Describing Prenatal Exposures and Evaluating Maternal and Infant Outcomes in Sentinel

SPER Webinar

#SPER_online_SENTINEL

9/13/2022

Agenda

01 **Introduction to the Sentinel System**
Jennifer Lyons

02 **Use of Multiple Sclerosis Drugs among Women with Live-birth Deliveries**
Jennifer Lyons

03 **Validation of an ICD-10-based Algorithm to Identify Stillbirth in the Sentinel System**
Susan Andrade

04 **Medication Use among Pregnancies with COVID-19 in the Sentinel System**
Mayura Shinde

The Sentinel Initiative and Real World Data

The FDA has two big jobs. One—are the medical products we use SAFE? Two—are the medical products we use EFFECTIVE? In other words, are medical products doing the job they are supposed to do?

FDA is looking into how real world data like that in Sentinel might help FDA answer these important questions. Much of this real world data comes from health insurance companies and patients themselves.

How does Sentinel Work?

- Sentinel gets information from insurance claims, electronic health records, and patient reports.
- Sentinel uses computer programs to see how groups of patients are doing.
- This real world evidence can show if patients are getting bad side effects and maybe also if products are working.

What kinds of questions?

- What medicines are patients taking and why?
- Are medicines helping or hurting some patients more than others?
- Do side effects interfere with patients' lives?
- Are patients taking medicines the way their doctors prescribed?

What about privacy?

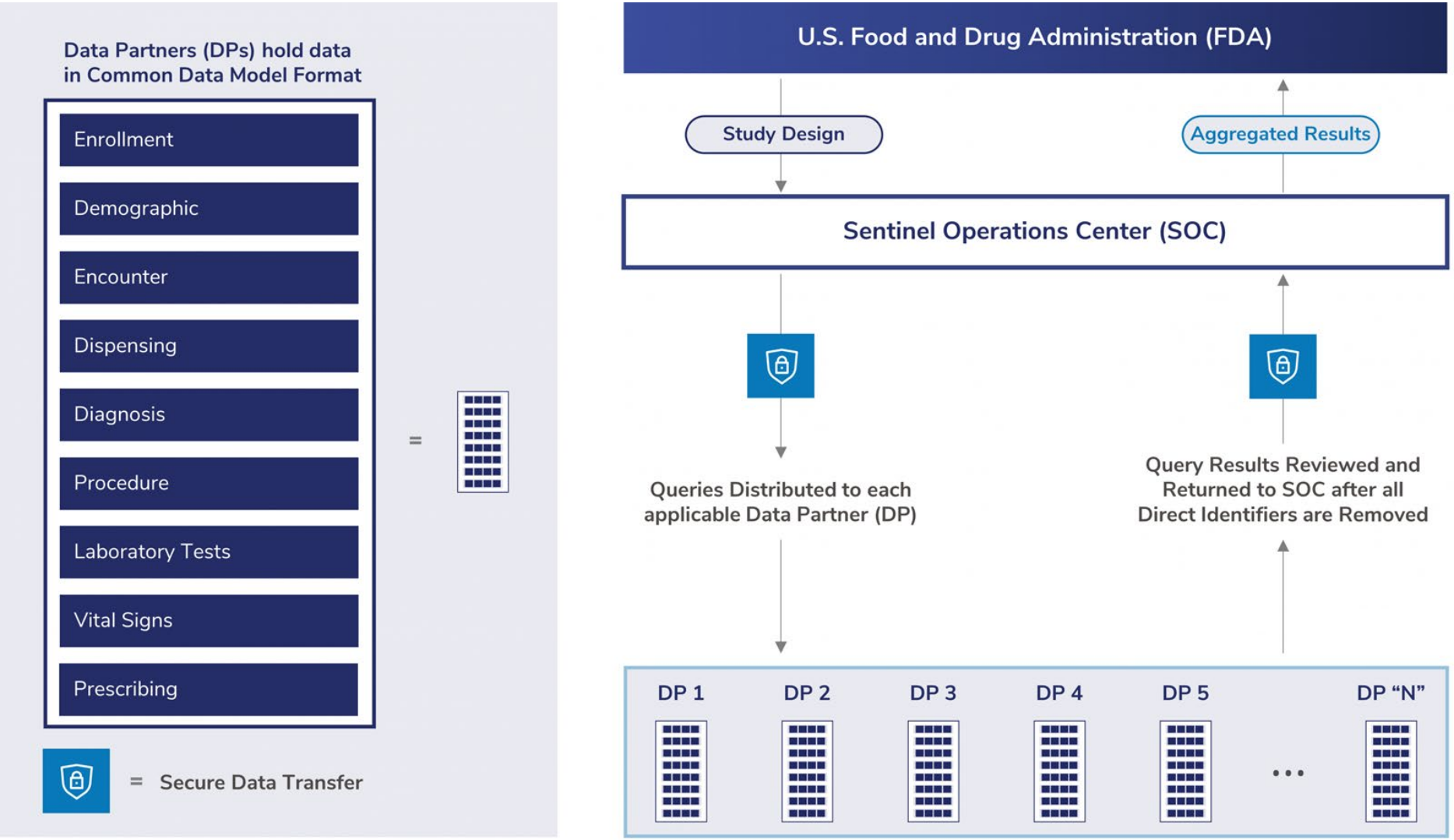
- No one looks at patients' names, addresses, phone numbers, or other identifying information.
- For more information please visit: https://www.sentinelinitiative.org/about/how-sentinel-protects-privacy-security

What happens next?

- FDA may use information from Sentinel to help determine whether medical products are safe and working.
- FDA warns patients and their doctors about bad side effects.
- If a patient has concerns about their medical products, they should contact their doctor.

https://www.sentinelinitiative.org/about/engaging-sentinels-stakeholders

Sentinel is a Distributed Data Network



https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data

Collaborating Organizations

Lead: Harvard Pilgrim Health Care Institute

DEPARTMENT OF POPULATION MEDICINE
HARVARD MEDICAL SCHOOL
Harvard Pilgrim Health Care Institute

Point32Health

Data & Scientific Partners

HealthCore
Humana
OPTUM
TennCare
RTI INTERNATIONAL
veradigm
Penn Medicine
CVSHealth Clinical Trial Services
aetna™
GDIT
OPTUM Labs
pcornet
ADVANCE Collaborative
MASSACHUSETTS
BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL
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Colorado
Hawaii
Mid-Atlantic
Northern California
Northwest
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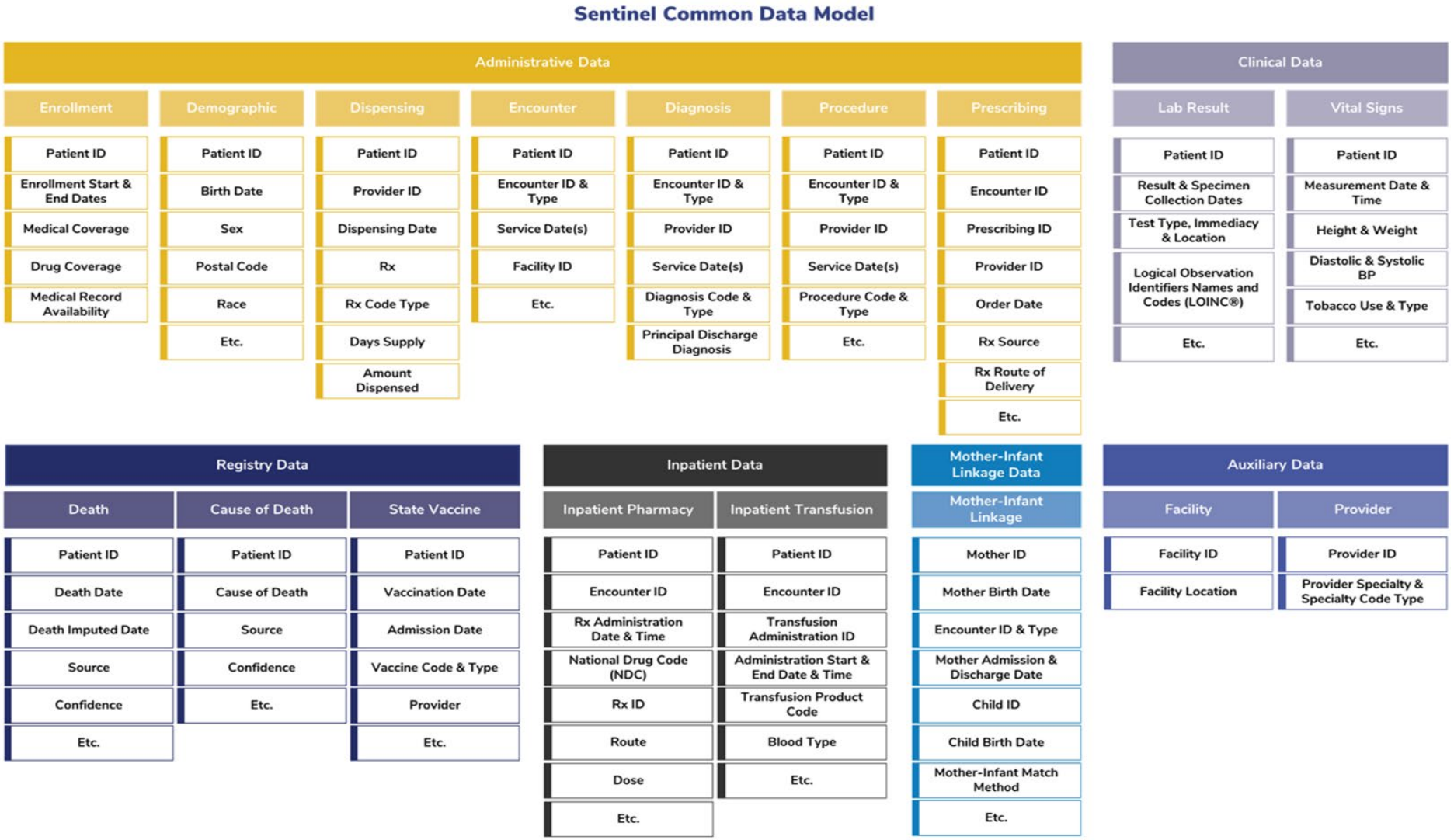
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
CMS CENTERS FOR MEDICARE & MEDICAID SERVICES
RUTGERS
NYC-CDRN New York City Clinical Data Research Network
UF College of Pharmacy UNIVERSITY of FLORIDA
VANDERBILT UNIVERSITY MEDICAL CENTER
The Meyers Primary Care Institute
KAISER PERMANENTE®
Kaiser Permanente Washington Health Research Institute
OneFlorida Clinical Research Consortium
REACHnet Research Action for Health Network
IBM Watson Health
PaTH Network patient empowered research
PEDSnet A Pediatric Learning Health System
HealthPartners Institute
SCHOOL OF PUBLIC HEALTH UNIVERSITY of WASHINGTON
UAB
HCA Healthcare
UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
STAR Stakeholders, Technology, and Research CRN
Duke Clinical Research Institute
THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH
TriNetX Sentinel Initiative

Available Data Elements



https://www.sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Single Patient Example Data in Model

DEMOGRAPHIC

PATID	BIRTH_DATE	SEX	HISPANIC	RACE	zip
PatID1	2/2/1984	F	N	5	32818

ENROLLMENT

PATID	ENR_START	ENR_END	MEDCOV	DRUGCOV
PatID1	7/1/2004	12/31/2006	Y	Y
PatID1	9/1/2007	6/30/2009	Y	Y

DISPENSING

PATID	RXDATE	NDC	RXSUP	RXAMT
PatID1	10/14/2005	00006074031	30	30
PatID1	10/14/2005	00185094098	30	30
PatID1	10/17/2005	00378015210	30	45
PatID1	10/17/2005	54092039101	30	30
PatID1	10/21/2005	00173073001	30	30
PatID1	10/21/2005	49884074311	30	30
PatID1	10/21/2005	58177026408	30	60
PatID1	10/22/2005	00093720656	30	30

ENCOUNTER

PATID	ENCOUNTERID	ADATE	DDATE	ENCTYPE
PatID1	EncID1	10/18/2005	10/20/2005	IP

DIAGNOSIS

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	DX	DX_CODETYPE	PDX
PatID1	EncID1	10/18/2005	Provider1	IP	296.2	9	P
PatID1	EncID1	10/18/2005	Provider1	IP	300.02	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	311	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	401.9	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	493.9	9	S
PatID1	EncID1	10/18/2005	Provider1	IP	715.9	9	S

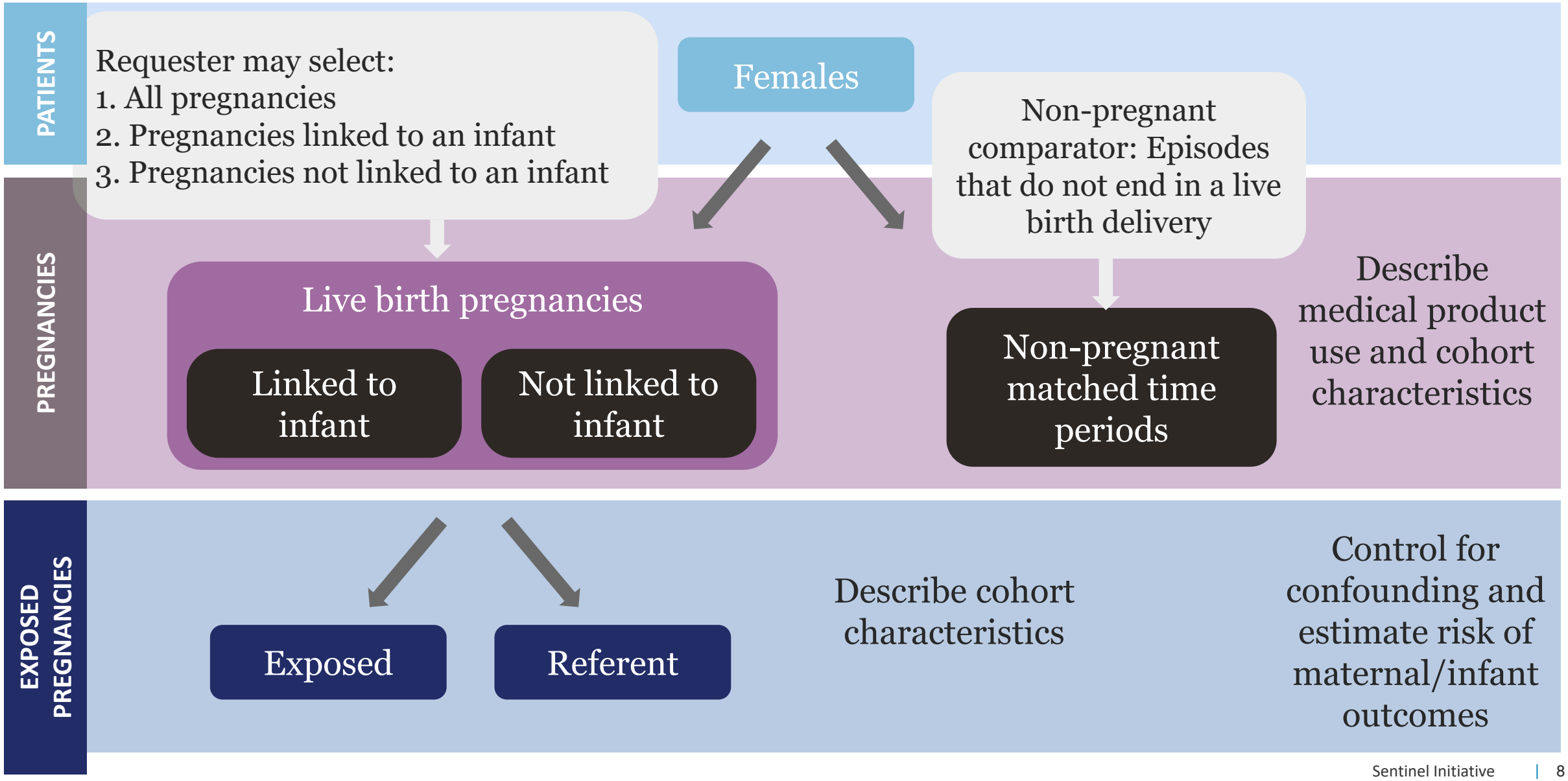
PROCEDURE

PATID	ENCOUNTERID	ADATE	PROVIDER	ENCTYPE	PX	PX_CODETYPE
PatID1	EncID1	10/18/2005	Provider1	IP	84443	C4

MOTHER-INFANT LINKAGE

MPATID	ADATE	DDATE	CPATID	CBIRTH_DATE	CSEX	CENR_START	BIRTH_TYPE	MATCHMETHOD
PatID1	5/3/2006	5/5/2006	PatID2	5/2/2006	M	6/1/2006	1	SI

Pregnancy Cohort Selection



Use of Multiple Sclerosis Drugs among Women with Live-birth Deliveries

Jennifer Lyons, PhD MPH

Sentinel Operations Center

Medication Safety in Pregnancy

- The safety of pregnant people and infants when exposed to medications is important
- Pregnant/breastfeeding individuals are excluded from most clinical trials
- Evidence on drug safety in and around pregnancy often comes from **post-marketing observational studies**.

Prospective, Product-Specific Pregnancy Registries for MS Drugs

Medicine	Medical Condition	Registry	How to contact	Status
Aubagio (teriflunomide)	Multiple Sclerosis	OTIS Autoimmune Diseases in Pregnancy Study	MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS) Website: https://mothertobaby.org/ongoing-study/aubagio/ Phone: 1-877-311-8972	Ongoing
Gilenya (fingolimod)	Multiple Sclerosis (MS)	The Gilenya Pregnancy Registry	Novartis Pharmaceuticals: 1-877-598-7237 Website: https://clinicaltrials.gov/ct2/show/NCT01285479 Phone: 1-877-598-7237	Ongoing
LEMTRADA (Alemtuzumab)	Multiple Sclerosis	LEMTRADA Pregnancy Exposure Registry	**Email:** pregnancyregistries@syneoshealth.com **Phone:** 1-866-758-2990	Ongoing
Mavenclad (cladribine tablets)	Multiple Sclerosis	Worldwide pregnancy surveillance	EMD Serono Research & Development Institute, Inc. an affiliate of Merck KGaA, Darmstadt, Germany **Website:** https://www.emdseronoclinicalsupport.com/ms-support	Ongoing

PRIM example: Geissbühler Y, Rezaallah B, Moore A. An alternative to product-specific pregnancy registries? PRIM; PRegnancy outcomes Intensive Monitoring. Reprod Toxicol. 2020 Jun;94:13-21. doi: 10.1016/j.reprotox.2020.03.004.

Prospective, Product-Specific Pregnancy Registries for MS Drugs

Drug	Pregnancy Registry Status	Study Period		Study Size	
		Planned	Actual	Planned	Actual
Alemtuzumab	Ongoing	2014-2021	N/A	185	Not reported
Dimethyl fumarate	Ongoing	2013-2021	2013-	310-375	Not reported
Fampridine, dalfampridine	Terminated	2012-2016	2012-2015	375	Not reported
Interferon b-1a (Biogen)	Completed	2004-2010	2004-2011	300	329
Interferon b-1a (EMD Serono)	Terminated	2002-2008	2002-2008	300	34
Interferon b-1b	Completed	2006-2010	2006-2012	420	113
Natalizumab	Completed	2007-2015	2007-2012	300	376
Teriflunomide	Ongoing	2015-2022	2015-	196	Not reported

Krueger WS, Anthony MS, Saltus CW, *et al*. Evaluating the Safety of Medication Exposures During Pregnancy: A Case Study of Study Designs and Data Sources in Multiple Sclerosis. *Drugs Real World Outcomes.* 2017 Jul 29. doi: 10.1007/s40801-017-0114-9

Sentinel: Multiple Sclerosis Drug Safety

- When registries aren't sufficient, we can turn to pregnancy cohorts nested within administrative claims databases

- Use Sentinel to:

    - Estimate use of MS drugs before, during and after pregnancy to help FDA review cohort size and outcomes for registries

    - Understand if it's feasible to evaluate MS drug safety in pregnant cohorts

Multiple Sclerosis Characteristics

- Immune-mediated chronic disease affecting more than 800,000 people in the United States
- Predominantly affects women (3:1)
- Most common disabling neurological disease among women of childbearing age
- Onset between 20 and 40 years of age
- Progressive, highly variable disease
- Treatable

→ Little is known about safety of MS treatment during pregnancy

Disease Modifying Therapy (DMT) During Pregnancy

Risks of stopping DMT

MS relapse/rebound

Symptoms worsen (fatigue, mobility)

Risks of continuing DMT

Fetal harm

May pass to infant via breastmilk

Nuance

- Pregnancy associated with **decreased** risk of relapse (3rd trimester)
- Postpartum associated with **increased** risk of relapse, but maybe less so if breastfeeding
- Relapse can be treated with corticosteroids, but only after first trimester

Vukusic S, Marignier R. Multiple sclerosis and pregnancy in the 'treatment era'. Nat Rev Neurol. 2015 May;11(5):280-9
anger-Gould AM. Pregnancy and Family Planning in Multiple Sclerosis. Continuum (Minneap Minn). 2019 Jun;25(3):773-792

Objective

The purpose of this study was to assess the patterns of MS drug use before, during, and after pregnancy in the Sentinel Distributed Database (SDD).

- Determine if enough pregnant users to support safety analyses in the SDD

Methods

Study Period: 1/1/2001 – all available data from each Data Partner

Age groups: 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49 years

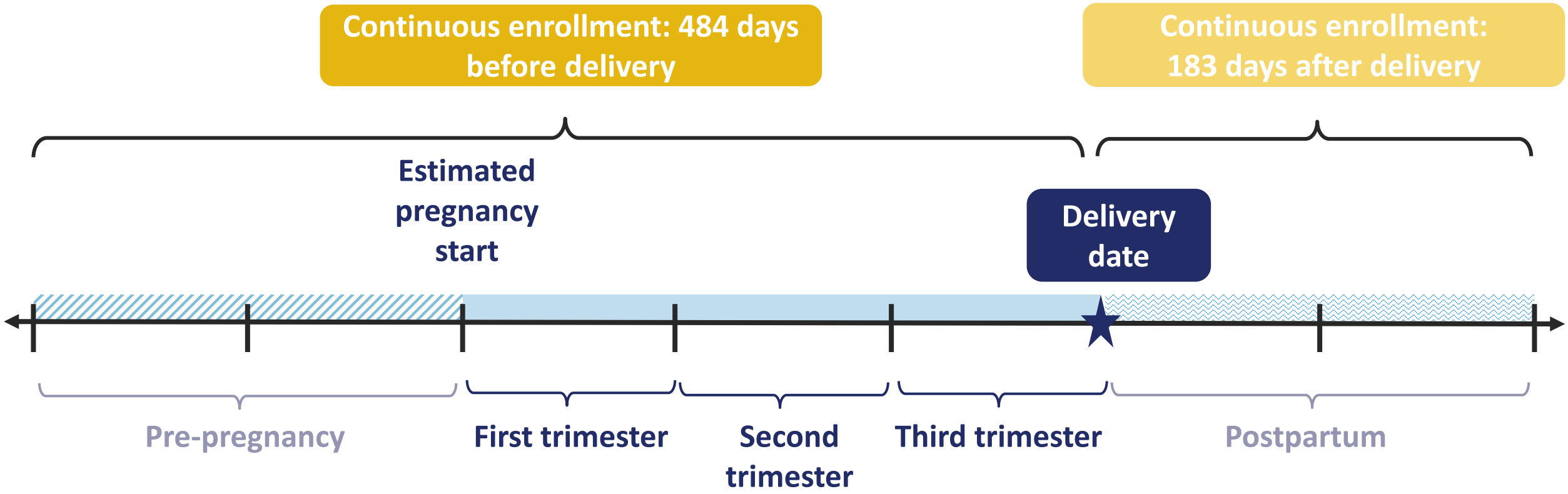
Enrollment Requirement Prior to Delivery Date: 484 Days
(301 day pregnancy + 183 day pre-pregnancy exposure assessment)

Enrollment Requirement Following Delivery Date: 183 Days

Matching: Pregnancy episodes to non-pregnant episodes (DP, age, calendar time of delivery)

MS Drugs Evaluated: Glatiramer Acetate, Interferon beta-1a, Dimethyl fumarate, Natalizumab, Interferon beta-1b, Fingolimod, Dalfampridine, Ocrelizumab, Teriflunomide, Peginterferon beta-1a, Alemtuzumab, Mitoxantrone, Cladribine, Siponimod, Diroximel fumarate

Methods

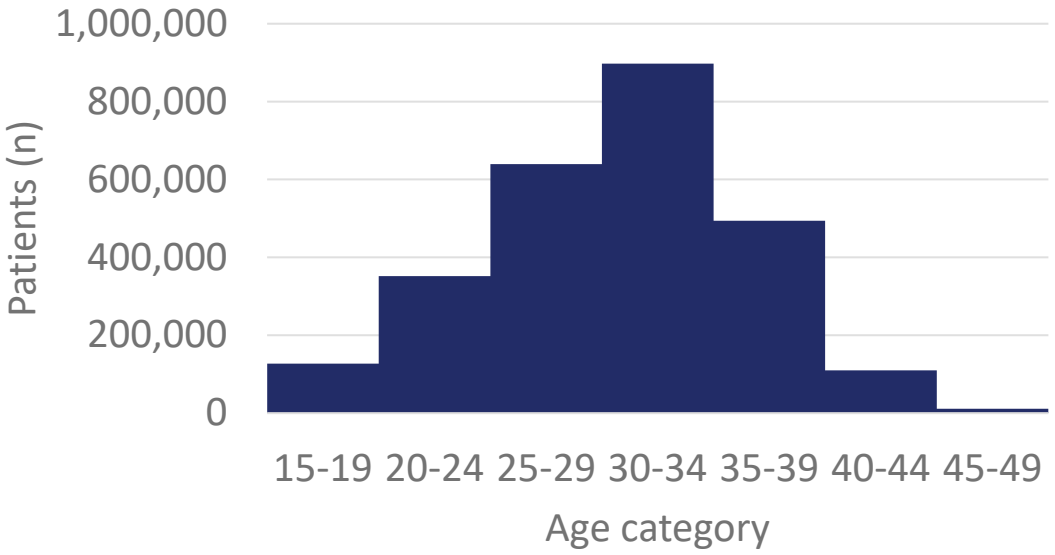

Continuous enrollment: 484 days before delivery
Continuous enrollment: 183 days after delivery
Estimated pregnancy start
Delivery date
Pre-pregnancy
First trimester
Second trimester
Third trimester
Postpartum

Demographic Characteristics

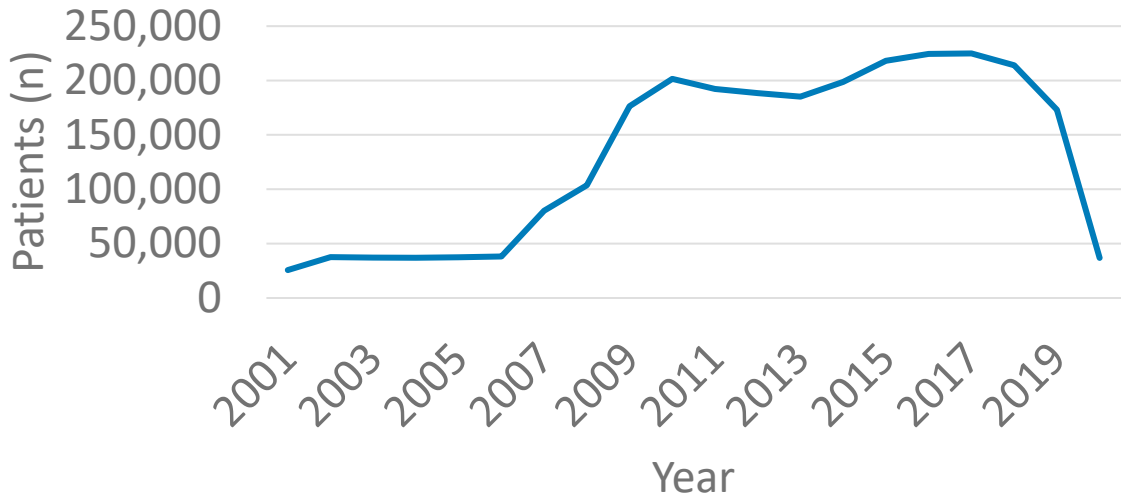
Cohort Size

	Pregnant cohort	Matched non-pregnant cohort
Patients	2,142,706	2,140,869
Episodes	2,630,485	2,630,485

Maternal Age



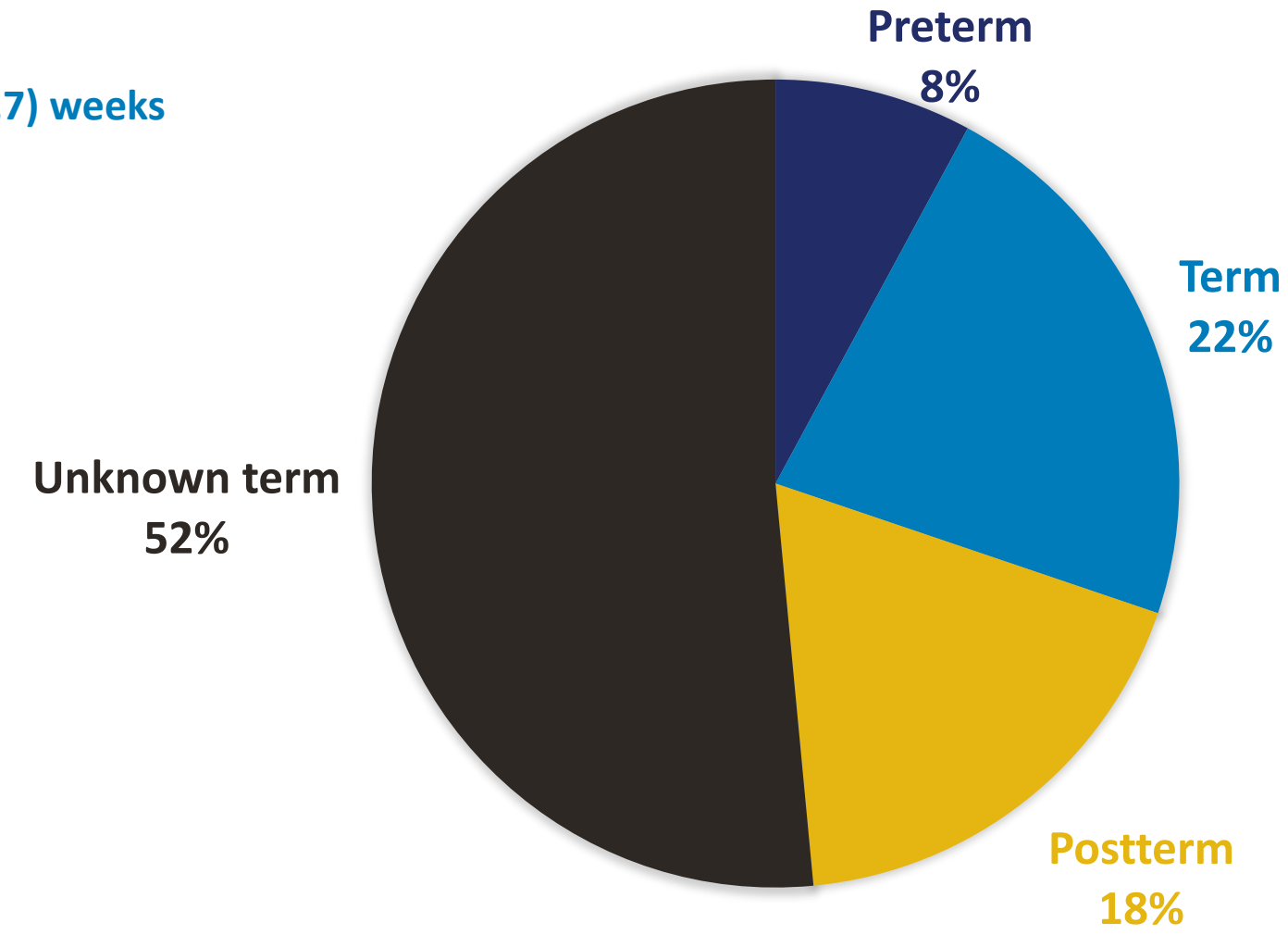
Year of delivery date (or matched index date)



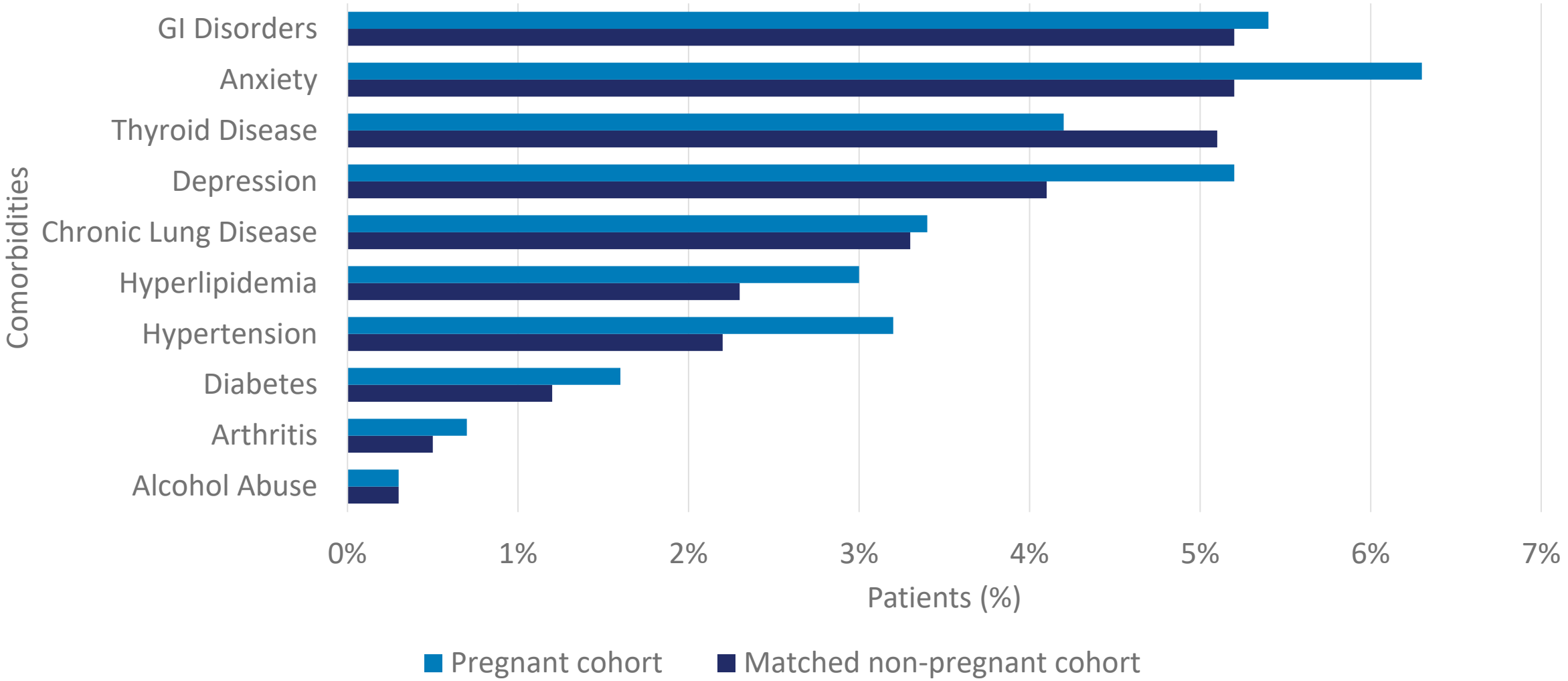
Pregnancy Characteristics

Mean gestational age at delivery 39.8 (1.7) weeks

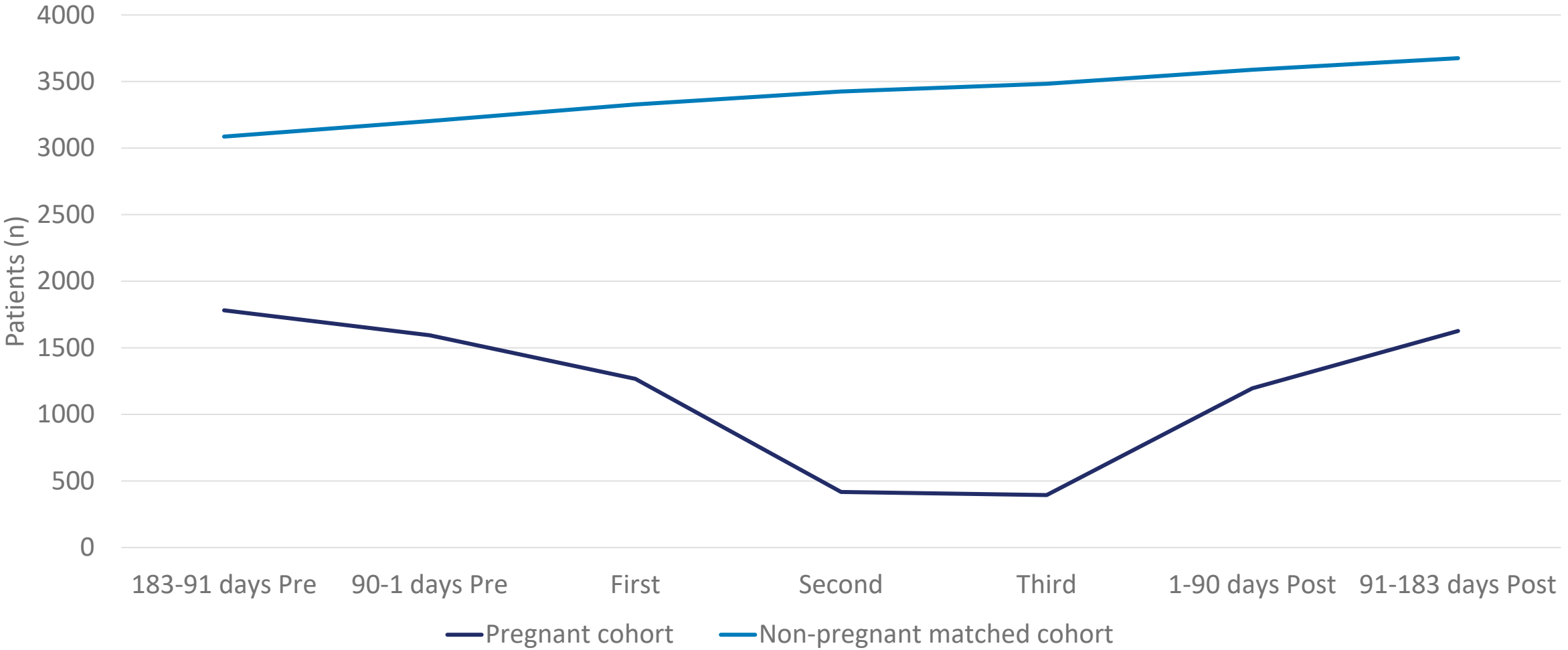
	Episodes	%
Preterm	207,182	7.9%
Term	587,400	22.3%
Postterm	480,646	18.3%
Unknown term	1,355,257	51.5%



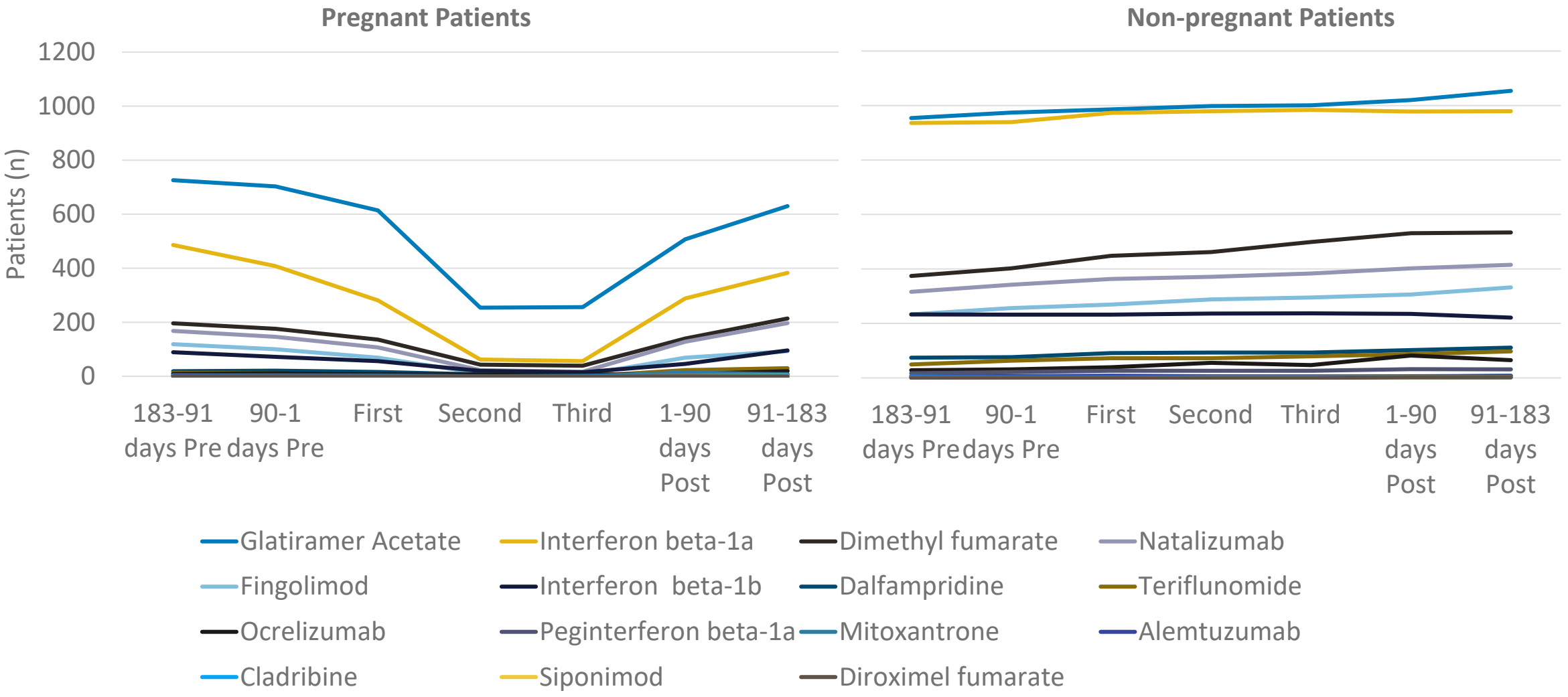
Health Characteristics



Any MS Drug Use Across Pregnancy (or matched) Episode

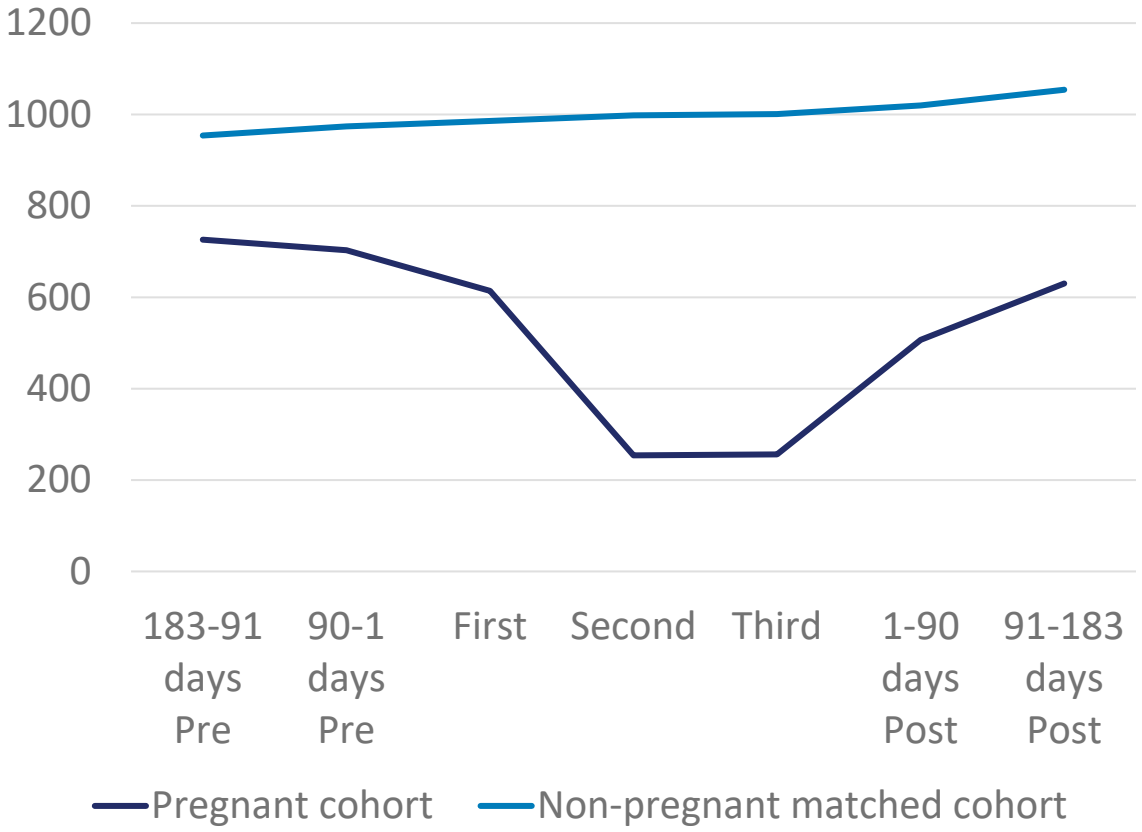


All MS Drug Use Across Pregnancy (or matched) Episode

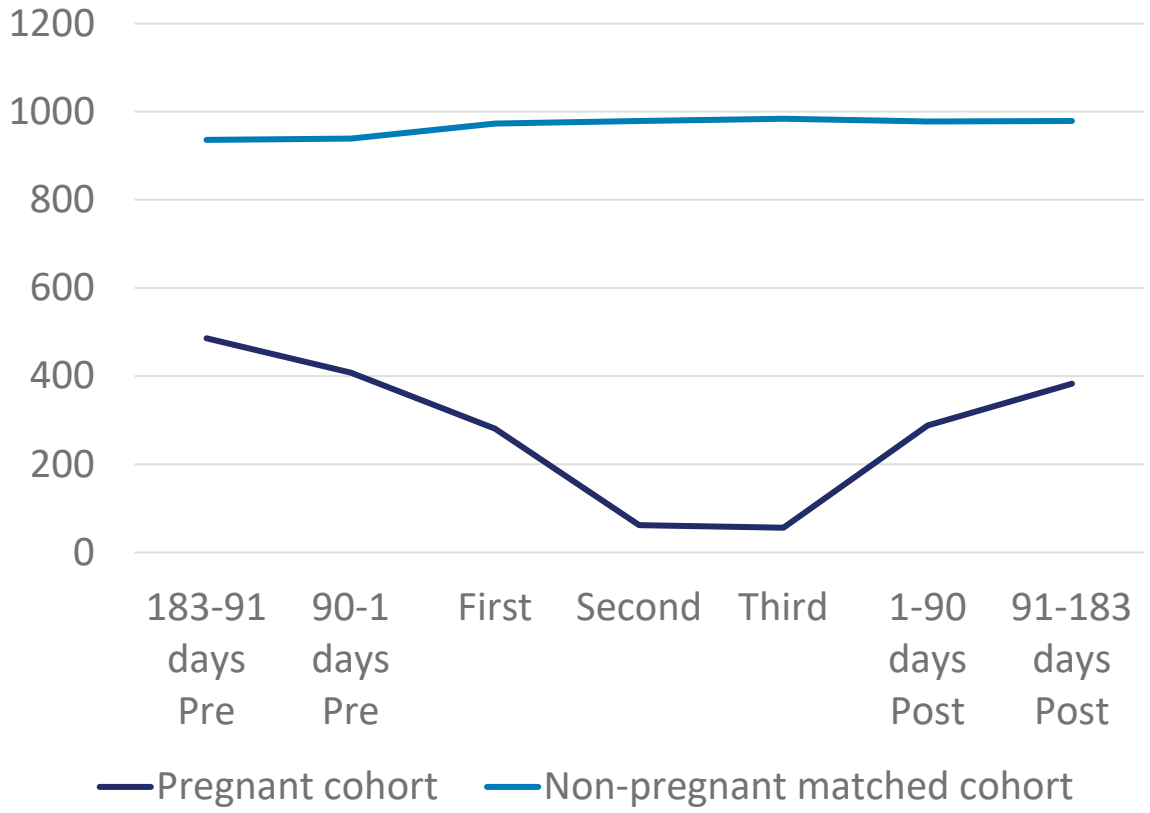


Most Common Drug Use Across Pregnancy (or matched) Episode

Glatiramer acetate

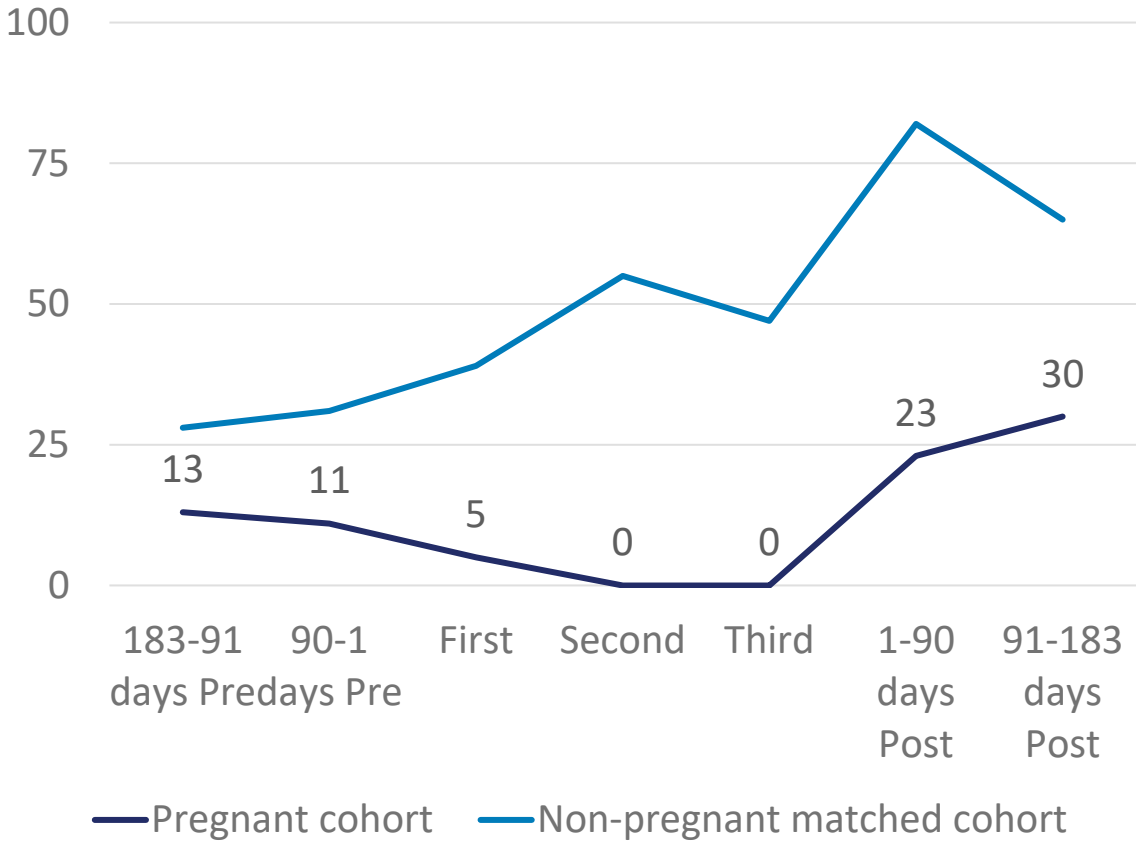


Interferon beta 1a

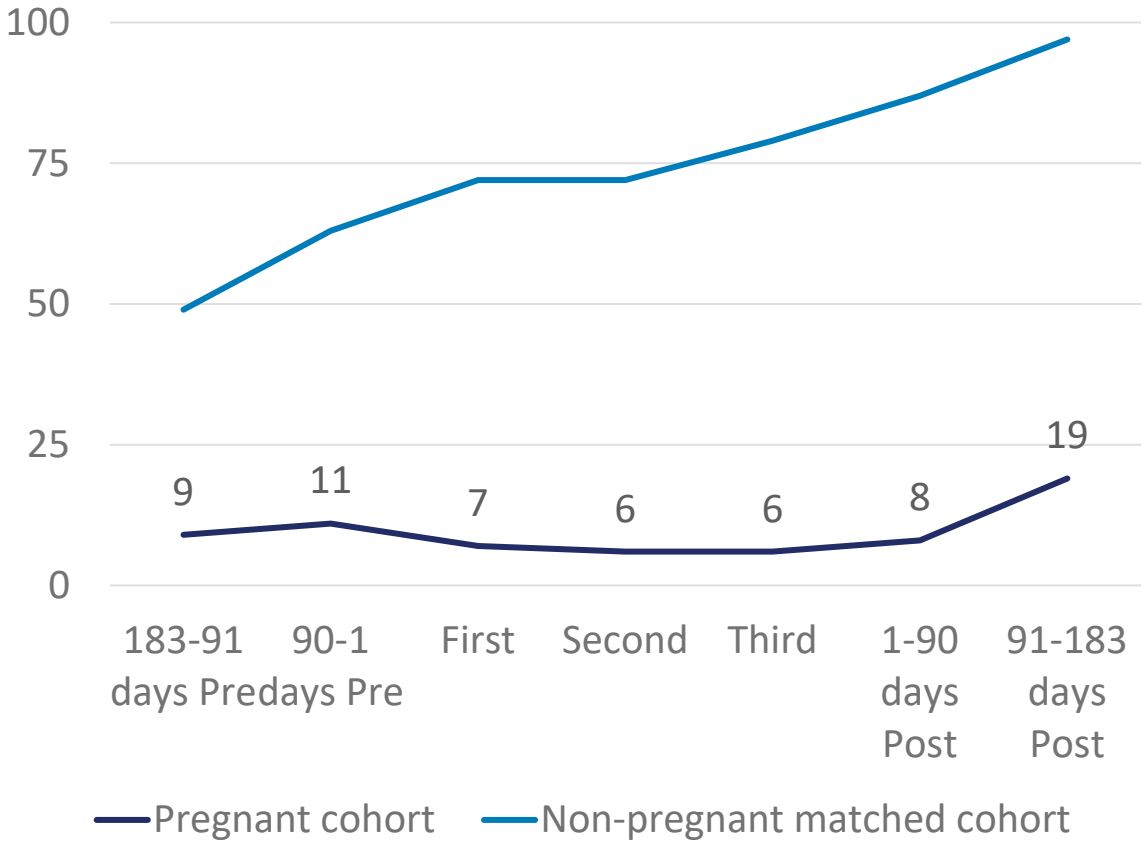


Least Common Drug Use Across Pregnancy (or matched) Episode

Ocrelizumab



Teriflunomide



Conclusions

- Among a cohort of patients with multiple sclerosis, pregnant patients have lower use of multiple sclerosis drugs than non-pregnant patients
  - This difference is apparent even 6 months before and after pregnancy
- Prevalence of different drugs varies
  - Higher for those on the market longer
- Safety studies may be possible for some drugs, but will be harder for those with low uptake

Acknowledgements

Sentinel Operations Center

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- Amanda Carruth
- Nicole Haug
- Rebecca Hawrusik
- Mayura Shinde
- Liz Siranosian

FDA

- Danijela Stojanovic
- Patricia Bright

Sentinel Data Partners

- CVS Health Clinical Trial Services, an affiliate of Aetna, a CVS Health Company, Blue Bell, PA
- HealthCore (Elevance Health), Wilmington, DE
- Humana Healthcare Research Inc., Louisville, KY
- Kaiser Permanente Northern California
- OptumInsight Life Sciences Inc., Boston, MA.
- Vanderbilt University Medical Center, Department of Health Policy, Nashville, TN, through the TennCare Division of the Tennessee Department of Finance & Administration

Sentinel

Validation of an ICD-10-based Algorithm to Identify Stillbirth in the Sentinel System

Susan E. Andrade, ScD

University of Massachusetts Chan Medical School

Background

- Fetal deaths include stillbirths and spontaneous abortions, which are generally differentiated by gestational age and/or birth weight
- Stillbirth data in the U.S. are commonly reported as fetal deaths at ≥ 20 weeks gestation
- Approximately 24,000 stillbirths occur in the U.S. annually, representing about 1% of all pregnancies*
- Few studies have developed and validated algorithms to identify stillbirths using administrative or claims data in U.S. populations

*MacDorman MF, Gregory ECW. Fetal and perinatal mortality: United States, 2013. National vital statistics reports; vol 64 no 8. Hyattsville, MD: National Center for Health Statistics. 2015

Objectives

- To develop an ICD-10-CM-based algorithm to identify cases of stillbirth using electronic healthcare data
  - Assess the positive predictive value (PPV) of the algorithm through medical chart review

Study Design

- Development of an ICD-10-CM based algorithm to identify cases of stillbirth using electronic health data
  - Code-based screening algorithm included diagnosis codes for stillbirth or a combination of intrauterine death or papyraceous fetus and a gestational age code ≥ 20 weeks
  - From the study population identified using this screening algorithm, three final algorithms were developed for evaluation
    - Selected criteria based upon clinical relevance and the distribution of individual diagnosis and procedure codes among both confirmed and non-confirmed potential stillbirth cases in the period 60 days prior to (and including) the index date and 60 days after the index date

Study Design (continued)

ICD-10-CM Diagnosis Codes

O31.00XX	**Papyraceous fetus, unspecified trimester**
O31.02XX	**Papyraceous fetus, second trimester**
O31.03XX	**Papyraceous fetus, third trimester**
O36.4XXX	**Maternal care for intrauterine death**
Z37.1	Single stillbirth
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.60	Multiple births, unspecified, some liveborn
Z37.61	Triplets, some liveborn
Z37.62	Quadruplets, some liveborn
Z37.63	Quintuplets, some liveborn
Z37.64	Sextuplets, some liveborn
Z37.69	Other multiple births, some liveborn
Z37.7	Other multiple births, all stillborn
P95	Stillbirth

Study Design (continued)

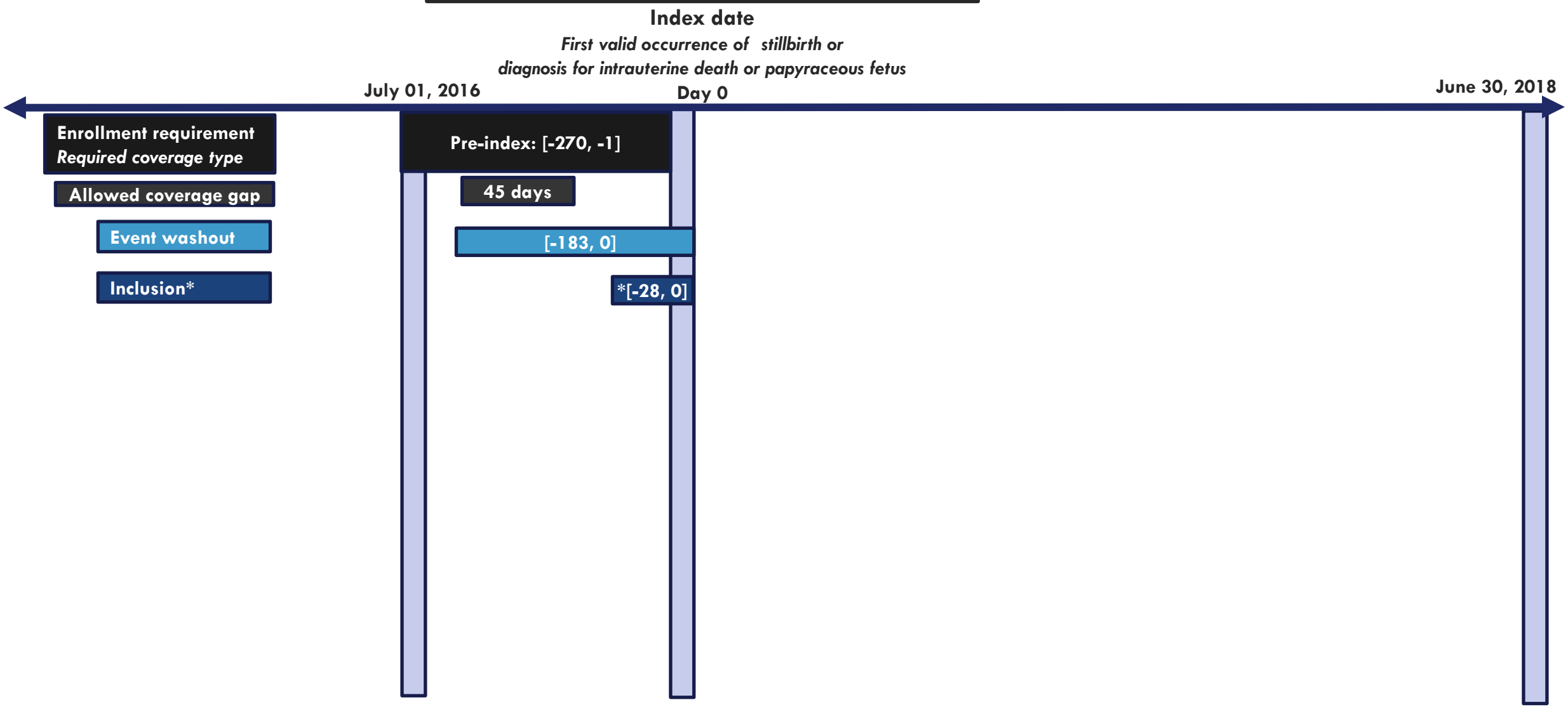
Code-based screening algorithm for identification of sample for chart abstraction and adjudication:

At least one ICD-10-CM code specifically describing **stillbirth/stillborn outcome of delivery** (Z37.1, Z37.3, Z37.4, Z37.6X, Z37.7, P95)

OR

At least one ICD-10-CM code for **intrauterine death or papyraceous fetus** (O36.4XXX and O31.0XXX) **PLUS an ICD-10-CM code indicating a gestational age greater than or equal to 20 weeks** (ICD-10-CM codes Z3A20-Z3A49) was recorded within the period 28 days before the code for intrauterine death or papyraceous fetus

Stillbirth potential cases identification



*Inclusion	**Cohort Restrictions
Diagnosis code ≥ 20-Week Gestation was required within 28 days of code for intrauterine death or papyraceous fetus	12-55 years of age on index date Females

Study Design (continued)

Algorithm 1.
Presence of an ICD-10-CM code for stillbirth/IUFD and an ICD-10-CM code indicating a gestational age greater than or equal to 20 weeks recorded within the period 28 days before (and including) the index date (encounter date for which the code for stillbirth/IUFD code was identified)
PLUS
[(At least two ICD-10-CM codes for stillbirth, IUFD, or continuing pregnancy after IUFD (unspecified trimester, second trimester, or third trimester) identified on the index date)
OR
(no other pregnancy outcome ICD-10-CM code [i.e. live birth, spontaneous abortion, induced abortion] identified on the index date)]

Algorithm 2.
Presence of an ICD-10-CM code for stillbirth/IUFD and an ICD-10-CM code indicating a gestational age greater than or equal to 20 weeks recorded within the period 28 days before (and including) the index date (encounter date for which the code for stillbirth/IUFD code was identified)
PLUS
[(At least two ICD-10-CM codes for stillbirth, IUFD, or continuing pregnancy after IUFD (unspecified trimester, second trimester, or third trimester) identified on or within 7 days after the index date)
OR
(no other pregnancy outcome ICD-10-CM code identified on the index date)]

Algorithm 3.
Presence of an ICD-10-CM code for stillbirth/IUFD and an ICD-10-CM code indicating a gestational age greater than or equal to 20 weeks recorded within the period 28 days before (and including) the index date (encounter date for which the code for stillbirth/IUFD code was identified)
PLUS
Exclude pregnancies with a procedure code for nursery services (revenue code 017x) or induced abortion identified on the index date

Study Design (continued)

- Retrospective study using data from three Data Partners (U.S. health systems) included in FDA's Sentinel System
  - A random sample of medical charts (N=169) was identified for chart abstraction and adjudication
  - Two physician adjudicators reviewed potential cases to determine whether a stillbirth event was definite/probable, the date of the event, and the gestational age at delivery
    - Clinical definition based upon the Brighton Collaboration Stillbirth Working Group guidelines*

*Tavares Da Silva F, et al. Vaccine. 2016;34(49):6057-6068

Analysis

- Positive predictive value (PPV) was calculated for the algorithms
  - Secondary analyses: PPV estimates stratified by demographic and encounter characteristics
- Among confirmed cases, agreement between the claims data and medical charts was determined for both the event date and gestational age (GA) at stillbirth

Results

- Data Partners requested charts for 153 of the 169 potential cases (90.5%) identified for review (those meeting code-based screening algorithm criteria)
- Obtained 110 of the 153 charts (71.9%) requested (61.5% of overall potential cases identified)
  - Distributions of maternal age and specific encounter characteristics were generally similar for potential cases with a chart and potential cases for whom the charts were unobtainable

Results (continued)

- Of the 110 potential cases identified by the code-based screening algorithm, 54 were confirmed stillbirth events (49.1%)
  - Majority were identified in the inpatient setting (90.7%; 49/54 confirmed cases)
  - All 54 confirmed cases had an ICD-10-CM diagnosis code indicating a GA ≥ 20 weeks

Results (continued)

- Of the 56 potential cases not confirmed to be stillbirth events
  - 22 (39.3%) spontaneous abortions
  - 19 (33.9%) liveborn infants or continuing pregnancies
  - 11 (19.6%) were terminations of pregnancy, including inductions of labor for pregnancy complications
  - 1 neonatal death shortly after birth
  - 3 cases were unable to determine diagnosis (insufficient/conflicting information in the chart)

Results (continued)

- Algorithm with the highest PPV was **Algorithm 1**
  - Of the 63 potential cases identified, 52 were confirmed stillbirth events (PPV=82.5%; 95% CI, 70.9%-91.0%)
  - 52 of total 54 confirmed cases (96.3%) were identified using Algorithm 1
- Algorithm 2: 52/64 potential cases identified were confirmed stillbirth events (PPV=81.3%; 95% CI, 69.5%-89.9%)
- Algorithm 3: 53/81 potential cases identified were confirmed stillbirth events (PPV= 65.4%; 95% CI, 54.0%-75.7%)

Results (continued)

Validation of Algorithm 1 for identification of stillbirth

Population	Number of charts reviewed	Number of cases confirmed	Positive predictive value (95% confidence interval)
Overall	63	52	82.5% (70.9%-91.0%)
Encounter type			
Inpatient	50	47	94.0% (83.5%-98.8%)
Ambulatory visit	11	4	36.4% (10.9%-69.2%)
Other ambulatory encounter type	2	1	50.0% (1.3%-98.7%)
ICD-10-CM coding			
Stillbirth	52	47	90.4% (79.0%-96.8%)
Intrauterine fetal death	57	48	84.2% (72.1%-92.5%)
Gestational age ≥ 20 weeks on index date	61	52	85.3% (73.8%-3.0%)
Data Partner			
DP 1	29	24	82.8% (64.2%-94.2%)
DP 2	27	22	81.5% (61.9%-93.7%)
DP 3	7	6	85.7% (42.1%-99.6%)

Results (continued)

Comparison of outcome dates and gestational age estimates in the claims and medical chart data

		Difference in days, claims data versus medical chart					
	Women with data recorded	Mean	Standard deviation	Within 3 days	Within 7 days	Within 14 days	Within 30 days
Outcome date comparison							
Delivery date	52	1.2	2.7	**49 (94%)**	**50 (96%)**	51 (98%)	52 (100%)
Date of fetal demise	44	0.8	2.1	**41 (93%)**	**4 (98%)**	44 (100%)	44 (100%)
Gestational age comparison							
Delivery date	52	3.4	4.5	**41 (79%)**	**47 (90%)**	50 (96%)	52 (100%)
Date of fetal demise	42	2.9	2.7	**31 (74%)**	**40 (95%)**	42 (100%)	42 (100%)

Strengths

- Size and diversity of the study population
  - Mostly commercial healthcare systems
- Validation of cases was performed by clinical adjudicators with expertise in obstetrics and gynecology using established guidelines for the clinical definition of stillbirth

Limitations

- Evaluated only women meeting our specified criteria which included codes suggestive of stillbirth
  - Could not evaluate the sensitivity and specificity of the algorithm
- 72% of medical records requested were obtained for chart review (62% of overall potential cases identified)
  - Distributions of characteristics were generally similar among potential cases for whom charts were available versus those for whom charts were not obtained

Conclusions

- Electronic healthcare data may be useful for signal detection of medical product exposures potentially associated with stillbirth
  - Algorithm 1 PPV=83%
    - Incorporated a combination of criteria including a code indicating a gestational age ≥ 20 weeks plus either > 1 stillbirth/IUFD-related code or no other pregnancy outcome code recorded on the index date
    - Vast majority of confirmed cases (52 of 54 total confirmed cases [96%]) were identified by this algorithm
  - ≥ 90% agreement within 7 days between claims data and medical charts for both the outcome date and gestational age at stillbirth

Workgroup Members

- **University of Massachusetts Chan Medical School:** Susan Andrade, ScD; Tiffany Moore-Simas, MD, MPH; Cassandra Saphirak, MA; Christopher Delude, BA; Mary Ellen Stansky, Timothy Konola, BA
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- **HealthCore (Elevance Health):** Kevin Haynes, PharmD, MS
- **CVS Health Clinical Trial Services:** Cheryl McMahill-Walraven, PhD
- **Kaiser Permanente Center for Integrated Health Care Research:** Connie M Trinacty, PhD
- **U.S. Food and Drug Administration (FDA):** Danijela Stojanovic, PhD, PharmD; Steven Bird, PhD, PharmD; Lockwood Taylor, PhD
- **Adjudicators:** Julianne Lauring, MD (University of Massachusetts Medical School); Erin Longley, MD (Community Health Care)

Thank You

Characterizing Medication Use Among Pregnancies with COVID-19 in the Sentinel System

Mayura Shinde, MPH, DrPH

Sentinel Operations Center

Background

Background

- Pregnant/breastfeeding patients are excluded from most clinical trials, importantly from initial COVID-19 vaccine and treatment trials
- Medication and vaccine safety is routinely assessed through post-marketing observational studies and pregnancy registries
- Several retrospective observational studies have characterized pregnant patients with COVID-19 but data on real-world utilization of medications is limited

CONSIGN

Covid-19 infectiOn aNd medicineS In preGNancy

- European Medicines Agency (EMA)-funded, international collaboration across various countries to understand the natural history of COVID-19 in pregnant people
    - Goal: to provide adequate data on the impact of COVID-19 in pregnancy to guide decision-making about vaccine indications, vaccination policies, and treatment options for COVID-19 disease and associated complications
- U.S. FDA's Sentinel System is one of several international collaborators, including the United Kingdom, Norway, Denmark, Germany, Spain, Italy, France, and Sweden

Study Objectives

CONSIGN Objectives

Objective 1:
Outpatient medication use

→ By trimester at time of ***diagnosis***

Objective 2:
COVID-19 severity and clinical outcomes

→ By trimester at time of ***diagnosis***

1a: Pregnant patients with COVID-19

1b: Pregnant patients without COVID-19

1c: Non-pregnant patients with COVID-19

2a: Pregnant patients with COVID-19

2b: Non-pregnant patients with COVID-19

Study Cohort Identification

COVID-19 Identification

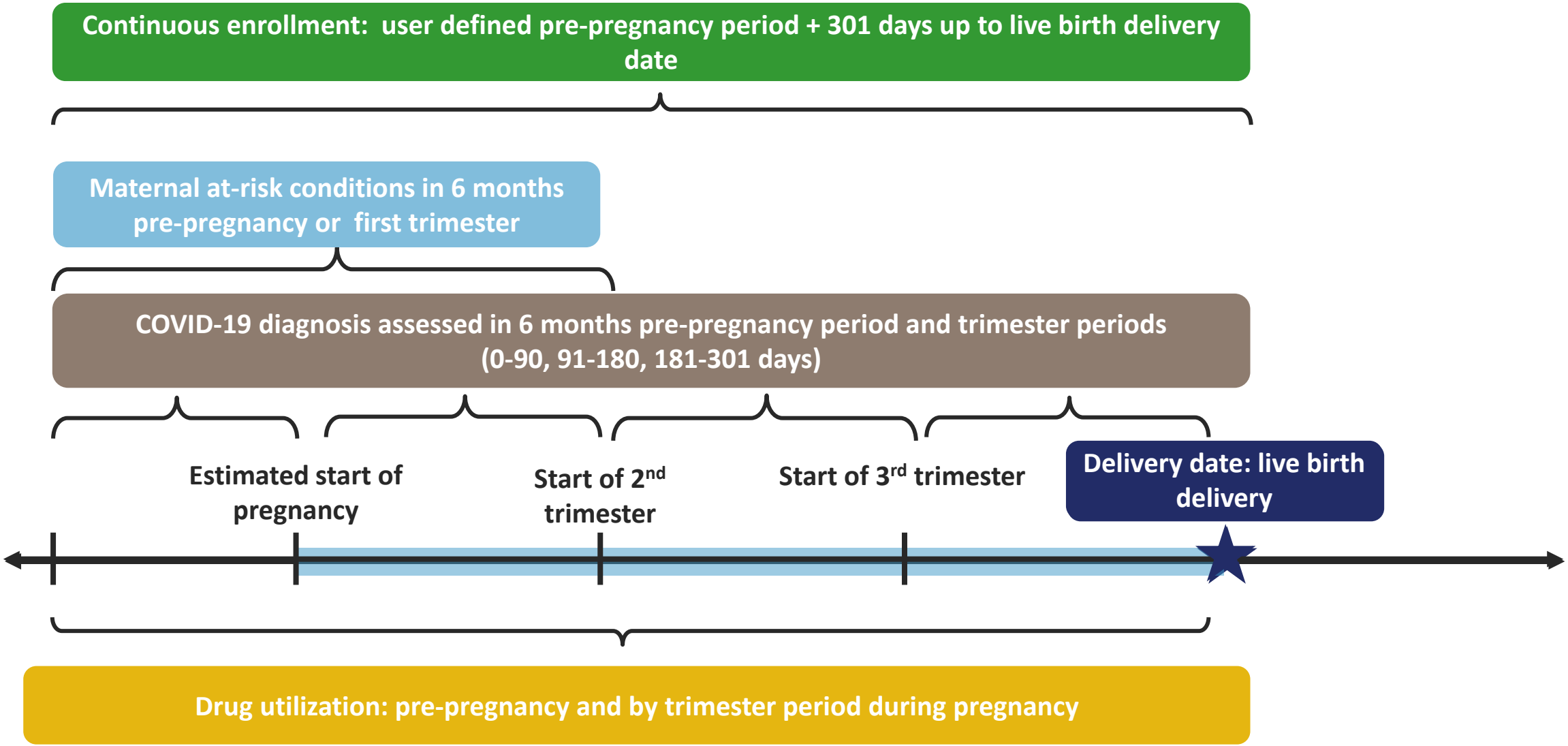
- COVID-19 related International Classification of Diseases (ICD)-10-Clinical Modification (CM) diagnosis codes,

  OR

- Positive result of reverse transcription polymerase chain reaction (RT-PCR) or other Nucleic Acid Amplification Test (NAAT) for severe acute respiratory syndrome (SARS)-CoV-2

Exposure	Code	Code type	Care setting	Description
Diagnosis	B34.2	ICD-10-CM	Inpatient	Coronavirus infection, unspecified site
Diagnosis	B97.21	ICD-10-CM	Inpatient	SARS-associated coronavirus as the cause of diseases classified elsewhere
Diagnosis	B97.29	ICD-10-CM	Inpatient	Other coronavirus as the cause of diseases classified elsewhere
Diagnosis	J12.81	ICD-10-CM	Inpatient	Pneumonia due to SARS-associated coronavirus
Diagnosis	U07.1	ICD-10-CM	Any	COVID-19, virus identified

Study Design



Results

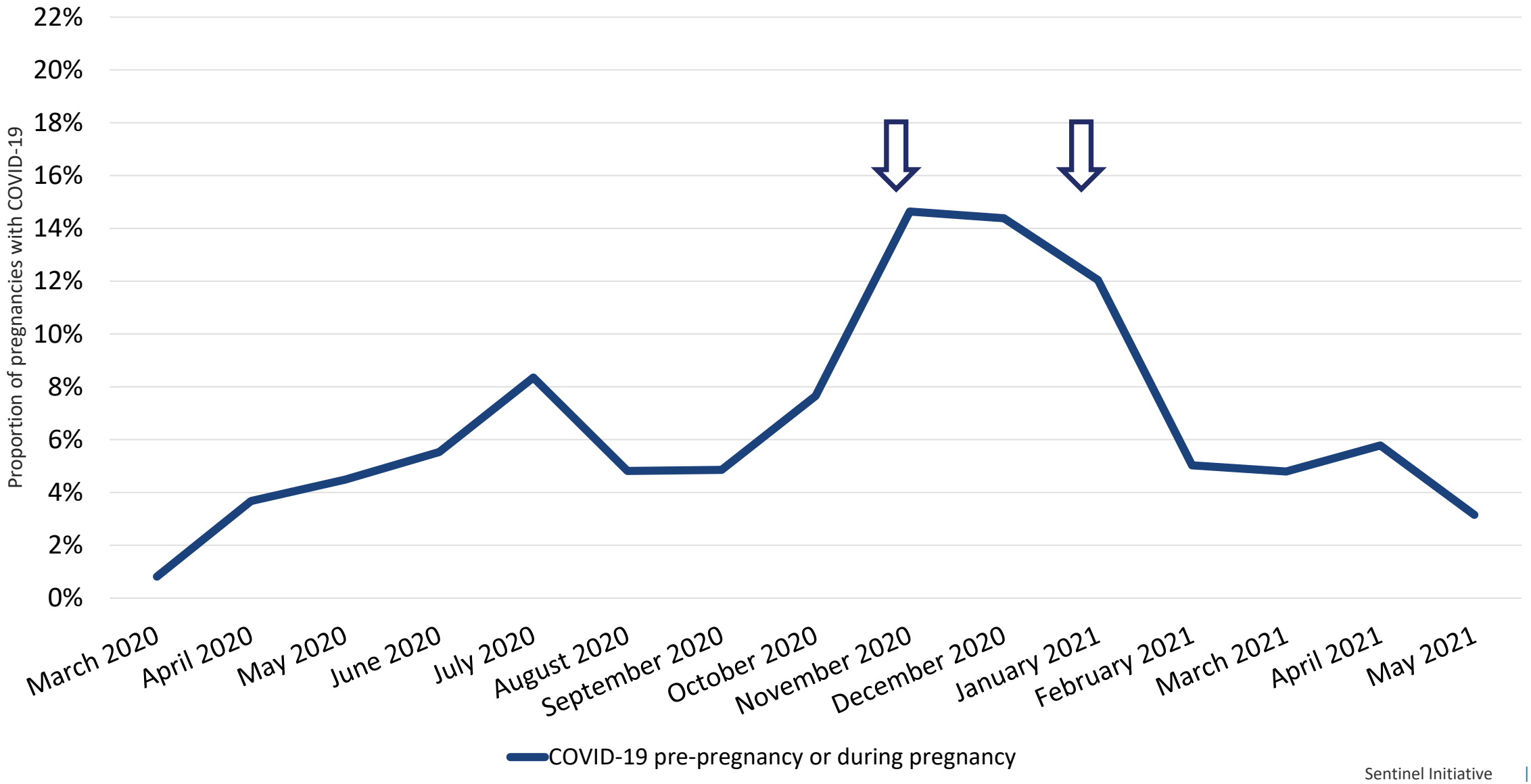
Study Cohorts in Sentinel between January 1, 2020 and May 31, 2021

	COVID-19 in 183 days pre-pregnancy	COVID-19 in first trimester	COVID-19 in second trimester	COVID-19 in third trimester	Total patients (pre-pregnancy or during pregnancy)
Pregnancies with COVID-19	143	270	664	1,942	2,747
Non-pregnant matched episodes[1] with COVID-19	143	270	663	1,936	2,744

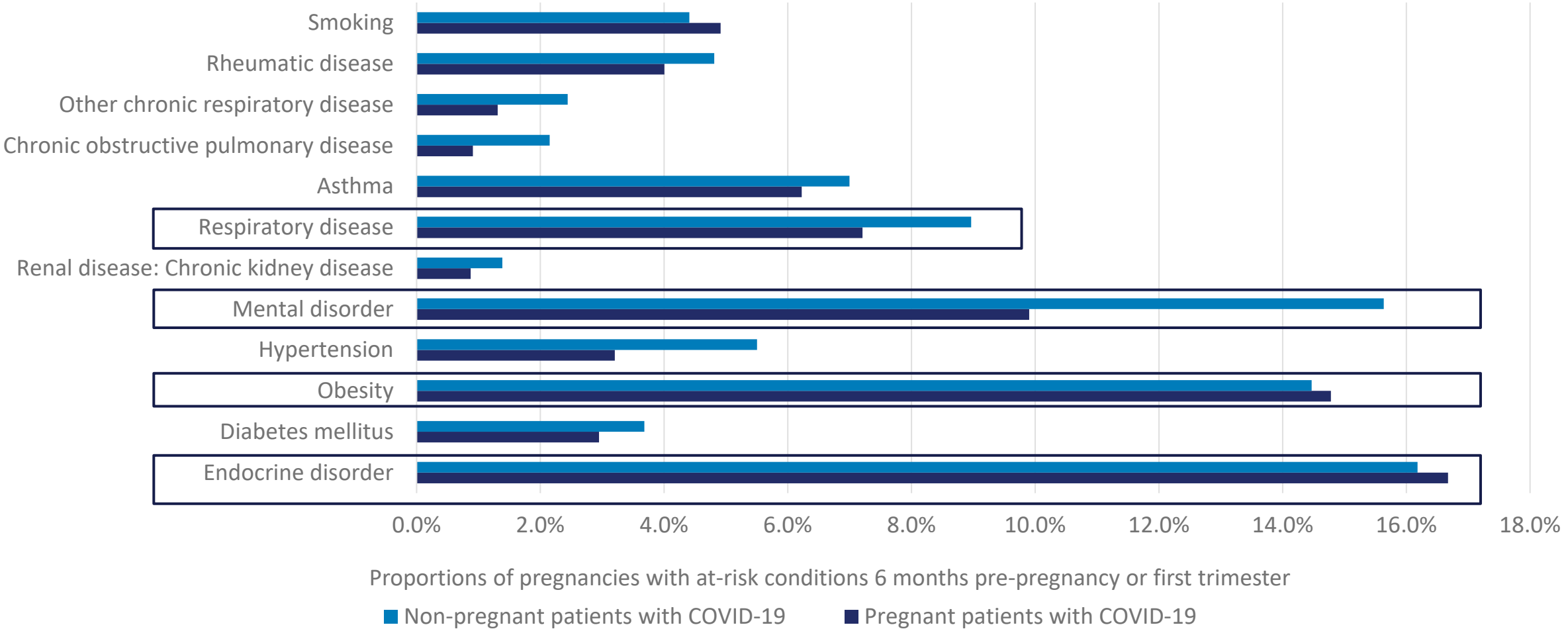
[1]For each identified pregnancy, patients were matched within Data Partner who had first enrollment episodes without live birth delivery that met all inclusion criteria, were the same age (integer), and where the eligible enrollment spans overlapped the entire pregnancy duration and 183 days pre-pregnancy period. Patients and comparator episodes were allowed to be used multiple times as controls, and patients with a pregnancy episode were allowed to contribute a separate comparator episode.

*Query period end dates were selected based on inpatient (IP) data availability per DP. Please refer to final report for a list of dates of available data for each DP.

COVID-19 Identification in Pregnant Patients During the Pandemic

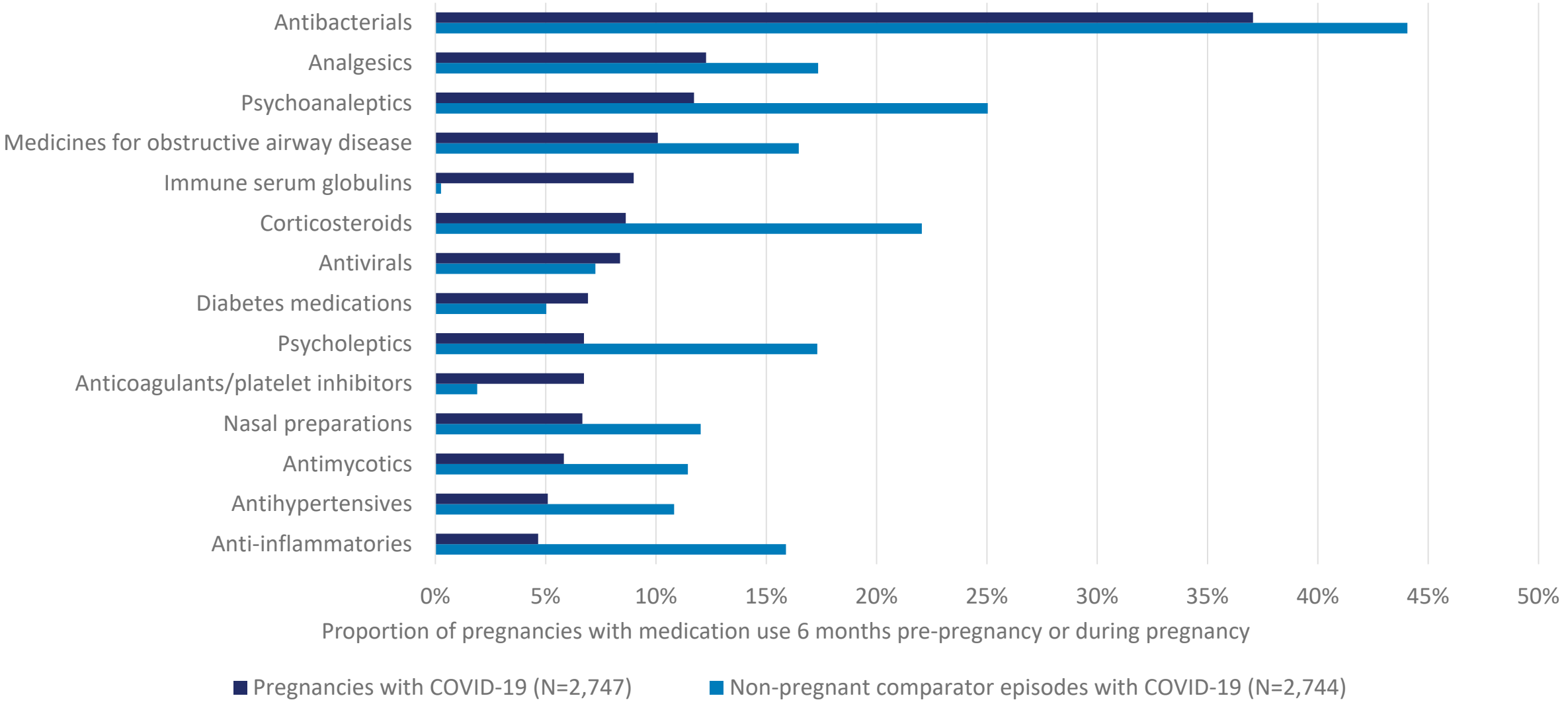


Baseline At-Risk Conditions



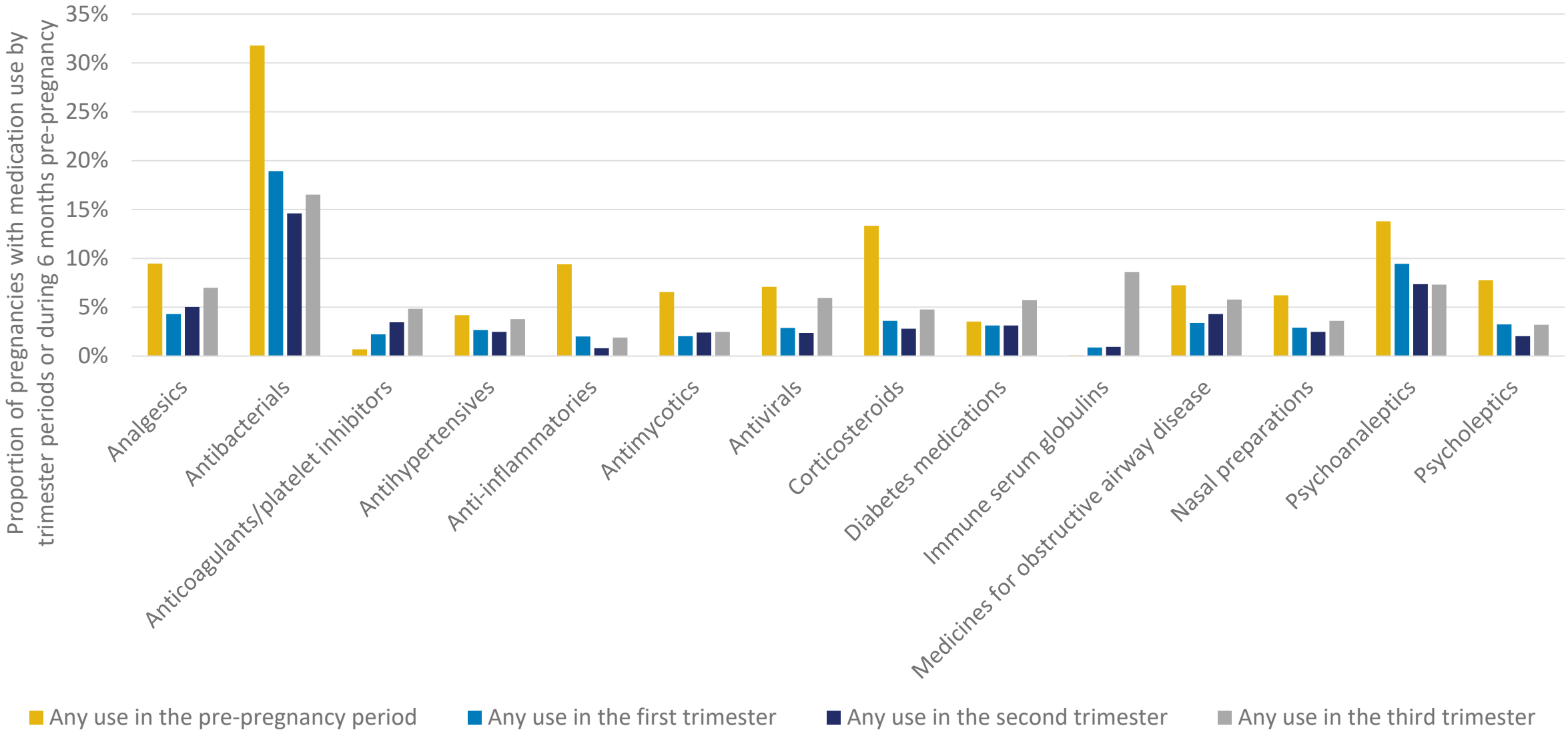
*At-risk conditions assessed in 6 months pre-pregnancy and first trimester of pregnancy in pregnant patients with COVID-19 and corresponding time periods in non-pregnant patients

Medication Use

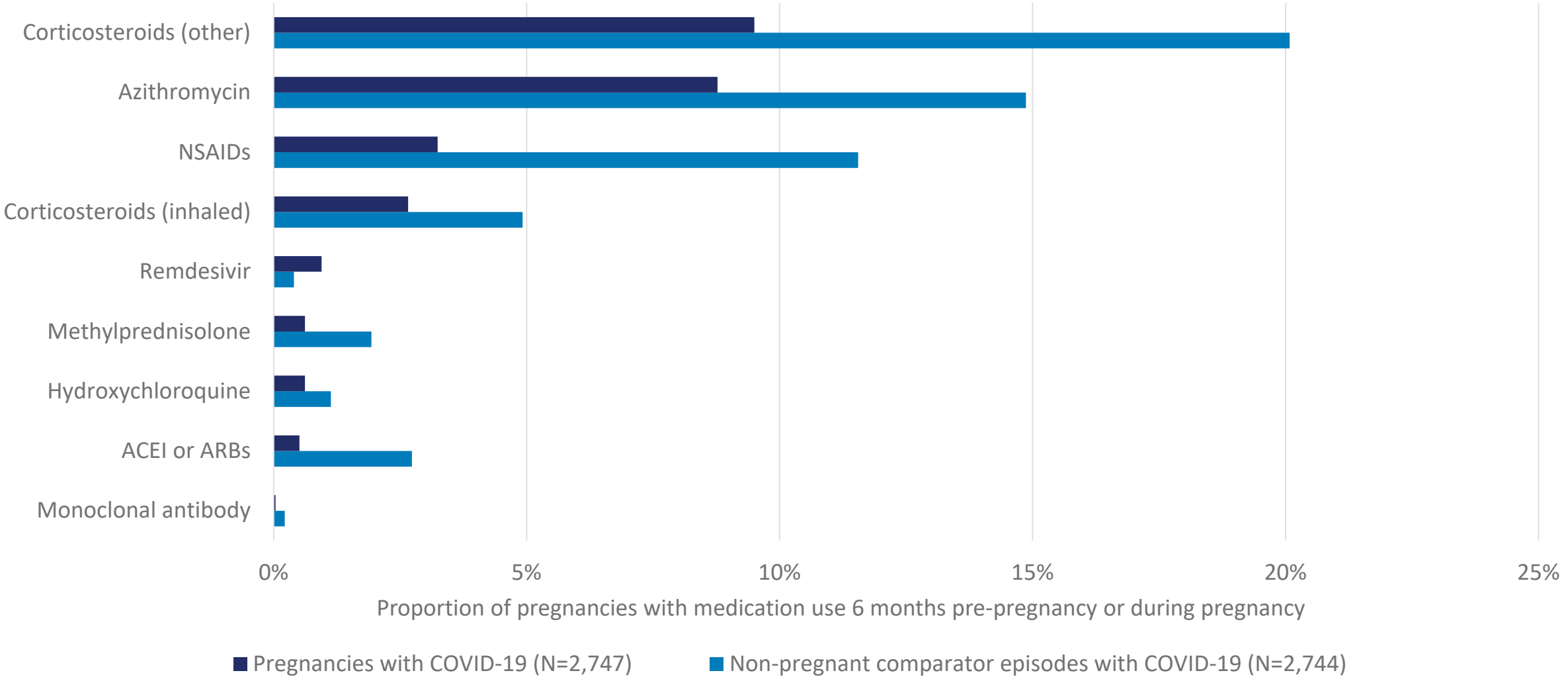


*Assessed pre-pregnancy or during pregnancy among pregnant patients with COVID-19 and corresponding time periods in non-pregnant patients with COVID-19

Medication Utilization by Trimester among Pregnant Patients with COVID-19



Potential COVID-19 Medications



*Assessed pre-pregnancy or during pregnancy among pregnant patients with COVID-19 and corresponding time periods in non-pregnant patients with COVID-19
NSAID- Non-steroidal anti-inflammatory drug; ACEI- Angiotensin converting enzyme inhibitors; ARB- Angiotensin receptor blockers

Conclusions

Conclusions

- We characterized pregnant patients with COVID-19 and described patterns of outpatient medication use among pregnant and non-pregnant patients with COVID-19
    - Corticosteroids, azithromycin, and NSAIDs more commonly used in non-pregnant patients with COVID-19
- Some interpretation considerations:

Pregnancy

- Immune system changes over the course of pregnancy
- Tendency to stop medication use at beginning of pregnancy and restart after delivery

Pandemic

- Geographic differences in COVID-19 prevalence
- Temporal differences in COVID-19 prevalence

Treatment

- Changes in COVID-19 testing, treatment patterns, and best clinical practices
- Changes in healthcare-seeking behavior throughout the pandemic
- Vaccine uptake over time (could not assess)

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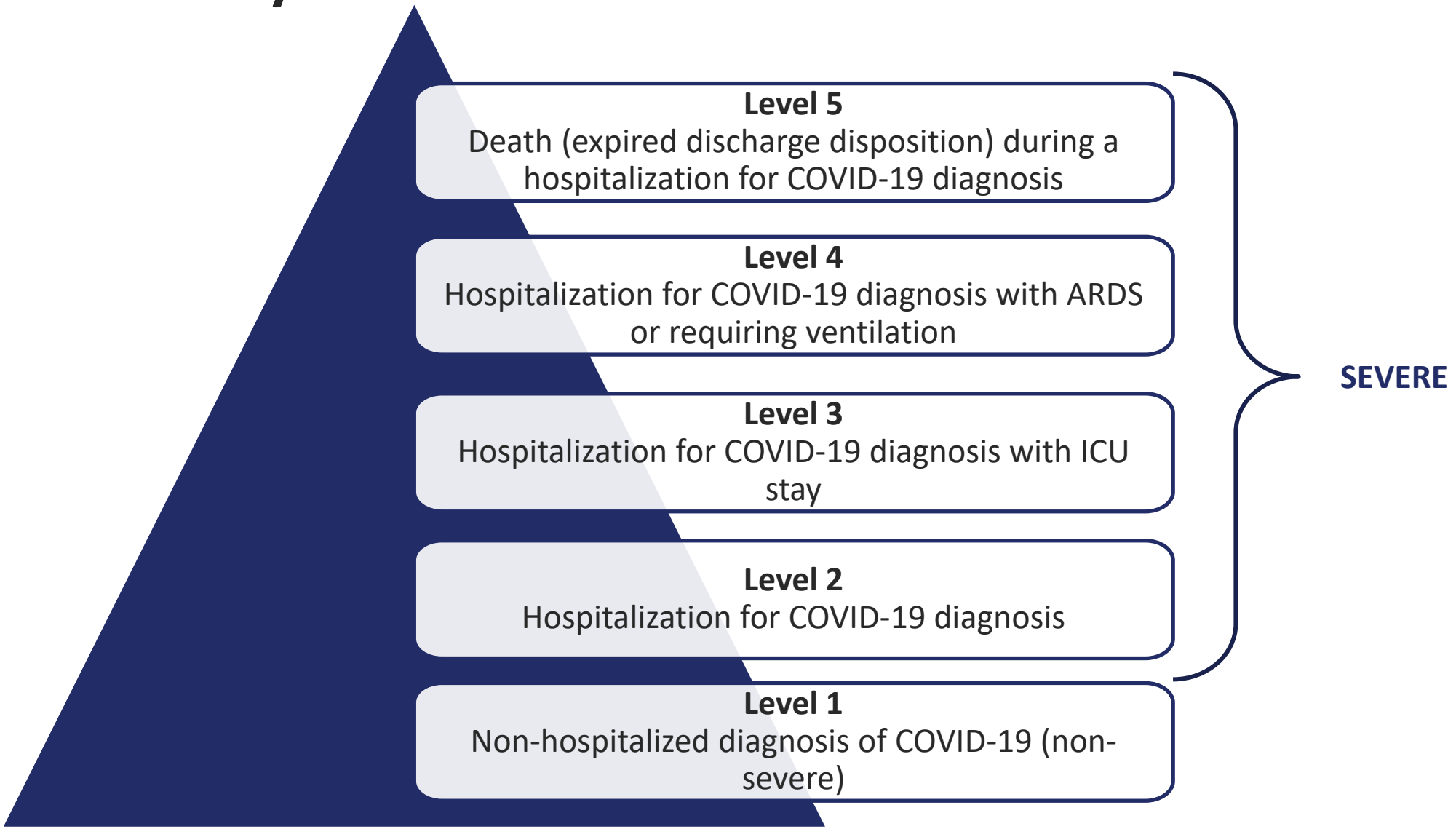
- Kaiser Permanente Northwest Center for Health Research, Portland, OR
- Kaiser Permanente Washington Health Research Institute, Seattle, WA

Thank You

Supplemental Slides

COVID-19 Severity



World Health Organization (WHO). Coronavirus disease (COVID-19) outbreak situation. Accessed 20.05.2020.
ARDS- Acute Respiratory Distress Syndrome

COVID-19 Severity