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

A Focus on Pediatric Populations

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Disclaimer

- The Sentinel Operations Center is funded by the FDA through the Department of Health and Human Services (HHS) Task order 75F40125F19015.
- The views expressed in this presentation represent those of the presenters and do not necessarily represent the official views of the U.S. FDA.
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- The Sentinel projects described herein are public health surveillance activities conducted under the authority of the U.S. FDA and, accordingly, are not subject to Institutional Review Board oversight.

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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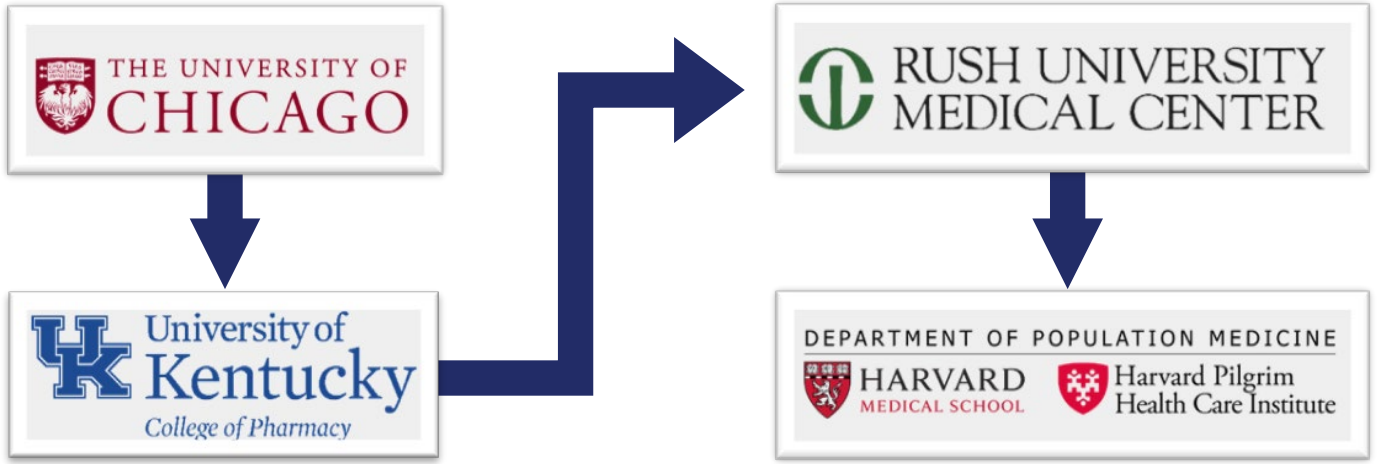
Experience



Research

Current portfolio includes Sentinel queries, industry-sponsored, and federally funded grant work.

Areas of interest include potentially inappropriate medication use in older adults; medication safety in pregnant and pediatric populations.

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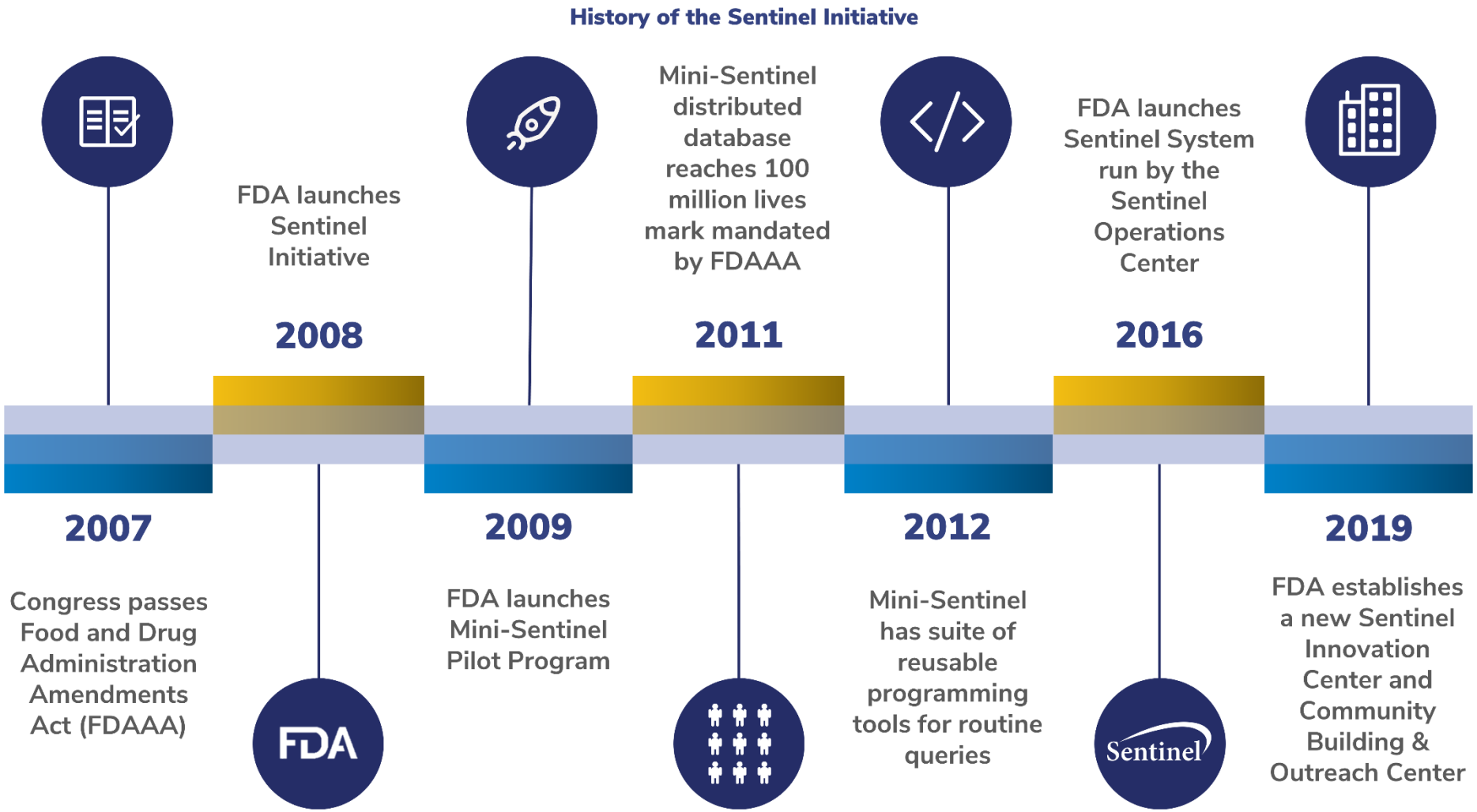
Agenda

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

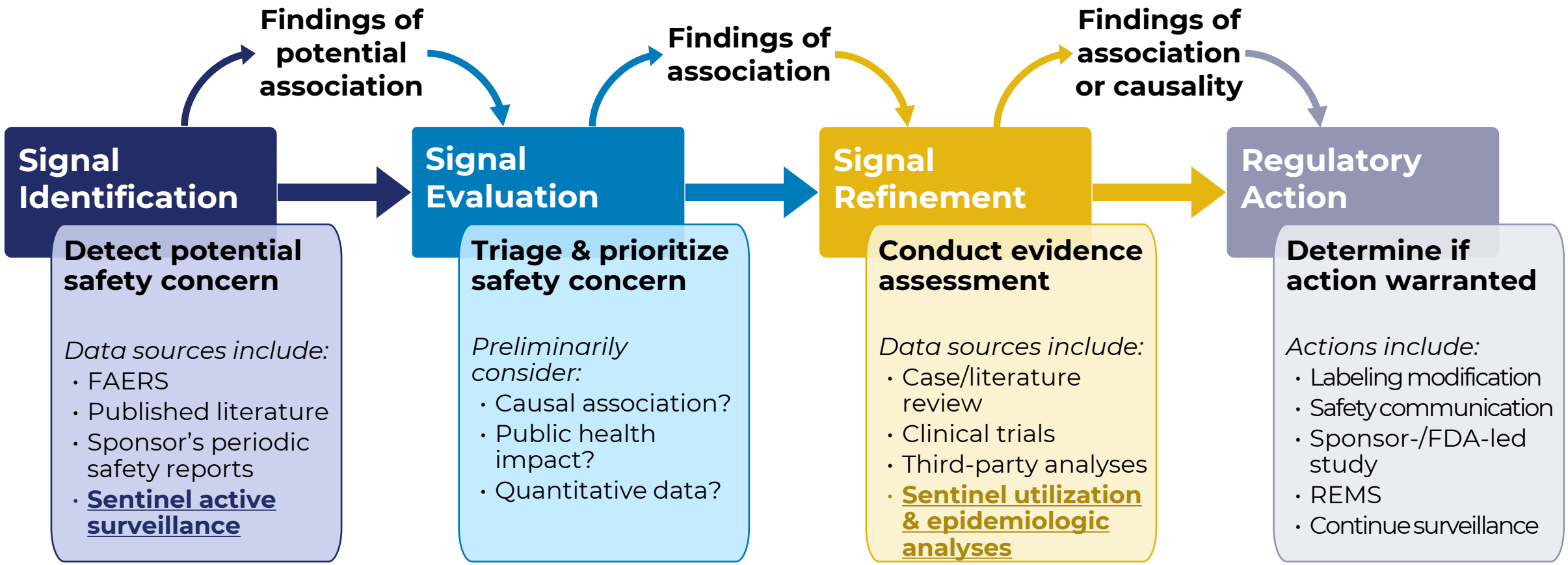
Introduction to Sentinel

History of the Sentinel Initiative



https://sentinelinitiative.org/about

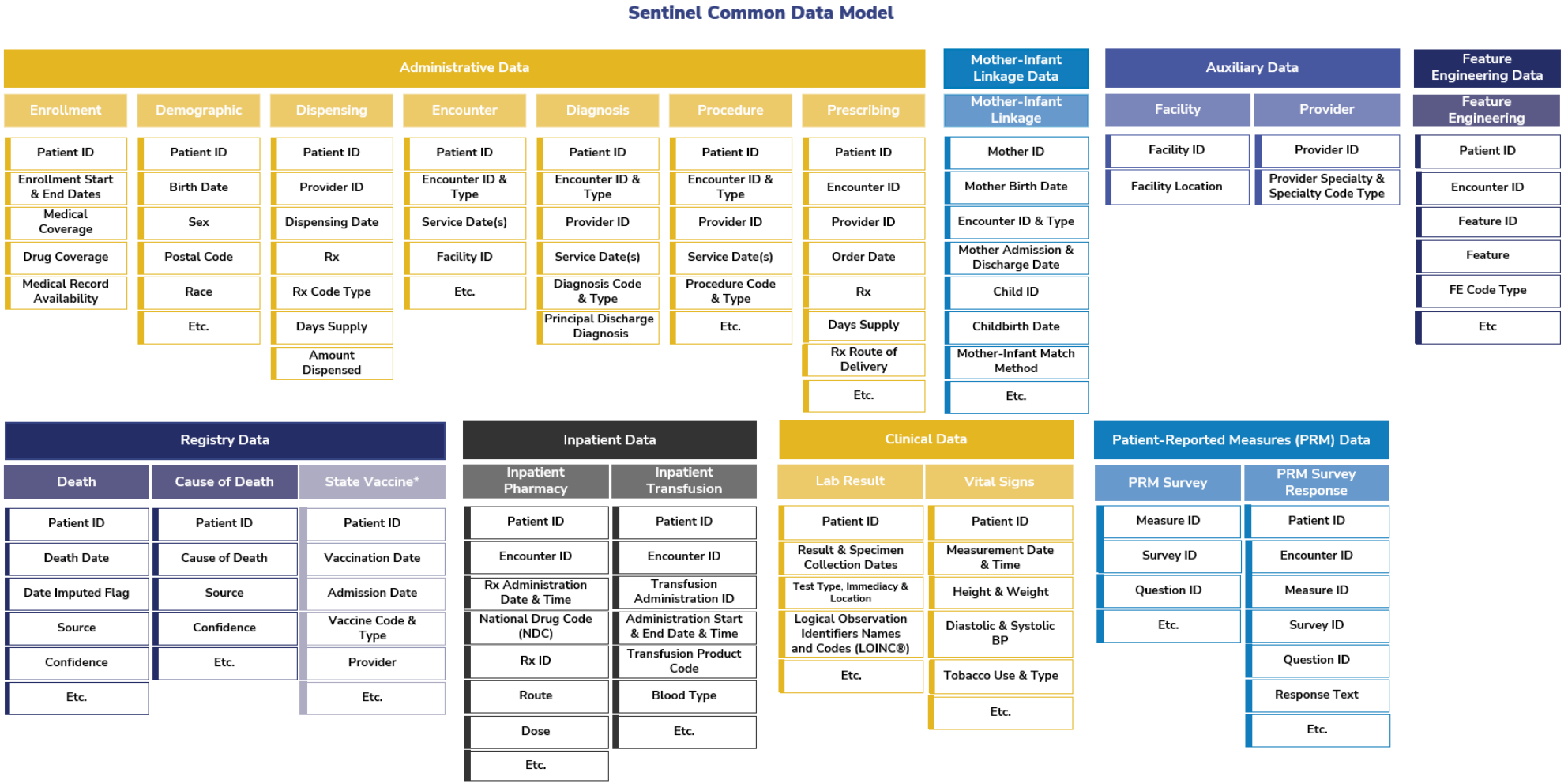
Sentinel's Role in FDA Drug Safety Pipeline



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

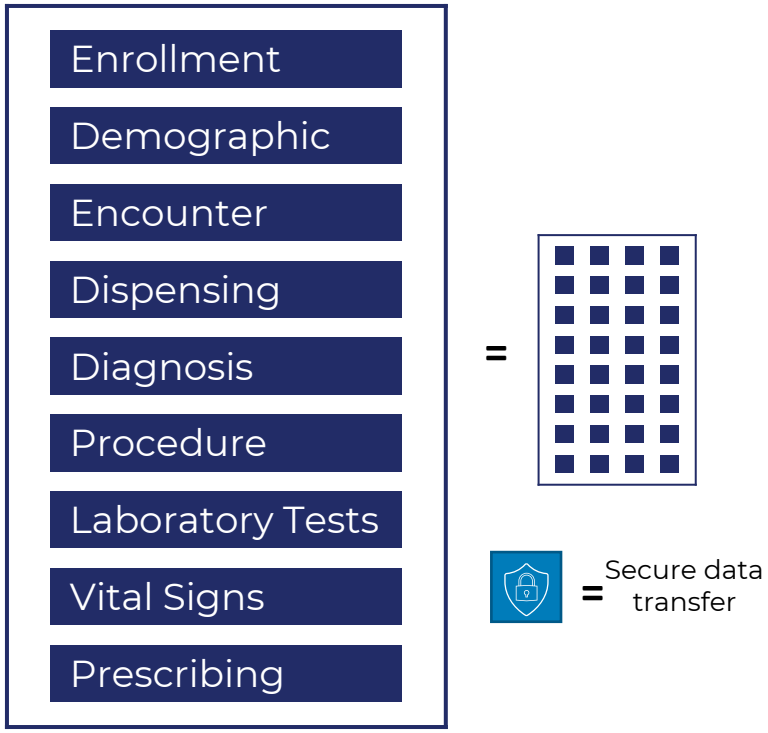
Sentinel Common Data Model

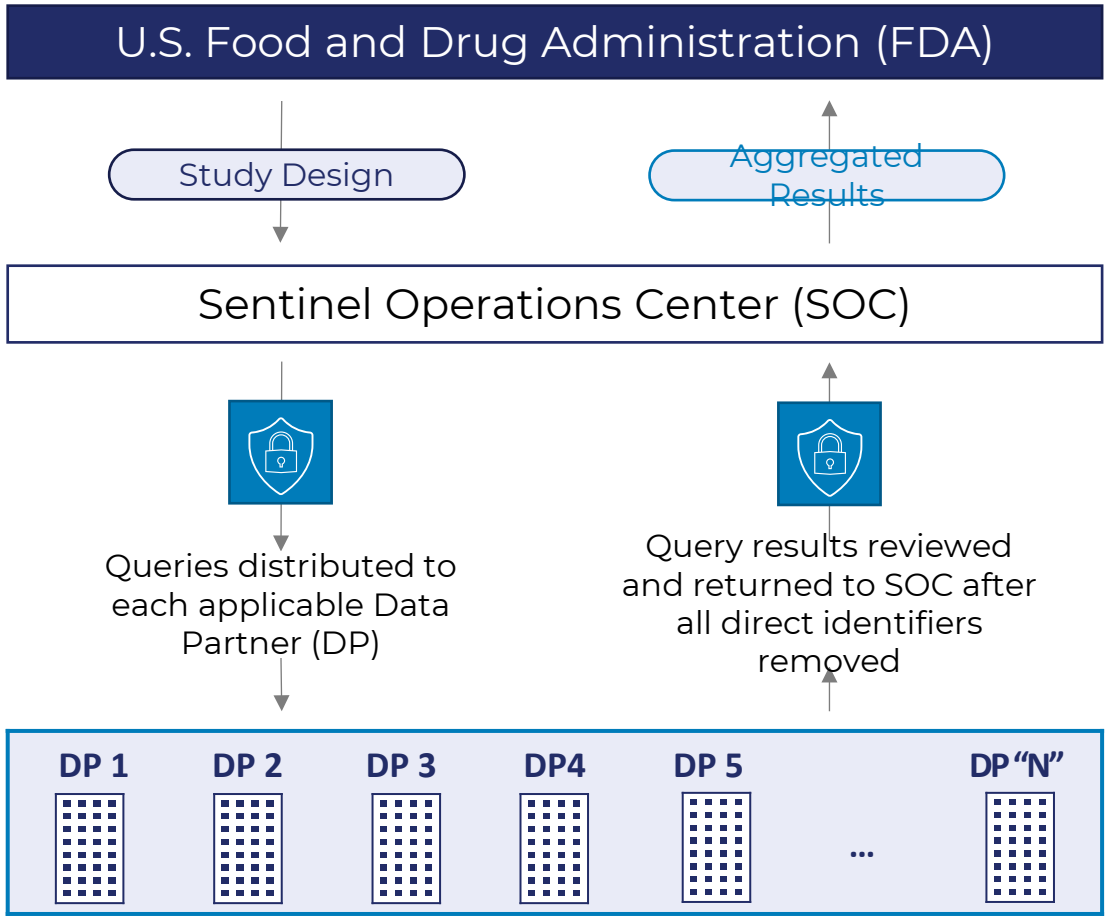


* The State Vaccine table has not been used since SCDM v6.0.
https://sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Sentinel Distributed Data Network

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

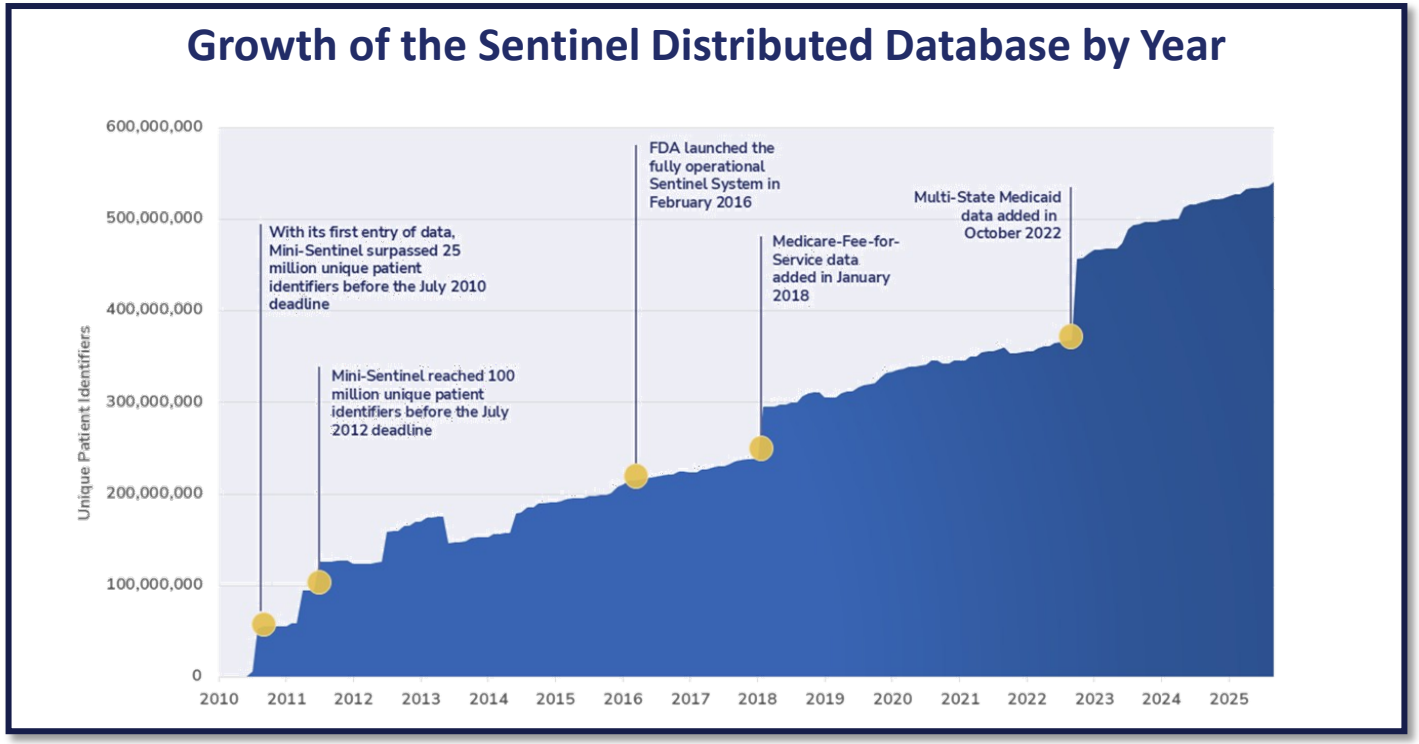




https://www.sentinelinitiative.org/about/how-sentinel-gets-its-data

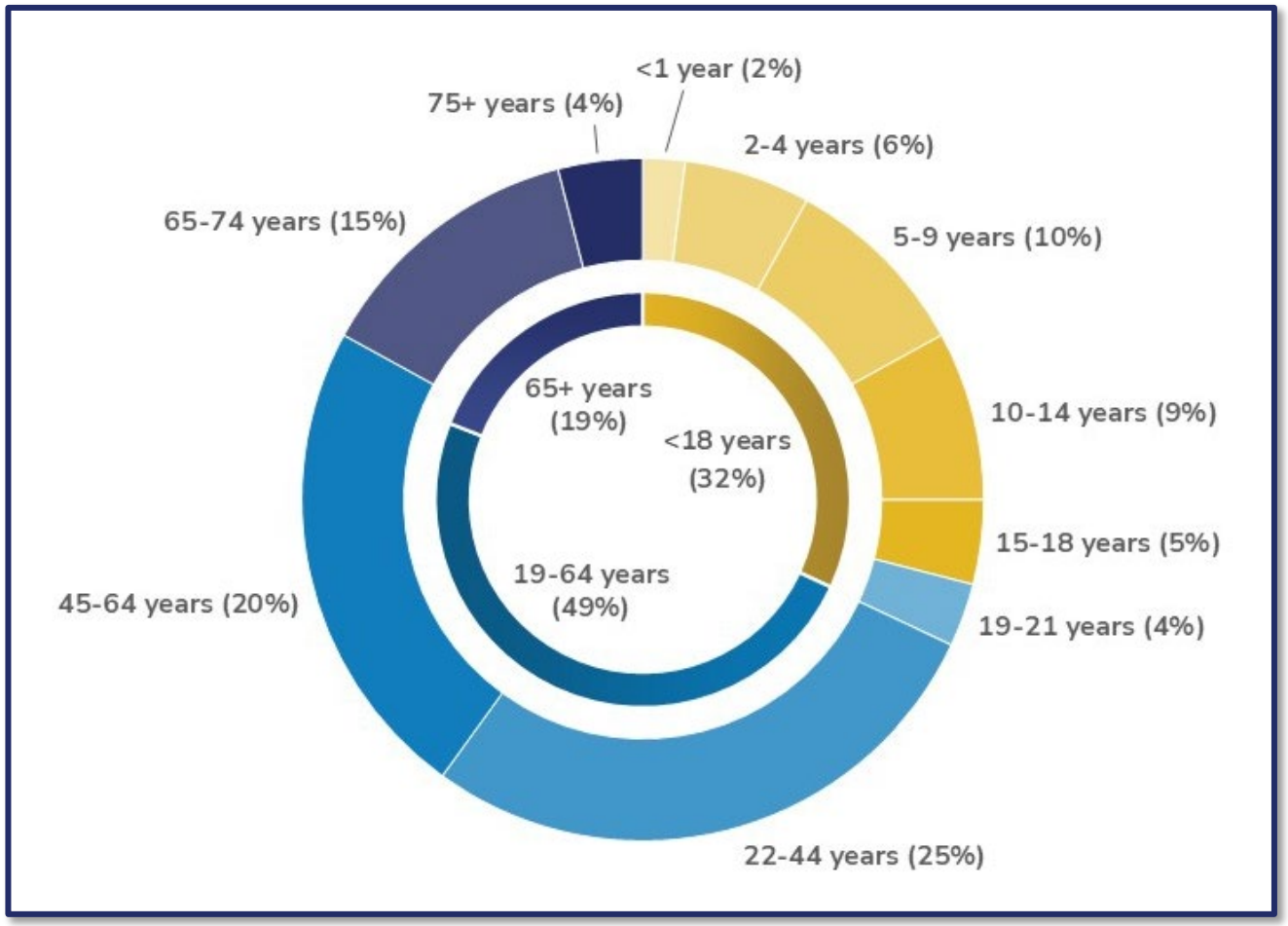
Sentinel Distributed Database Growth

- Sentinel Distributed Database came online in 2010
- Now contains >540 million unique patient IDs from enrolled 2000 – 2025
  - ~405 million have ≥1 day of medical and drug coverage
  - ~139 million currently accruing new data
  - **~13.5 million live birth deliveries with a mother-infant linkage**



Current as of October 2025; https://sentinelinitiative.org/about/key-database-statistics

Active Members Age Distribution



Data for all members' who are currently enrolled (~139M) as of the first day of most recent enrollment span; Last updated of October 2025.
https://www.sentinelinitiative.org/about/key-database-statistics

Pediatric Members in the Sentinel Distributed Database

A Characterization of Sentinel's Young

Study Design: Cohort Selection

- Included all pediatric members in the SDD with ≥ 1 day of medical & drug coverage
- Age-based cohorts based categories used by FDA's Office of Pediatric Therapeutics:
  - Infants & toddlers: 29 days – 24 months of age
  - Young children: 2 – 5 years of age
  - Older children: 6 – 11 years of age
  - Early adolescents: 12 – 17 years of age
  - Late adolescents: 18 – 21 years of age
- Members were included in age-based cohorts on the first day they were eligible and described in their first year in each cohort.
  - Consider a member with DOB 6/15/2005 who enrolls on 1/1/2010 & disenrolls on 12/31/2020.

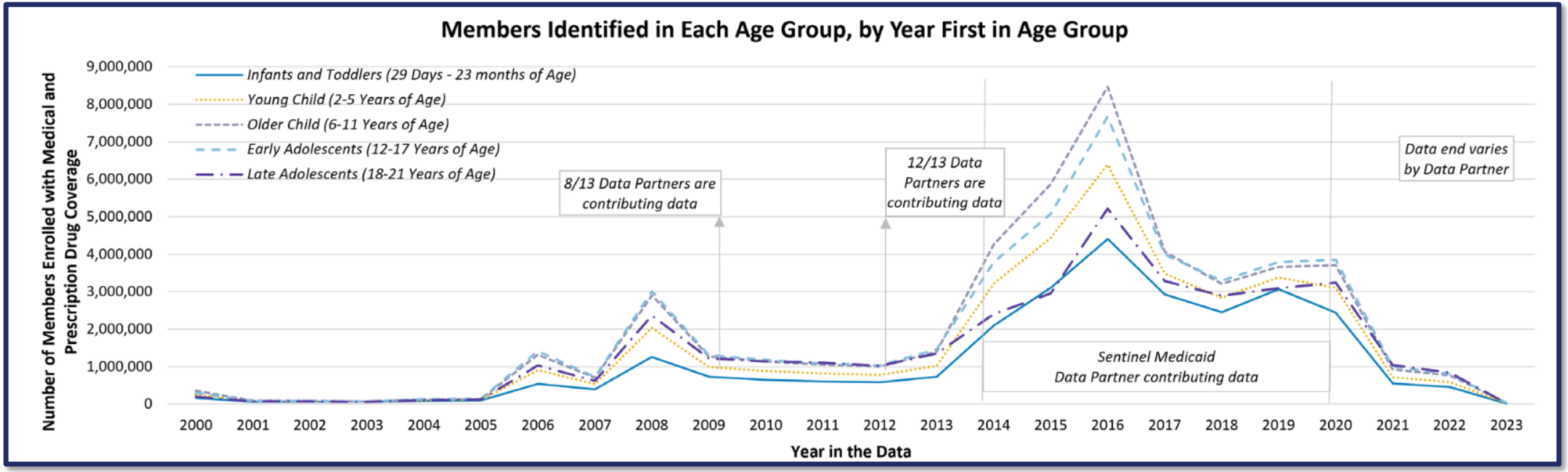
Cohort	Entry	Characterization
Young children	1/1/2010 @ 4 YO	1/1 – 12/31/2010
Older children	6/15/2011 @ 6 YO	6/15/2011 – 6/14/2012
Early adolescents	6/15/2017 @ 12 YO	6/15/2017 – 6/14/2018

SDD: Sentinel Distributed Database

Study Design: Data

- Included all available data from January 1, 2000 (min) to May 8, 2023 (max)

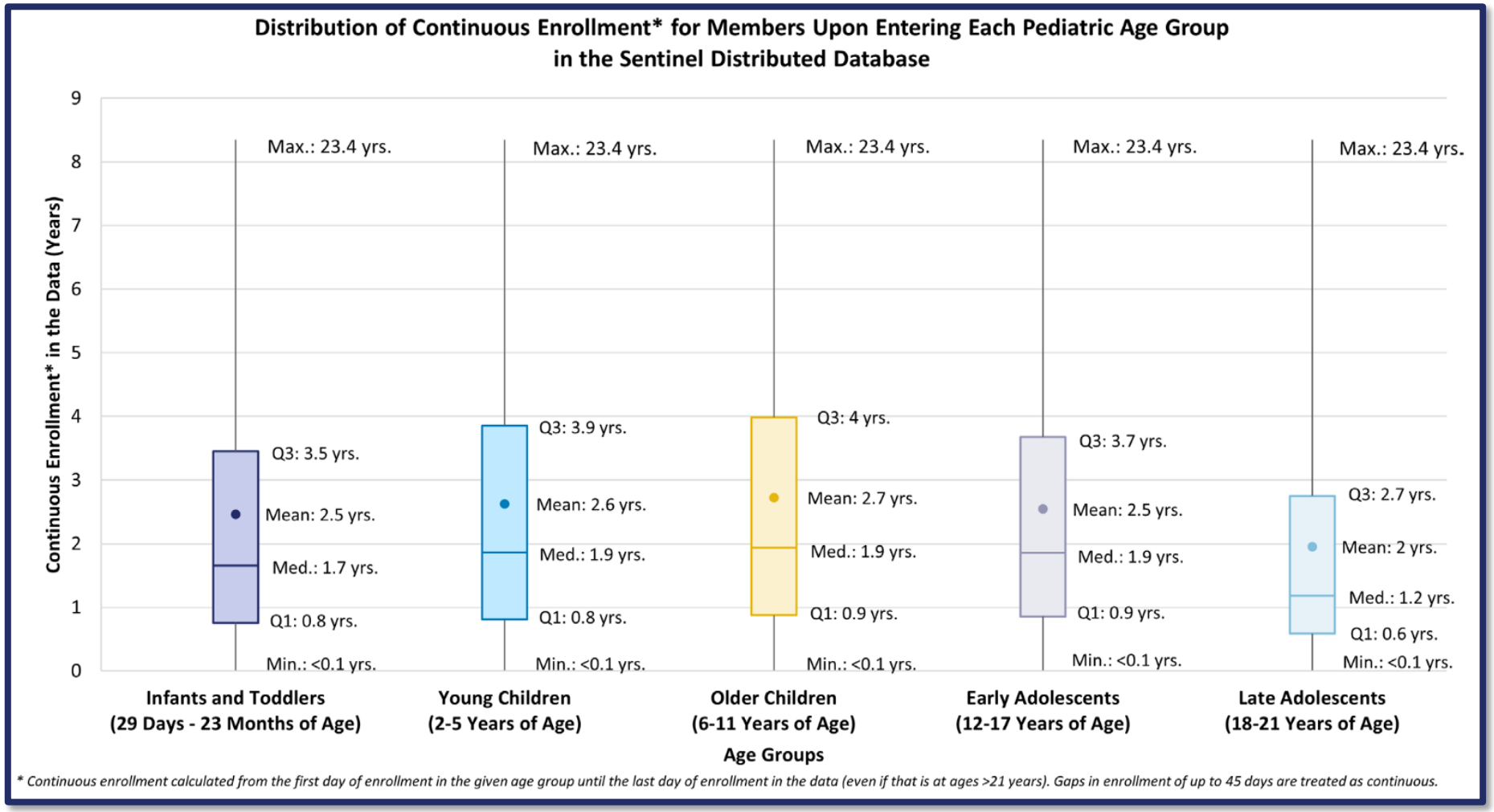
Enrollment Over Time



Data covering years 2000-2023 from all 13 Data Partners contributing to the Sentinel Distributed Database

Michnick AI, Barrett K, Brisbane G, et al. "Capturing Pediatric Health and Medication Use in a US National Health Data Network." *Pharmacoepidemiology and Drug Safety*. 2025;34(9):e70217. doi:10.1002/pds.70217

Length of Time Enrolled



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Demographics and Healthcare Utilization

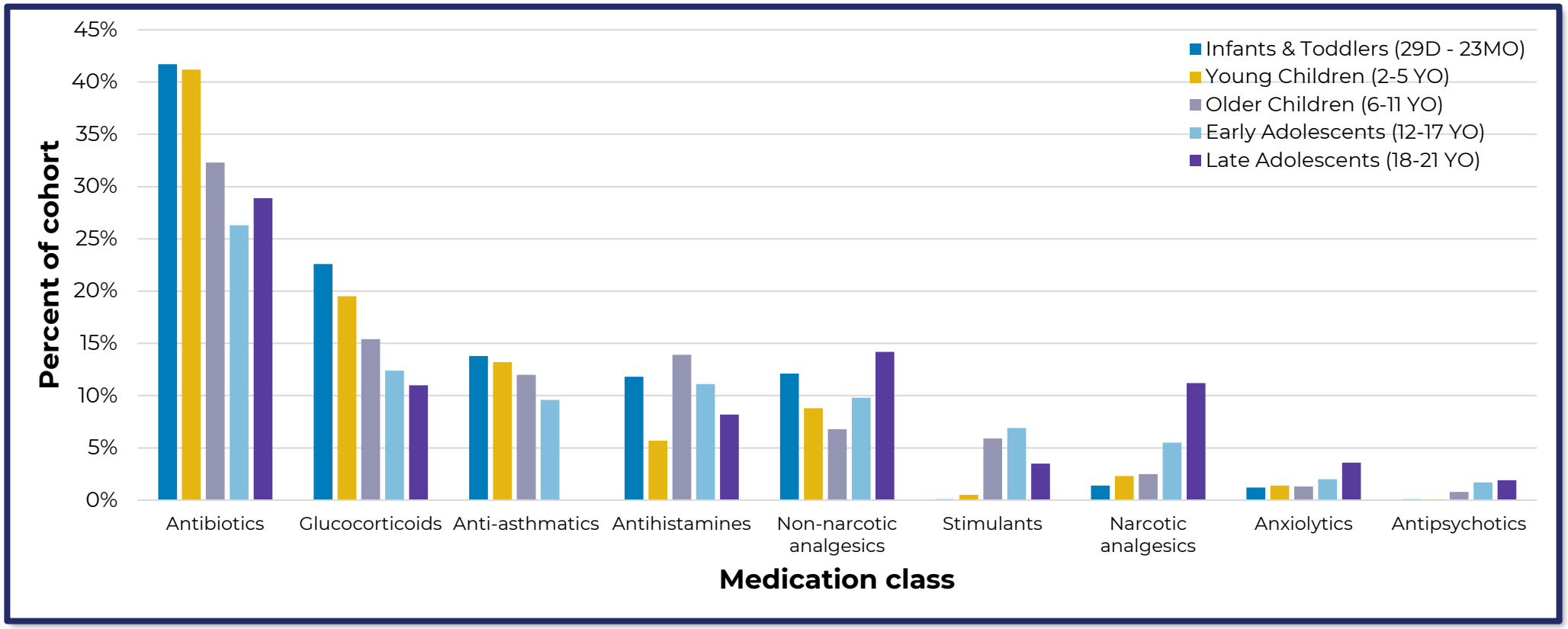
	Infants & Toddlers (29 DO – 23 MO)	Young Children (2-5 YO)	Older Children (6-11 YO)	Early Adolescents (12-17 YO)	Late Adolescents (18-21 YO)
Ever enrolled, N	27,569,755	36,832,277	46,661,185	45,354,705	35,499,458
Age in years, mean (SD)	0.5 ± 0.6	3.1 ± 1.3	7.8 ± 1.9	13.8 ± 1.9	19.1 ± 1.3
Known Race, %	35.2%	36.3%	35.7%	34.2%	30.0%
Non-White Race, %	41.4%	41.3%	41.2%	41.1%	40.7%
Female, %	48.8%	48.8%	48.8%	49.0%	51.2%
Annual #, mean (SD)					
Ambulatory encounters	7.6 (8.0)	5.3 (10.7)	4.9 (10.1)	5.1 (10.0)	4.2 (8.5)
Dispensed prescriptions	3.4 (7.4)	2.9 (6.0)	3.2 (7.2)	3.7 (8.5)	4.1 (8.6)
Dispensed drug classes	2.0 (2.5)	1.7 (2.3)	1.5 (2.2)	1.6 (2.4)	1.8 (2.7)

Data covering years 2000-2023 from all 13 Data Partners contributing to the Sentinel Distributed Database

Michnick AI, Barrett K, Brisbane G, et al. “Capturing Pediatric Health and Medication Use in a US National Health Data Network.” *Pharmacoepidemiology and Drug Safety*. 2025;34(9):e70217. doi:10.1002/pds.70217

Prescription Medication Use

- Measured **first-year point prevalence**: percent of members with ≥1 record for given characteristic during their first year in the age group



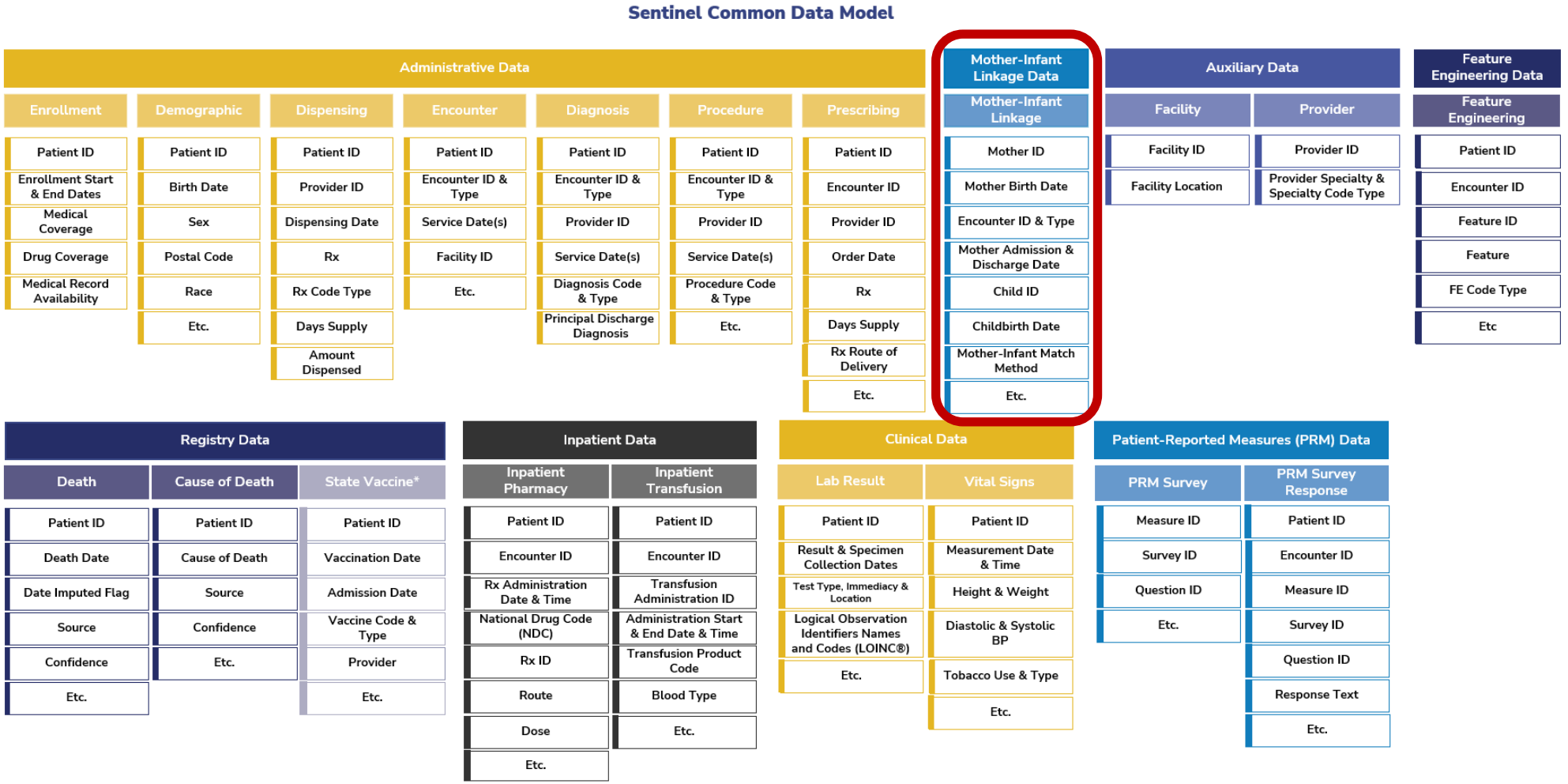
Data covering years 2000-2023 from all 13 Data Partners contributing to the Sentinel Distributed Database

Michnick AI, Barrett K, Brisbane G, et al. "Capturing Pediatric Health and Medication Use in a US National Health Data Network." *Pharmacoepidemiology and Drug Safety*. 2025;34(9):e70217. doi:10.1002/pds.70217

Mother-Infant Linkages in the Sentinel Distributed Database

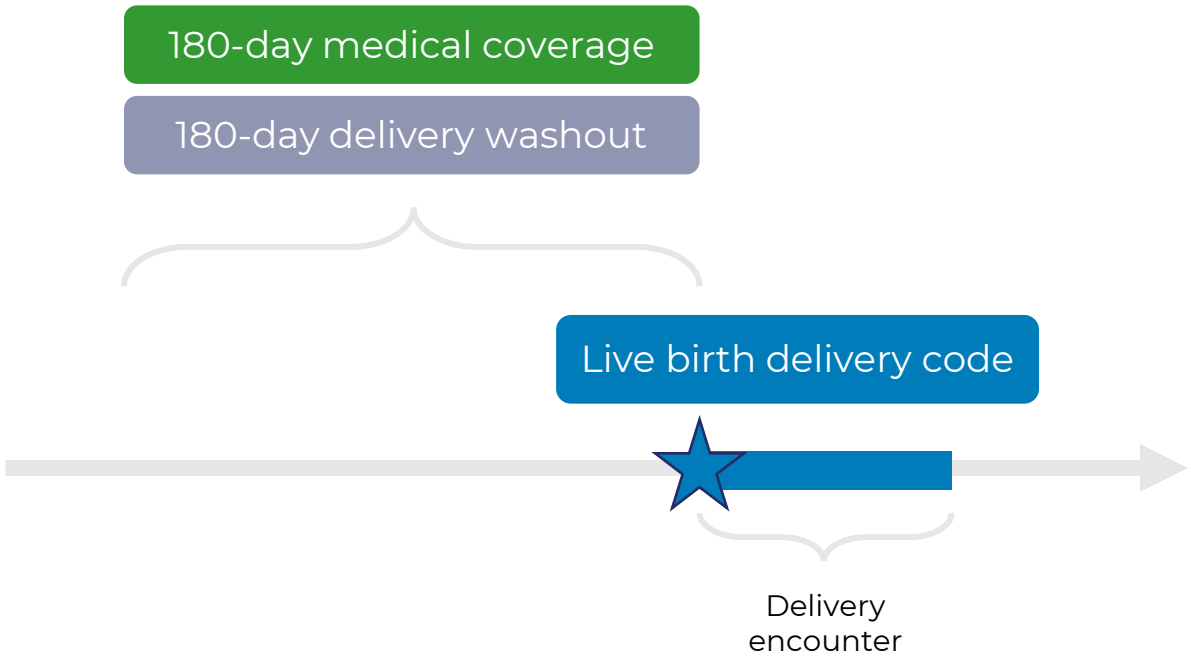
A Characterization of Sentinel's Youngest

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

Identifying Deliveries

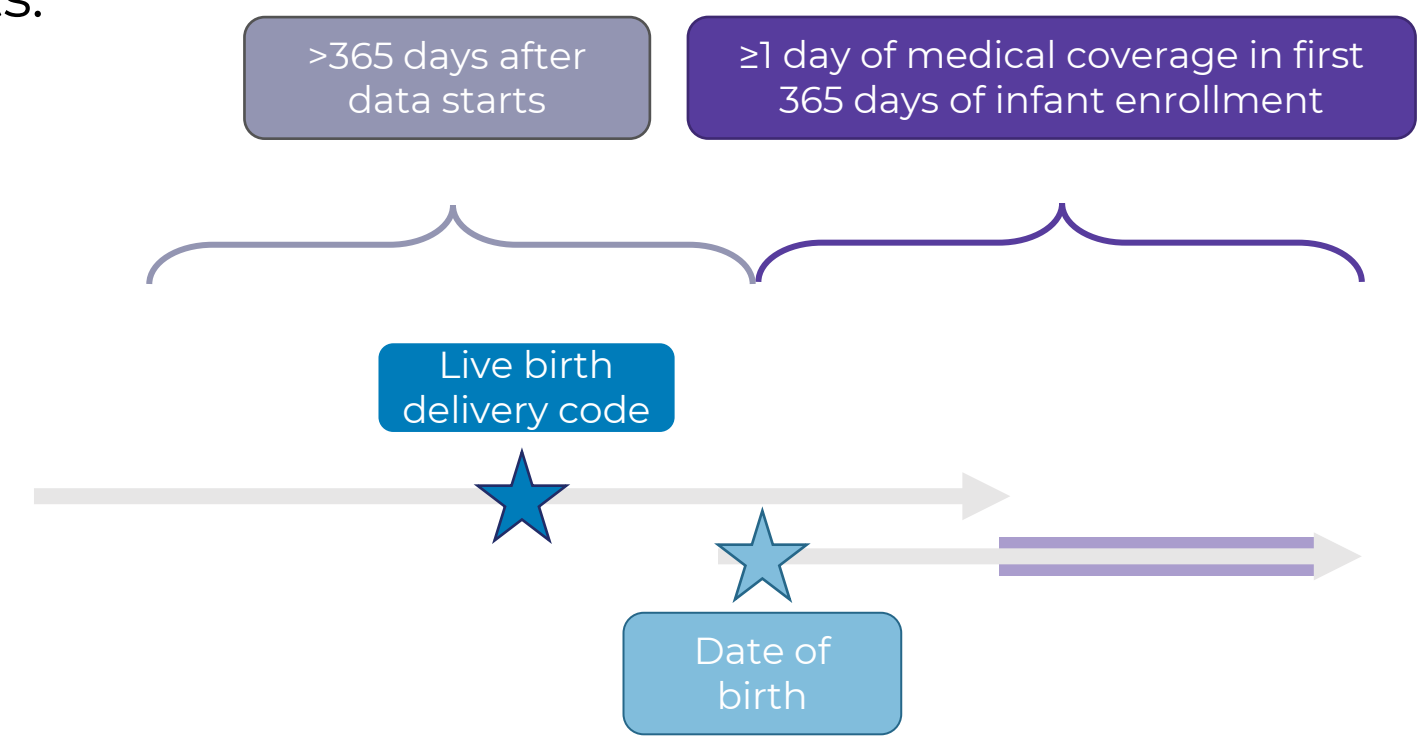


- Information recorded for mothers:
  - Patient ID
  - Birth date
  - Age
  - ID for delivery encounter
  - Delivery encounter type
  - Delivery encounter admission date
  - Delivery encounter discharge date
  - Singleton or multiple delivery
    - Codes from the delivery encounter

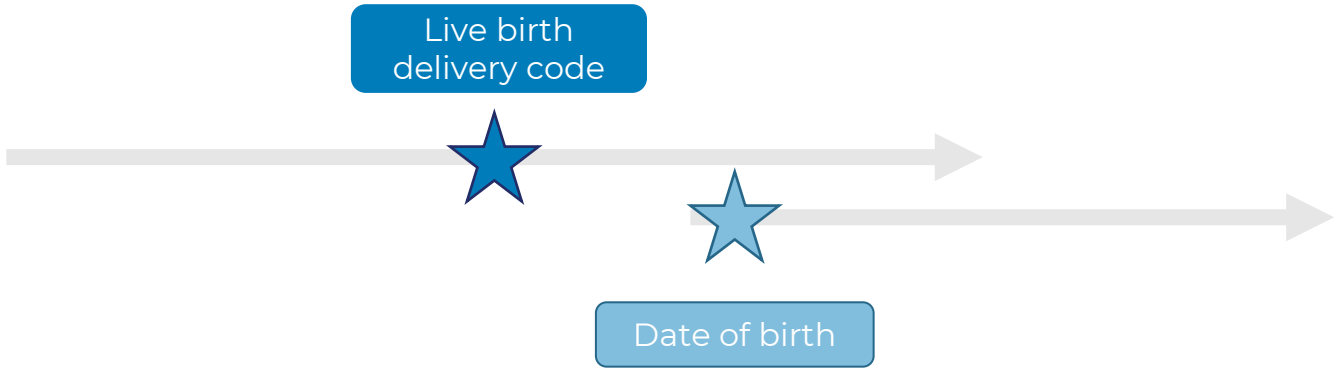
** Also required: female, ages 10-54 years at delivery admission*

Identifying Infants

- Information recorded for infants:
  - Patient ID
  - Birth date
  - Sex
  - Date of first enrollment



Linking Deliveries and Infants

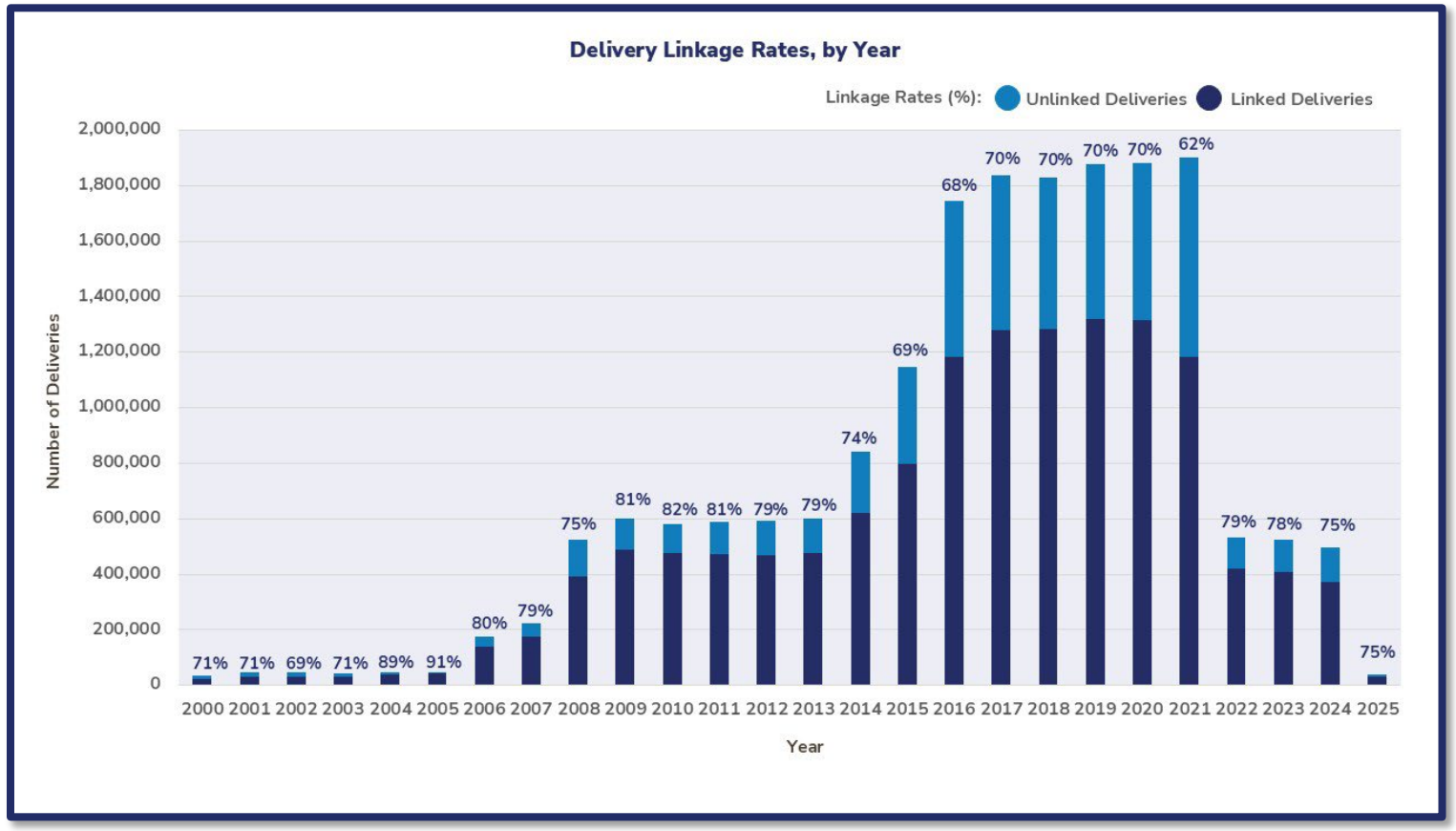


Successful Match Methods	Unsuccessful Match Reasons
Family subscriber number	No subscriber or family IDs available
Last name and address match	No name or address available
Birth certificate	Neither family IDs nor name/address available
DP-maintained birth registry	No linkage attempted
Other	

Deterministic

Probabilistic

Mother-Infant Linkage Table

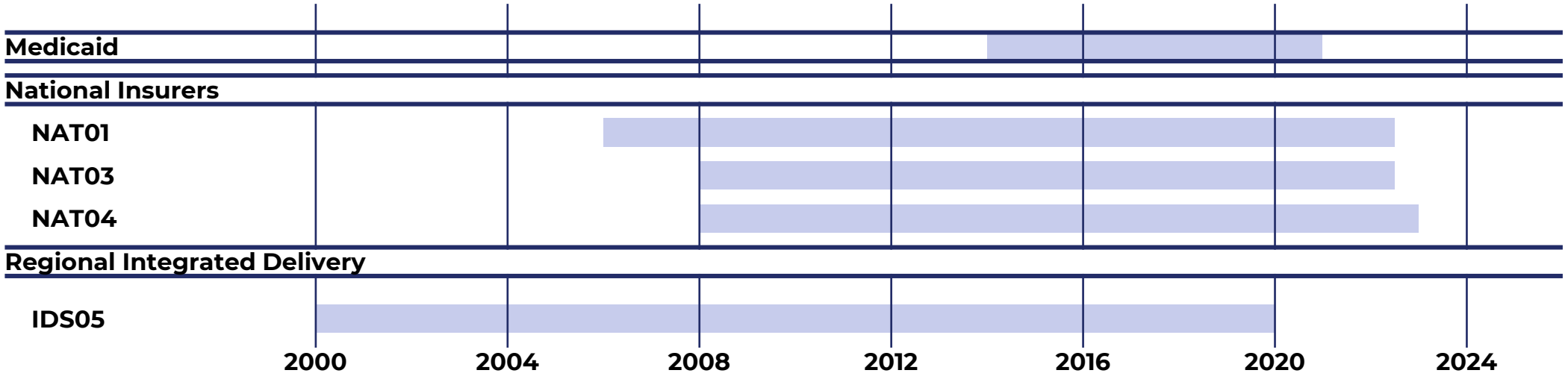


- **Factors impacting linkage rates**
  - Mother/infant on different insurance plans
  - Strict mother enrollment requirement
  - Low tolerance for potentially incorrect linkages

Data for all Data Partners that contribute to the Mother-Infant Linkage table in the Sentinel Distributed Database; Last updated of October 2025.
https://www.sentinelinitiative.org/about/key-database-statistics

Study Design

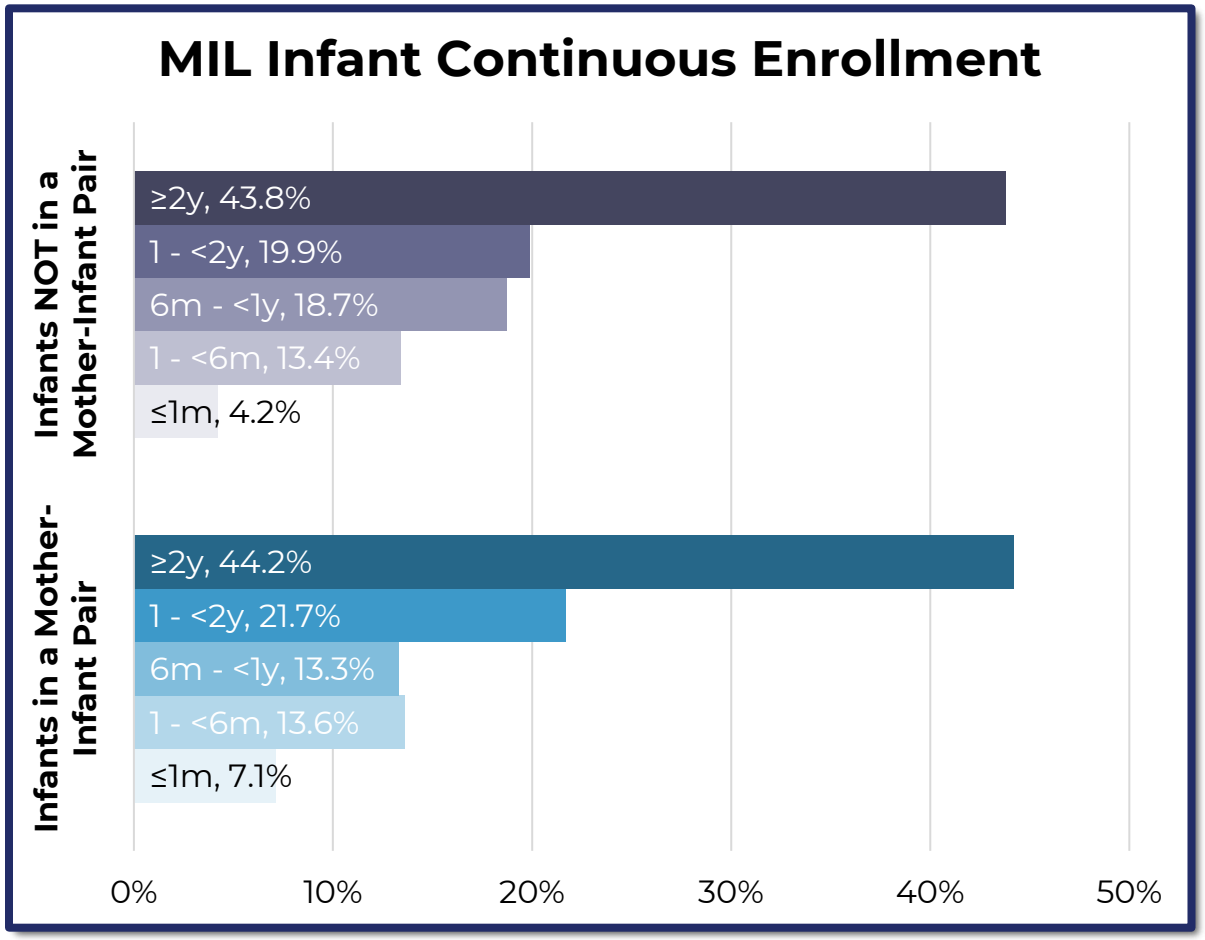
- Included all infants (aged <29 days) in the MIL table with ≥ 1 day of medical & drug coverage, describing characteristics in (1) the first 28 days of life [neonatal period], and (2) days 29-365 of life [non-neonatal period]
- Included all available data from January 1, 2000 (min) to April 30, 2023 (max)



SDD: Sentinel Distributed Database

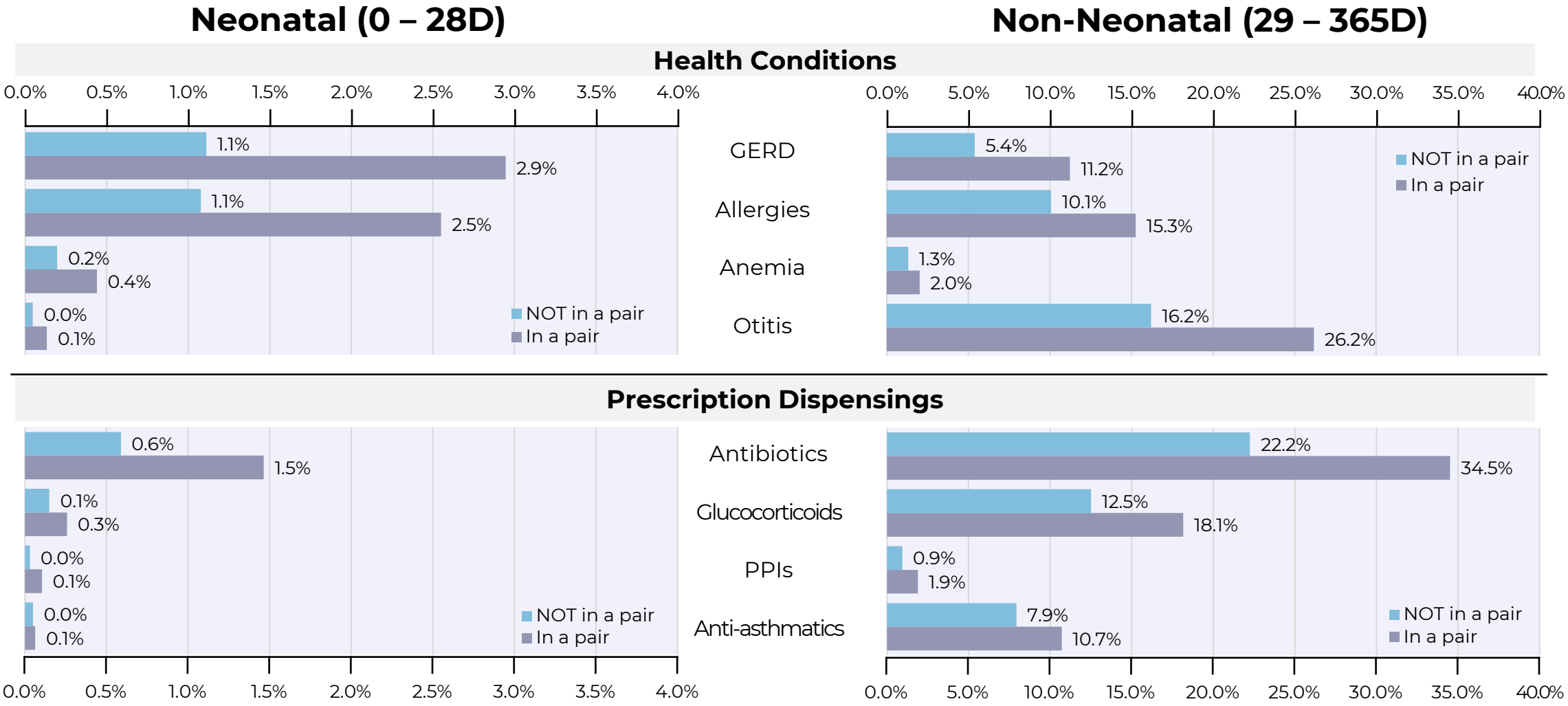
Infant Enrollment

- Identified **22,820,930 infants** in the MIL tables
- 5,433,164 infants were in a **mother-infant pair**
  - *90.4% of infants in a pair were from singleton deliveries*
- ~44% of infants have >2 years continuous enrollment



Data covering years 2000-2023 from all 5 Data Partners contributing to the Mother-Infant Linkage (MIL) table in the Sentinel Distributed Database (SDD)
Sentinel Operations Center; https://www.sentinelinitiative.org/sites/default/files/documents/Final_cder_mpl1p_wp076_Report_1.pdf

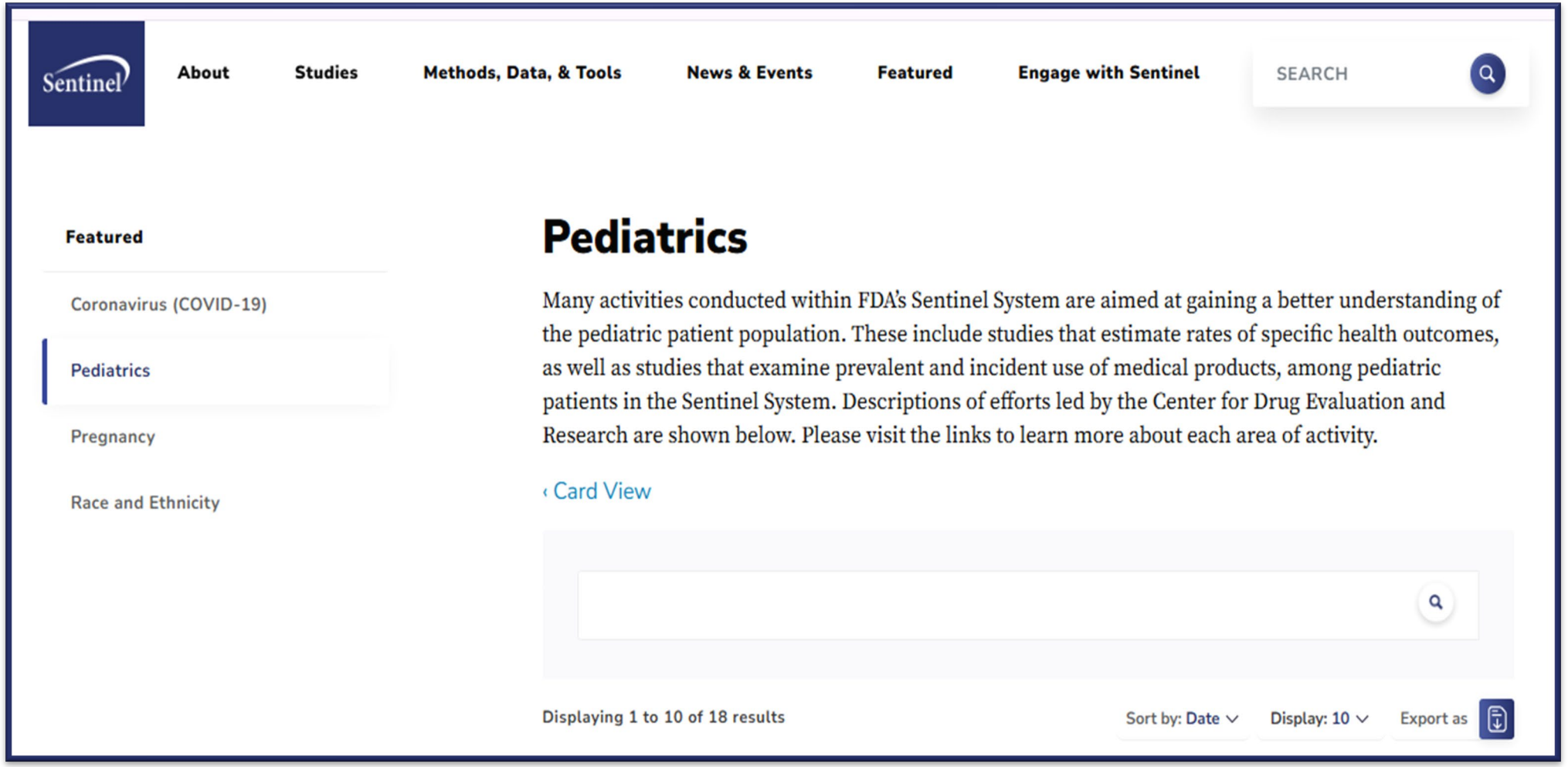
Health Conditions and Prescription Dispensings



Data covering years 2000-2023 from all 5 Data Partners contributing to the Mother-Infant Linkage (MIL) table in the Sentinel Distributed Database (SDD)
Sentinel Operations Center; https://www.sentinelinitiative.org/sites/default/files/documents/Final_cder_mpl1p_wp076_Report_1.pdf

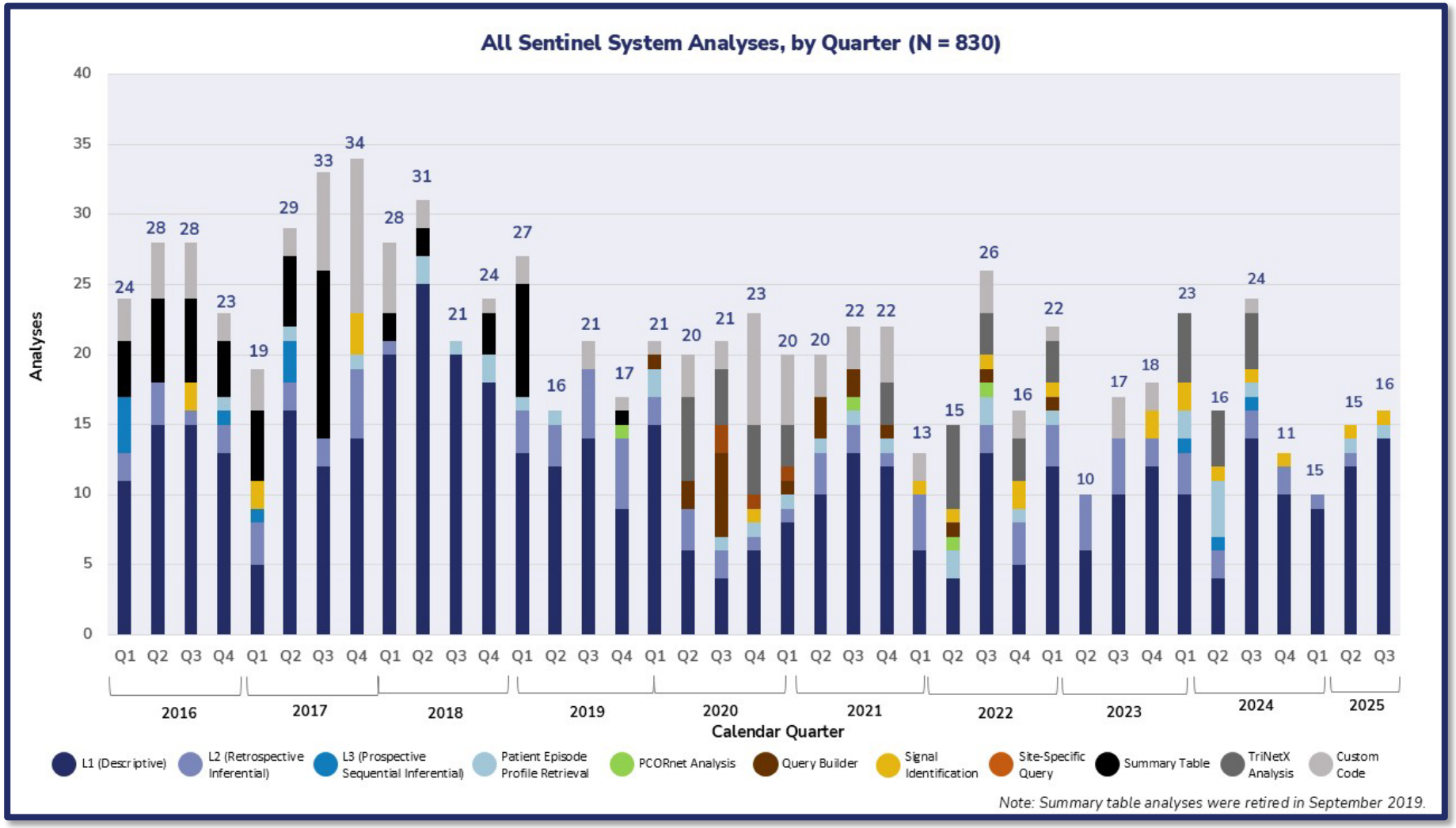
Assessing Pediatric Populations in Sentinel

Featured Topic



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

Distribution of Analyses by Quarter



Select Pediatric-Focused Assessments

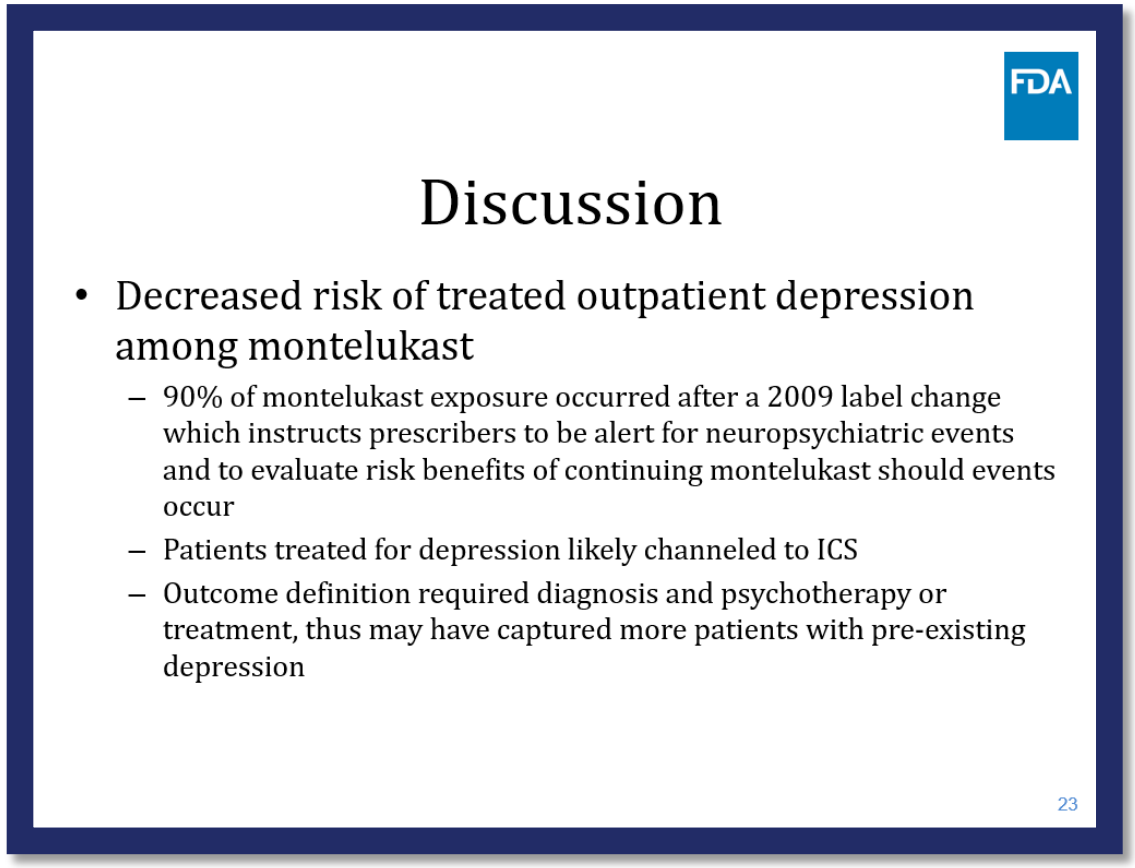
Study Name	Year
Use of Angiotensin-Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARB) in a Pediatric Population	2016
Respiratory syncytial virus (RSV) in pediatrics	2016
Interleukin-1/Interleukin-6 Inhibitors & ILD/PAH	2018
Risk of neuropsychiatric adverse events among montelukast users	2019
Risk of suicide and all-cause mortality among montelukast users	2019
Use of typical and atypical antipsychotics among inpatient infants	2019
IV Iron Use and Stillbirth in Pregnancy	2019
Risk of cardiac malformations after in utero exposure to NUVIGIL® (armodafinil)[C-IV]/PROVIGIL® (modafinil)	2020
Hypertension in Pediatric Patients: A Descriptive Analysis	2020
Oral Clefts following Topiramate Use during the First Trimester of Pregnancy	2020
Drug Utilization in Patients with Polyarticular Juvenile Idiopathic Arthritis (pJIA): A Descriptive Analysis	2020
Valganciclovir Use in Children with Congenital Cytomegalovirus Infection	2021
Treatment and Care Received by Children Hospitalized with COVID-19 in a Large Hospital Network in the United States	2021
Epidiolex (Prescription Cannabidiol) Utilization Patterns: A Descriptive Analysis	2021

Study Name	Year
Utilization of Beta Blockers in the Pediatric Population: A Descriptive Analysis	2022
Counts and Characteristics of Individuals 25 Years Old or Younger With Drug-Device or Biologic-Device Combination Use: A Descriptive Analysis	2022
Risk of Non-Cardiac Congenital Malformations Following Armodafinil or Modafinil Use: A Propensity Score Matched Analysis	2022
Risk of Adverse Neonatal Health Outcomes Among Pregnant Patients With and Without COVID-19: A Propensity Score Matched Analysis	2023
Risk of cardiac and urinary malformations after in utero exposure to GILENYA® (fingolimod)	2023
Pediatric Utilization of New Molecular Entities (NMEs): A Summary of Early Post-Marketing Uptake in the Sentinel Distributed Database	2023
Characterization of Pediatric Demographics and Enrollment in the Sentinel Distributed Database: An Updated Descriptive Analysis	2024
Characterization of Infants in the Mother-Infant Linkage Table in the Sentinel Distributed Database: An Updated Descriptive Analysis	2024
Chart Review of Major Congenital Malformations	2025
Assessing the Performance of Major Congenital Malformations as a Composite Outcome in Signal Detection and Evaluation	2025
Utilization of orally ingestible sodium fluoride drug products	2026

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



BLA: Biologics license application; NDA: New drug application
https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/neuropsychiatric-events-following-montelukast-use-propensity

Pregnant Women with Heart Failure (HF)

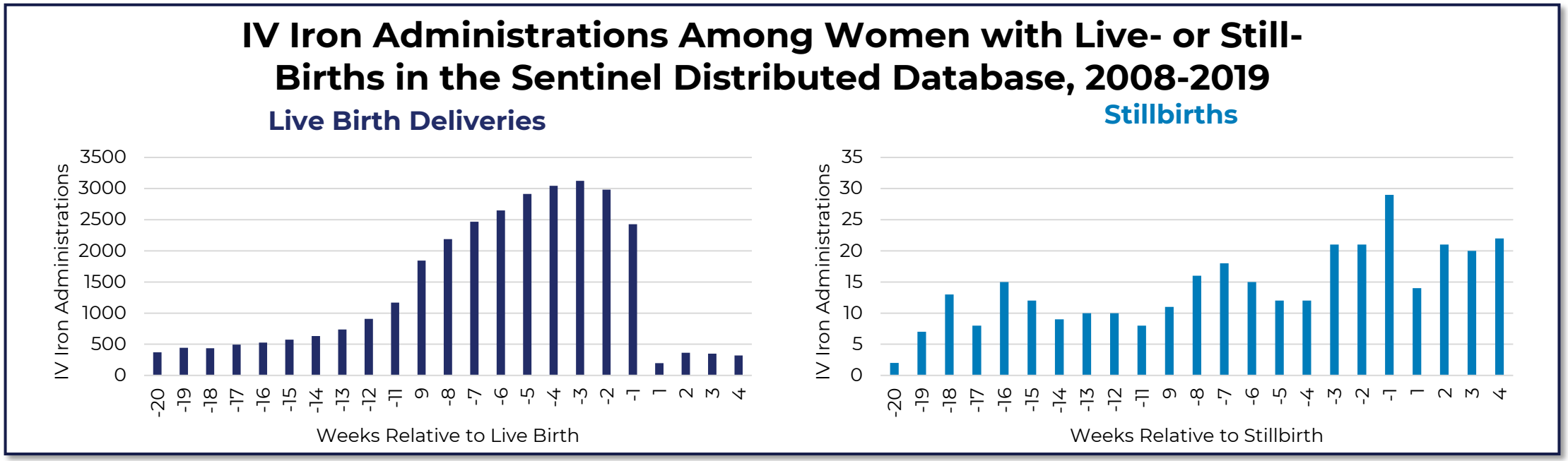
- **Safety concern source**: (s)NDA/(s)BLA
- **Regulatory Question**: Should a REMS program be required for vericiguat?
- **Regulatory Outcome**: Contributed to the review team's determination that labeling would provide sufficient information

	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%

REMS: Risk evaluation and mitigation system
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)



FAERS: FDA adverse event reporting system
https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/intravenous-iv-iron-utilization-among-pregnant-women

Valganciclovir for Congenital Cytomegalovirus (cCMV)

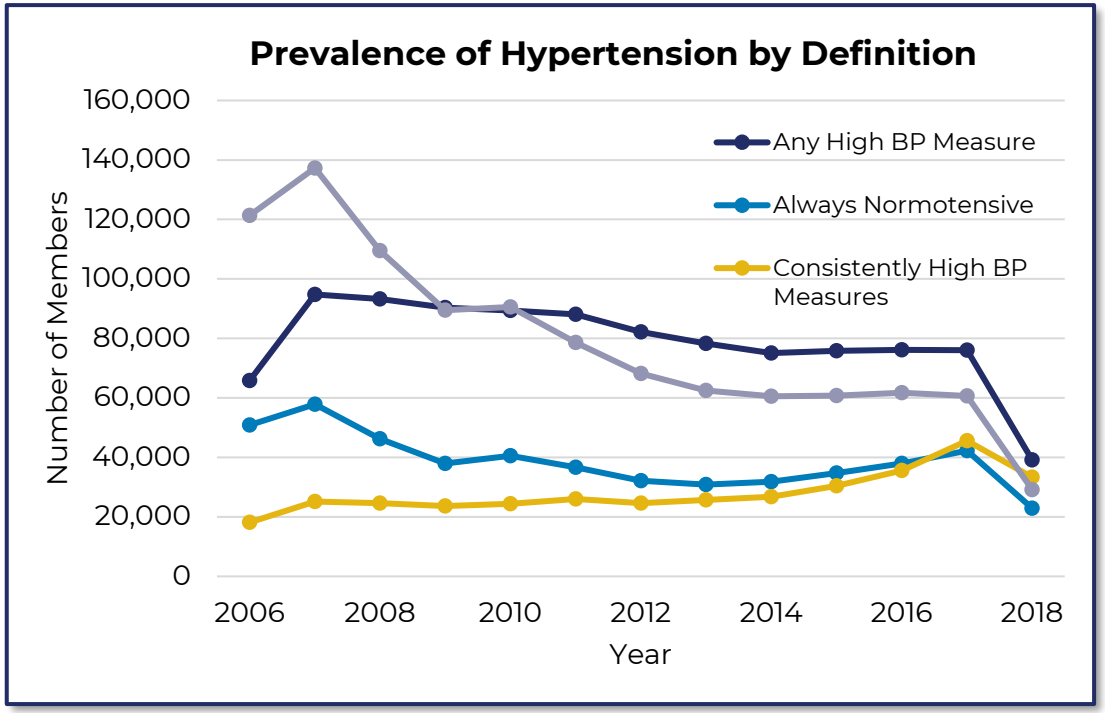
- **Safety concern source**: FAERS, Medical Literature, Foreign Regulatory Agency
- **Regulatory Question**: Can Sentinel replace sponsor's post-marketing commitments to assess use to treat congenital cytomegalovirus?
- **Regulatory Outcome**: None; results highlight the limitations of real-world data and support the need for clinical trials to study valganciclovir for cCMV

	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)

FAERS: FDA adverse events reporting system; G-CSF: granulocyte colony stimulating factor; pRBC: Packed red blood cells
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

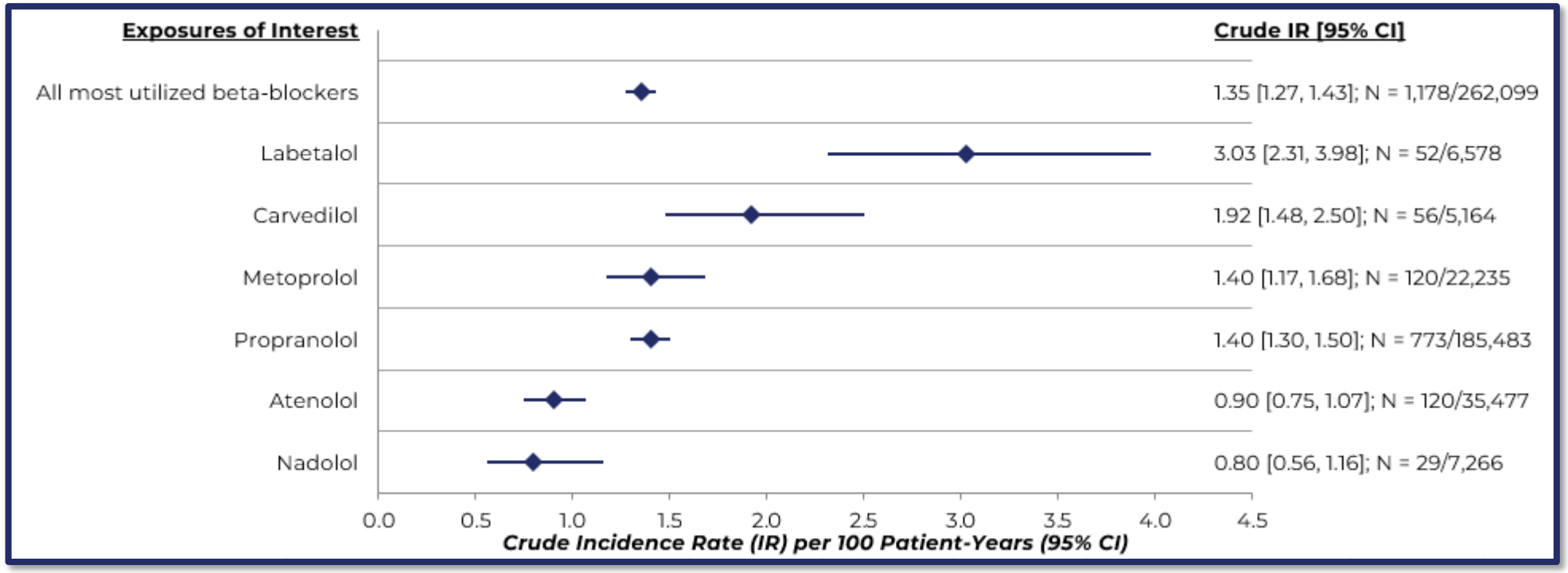


	Definition 1		Definition 2		Definition 3	
	HTN DX	No HTN DX	1 IP or 2 OP HTN DX	<1 IP or <2 OP HTN DX	DX for ↑ BP w/o HTN DX	No DX for ↑ BP
Hypertensive BP Measure	2,995 (0.6%)	507,412 (99.4%)	1,506 (0.3%)	508,901 (99.7%)	1,643 (0.3%)	512,249 (99.7%)

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

Beta Blockers and Hypoglycemia in Children

- **Safety concern source**: FAERS
- **Regulatory Question**: What is the risk of hypoglycemia w/beta blockers in pediatrics?
- **Regulatory Outcome**: Label Change – Warnings & Precautions / Patient Counseling



FAERS: FDA adverse events reporting system
https://sentinelinitiative.org/studies/drugs/beta-blockers

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

A Focus on Pediatric Populations

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