Prevalence of major congenital malformations among the insured population in the United States using seven algorithms

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Background

- Major congenital malformations are important drug safety outcomes

- Drug safety in pregnancy is typically determined through postmarketing surveillance in the United States

- There is no unified definition of the concept of composite major congenital malformations in postmarketing safety studies
  - Definitions may vary by data source and interpretation of "major"

- Estimates of the prevalence of major congenital malformations may vary by the definition used

Objectives

- Compare prevalence estimates of major congenital malformations derived using various algorithms compatible with administrative claims data in the U.S.

Algorithms defining major malformations (1/3)
Source: population-based surveillance programs

MACDP-47[1]

- Major malformations reported by NBDPN/CDC
- Defined using ICD or modified ICD (CDC/BPA) diagnosis codes

MACDP-29[2]

- Subset of 29 defects that have consistent diagnostic accuracy at or soon after birth

NBDPN: National Birth Defects Prevention Network
CDC: U.S. Centers for Disease Control and Prevention
ICD: International Classification of Diseases
BPA: British Paediatric Association
MACDP: Metropolitan Atlanta Congenital Defects Program

Algorithms defining major malformations (2/3)
Source: literature

Kharbanda et al.,[3]	• Major structural malformations consistent with GAIA definitions in the context of vaccine safety
Bérard et al.,[4]	• Major congenital malformations validated against medical charts in Quebec
Chomistek et al.,[5]	• Excluded minor malformations from various population-based surveillance programs to identify major malformations

GAIA: Global Alignment of Immunization Safety Assessment in Pregnancy

Algorithms defining major malformations (3/3)

Source: completed or ongoing in-house projects (not yet published)

CONSIGN (**C**OVID-19 Infecti**O**n a**N**d Medicine**S I**n Pre**GN**ancy)[6]

- References CDC's definition in Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET)

BOOST-HP (**B**ig data appr**O**aches f**O**r **S**afe **T**herapeutics in **H**ealthy **P**regnancy)[7]

- Major structural defects excluding those with known etiologies as determined by clinician review

Methods

- Data:
  - Merative™ MarketScan® Research Databases
  - Longitudinal administrative data for commercially insured members and their dependents in the United States

- Mother-infant linked live births cohort:
  - Singleton livebirth deliveries among mothers aged 12-54 years occurring between 2015-2024 where the infant is linked to the mother using a deterministic match
  - Continuous enrollment requirement: 3 months prior to the estimated start of pregnancy through the end of pregnancy

Analysis

- Major congenital malformations defined according to each algorithm:
  - Primary: ≥ 2 diagnosis codes in 180 days post-delivery
  - Sensitivity: ≥ 1 or ≥ 2 diagnosis codes in 90 or 180 days post-delivery

- Prevalence estimated as number of live births with major congenital malformations divided by the number of linked live births in the database (2015-2024)

Cohort characteristics

- 719,281 mother-infant pairs meeting eligibility requirements of age and enrollment

- Average maternal age: 31.8 (± 4.4) years
  - 12-22 years: 1.7%
  - 23-34 years: 75.0%
  - 35-44 years: 23.1%
  - 45-54 years: 0.3%

- Average gestational age at birth: 38.8 (± 1.9) weeks

Prevalence estimates of major congenital malformations

Primary analysis: ≥ 2 codes in 180 days post-delivery

Source	Algorithm	Evidence of major congenital malformations (n)	Malformations per 100 live births
Population-based surveillance programs	MACDP-47[1]	23,279	3.24
	MACDP-29[2]	6,414	0.89
Literature	Kharbanda et al.,[3]	13,295	1.85
	Bérard et al.,[4]	27,756	3.86
	Chomistek et al.,[5]	122,507	17.03
Completed or ongoing in-house projects (not yet published)	CONSIGN[6]	117,636	16.35
	BOOST-HP[7]	26,966	3.75

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Prevalence estimates of major congenital malformations

Sensitivity analysis: ≥ 2 codes in 90 days post-delivery

Source	Algorithm	Evidence of major congenital malformations (n)	Malformations per 100 live births
Population-based surveillance programs	MACDP-47[1]	19,535	2.72
	MACDP-29[2]	5,621	0.78
Literature	Kharbanda et al.,[3]	11,796	1.64
	Bérard et al.,[4]	23,034	3.20
	Chomistek et al.,[5]	96,176	13.37
Completed or ongoing in-house projects (not yet published)	CONSIGN[6]	92,420	12.85
	BOOST[7]	22,396	3.11

Prevalence was higher in other sensitivity analyses requiring ≥1 code:
- Within 180 days: 1.5 – 33.6 per 100 live births, ranked in same order
- Within 90 days: 1.4 - 29.6 per 100 live births, ranked in same order

Discussion

- 3 of 7 algorithms (MACDP-47, BOOST-HP and Berard) yielded prevalence of major congenital malformations comparable to that reported by the U.S. Centers for Disease Control and Prevention (3-4%)

- Variation in prevalence of major malformations across algorithms was driven by the inclusion of structural malformations otherwise deemed minor
  - Examples include: Q38.1: ankyloglossia (tongue-tie) and Q67.3: plagiocephaly (flat head syndrome)

Selection criteria for malformations in safety studies

- Background rates of malformations will appear higher when using a liberal definition of malformations, making it harder to detect the increased risk of a rare event

- Examples of malformations typically excluded when evaluating malformations as drug safety outcomes[8]:
  - Genetic disorders
  - Chromosomal abnormalities
  - **Minor anomalies**
  - Birth marks
  - **Positional deformities**
  - Prematurity-related physical features
  - Physiologic findings
  - Functional abnormalities
  - Findings from newborn screening

Future research

- 47 major defects reported on by the NBDPN in collaboration with CDC ('MACDP-47) can be identified using ICD-9-CM or ICD-10-CM diagnosis codes as well as modified ICD diagnosis codes in the CDC/BPA vocabulary making it easy to harmonize the definition of major malformations across various sources of data used for postmarketing drug safety research in pregnant populations

- Ongoing validation of the MACDP-47 algorithm against gold standard of medical records within the FDA's Sentinel Initiative

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Questions?

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