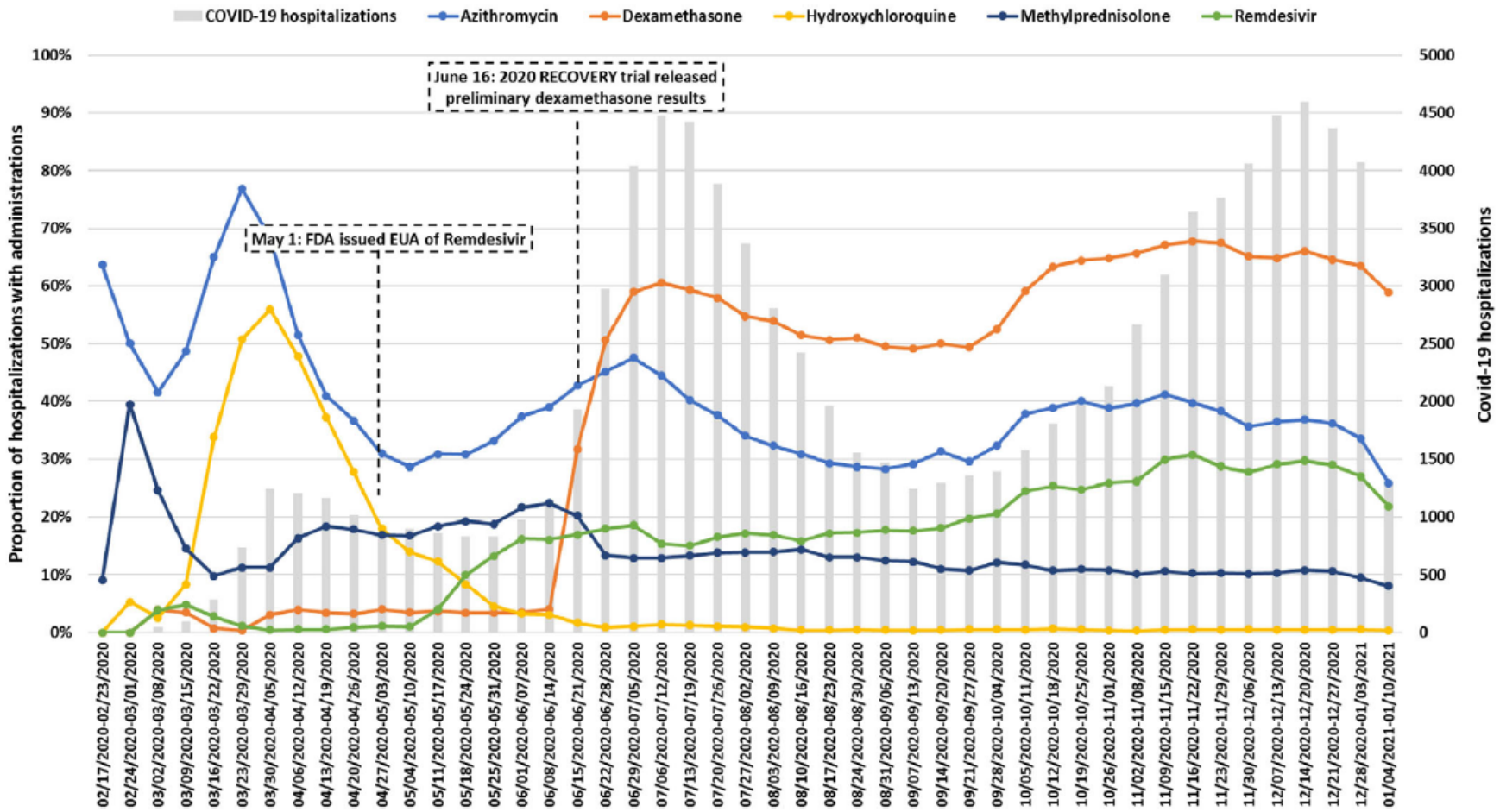


FIGURE 1 Proportion of COVID-19 hospitalizations with administration of select medications, by week, February 20, 2020-January 10, 2021, HCA Healthcare Sentinel System data. The gray bars represent COVID-19 hospitalizations independent of medication administrations. The US Food and Drug Administration issued an emergency use authorization (EUA) for remdesivir on May 1, 2020.[26] Preliminary results from the RECOVERY trial on dexamethasone were released June 16, 2020[27] [Colour figure can be viewed at wileyonlinelibrary.com]

Cocoros NM, et al. A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System. Pharmacoepidemiol Drug Saf. 2021 Jul;30(7):827-837. doi: 10.1002/pds.5240. Epub 2021 Apr 18. PMID: 33797815.

Considerations for Identifying Inpatient Medication Administrations

- **Determine which variables are standardized, and if capture differs across hospitals**
  - NDC or RxNorm may not be available – may need brand and generic names
  - Dose and route may not be standardized
  - Work with clinical experts, to ensure complete capture

- **Consult with data partner about limitations, examples**
  - Intra-operatively administered medications may not be captured
    - Pre- and post-op captured
  - Multiple-medication IV-administered preparations, may not be represented
  - Total parenteral nutrition not always be captured
  - NDCs captured may not always represent the product manufacturer

Considerations for Identifying Oxygen-related Therapy

- Important for COVID-19, previously not usually included in pharmacoepidemiology studies
- Initially observed just 28% of patients with COVID-19 had evidence of oxygen-related therapy in coded data - under capture
- Solution- worked with clinical experts to determine where this information resides
  - Oxygen-related nursing documentation, devices and other notes
- Supplemented analyses with information derived from oxygen-related nursing documentation and leveraged mappings completed by clinical experts
- Significantly improved granularity and capture of oxygen-related therapy, compared to procedure codes for mechanical ventilation and supplemental oxygen

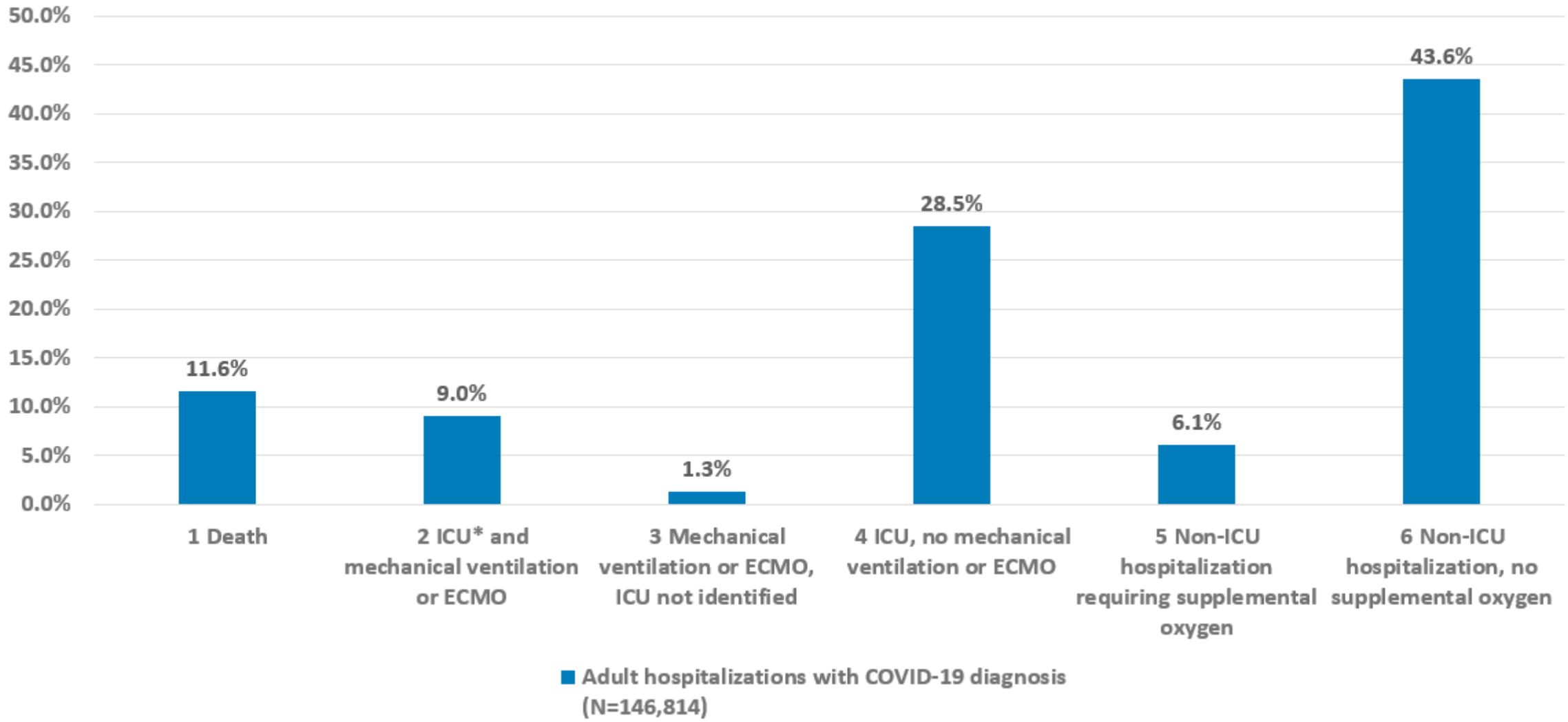
Oxygen-Related Therapy in Hospitalized Adult Patients with COVID-19 Diagnosis, Feb 2020 – Mar 2021

Oxygen-related care, nursing documentation[1]	Hospitalizations with COVID-19 diagnosis (N=137,565) %
Bilevel Positive Airway Pressure (BiPAP)	15%
High flow nasal cannula	24%
Nasal cannula (routine)	74%
Non-rebreather	20%
Oxygen conserving device	4%
Simple mask	13%
Ventilator*	14%
Any oxygen	78%
Any oxygen or ventilator	79%

- Nursing documentation improved both granularity and capture of oxygen-related therapy
- 79% were ventilated or on supplemental oxygen (compared to 28% in code-based definitions)
- Capture of invasive mechanical ventilation did not significantly change when using nursing documentation

[1]Data derived from oxygen-related nursing documentation, leveraging mappings from clinical experts.

Complications: Ordinal Endpoints (Using Coded Data)



*Intensive care unit (ICU) stays identified with revenue codes

Severity of COVID-19 at Diagnosis: Scheme #2

COVID-19 Severity	Criteria	Example estimate of ordinal endpoints
Mild	Not hospitalized	N/A as all patients were hospitalized
Moderate	Hospitalized, but not admitted to ICU or mechanically ventilated	50%
Severe	Hospitalized *plus* either admitted to ICU or mechanically ventilated	39%
Death	Discharged expired	11%

Summary

- Inpatient EHR data provide important clinical information, but requires deep understanding of underlying source data, workflows, and documentation
  - Comprehensive identification of medications or laboratory results requires careful mapping, and frequent updates to comprehensively identify in heterogenous systems
  - Consult with clinical experts, and with system creating data

- Challenges of real-time epidemiology- data lags, completeness*
  - Carefully consider data lags, completeness and how to address in your study
  - Often unable to examine patient characteristics, medication use, or care delivered before or after hospitalization without linking to another data source
  - No substitute for careful planning, investigating how to define exposures outcomes, and which covariates are captured will within EHR
  - Coded data have limitations, may need to use other clinical data streams to capture important variables (e.g., oxygen related therapy)

*Pottegård, A, Kurz, X, Moore, N, Christiansen, CF, Klungel, O. Considerations for pharmacoepidemiological analyses in the SARS-CoV-2 pandemic. *Pharmacoepidemiol Drug Saf*. 2020; 29: 825– 831. https://doi-org.ezp-prod1.hul.harvard.edu/10.1002/pds.5029

Acknowledgements

Harvard Pilgrim Health Care Institute

Austin Cosgrove, Edward Rosen, Katie Haffenreffer, Meg Her, Mayura Shinde, Christian Hague, Julia Fearrington, Jennifer Noble, Judith Maro, Richard Platt, and many others

Many colleagues at HCA Healthcare

US Food and Drug Administration

Sarah Dutcher, Natasha Pratt, Catherine Corey, Brian Kit

Sentinel

Studying COVID-19 Using Claims Data

Noelle M. Cocoros, DSc, MPH

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Harvard Pilgrim Health Care Institute

DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL

Harvard Pilgrim Health Care Institute

Study Synopsis: Natural History of Coagulopathy in COVID-19

Vincent Lo Re III, MD, MSCE,[1,2] Sarah K. Dutcher, PhD,[3] Silvia Perez-Vilar, PharmD, PhD,[3] Dena M. Carbonari, MS,[2] Sean Hennessy, PharmD, PhD,[2] Maria E. Kempner, BA,[4] Brian Kit, MD,[3] Jenice Ko, BS,[4] Allyson M. Pishko, MD, MSCE,[5] Meighan Rogers Driscoll, MPH,[4] Jeffrey Brown, PhD[4], Noelle Cocoros, DSc, MPH[4]

Affiliations 1. Division of Infectious Diseases, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 2. Department of Biostatistics, Epidemiology, and Informatics, Center for Clinical Epidemiology and Biostatistics, Center for Pharmacoepidemiology Research and Training, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; 3. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; 4. Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; 5. Division of Hematology and Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

US Claims Data in the Time of COVID-19

Claims data provide

- Longitudinality and information on medically attended, billed care
- Patient history not available in EHR-only data sources

Important Challenges and Considerations
Data completeness and timeliness (lags)
Cohort identification
Laboratory test results
Inpatient care – completeness, timing of ‘events’/care
Certain complications of interest, severity
Death data completeness and timeliness
Generalizability

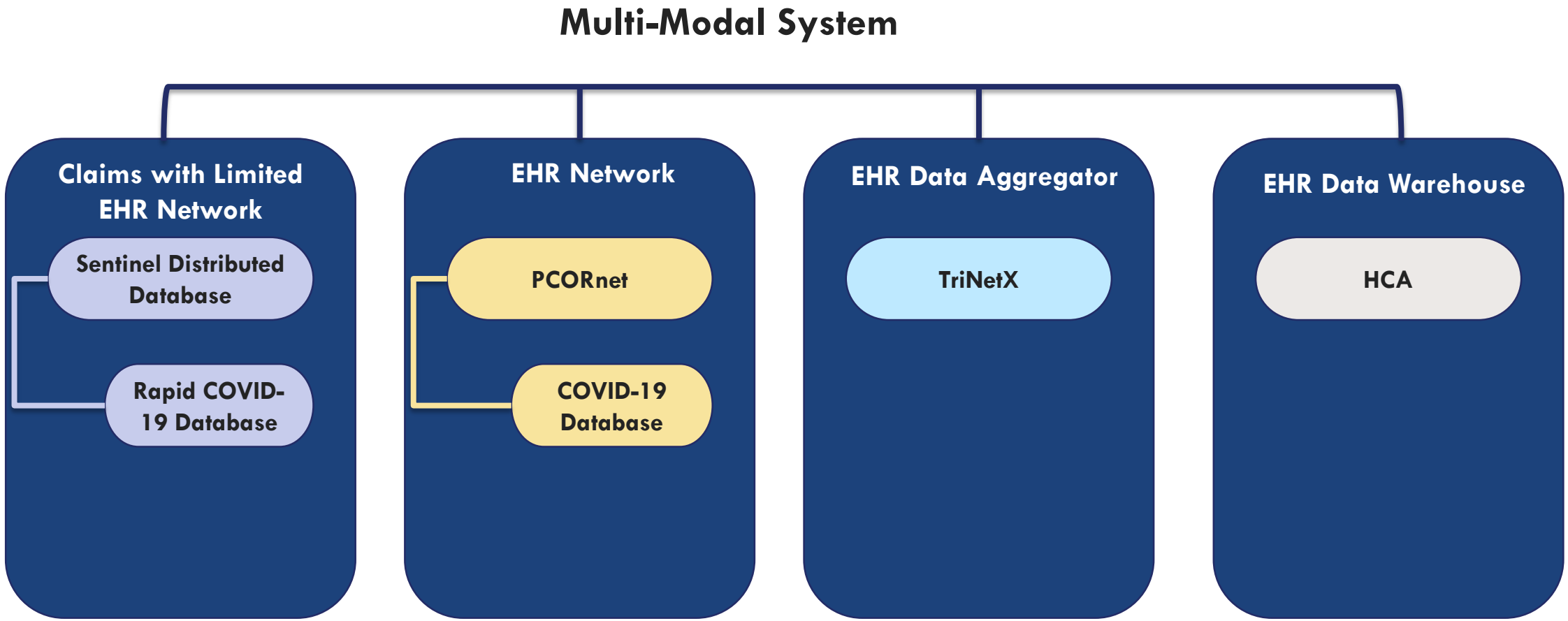
How Fresh and Complete Can the Data Be?

- The Sentinel Rapid Distributed Database was created for COVID-19
  - Two national health plans, four integrated delivery systems

- When working with “fresh data” – must balance freshness with completeness

- Time to complete data varies by care setting and specific partner/source
  - Qualitative assessment: We asked the data partners how long to complete data
  - Quantitative assessment: We look at the data and calculate an 80% completeness threshold
  - Adjust study detail as needed – e.g., max follow up time

Currently Available Data Sources for Sentinel



Rapid COVID-19 Sentinel Distributed Database

- Over 55 million patient IDs
- All patients with records in 2020 contribute data, regardless of COVID-19 status

Humana Healthcare Research

KAISER PERMANENTE® Center for Health Research

KAISER PERMANENTE® Washington

aetna®

HealthPartners Institute

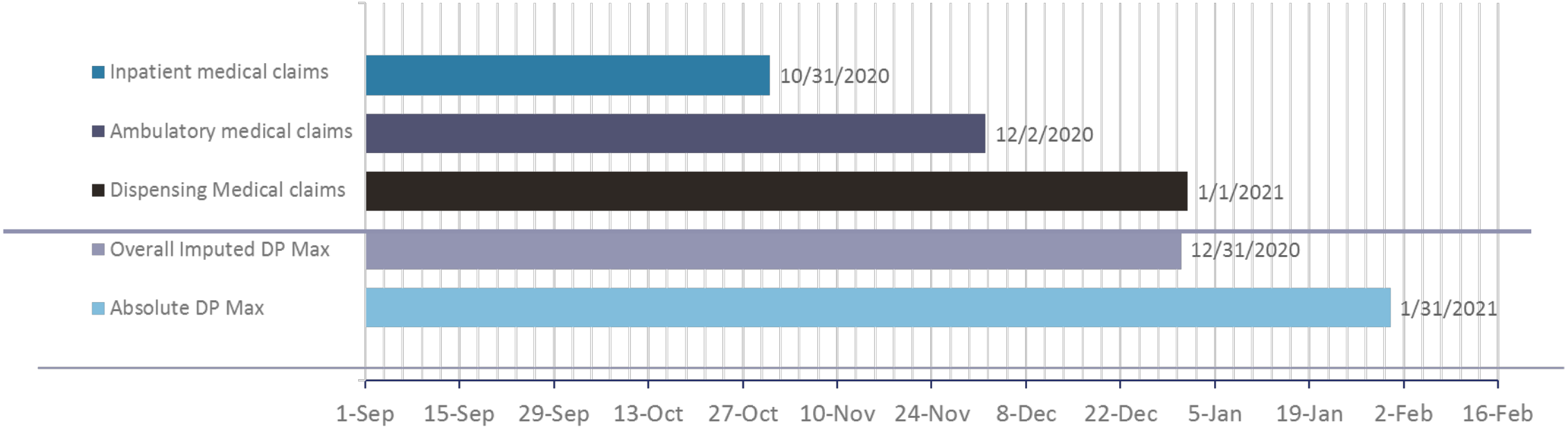
KAISER PERMANENTE® Institute for Health Research

Rapid COVID-19 Sentinel Distributed Database as of June

Data Partner	Patients with at least 1 COVID lab	COVID PCR labs	COVID diagnoses (U07.1)	80% Completeness Target	Freshest Data
DP01*	2,380,405	3,452,518	2,255,409	03/31/21	04/15/21
DP02*	746,578	1,198,117	2,076,788	03/31/21	04/30/21
DP03	224,927	358,918	32,732	04/30/21	05/11/21
DP04	396,916	625,973	89,915	03/31/21	05/14/21
DP05	180,251	371,821	39,491	04/30/21	05/07/21
TOTAL	**3.9 M**	**5.9 M**	**4.2 M**		

*Laboratory results are not generally available for the whole population

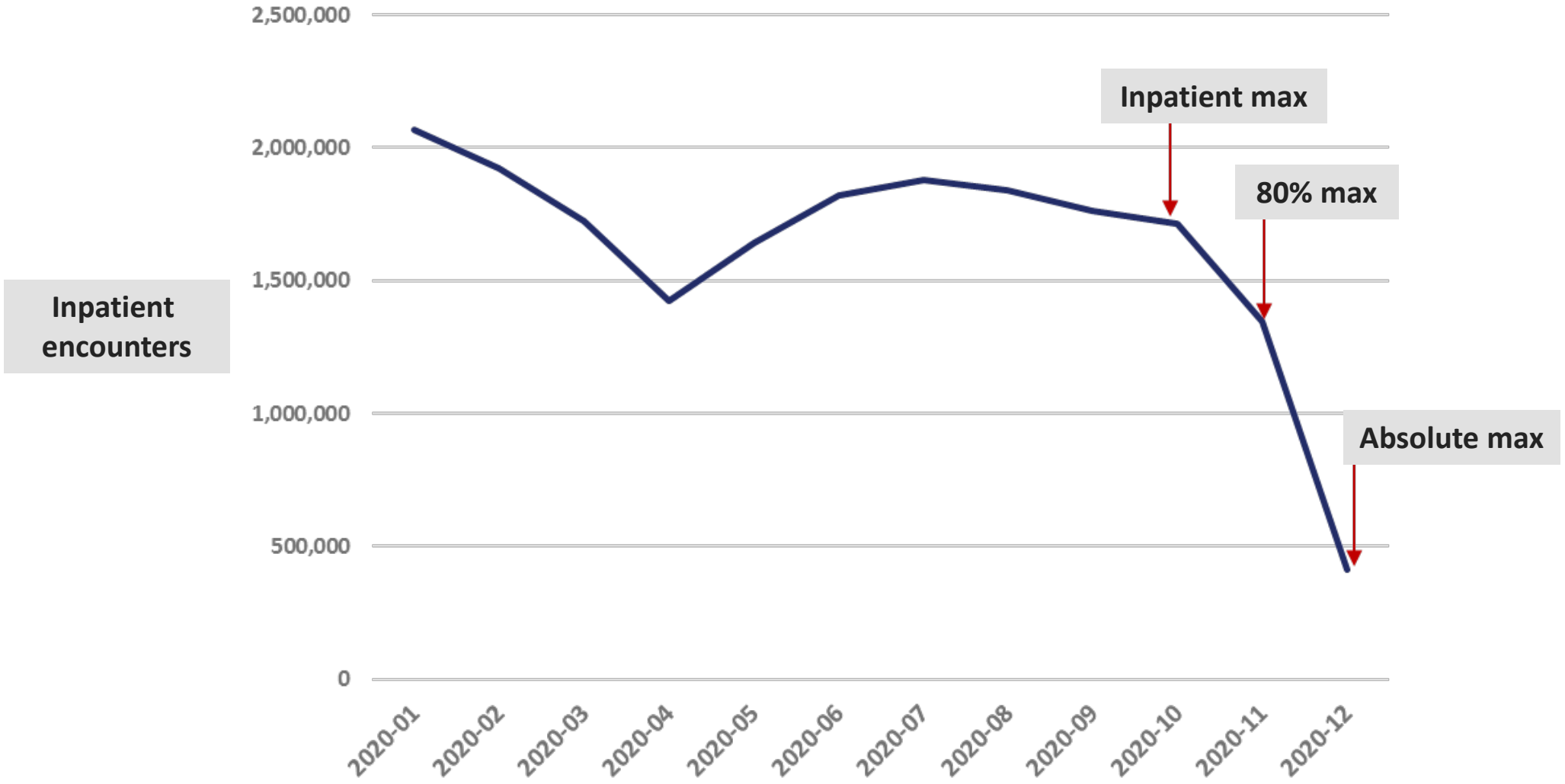
Data Completeness by Encounter Type: National Insurer



Partners are providing the *freshest feasible data* each time they refresh - data on the right tail are incomplete

- **Overall max -** latest year-month with a record count within an 80% threshold of the prior month; the last day of the month is the "maximum" date
- **Absolute max -** latest date for which any records are included; data between the overall and imputed max dates may be sparse

Data Lags for Inpatient Claims, National Insurer



How Fresh and Complete Can the Data Be?

- When working with “fresh data” – must balance freshness with completeness
- Time to complete data varies by care setting and specific partner/source
- To estimate accurate incidence rates: building in up to 4-month lag for inpatient claims for the Natural History of Coagulopathy project
- Use closed/adjudicated claims only to avoid flux

Cohort Identification – Major Considerations of Laboratory Tests

Availability of labs by care setting varies by partner

e.g., national claims partner have little inpatient lab results

Some partners have LOINCS*, some do not

Curate and update LOINC list routinely

Currently NAAT tests are limited to qualitative diagnostic tests

Data quality must be reviewed

Examine mapping from source data to CDM

Clinical labs relevant for *Coagulopathy* also being reviewed

*Logical Observation Identifiers Names and Codes, https://loinc.org/sars-coronavirus-2/

		DP 1		DP 2	
		count	% total	count	% total
COVID-19 TEST TYPE	NAAT	406,240	100	599,789	99.9
	blank	.	.	99	0.02
TEST ORDER DATE	0	.	.	220,743	36.8
	1	406,240	100	379,145	63.2
SPECIMEN DATE	0	410	0.10	220,919	36.8
	1	405,830	99.9	378,969	63.2
RESULT DATE	1	406,240	100	599,888	100
LOINC	94309-2	406,227	100	9,728	1.62
	94500-6	.	.	201,025	33.5
	94531-1	.	.	389	0.06
	94533-7	.	.	20,434	3.4
	94534-5	.	.	4,037	0.6
	94559-2	.	.	269,305	44.9
	94565-9	.	.	2,933	0.5
	blank	.	.	84,759	14.1
RESULT	BORDERLINE	.	.	1,250	0.2
	NEGATIVE	374,961	92.3	559,158	93.2
	POSITIVE	31,107	7.7	39,360	6.6
	UNDETERMINED	172	0.04	119	0.02
PATIENT LOCATION	INPATIENT	29,144	7.17	220,743	36.8
	OUTPATIENT	377,096	92.8	363,132	60.5
	UKNOWN	.	.	16,013	2.7

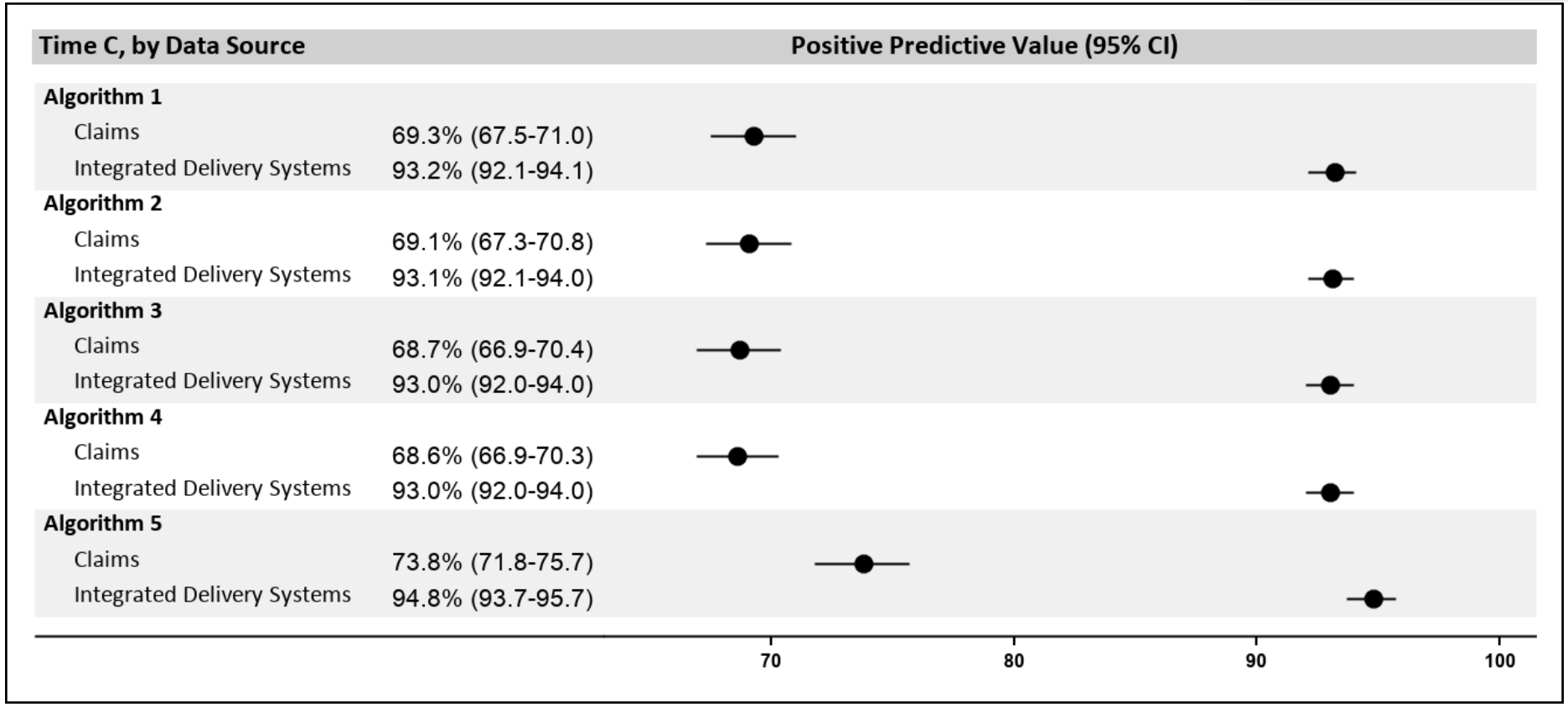
*Logical Observation Identifiers Names and Codes, https://loinc.org/sars-coronavirus-2/

Cohort Identification – Diagnosis Codes

Validation of claims-based algorithms to identify hospitalized COVID-19 events within the FDA Sentinel System – S. Kluberg et al., ICPE 2020

Overall PPV of 81% for U07.1 (Algorithm 1)

Algorithm 1: U07.1
Algorithm 2: U07.1 or B97.29
Algorithm 3: U07.1 or B97.29 or B34.2
Algorithm 4: U07.1 or B97.29 or B34.2 or J12.81 or B97.21
Algorithm 5: [U07.1 or B97.29] and [pneumonia or ARDS]



Challenges with Inpatient Care in Claims Data

Clinical laboratory tests / results – incomplete

Timing of diagnoses, procedures, medications – difficult to identify

Treatment vs prophylaxis of certain medications – e.g., anticoagulants

Certain indicators of severity, endpoints, and care – difficult to identify

- Non-invasive mechanical ventilation, O2 use under captured; ICU; # days organ free support

Mortality Data

In-hospital death

Expected to be well captured – take into account lagged data

Discharge disposition – alive, expired, unknown

Out of hospital death

Timing / availability varies by data source, partner type, specific partner

Cause of death

Sources: national death index, state registries, local sources, tumor registries; Timeliness is a limitation

Generalizability and Other Data 'Fitness' Considerations

- How generalizable do you need your findings to be?
  - Special populations – e.g., nursing home residents

- Validated ICD-10 algorithms lacking for many outcomes (including thrombotic events)
  - Always do mapping and careful review of codes
  - Use Master Protocol where applicable

- Changes in care seeking and medical utilization during COVID will impact patient history in COVID and future non-COVID studies

- Race and Hispanic ethnicity data – completeness, provenance

Summary - Claims Data for COVID-19

Strike a balance data completeness and freshness
Cohort identification – diagnoses and/or lab-confirmed
Laboratory test results – care setting, quality
Inpatient care – completeness, timing of ‘events’/care
Certain complications of interest, severity
Death data completeness and timeliness
Generalizability – what matters most?

Acknowledgements

Harvard Pilgrim Health Care Institute

Candace Fuller, Laura Shockro, Tawil Contreras, Suzanne Carter, Christine Halbig, Maria Kempner, Laura Hou, Meighan Rogers Driscoll, Jenice Ko, Sampada Nandyala, Daniel Scarnecchia, Lauren Zichittella, Neesha Nathwani

Colleagues at Aetna, Humana, KPWA, KPCO, KPNW, HealthPartners

Natural History of Coagulopathy project workgroup members

US Food and Drug Administration

Sarah Dutcher, Catherine Corey

FDA Collaborations with Researchers, Data Providers, and Regulatory Agencies

Silvia Perez-Vilar, PhD, PharmD
Senior Epidemiologist, Division of Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA COLLABORATIONS WITH RESEARCHERS, DATA PROVIDERS, AND REGULATORY AGENCIES

OUTLINE

01 **The Agency**

- Office of Surveillance and Epidemiology
  - FDA's Sentinel
- Office of the Commissioner

02 **Other Federal Agencies**

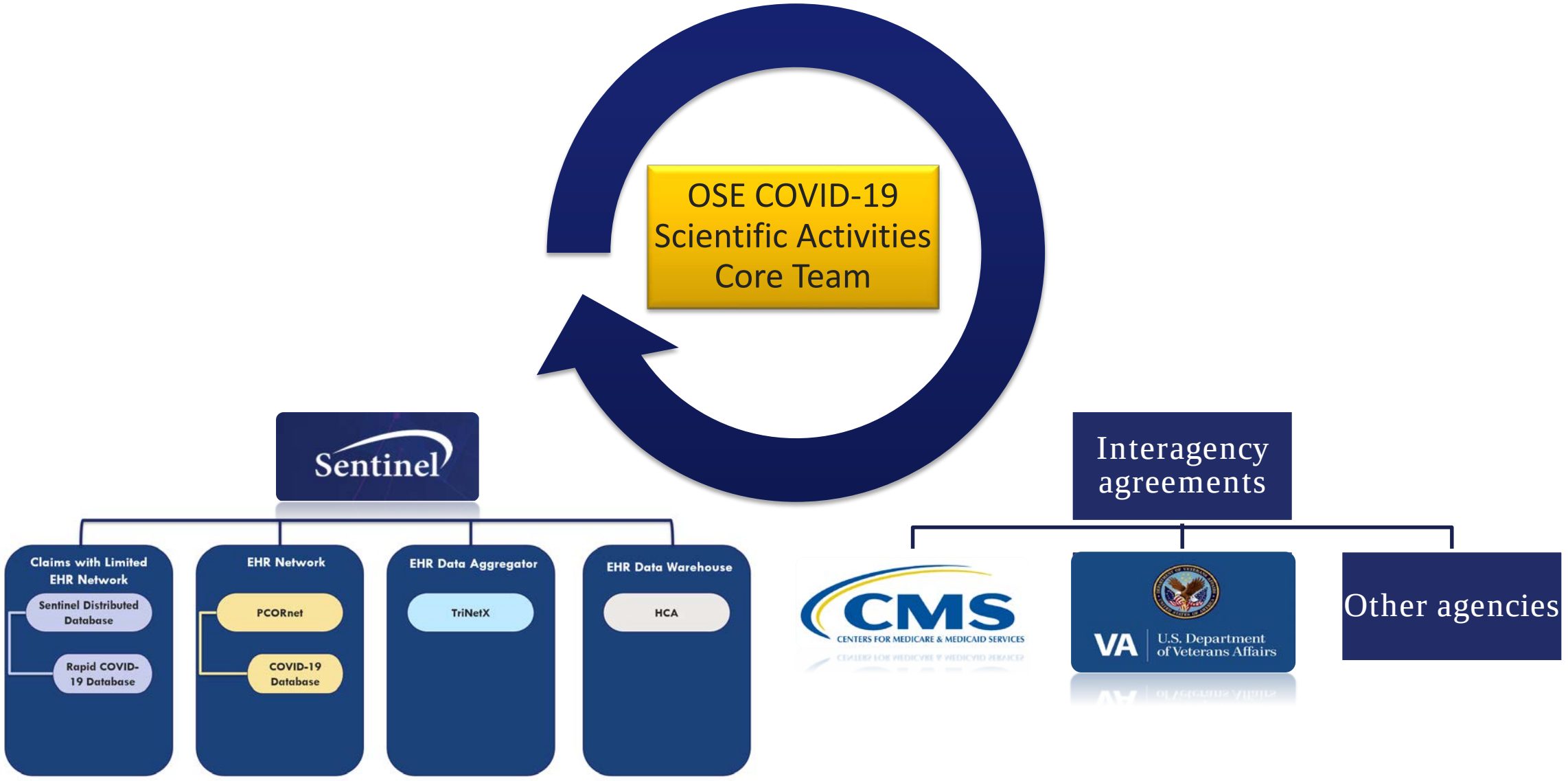
- Centers for Medicare & Medicaid Services
- Veterans Affairs

03 **Researchers and Data Providers**

- Reagan Udall Foundation
- Research Collaboration Agreements

04 **International Agencies**

- EMA, Health Canada
- International Coalition of Medicines Regulatory Authorities (ICMRA)


OSE COVID-19 Scientific Activities Core Team
Sentinel
Claims with Limited EHR Network
Sentinel Distributed Database
Rapid COVID-19 Database
EHR Network
PCORnet
COVID-19 Database
EHR Data Aggregator
TriNetX
EHR Data Warehouse
HCA
Interagency agreements
CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES
VA
U.S. Department of Veterans Affairs
Other agencies

FDA U.S. FOOD & DRUG ADMINISTRATION

Use of RWD to advance the understanding of the natural history of COVID-19 in specific patient populations, as well as treatment and diagnostic patterns

Development of methods and tools to improve and streamline clinical and post-marketing evaluation of FDA-regulated products in the context of the COVID-19 pandemic

Selected Vendors	Data Asset
IQVIA	IQVIA/CARE
MITRE	Health Catalyst & Cerner
Aetion	HealthVerity & Optum EHR
UC Health*	University of California Health System

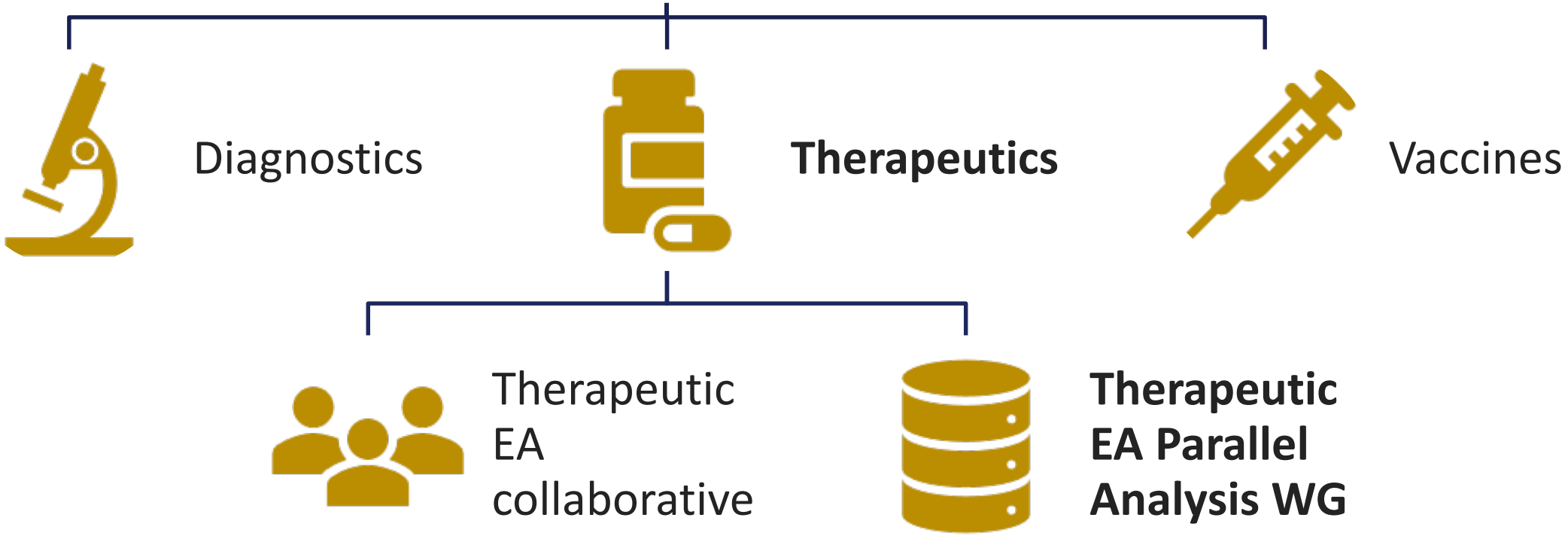
* Within the Center of Excellence in Regulatory Science and Innovation (CERSI)

Agile mode, with weekly cadence mtgs & dedicated teams (FDA & vendor)

REAGAN-UDALL FOUNDATION for the Food and Drug Administration

FRIENDS of CANCER RESEARCH

COVID-19 Evidence Accelerator (EA)



https://www.evidenceaccelerator.org/

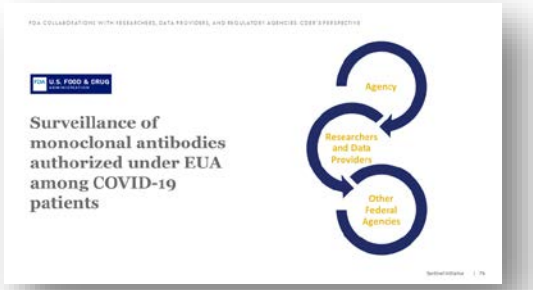
International Coalition of Medicines Regulatory Authorities

Voluntary, executive-level, strategic coordinating, advocacy and leadership entity of regulatory authorities that during the ongoing COVID-19 pandemic is acting as a **forum to support strategic coordination and international cooperation among global medicine regulatory authorities**

International regulators agreed to cooperate in building international clinical cohorts of COVID-19 patients to conduct research using RWE, share expertise, and increase study power and data quality in order to meet regulatory requirements and address existing knowledge gaps

http://www.icmra.info/drupal/en

Surveillance of monoclonal antibodies authorized under EUA among COVID-19 patients



IMPORTANCE: Given the circumstances of emergency during the COVID-19 pandemic, Emergency Use Authorization (EUA) is granted to a number of COVID-19 drugs that meet legal criteria for issuance. Per section 564(e)(1)(A)(iii) of Federal Food, Drug, and Cosmetic Act, safety monitoring for such drugs is required to the extent practicable in the EUA conditions.

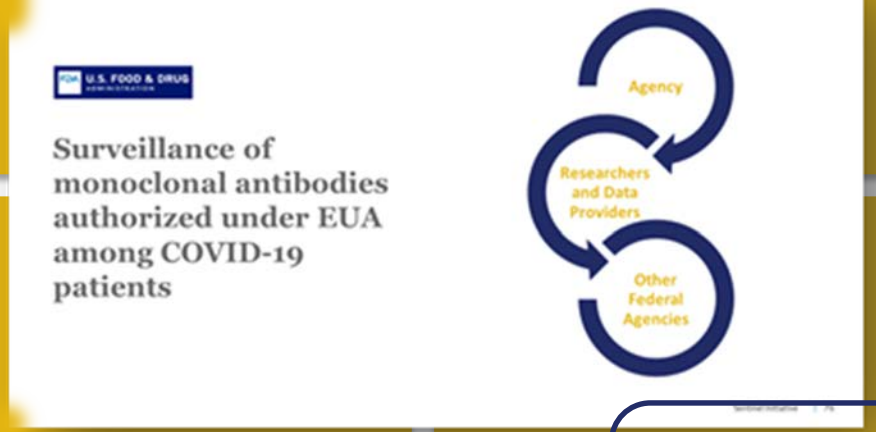
OBJECTIVE:

1. To conduct monitoring of the uptake of EUA monoclonal antibodies
2. Depending upon drug uptake, if deemed feasible, to conduct monitoring of prespecified safety signal(s)
3. If a signal is detected, to conduct signal refinement and evaluation analyses

Sentinel

Rapid COVID-19 Database

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES



VA | U.S. Department of Veterans Affairs

Agency

Help inform regulatory decision-making

Application to other EUAs

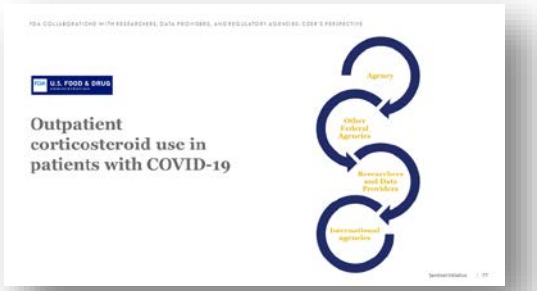
Researchers and data providers

FDA's severity definition and master protocol

Other Federal Agencies

Help inform decision-making

Outpatient corticosteroid use in patients with COVID-19



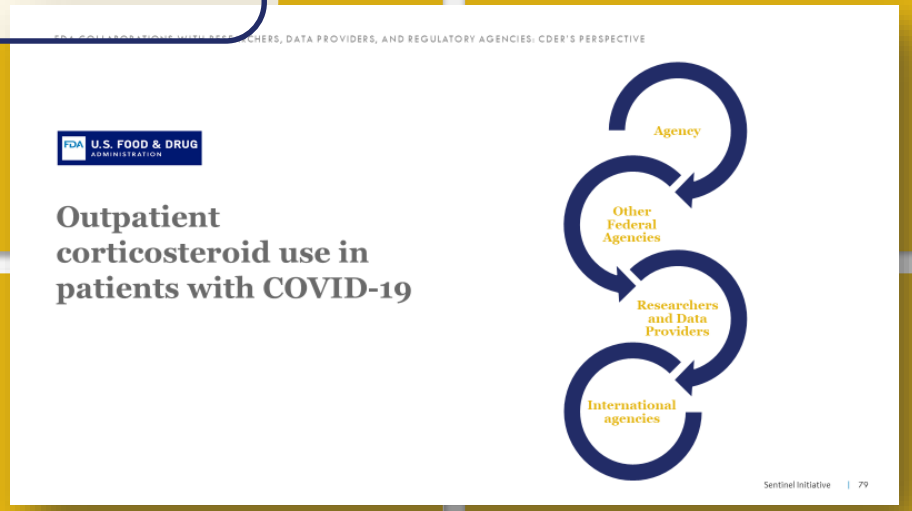
IMPORTANCE: The National Institutes of Health (NIH) coronavirus disease 2019 (COVID-19) treatment guidelines advise against corticosteroid use in non-hospitalized patients with mild to moderate COVID-19, in the absence of another indication

OBJECTIVE: To examine utilization patterns, characteristics, and outcomes among COVID-19 patients who have evidence of corticosteroid initiation in U.S. outpatient settings

Sentinel

Rapid COVID-19 Database

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES



healthverity

Research collaboration agreement between FDA and Aetion, Inc.

VA | U.S. Department of Veterans Affairs

Agency

Help inform regulatory decision-making

Other Federal Agencies

Results presented to the NIH COVID-19 Treatment Guidelines Panel

Help inform decision-making

Researchers and data providers

Ongoing publication

FDA's severity definition and master protocol

International Agencies

Results presented to ICMRA

Master protocol and Sentinel's SAS code shared with Health Canada


Sentinel

Study Synopsis: Natural History of Coagulopathy in COVID-19

Vincent Lo Re III, MD, MSCE,[1,2] Sarah K. Dutcher, PhD,[3] Silvia Perez-Vilar, PharmD, PhD,[3] Dena M. Carbonari, MS,[2] Sean Hennessy, PharmD, PhD,[2] Maria E. Kempner, BA,[4] Brian Kit, MD,[3] Jenice Ko, BS,[4] Allyson M. Pishko, MD, MSCE,[5] Meighan Rogers Driscoll, MPH,[4] Jeffrey Brown, PhD[4], Noelle Cocoros, DSc, MPH[4]

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https://www.sentinelinitiative.org/methods-data-tools/methods/assessment-natural-history-coagulopathy-covid-19


Sentinel

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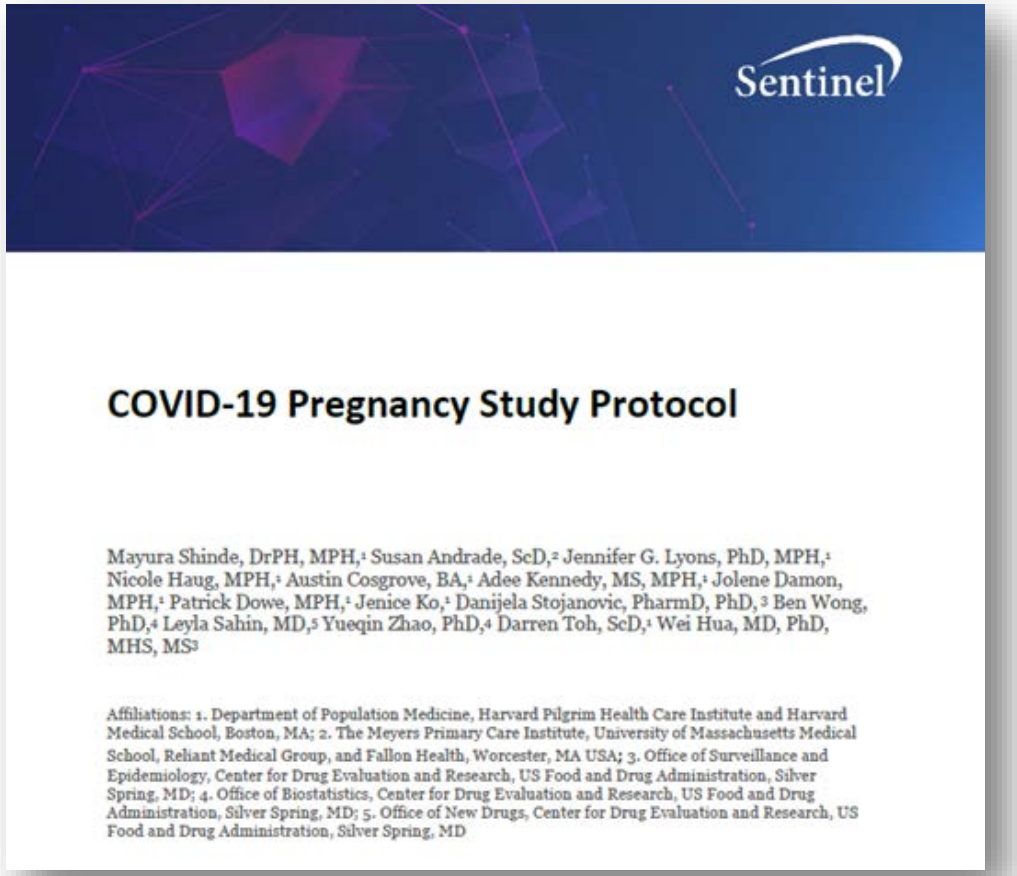
IMPORTANCE: There are major knowledge gaps on the incidence, determinants, and consequences of arterial and venous thrombotic complications with COVID-19

AIMS:

1. Determine the 90-day incidence of arterial and venous thrombotic complications with COVID-19 and subsequent risk of death within 90 days of the event
2. Evaluate patient characteristics present prior to COVID-19 diagnosis as risk factors for arterial and venous thrombotic events
3. Compare the 90-day risk of arterial and venous thrombotic events between health plan members diagnosed with COVID-19 and those diagnosed with influenza

https://www.sentinelinitiative.org/methods-data-tools/methods/assessment-natural-history-coagulopathy-covid-19

https://www.sentinelinitiative.org/methods-data-tools/methods/assessment-natural-history-coagulopathy-covid-19
http://www.encepp.eu/encepp/viewResource.htm?id=40415


Sentinel

COVID-19 Pregnancy Study Protocol

Mayura Shinde, DrPH, MPH,[1] Susan Andrade, ScD,[2] Jennifer G. Lyons, PhD, MPH,[1] Nicole Haug, MPH,[1] Austin Cosgrove, BA,[1] Adee Kennedy, MS, MPH,[1] Jolene Damon, MPH,[1] Patrick Dowe, MPH,[1] Jenice Ko,[1] Danijela Stojanovic, PharmD, PhD,[3] Ben Wong, PhD,[4] Leyla Sahin, MD,[5] Yueqin Zhao, PhD,[4] Darren Toh, ScD,[1] Wei Hua, MD, PhD, MHS, MS[3]

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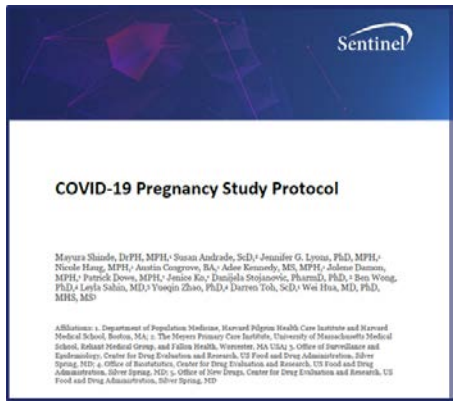
https://www.sentinelinitiative.org/methods-data-tools/methods/covid-19-pregnancy-study-implementation



IMPORTANCE: Little information is available to support understanding the natural history of COVID-19 disease in pregnant women, or the impact of COVID-19 treatment upon pregnant women or the developing fetus

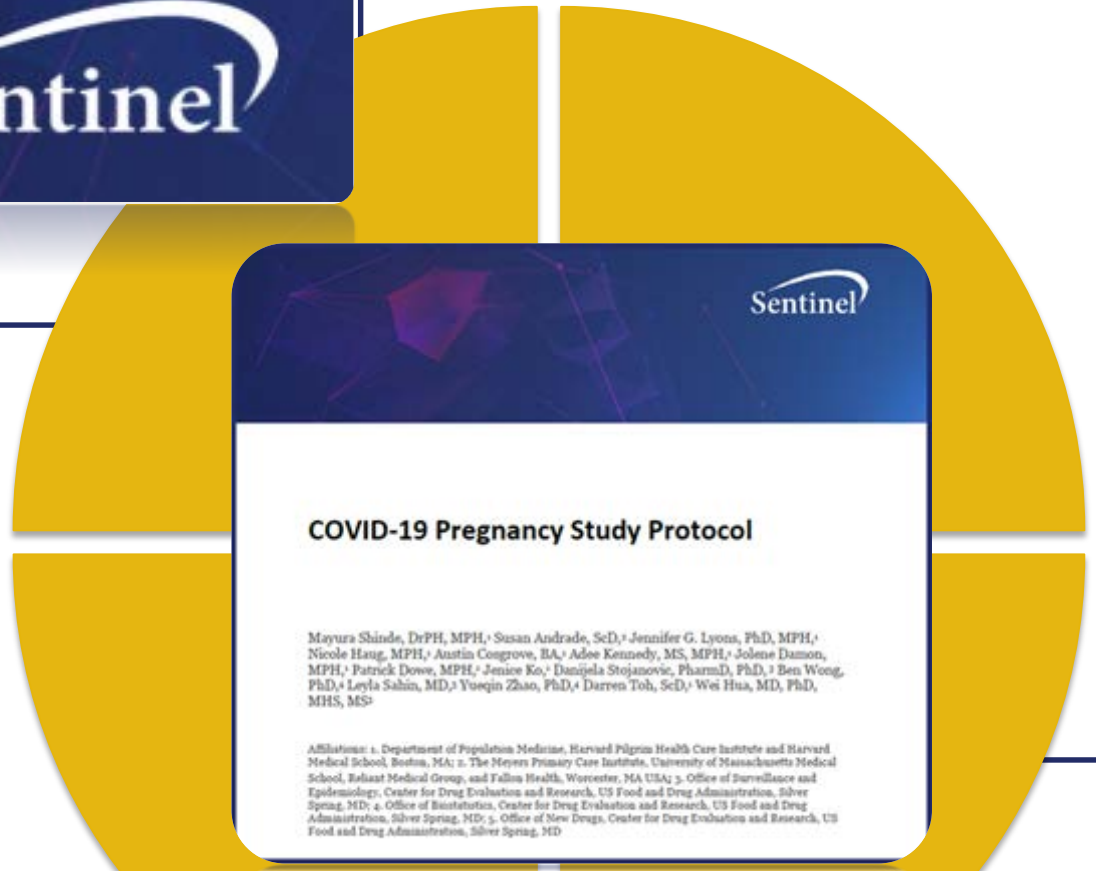
OBJECTIVES:

(1) To estimate the prevalence of medicines used and compare this among pregnant women with COVID-19, pregnant women without COVID-19, and non-pregnant women with COVID-19

(2) To describe severity and clinical outcomes of COVID-19 disease in pregnant women with COVID-19, according to treatments received during pregnancy, and compare these data with those of nonpregnant women of reproductive age with COVID-19

https://www.sentinelinitiative.org/methods-data-tools/methods/covid-19-pregnancy-study-implementation

Sentinel



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA-funded CONSIGN (“COVID-19 infectiOn aNd medicineS In pregnancy”), which will be implemented in varied data sources across eight European countries.

ICMRA
International Coalition of Medicines Regulatory Authorities

https://www.sentinelinitiative.org/methods-data-tools/methods/covid-19-pregnancy-study-implementation
http://www.encepp.eu/encepp/viewResource.htm?id=39439

Agency

Help inform regulatory decision-making

Researchers and Data Providers

Parallel analyses

Upcoming publications

International Agencies

International meta-analysis

Different health systems/ environments

Consistency of findings

Efficiency of regulatory processes and decision-making

SUMMARY

- Strengthening of existing systems/efforts already in place prior to the pandemic
- Timely collaborations within and across agencies
- Information sharing
- Coordination leading to parallel and/or joint analyses
- Validation of databases for future use

Acknowledgements

Marie Bradley, Wei Hua, Natasha Pratt, Monique Falconer, Efe Eworuke, David J Graham, Sarah Dutcher, Catherine Corey, Brian Kit, Simone Pinheiro, Michael Blum, Robert Ball, Gerald Dal Pan

Office of Surveillance and Epidemiology

Sentinel

SOC, Vin Lo Re and colleagues at Penn, Aetna, Humana, KPWA, KPCO, KPNW, HealthPartners

Francesca E Cunningham, Diane Dong, Rongping Zhang, Kwan Hur

Veterans Affairs

Centers for Medicare & Medicaid Services

Jeffrey Kelman

Acumen

Aloka Chakravarty, Laura Roe, Tamar Lasky, Nevine Zariffa, Joseph Franklin, Amy Abernethy, Donna Rivera

Aetion (RCA) and contractors

Office of the Commissioner

Office of New Drugs & Office of Biostatistics

Robert Busch, Leyla Sahin, Hana Lee, Ben Wong, Yueqin Zhao

Susan Winckler, Jeff Allen, Amar Bhat, Carla Rodriguez-Watson,

Evidence Accelerators

Reagan Udall Foundation

International Coalition of Medicines Regulatory Authorities

EMA, Health Canada, and their contractors

Discussion