Sentinel

Active Surveillance of Medical Product Use in the FDA's Sentinel System:

A Focus on Pediatric Populations

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Acknowledgements

- Sentinel is an enormous effort that would not be possible without the hard work of many collaborators and colleagues. Many thanks are due to:
  - FDA Sentinel Core Team and Sentinel System Users
  - Sentinel Operations Center Colleagues
  - Sentinel Data Partners who provided data used in the analyses described herein

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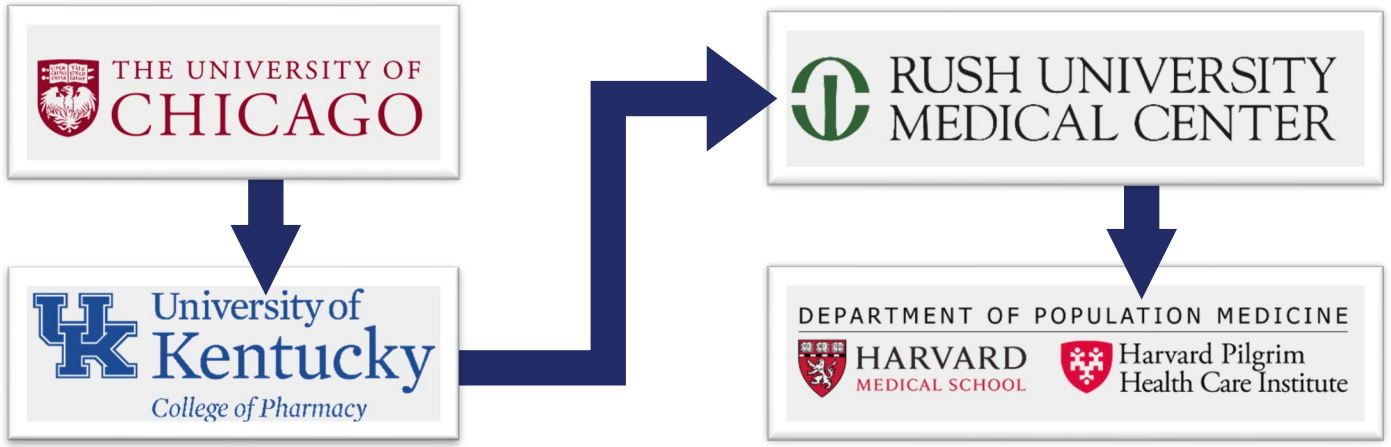
Experience



Research

Current portfolio contains routine and COVID-19 specific Sentinel queries, as well as federally funded grant work

Doctoral dissertation investigated impact of potentially inappropriate medication use on cognitive outcomes among older adults

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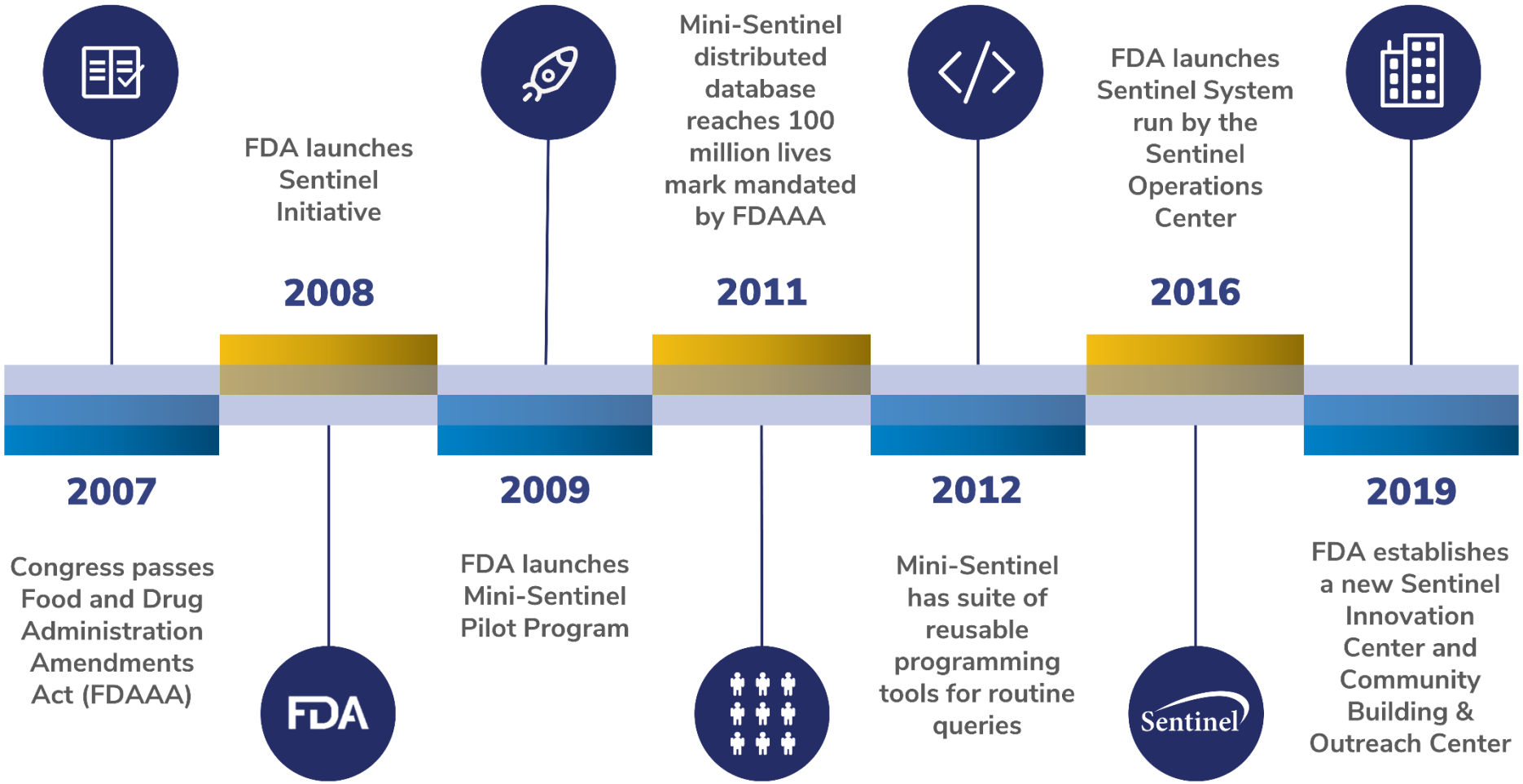
Agenda

1. Introduction to the Sentinel System
2. Characterizing the Pediatric Population in Sentinel
3. A Brief Review of Select Pediatric-Focused Sentinel Assessments

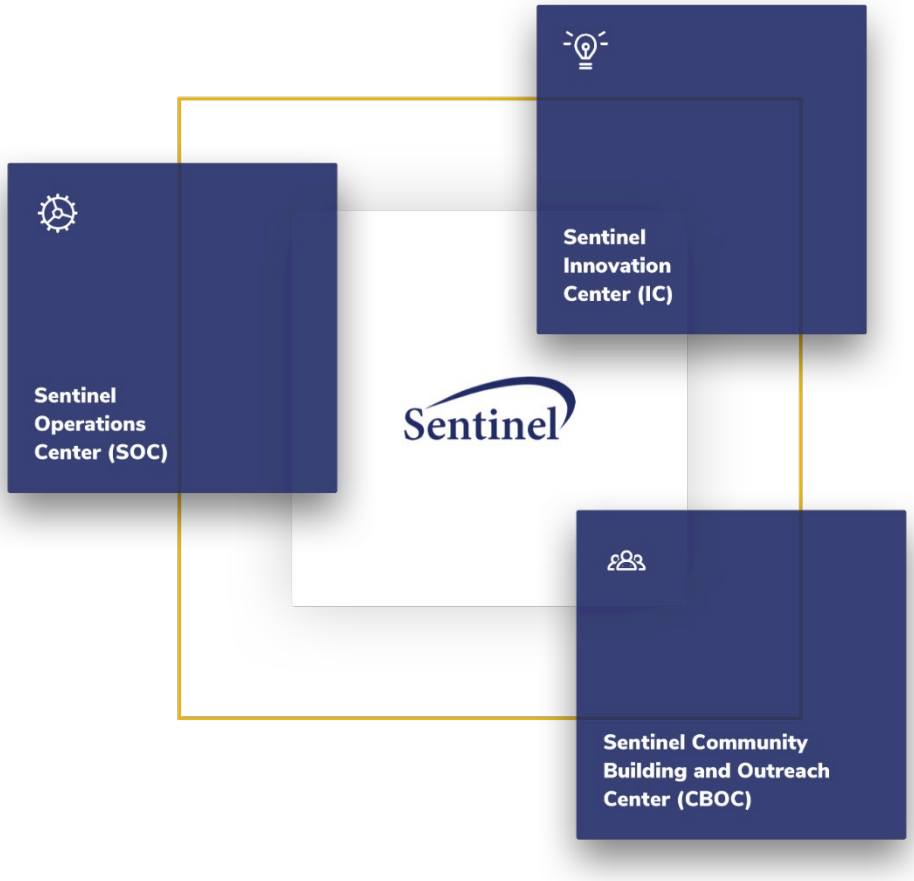

Introduction to Sentinel

History of the Sentinel Initiative



https://sentinelinitiative.org/about

Sentinel System Structure



- Sentinel System created to meet 2007 Congressional mandate to "create an **active postmarket drug safety surveillance system**"
- Led by FDA's **Office of Surveillance and Epidemiology** in the **Center for Drug Evaluation and Research**
- Three centers collaborate to proactively assess safety of approved drugs under real-world conditions

https://www.sentinelinitiative.org/about/sentinel-structure

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?

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 prescribe?

What about privacy?

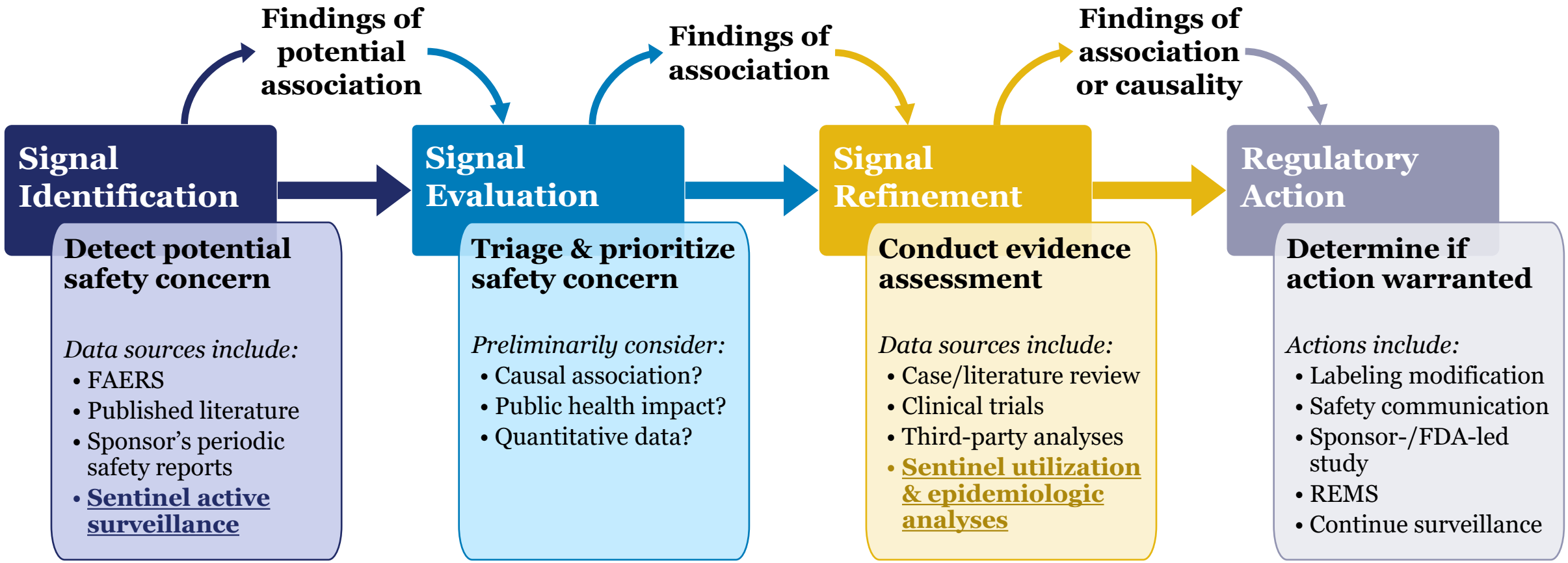
- No one looks at patients' names, addresses, phone numbers, or other identifying information.
- For more information, please visit: SentinelInitiative.org

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's Role in FDA Drug Safety Pipeline



Sentinel's Role in FDA Regulation

- FDA conducts safety studies in Sentinel for the following purposes:
  - **Assess known** serious risk related to the use of the drug
  - **Identify signals** of unexpected serious risk related to use of the drug
  - **Assess signals** of serious risk related to the use of the drug
- Sentinel drug safety studies contribute to FDA's regulatory process:
  - Provide data to address or alleviate new drug safety concerns
  - Contribute evidence to support Drug Safety Communication, Label Change, risk management strategy, or Advisory Committee deliberation
  - Respond to a citizen's petition

https://www.sentinelinitiative.org/studies/drugs

Key Components in Sentinel

- Two main components are key to success in the Sentinel System
  - A **distributed database of standardized** claims and claims linked with electronic health records (EHR) data
  - State-of-the-art **analysis tools** to monitor the safety of medications
- These components allow for efficient multi-site safety analyses

Operations Center Collaborations

Lead: Harvard Pilgrim - Health Care Institute

DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL | Harvard Pilgrim Health Care Institute

a Point32Health company

TN Division of TennCare

Elevance Health

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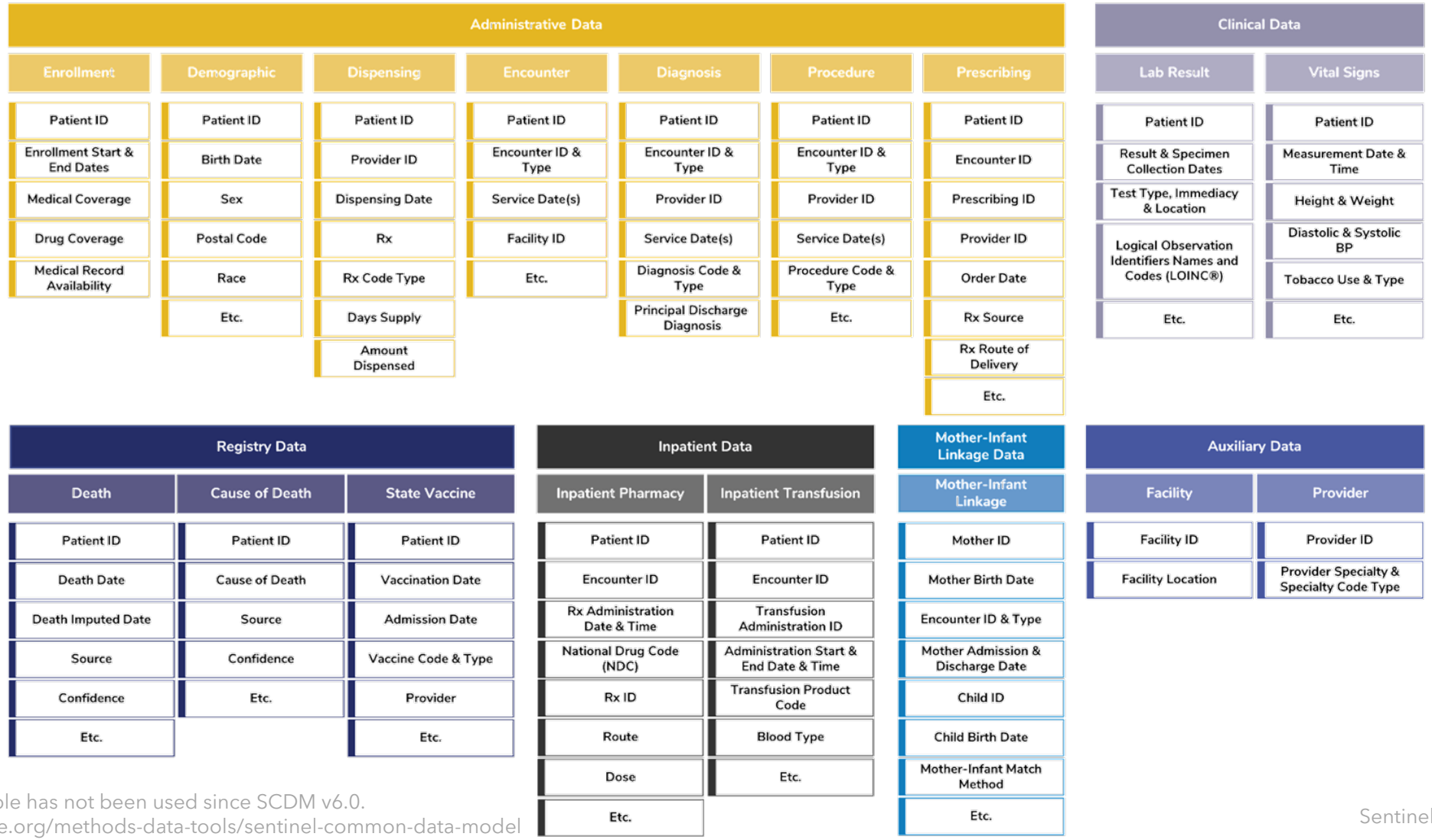
Department of Population Health Sciences
Duke University School of Medicine

Brigham and Women's Hospital
Founding Member, Mass General Brigham

CCEB

Perelman School of Medicine
University of Pennsylvania

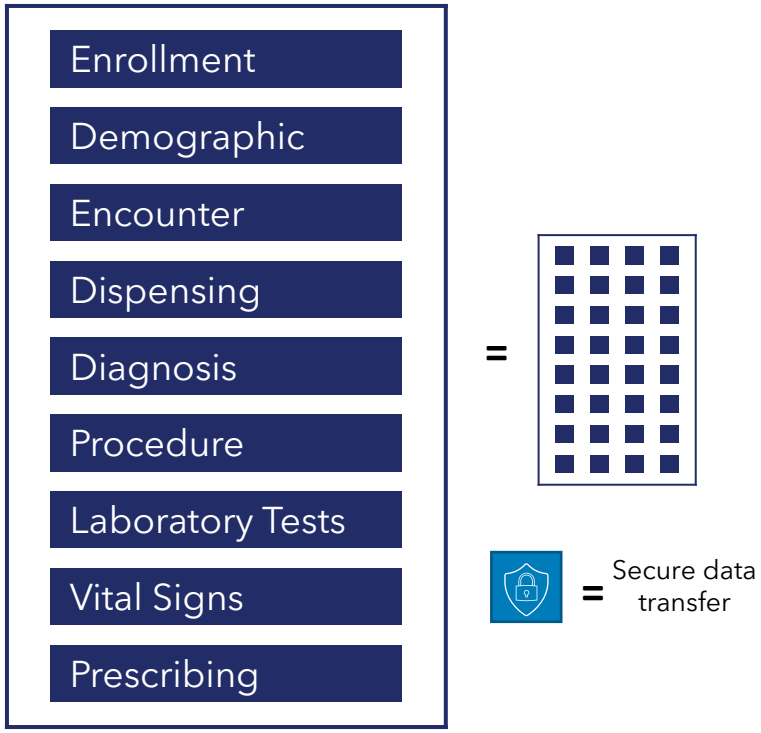
Sentinel Common Data Model

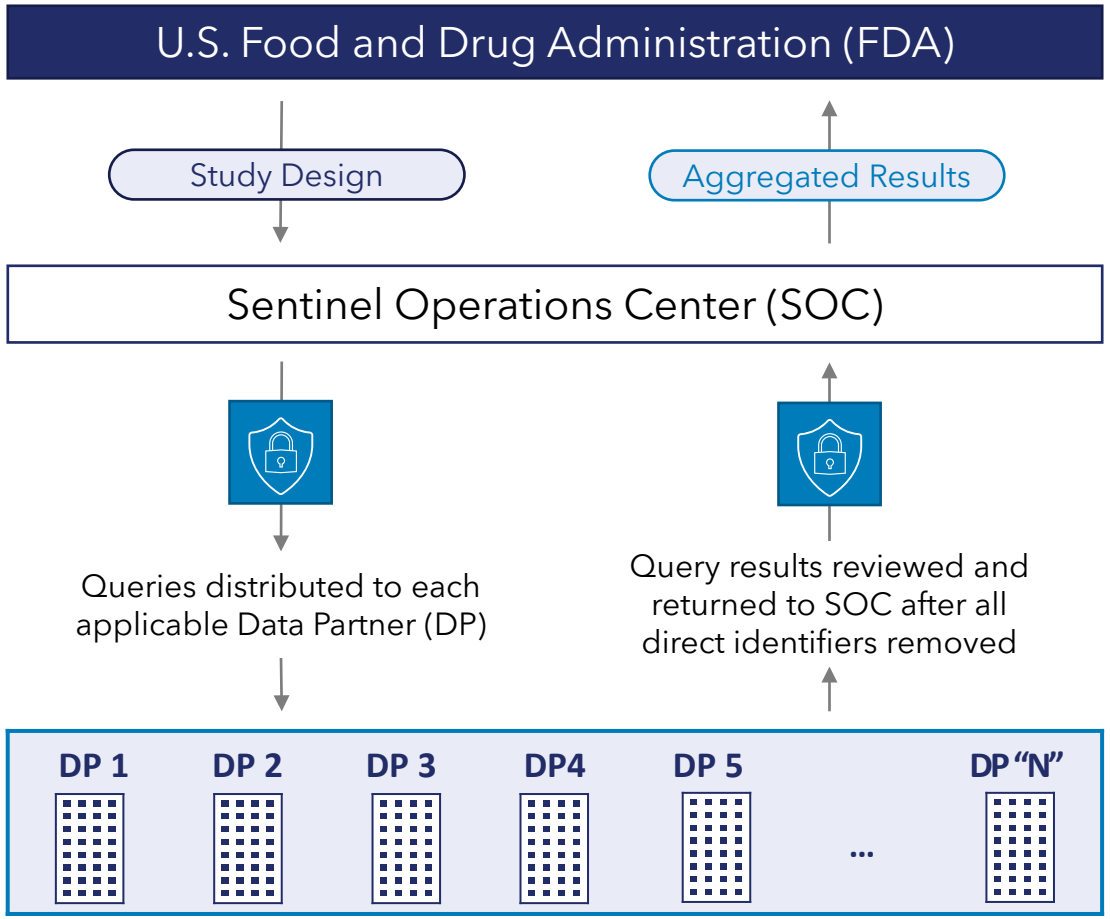


* The State Vaccine table has not been used since SCDM v6.0.
https://sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Sentinel Distributed Data Network

- Data Partners hold data in the Sentinel Common Data Model format

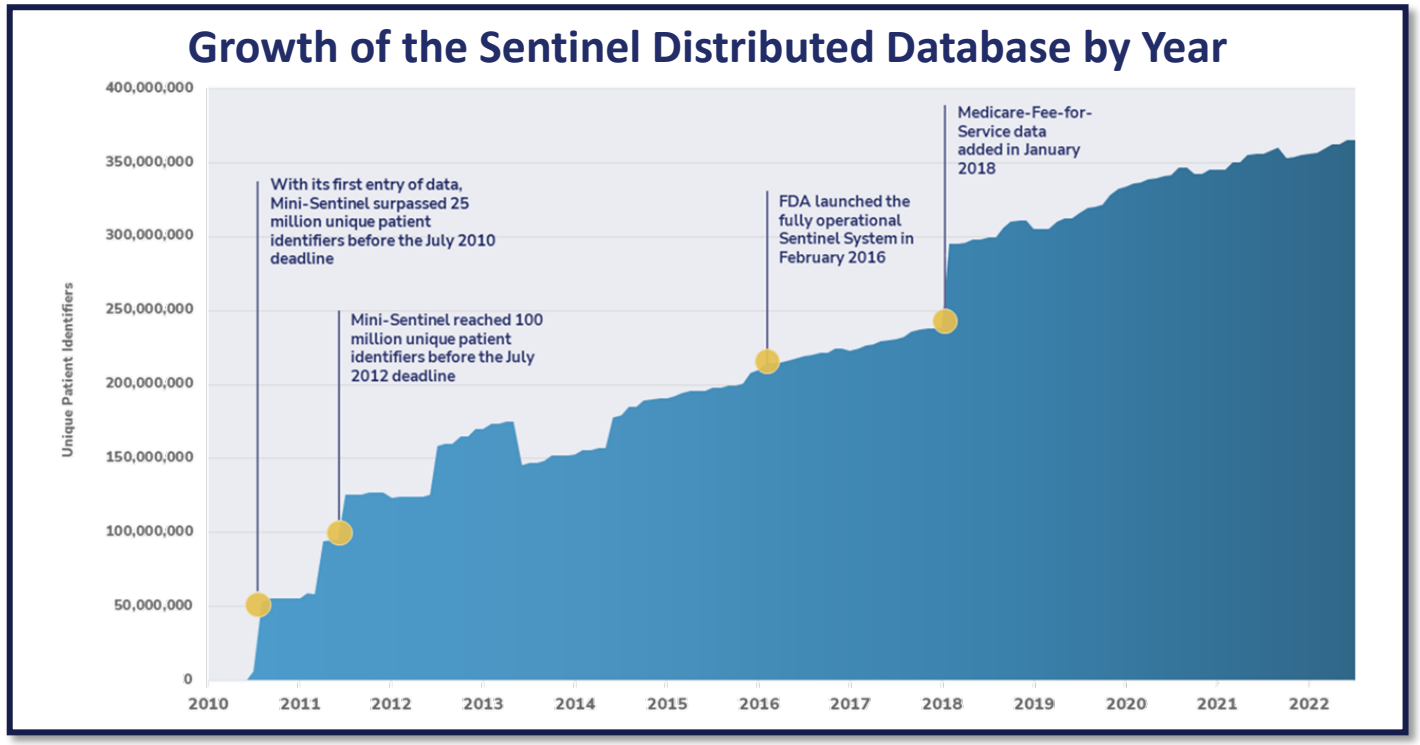




https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data

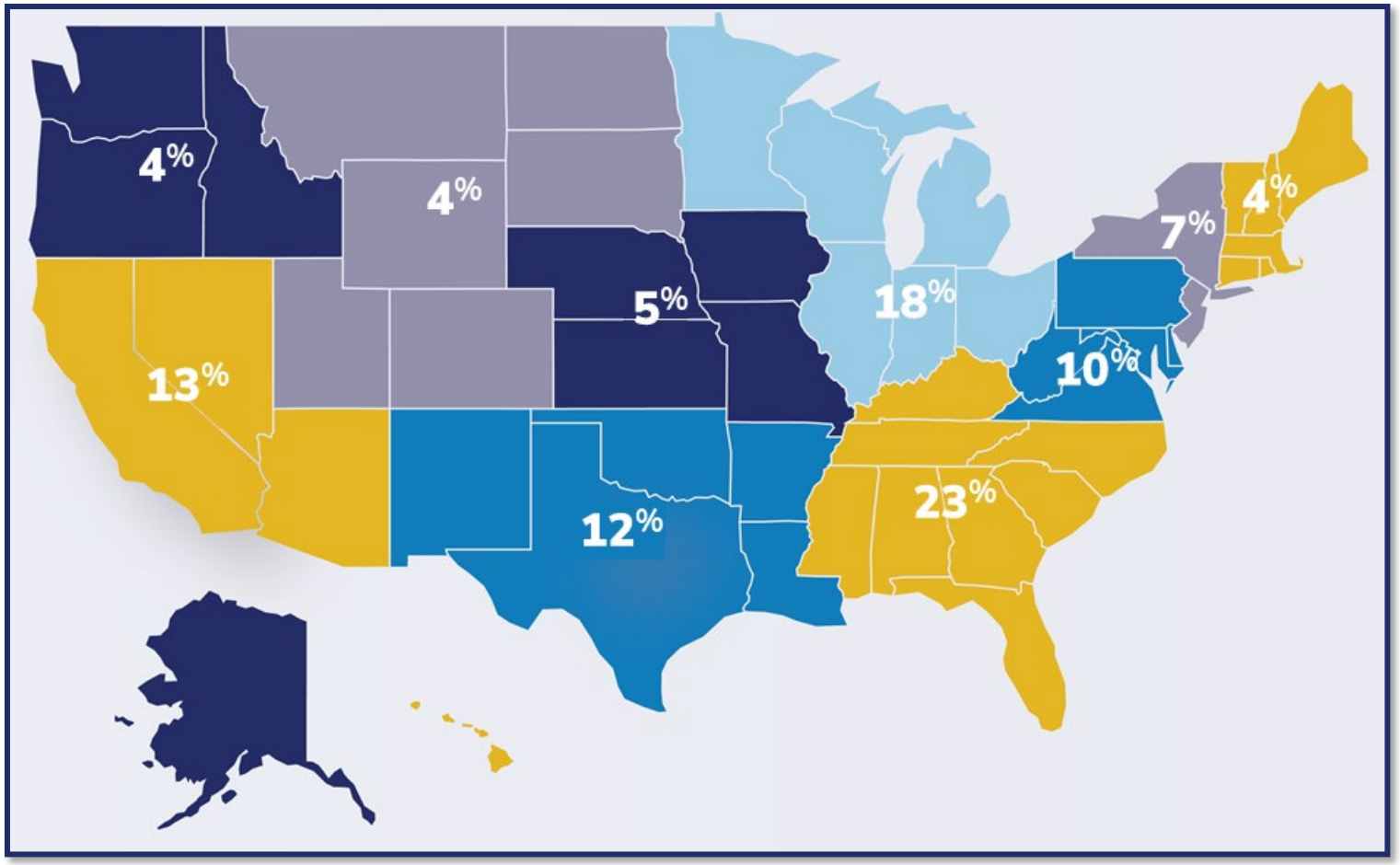
Sentinel Distributed Database Growth

- Sentinel Distributed Database came online in 2010
- Now contains ~365 million unique patient IDs from enrolled 2000 – 2022
  - ~240 million have ≥1 day of medical and drug coverage
  - ~63 million currently accruing new data
  - ~10 million live birth deliveries with a mother-infant linkage



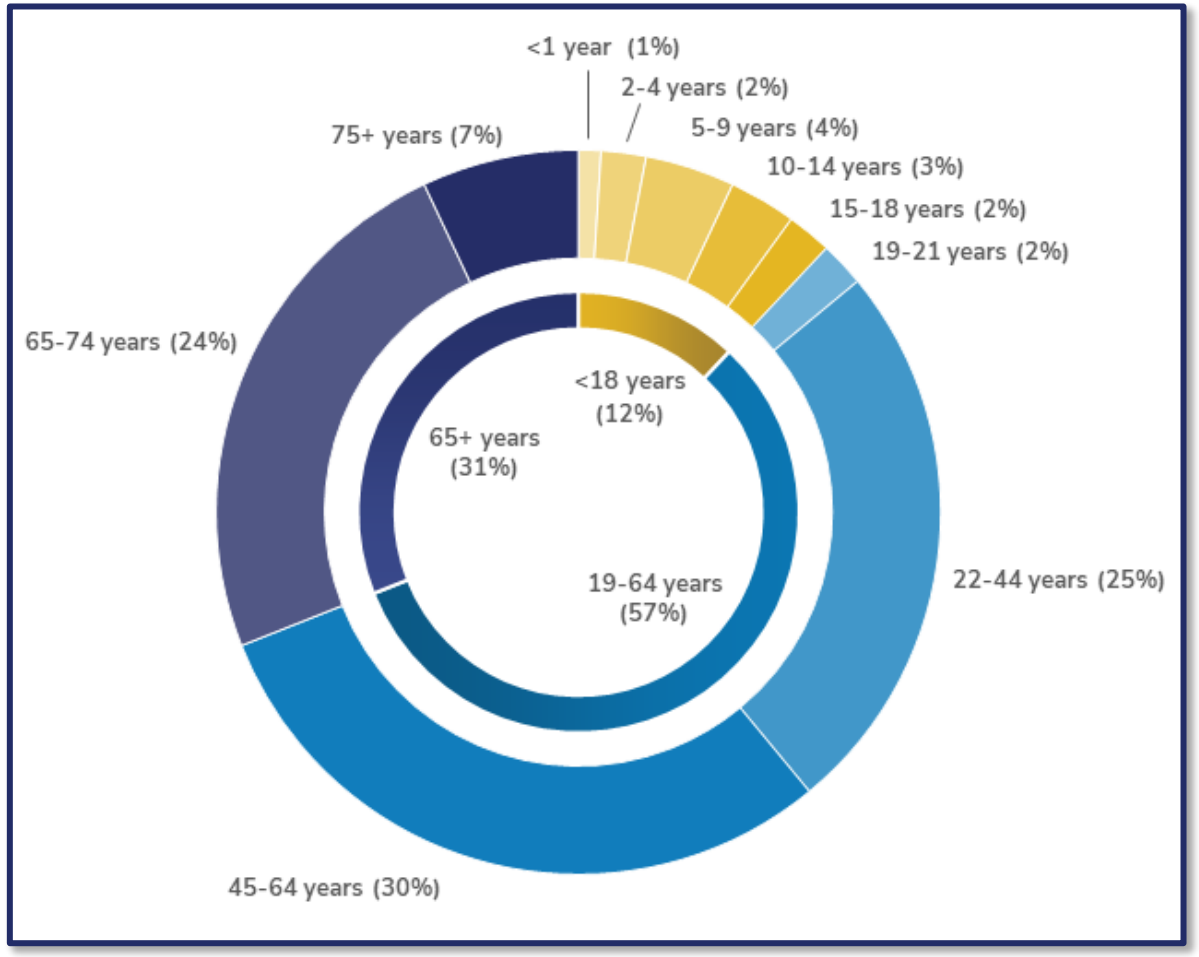
Current as of July 2022; https://sentinelinitiative.org/about/key-database-statistics

Members Geographic Distribution



Data for all members' with at least one day of medical and drug coverage based on the first day of most recent enrollment span; Data updated July 2022.
https://www.sentinelinitiative.org/about/key-database-statistics

Active Members Age Distribution

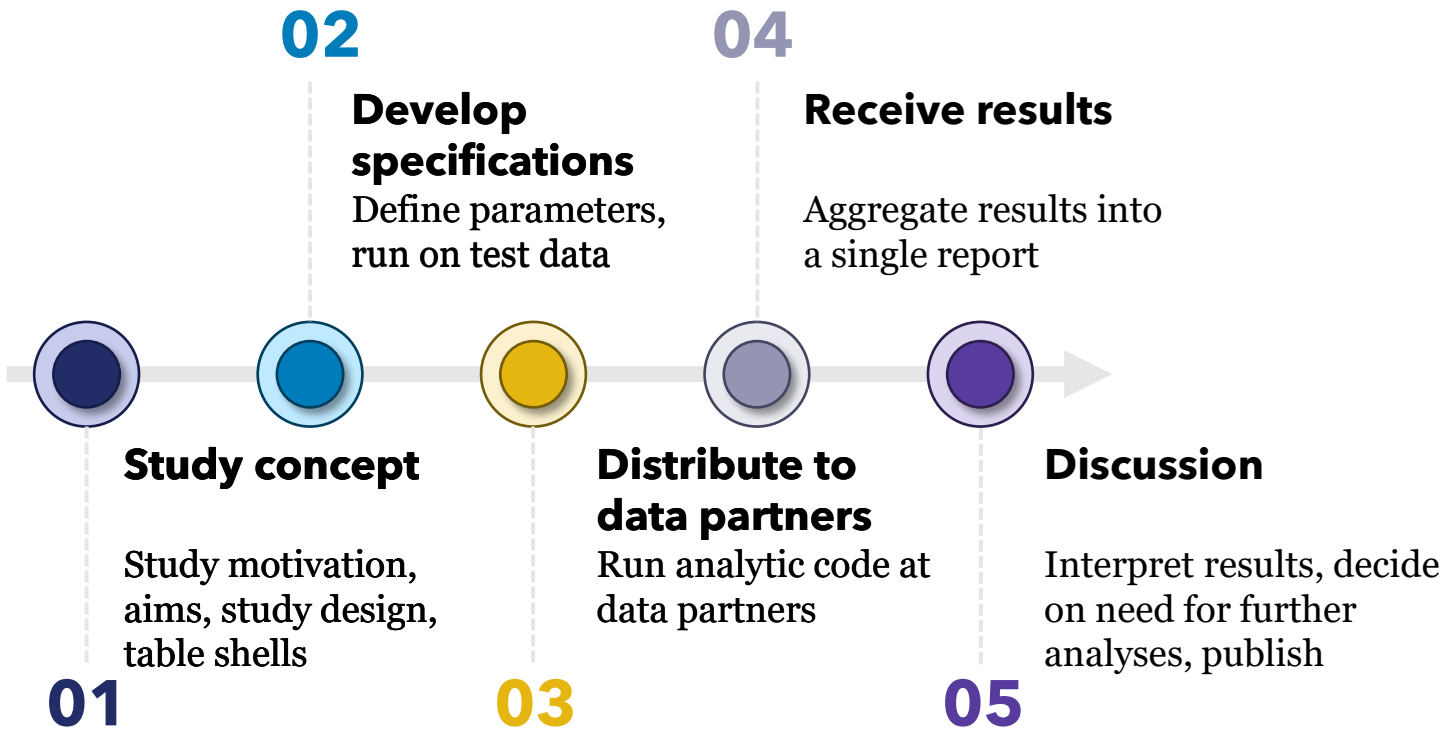


Data for all members' who are currently enrolled (~63M) as of the first day of most recent enrollment span; Last updated of July 2022
https://www.sentinelinitiative.org/about/key-database-statistics

Analytic Tools and Modules

A key component of the Sentinel System

Developing a Sentinel Study

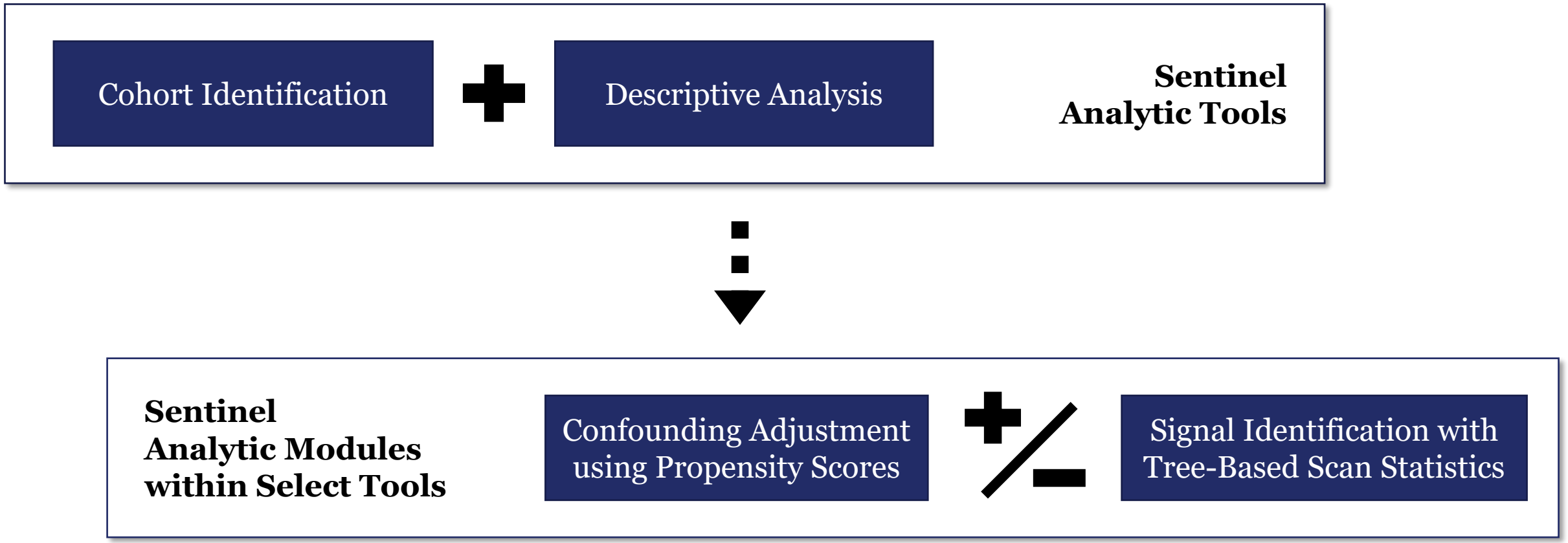


02 Most labor-intensive; requires code list review and fitting tools to study question

03 Analytic package contains all SAS code and parameters; posted online

05 All results are posted online, with any data partner-specific results masked

Conducting Analyses in Sentinel



Reporting Sentinel Analysis Findings

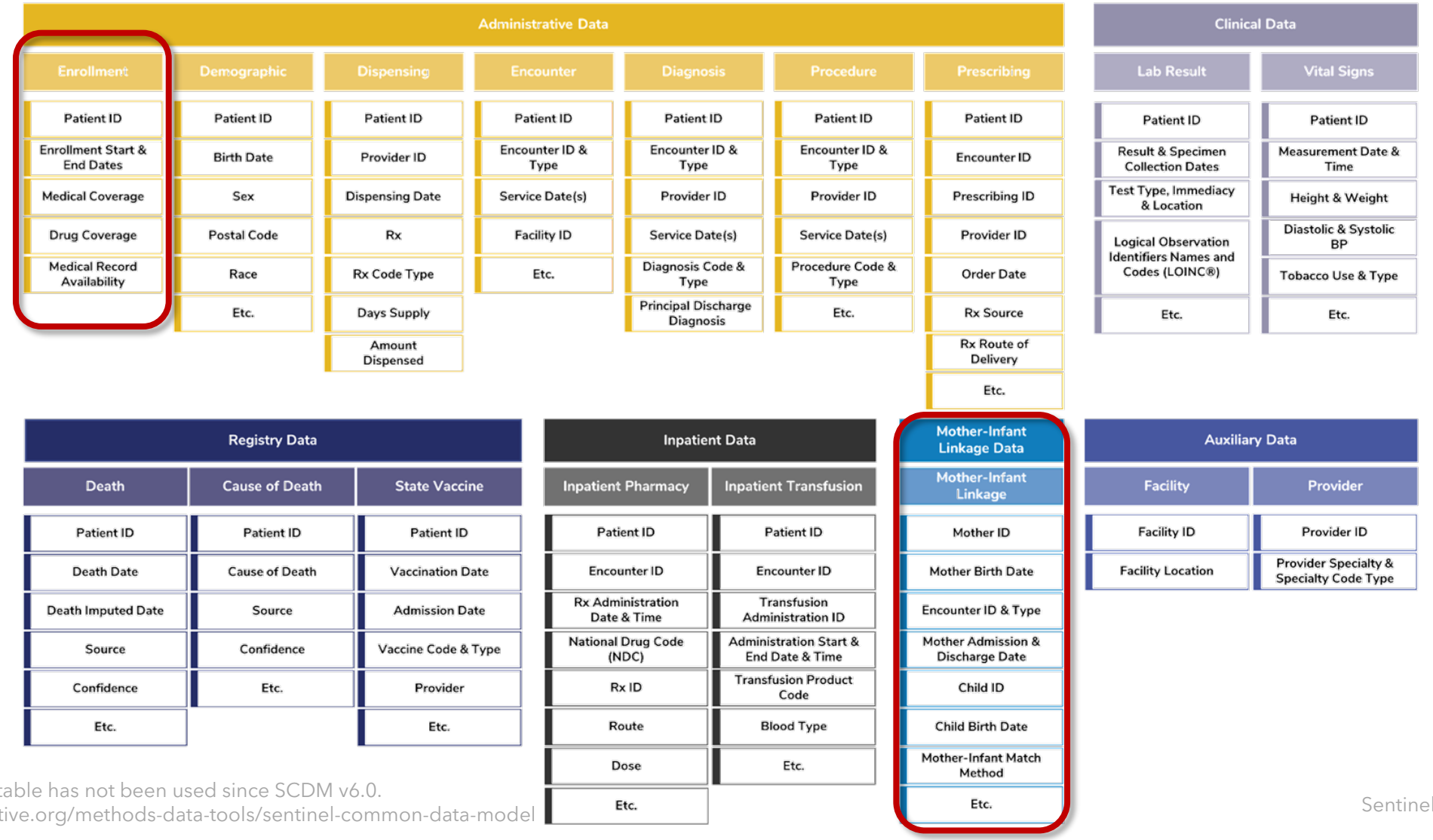
- After obtaining study results, Sentinel Operations Center aggregates across all contributing Data Partners

- A single Reporting Tool outputs findings in summary tables and figures
  - Option to output to Excel Workbook or PDF
  - Templated SAS code with parameterizable customizations

Pediatric Members in the Sentinel Distributed Database

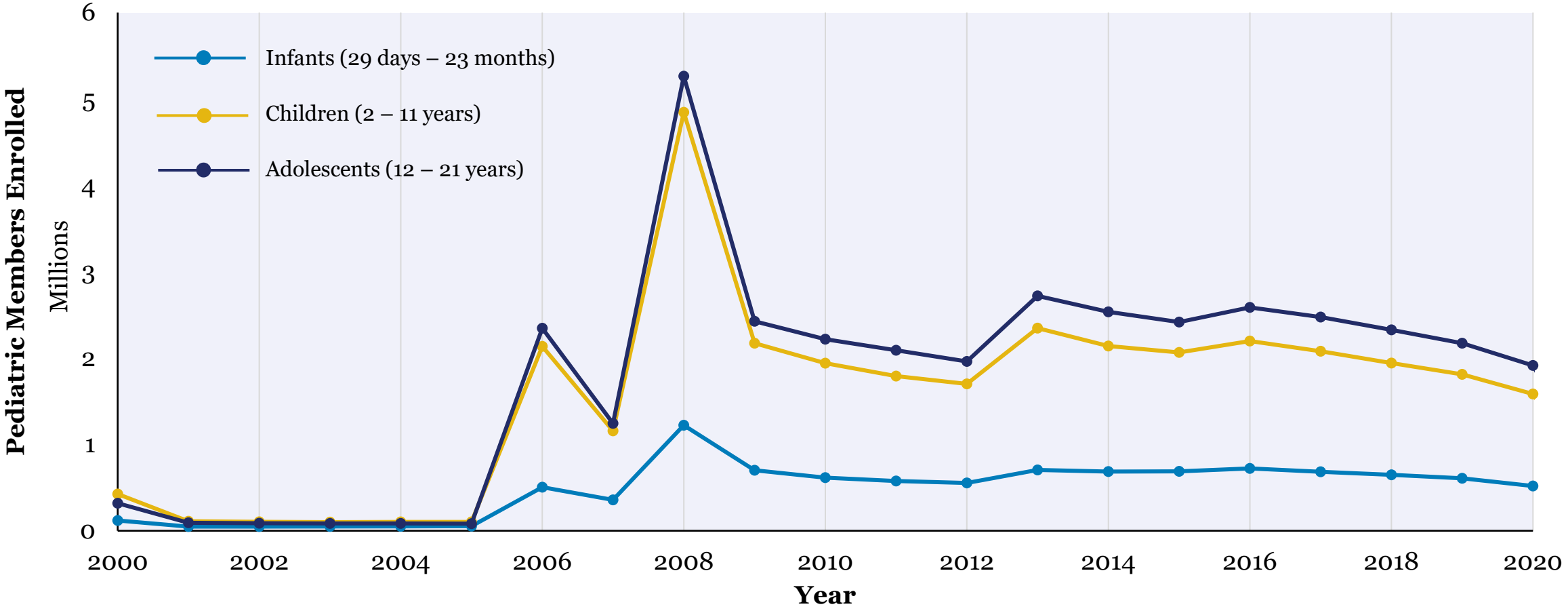
A Characterization of Sentinel's Youngest

Sentinel Common Data Model



* The State Vaccine table has not been used since SCDM v6.0.
https://sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Pediatric Member Enrollment by Year



Data as of January 2022 covering years 2000-2020 from five data partners comprising 95% of full Sentinel Distributed Database (prior to Medicaid data addition)
https://www.sentinelinitiative.org/news-events/publications-presentations/characterizing-pediatric-members-sentinel-distributed

Demographics and Healthcare Utilization

	Infants (29d – 23m)	Children (2 – 11 y)	Adolescents (12 – 21 y)
Ever enrolled, N (%)	10,273,860	33,247,274	37,925,029
Known Race, N (%)	881,027 (8.5)	2,709,211 (8.1)	3,049,895 (8.0)
Non-White Race, N (% of Known)	276,518 (31.9)	778,959 (28.7)	807,091 (26.5)
Female, N (%)	5,001,985 (48.7)	16,247,762 (48.9)	18,640,296 (49.2)
Mean (SD) annual number of:			
Ambulatory encounters	7.6 (7.1)	3.7-4.4 (7.2-7.5)	3.5-4.2 (6.8-7.4)
Dispensed prescriptions	2.9 (8.7)	2.4 (4.5-5.2)	3.0-3.9 (6.5-7.5)
Dispensed drug classes	1.6 (2.0)	1.2-1.4 (1.8-1.9)	1.4-1.7 (2.1-2.5)

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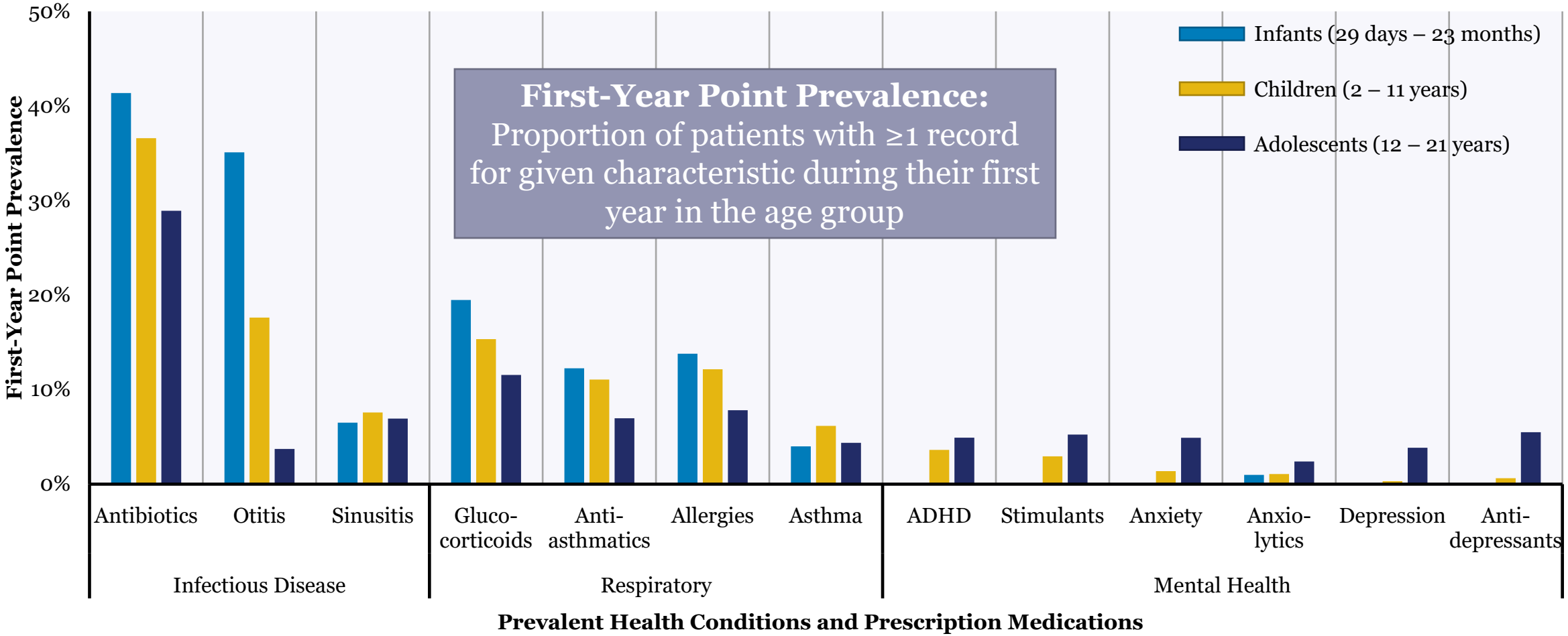
RX Medications and Health Conditions



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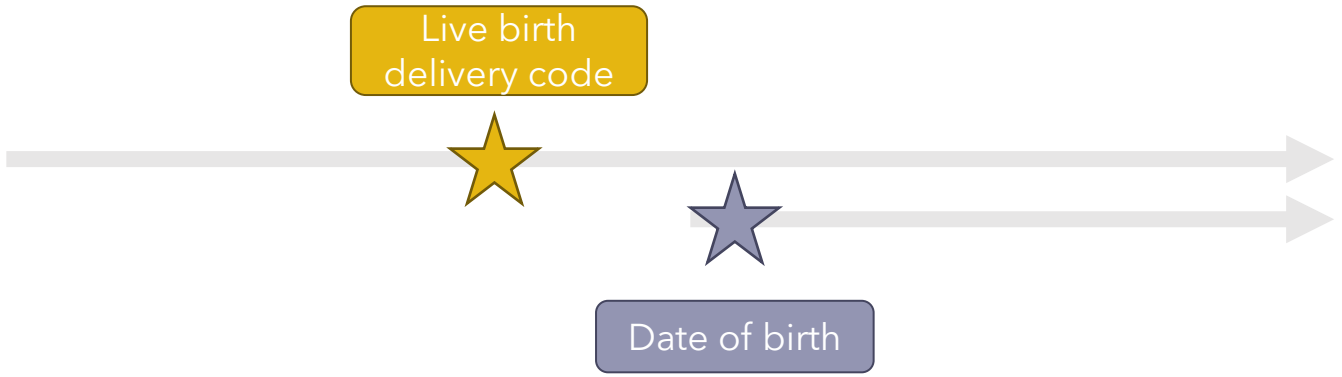
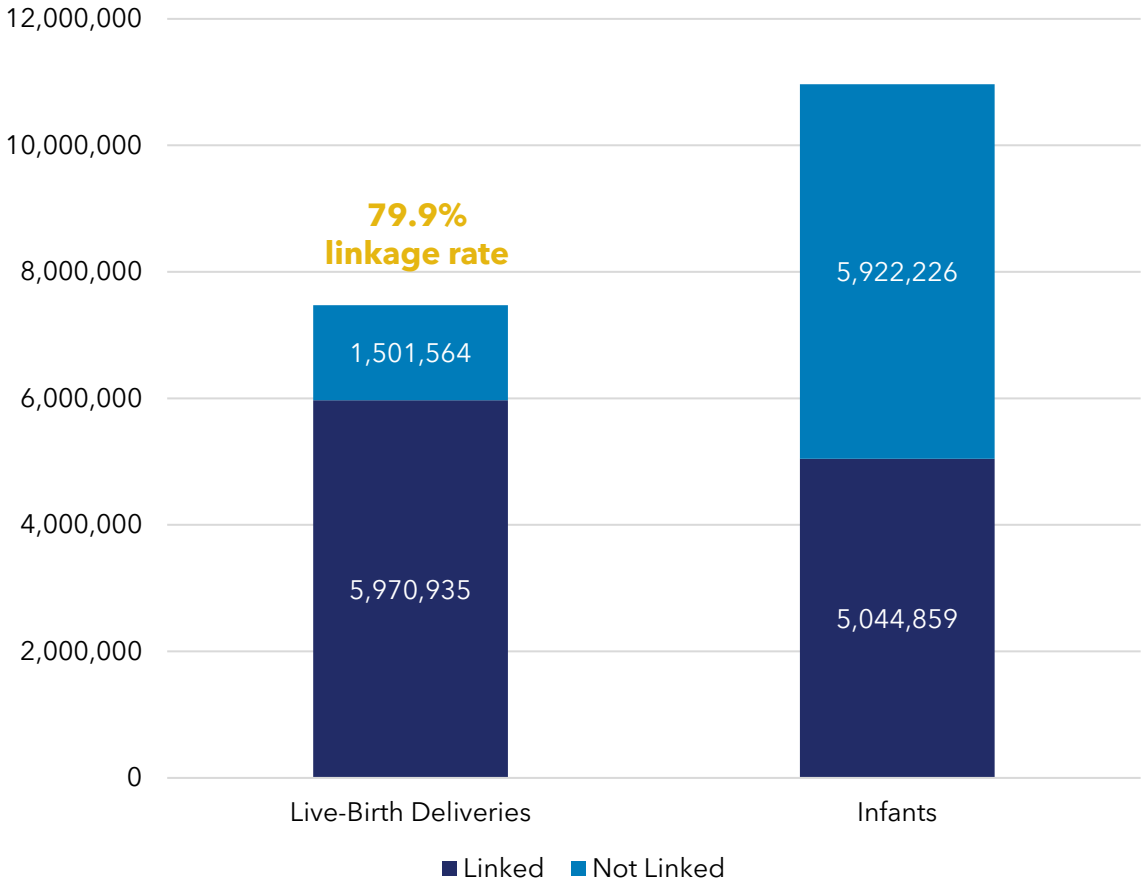
Linking Deliveries and Infants



Successful Match Methods	Unsuccessful Match Reasons
Family subscriber number	No subscriber or family IDs available
Last name and address match	No name or address available
Birth certificate*	Neither family IDs nor name/address available
DP-maintained birth registry*	No linkage attempted
Other	

* No default SDD DPs use these methods to match

Final Mother-Infant Linkage Table

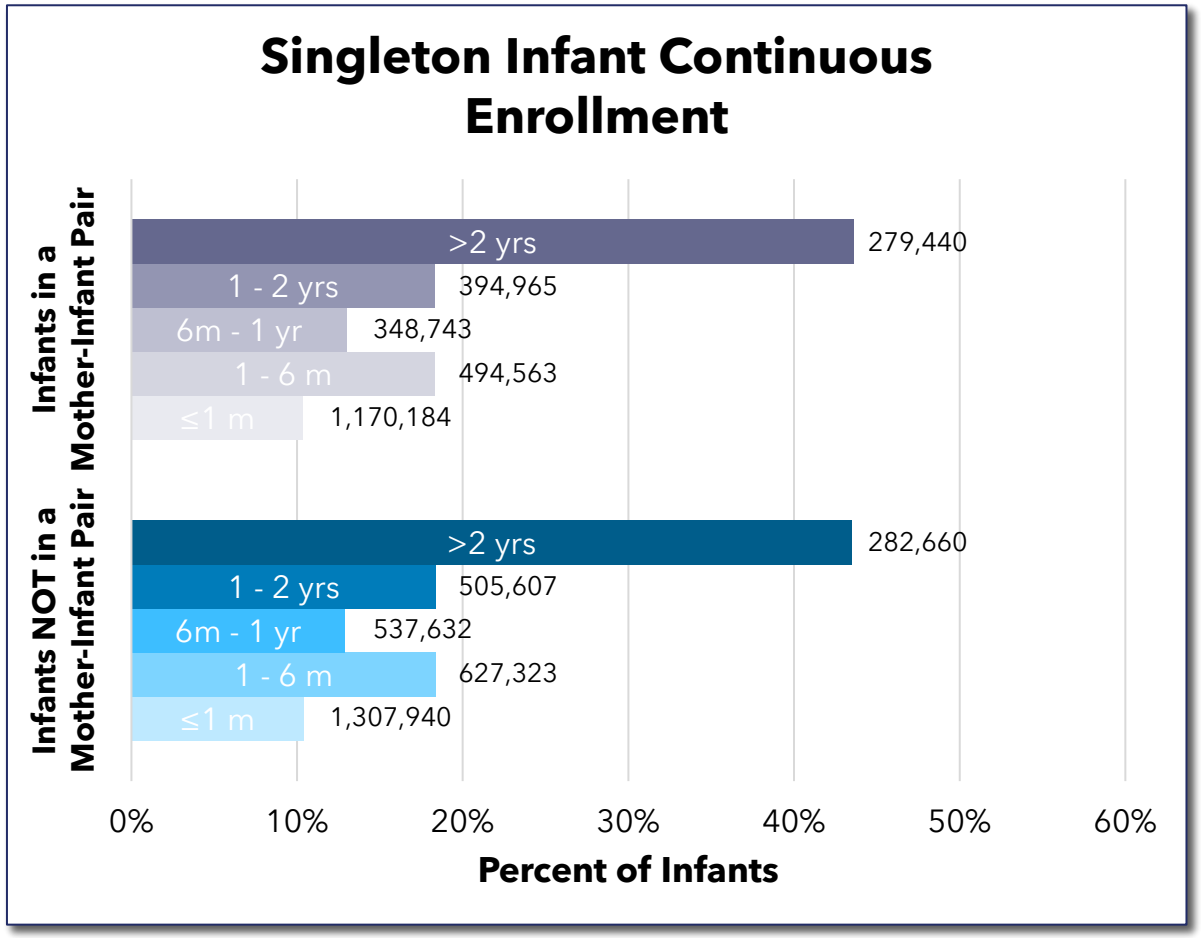


- **Factors impacting linkage rates**
  - Mother/infant on different insurance plans
  - Strict mother enrollment requirement
  - Low tolerance for potentially incorrect linkages

Data as of January 2022 covering years 2000-2020 from five data partners comprising 95% of full Sentinel Distributed Database (prior to Medicaid data addition)

Infant Enrollment

- Identified **6,131,472 infants** in the MIL tables
- 2,868,310 infants were in a **mother-infant pair**
  - *93.7% of infants in a pair were from singleton deliveries*
- ~44% of infants have >2 years continuous enrollment



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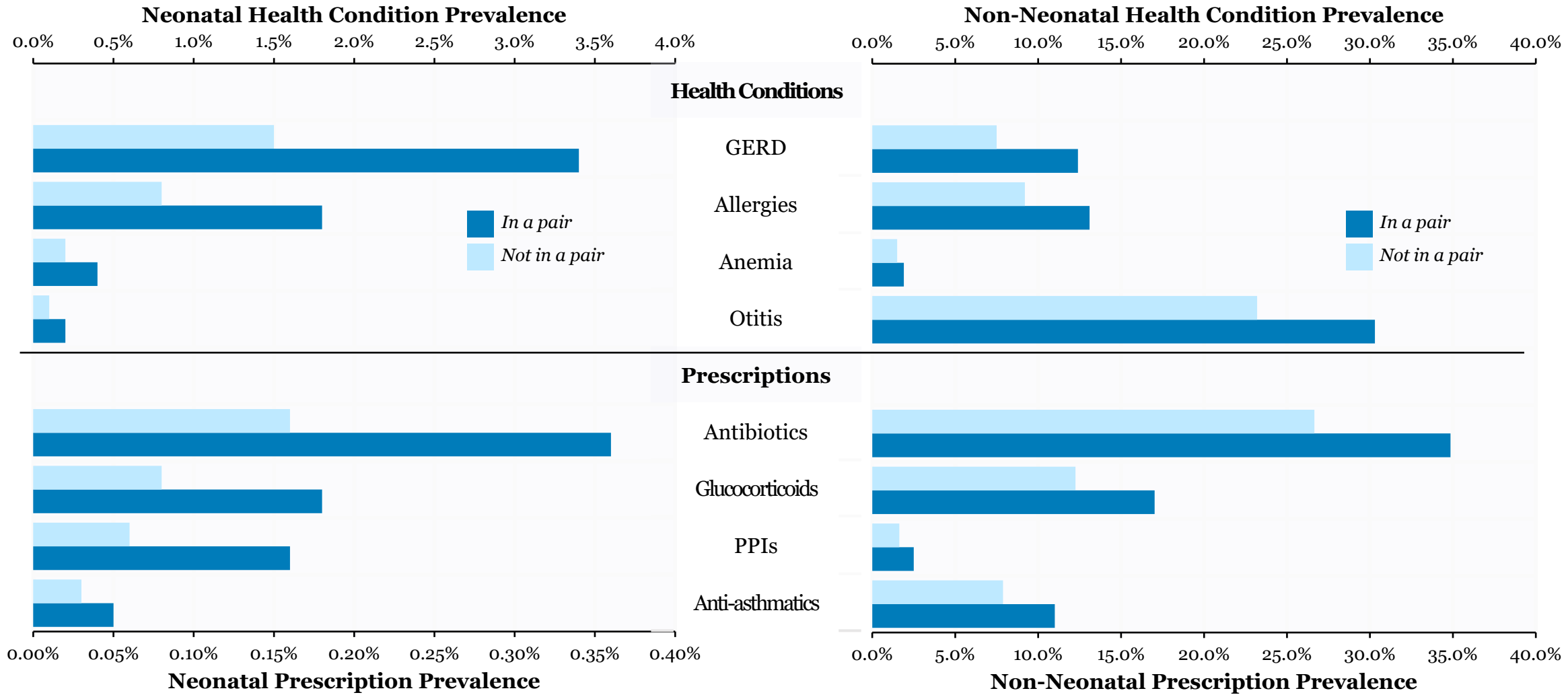
RX Medications and Health Conditions



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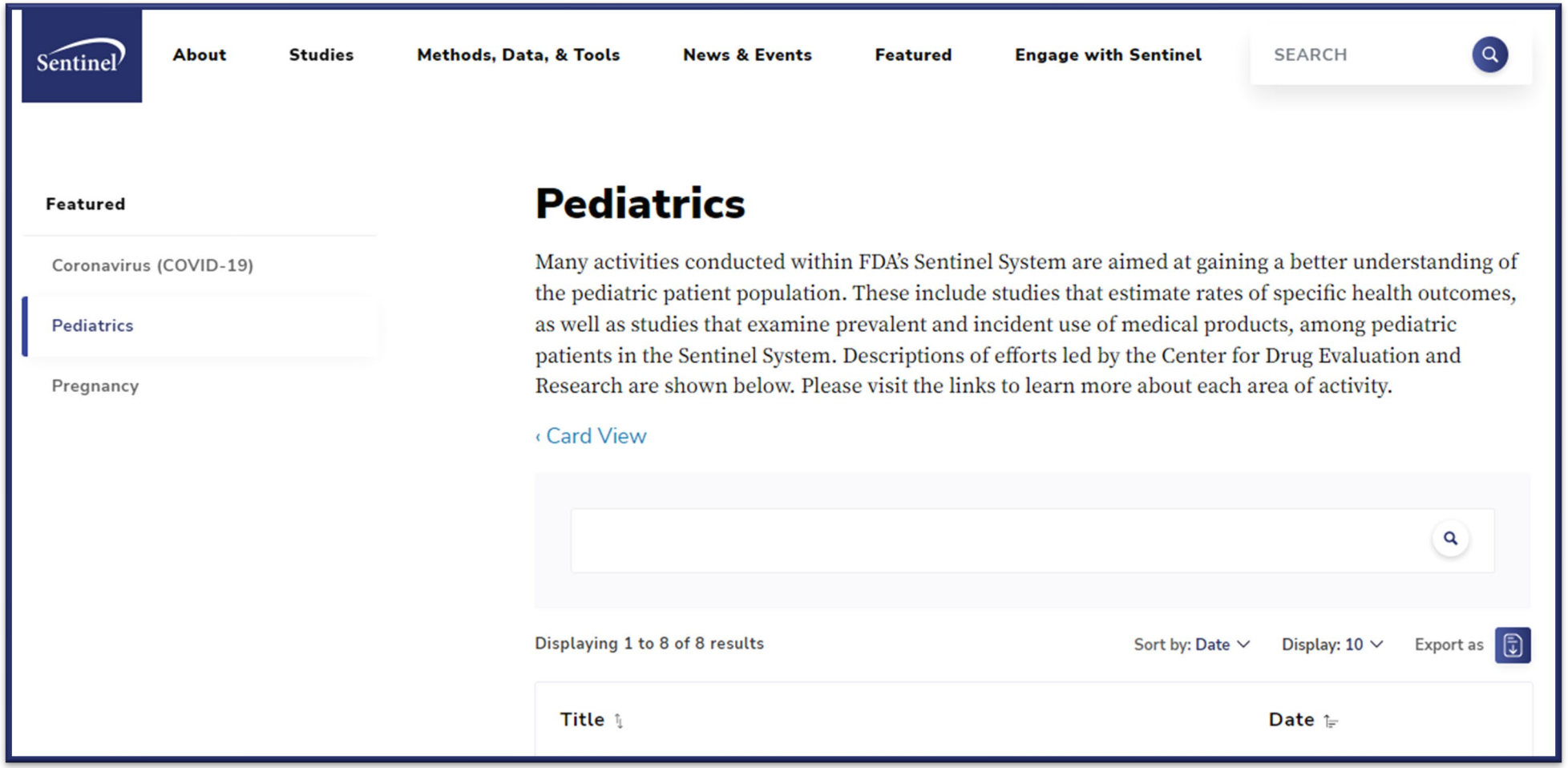
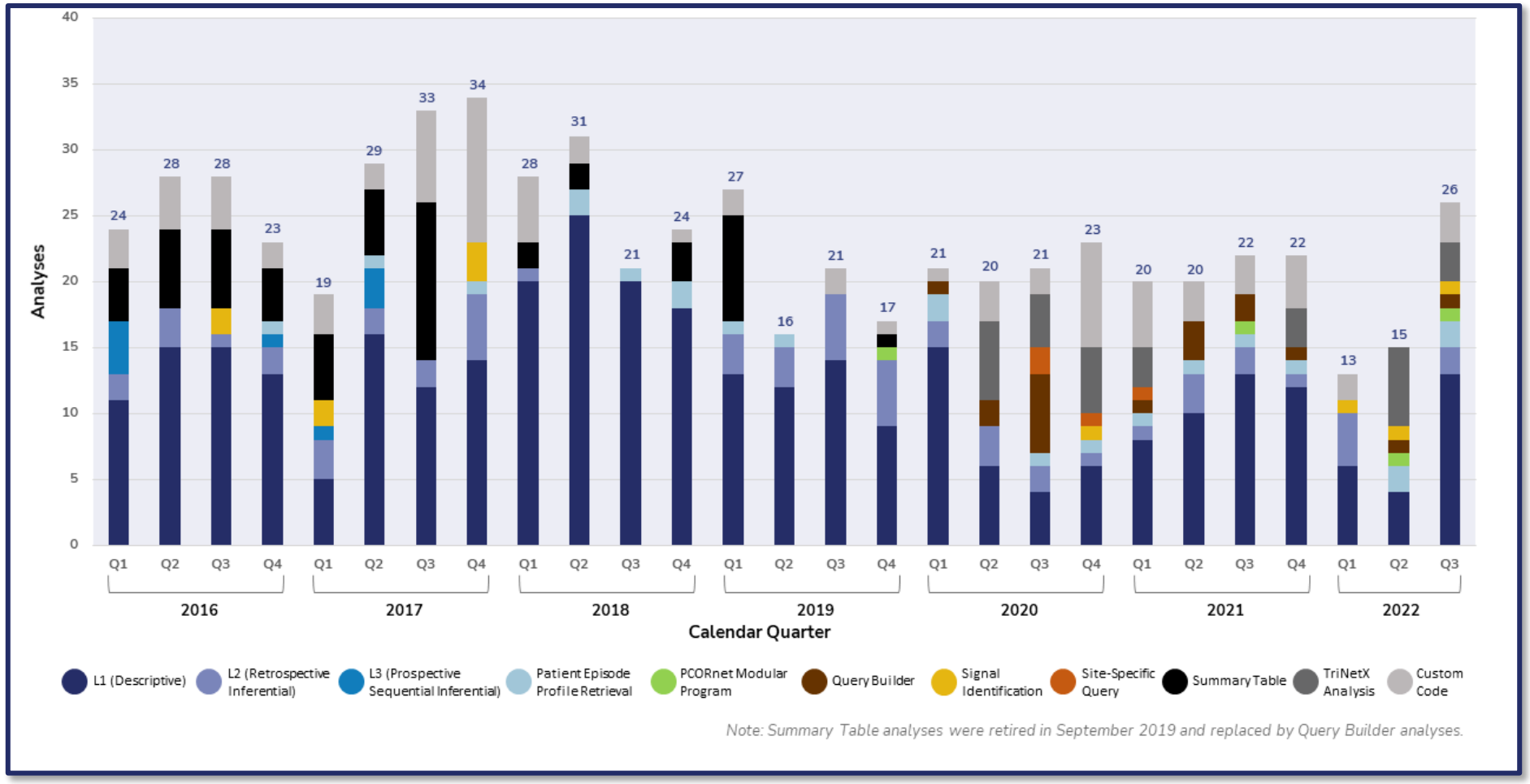
Assessing Pediatric Populations in Sentinel

Featured Topic



https://www.sentinelinitiative.org/featured-topics/pediatrics

Distribution of Analyses by Quarter



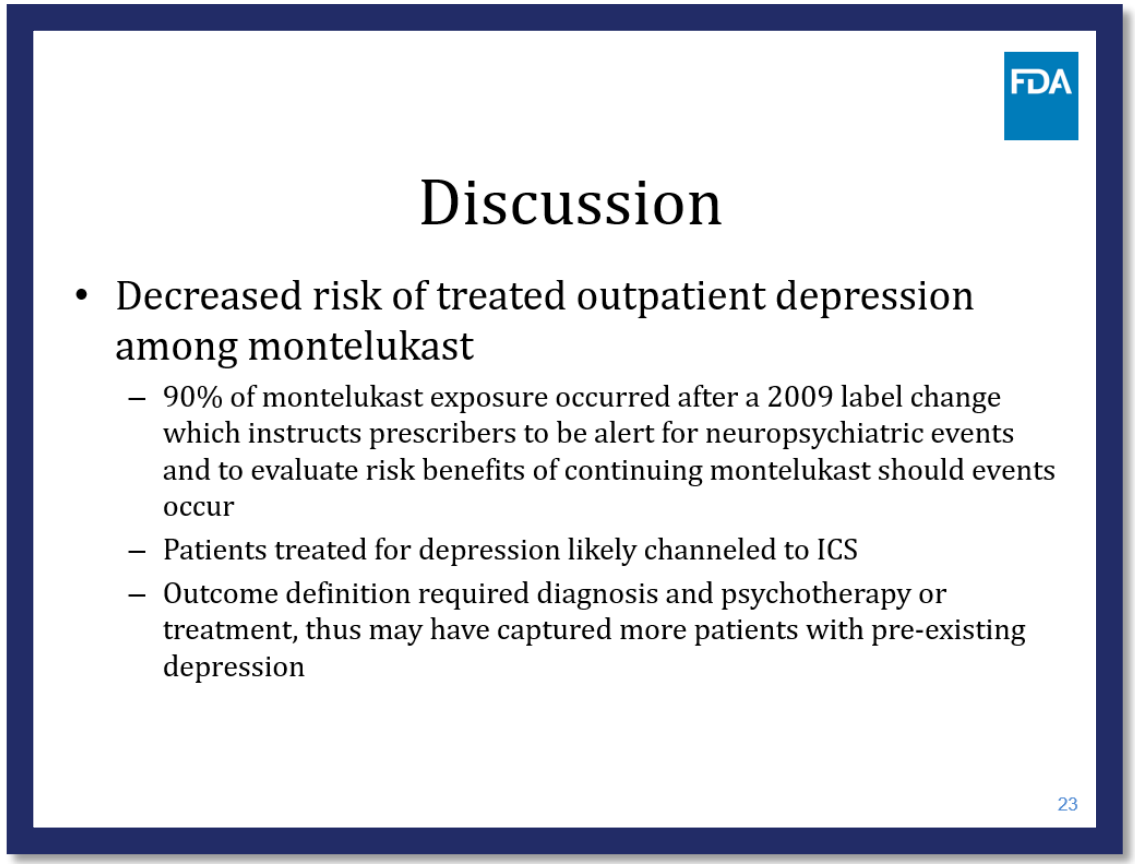
Summary of Pediatric-Focused Assessments

Study Name	Year
Intussusception Risk after Rotavirus Vaccination in U.S. Infants	2013
Use of Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARB) in a Pediatric Population	2016
Respiratory syncytial virus (RSV) in pediatrics	2016
Interleukin-1/Interleukin-6 Inhibitors & ILD/PAH	2018
Risk of neuropsychiatric adverse events among montelukast users	2019
Risk of suicide and all-cause mortality among montelukast users	2019
Use of typical and atypical antipsychotics among inpatient infants	2019
Hypertension in pediatric population	2019
IV Iron Use and Stillbirth in Pregnancy	2019
Risk of cardiac malformations after in utero exposure to NUVIGIL® (armodafinil)[C-IV]/PROVIGIL® (modafinil)	2020
Oral Clefts following Topiramate Use during the First Trimester of Pregnancy	2020
Characteristics and Outcomes of Pregnant Women with Heart Failure	2020
Valganciclovir Use in Children with Congenital Cytomegalovirus Infection	2021
Risk of cardiac and urinary malformations after in utero exposure to GILENYA® (fingolimod)	2023

See SentinelInitiave.Org for more information on each assessment

Montelukast and Neuropsychiatric Events

- **Safety concern source**: (s)NDA/(s)BLA
- **Regulatory Question**: Should the warnings for risk of neuropsychiatric events be strengthened?
- **Regulatory Outcome**: Used in Advisory Committee Meeting and supported label change to add Boxed Warning



https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/neuropsychiatric-events-following-montelukast-use-propensity

Pregnant Women with Heart Failure

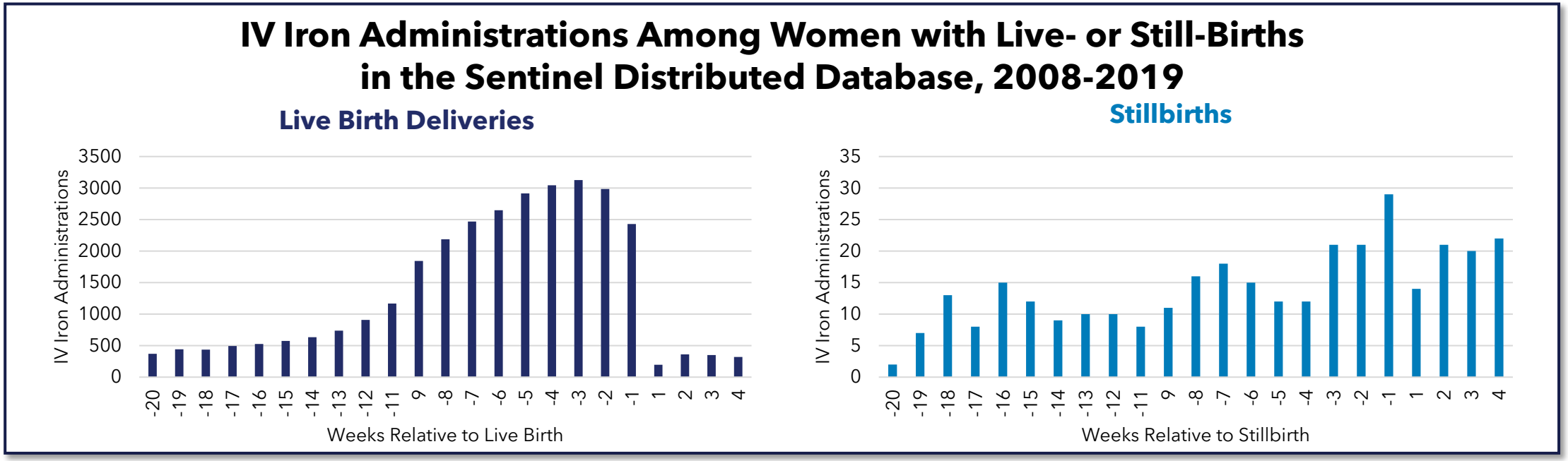
- **Safety concern source**: (s)NDA/(s)BLA
- **Regulatory Question**: Should a REMS program be required for vericiguat?
- **Regulatory Outcome**: Contributed to the review team's determination that labeling would provide sufficient information

	Pregnancies among women with HF (N = 489 pregnancies)		Pregnancies among women without HF (N = 1,076,117 pregnancies)	
	N	%	N	%
Infant outcomes				
Small for gestational age (SGA) [0, 30]	8	1.6%	18,998	1.8%
Congenital cardiac malformation [0, 90]	7	1.4%	726	0.1%
Ventricular septal defect	0	0.0%	7	< 0.1%
Right ventricular outflow tract obstruction	0	0.0%	< 5	< 0.1%
Other cardiac malformation	7	1.4%	721	0.1%
Any major malformation [0, 90]	8	1.6%	2,878	0.3%

https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/pregnancy-among-women-heart-failure-descriptive-analysis

IV Iron in Pregnant Women

- **Safety concern source**: FAERS
- **Regulatory Question**: Are there severe adverse effects associated with near-delivery administration of IV iron projects?
- **Regulatory Outcome**: Label Change - Use in Specific Populations (Pregnancy and Lactation)



https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/intravenous-iv-iron-utilization-among-pregnant-women

Valganciclovir for cCMV

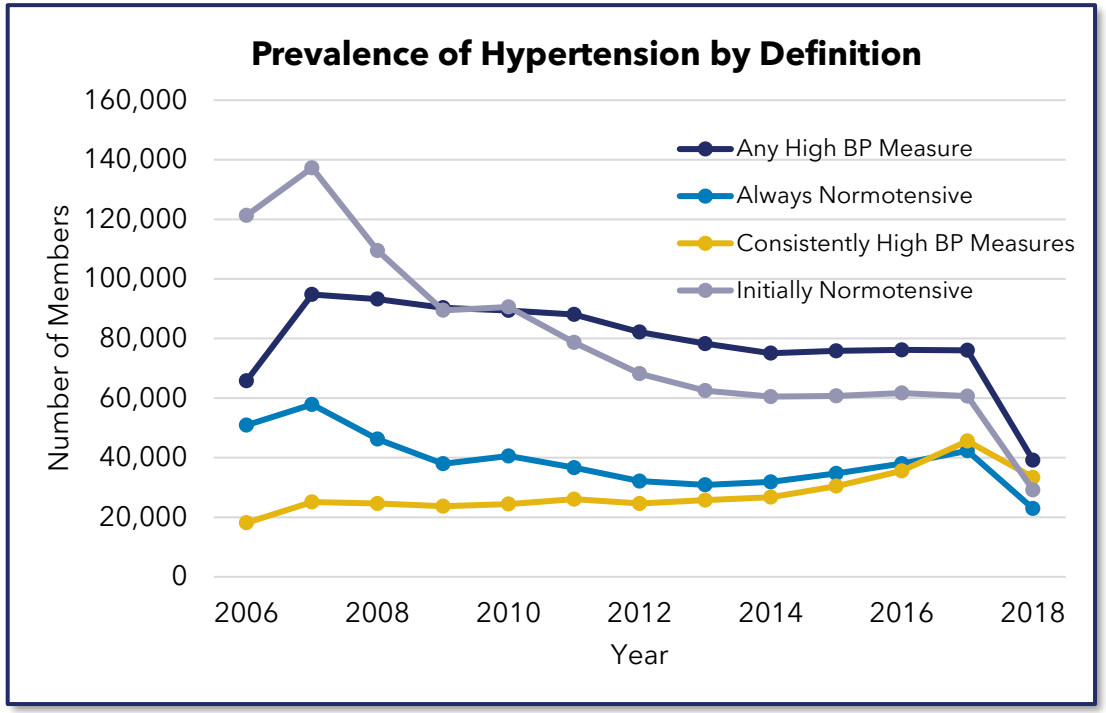
- **Safety concern source**: FAERS, Medical Literature, Foreign Regulatory Agency
- **Regulatory Question**: Can Sentinel replace sponsor's post-marketing commitments to assess use to treat congenital cytomegalovirus?
- **Regulatory Outcome**: Ongoing

	Group 1: All infants N = 1,500	Group 2: (v)GCV w/i 45 days N=221
Demographic Characteristics		
Age, mean (SD)	7.6 (11.5)	9.0 (12.3)
Female	691 (46.1)	105 (47.5)
Clinical Symptoms at Baseline		
Jaundice	731 (48.7)	105 (47.5)
Petechiae	84 (5.6)	33 (14.9)
Hepatomegaly	73 (4.9)	18 (18.1)
Splenomegaly	53 (3.5)	18 (18.1)
Microcephaly	123 (8.2)	36 (16.3)
Thrombocytopenia	542 (36.1)	97 (43.9)
Brain abnormality	279 (18.6)	75 (34.0)
Hematological Safety Outcomes (180 days)		
Neutropenia	244 (16.3)	57 (25.8)
G-CSF†	12 (0.8)	7 (3.2)
pRBC transfusion‡	122 (8.1)	7 (3.2)
Platelet transfusion	90 (6.0)	14 (6.3)
Hearing Loss		
Baseline	132 (8.8)	49 (22.2)
180 Days	318 (21.2)	124 (56.1)

https://www.sentinelinitiative.org/methods-data-tools/health-outcomes-interest/valganciclovir-use-children-congenital-cytomegalovirus

Pediatric Hypertension

- **Safety concern source**: Literature
- **Regulatory Question**: Can Sentinel be used to identify and assess pediatric hypertension?
- **Regulatory Outcome**: Provided guidance for the use of real-world data in future pediatric hypertension studies



	Definition 1		Definition 2		Definition 3	
	HTN DX	No HTN DX	1 IP or 2 OP HTN DX	<1 IP or <2 OP HTN DX	DX for ↑ BP w/o HTN DX	No DX for ↑ BP
Hypertensive BP Measure	2,995 (0.6%)	507,412 (99.4%)	1,506 (0.3%)	508,901 (99.7%)	1,643 (0.3%)	512,249 (99.7%)

https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/hypertension-pediatric-patients-descriptive-analysis

KEY TAKEAWAYS

- FDA is committed to ensuring medical product safety in pediatric populations.
- The Sentinel Distributed Database is large and comprehensive enough to assess drug utilization and conduct pediatric pharmacoepidemiology studies.
- Sentinel has a track record of conducting meaningful analyses leading to regulatory decision making for medical products used in pediatrics.

The Sentinel Initiative is a crucial component of FDA's drug safety program, and is well-suited to assess medical product use relevant to pediatric populations.

Sentinel's commitment to transparency allows the public access to tools and analysis results.

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Sentinel

Active Surveillance of Medical Product Use in the FDA's Sentinel System:

A Focus on Pediatric Populations

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24 March 2023