SURVEILLANCE OF MAJOR BIRTH DEFECTS IN NON-LIVE BIRTH PREGNANCY OUTCOMES

EPIDEMIOLOGICAL CONSIDERATIONS

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Objectives

- Provide overview for calculation of birth defect prevalence
- Discuss benefits of including non-live birth data for data analysis and epidemiological assessments
- Present some of the challenges of using non-live birth data
- Present potential ways to address the challenges with non-live birth data
- Discuss the gold standard vs. realistic alternatives

Acronyms:
BD – Birth defects
NBDPN – National Birth Defects Prevention Network
NTD – Neural Tube Defects

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Overview of Calculation for Birth Defect Prevalence

- Case counts
- Prevalence estimates (overall & stratum-specific)
  - 95% confidence intervals
- Prevalence calculation
  - NBDPN recommendation:

$$\frac{\text{BD Cases}}{\text{All Live Births in Same Population}} \quad \frac{\text{(Live Births + Fetal Deaths + Miscarriages + Terminations + Unknowns)}}{\text{x } 10{,}000}$$

Anencephaly (Arizona, 2011-2015): $\frac{42+33}{427{,}550} \times 10{,}000 =$ **1.75 cases per 10,000 live births**

(Mason et al., 2005; NBDPN Guidelines, 2004)

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Benefits of Including Non-Live Birth Data

1) More complete case ascertainment
- Reduces risk of under-reporting that could occur with just live birth data
- 1 BD case for every 33 pregnancies, yet 1 BD case for every 5 **stillborn** fetuses
- Odds of **elective termination** are 126 times higher for fetuses with severe non-neurologic malformations
- Odds of **elective termination** are 300 times higher for fetuses with serious neurologic malformations
- Over 40% of pregnancies with neural tube defects were **electively terminated** after prenatal diagnosis (South Carolina, California)
- Scant data in BD cases among **miscarriages**
  - Chromosomal abnormalities and NTDs

(Rynn, 2008; Hoyert, 2016; Gregory, 2013; Stillbirth Collaborative Research Network Writing Group 2011; Shechtman, 2002; Allen, 1996; Velie, 1996)

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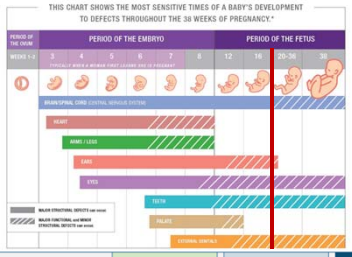
Benefits of Including Non-Live Birth Data

1) More complete case ascertainment
- Miscarriages…



(mothertobaby.org)

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Benefits of Including Non-Live Birth Data

1) More complete case ascertainment
- Arizona example
- Anencephaly prevalence estimate, 2011-2015

$$\frac{\text{BD live birth cases}}{\text{All live births in Arizona}} \times 10{,}000 = \text{Prevalence Estimates} \qquad \frac{42}{427{,}550} \times 10{,}000 = \textbf{.98 cases per 10,000 live births}$$

$$\frac{\text{BD live birth + BD fetal death cases}}{\text{All live births in Arizona}} \times 10{,}000 = \text{Prevalence Estimates} \qquad \frac{42 + 33}{427{,}550} \times 10{,}000 = \textbf{1.75 cases per 10,000 live births}$$

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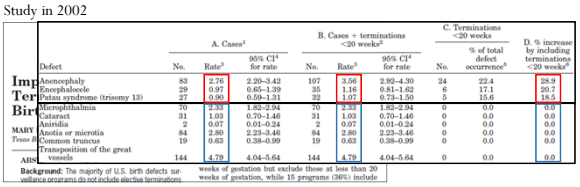
Benefits of Including Non-Live Birth Data

1) More complete case ascertainment
   - Texas example
   - Study in 2002



Defect	A. Cases[1] No.	A. Cases[1] Rate[3]	A. Cases[1] 95% CI[4] for rate	B. Cases + terminations <20 weeks[2] No.	B. Cases + terminations <20 weeks[2] Rate[3]	B. Cases + terminations <20 weeks[2] 95% CI[4] for rate	C. Terminations <20 weeks No.	C. Terminations <20 weeks % of total defect occurrence[5]	D. % increase by including terminations <20 weeks[6]
Anencephaly	83	2.76	2.20–3.42	107	3.56	2.92–4.30	24	22.4	28.9
Encephalocele	29	0.97	0.65–1.39	35	1.16	0.81–1.62	6	17.1	20.7
Patau syndrome (trisomy 13)	27	0.90	0.59–1.31	32	1.07	0.73–1.50	5	15.6	18.5
Microphthalmia	70	2.33	1.82–2.94	70	2.33	1.82–2.94	0	0.0	0.0
Cataract	31	1.03	0.70–1.46	31	1.03	0.70–1.46	0	0.0	0.0
Aniridia	2	0.07	0.01–0.24	2	0.07	0.01–0.24	0	0.0	0.0
Anotia or microtia	84	2.80	2.23–3.46	84	2.80	2.23–3.46	0	0.0	0.0
Common truncus	19	0.63	0.38–0.99	19	0.63	0.38–0.99	0	0.0	0.0
Transposition of the great vessels	144	4.79	4.04–5.64	144	4.79	4.04–5.64	0	0.0	0.0

Background: The majority of U.S. birth defects surveillance programs do not include elective terminations

weeks of gestation but exclude those at less than 20 weeks of gestation, while 15 programs (36%) include

Excluding non-live birth data can lead to an underestimation of prevalence estimates

(Ethen and Canfield, 2002)

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Benefits of Including Non-Live Birth Data

2) More accurate evaluation of prevention efforts
   - If non-live births are excluded, it can lead to underestimation of prevalence estimates and possible overestimation of success of prevention efforts.

3) Reduces potential bias in epidemiologic studies of birth defects
   - If there are exposures and/or events of interest associated with the decision to terminate a pregnancy or a stillbirth, excluding non-live births could bias findings.

4) Assess & monitor terminations over time
   - Cannot assume a consistent proportion of BD cases will result in terminations; thus, exclusion of elective terminations can underestimate prevalence.

(NBDPN Guidelines, 2012; Cragan and Khoury, 2000)

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Some Challenges of Using Non-Live Birth Data

1) Classification/categories for non-live birth outcomes
   - Not knowing, or being able to provide, accurate birth outcome (i.e. stillbirth vs miscarriage vs termination)

2) Inflation of prevalence estimates
   - Certain BDs need a post-delivery confirmation or are poorly identified prenatally (e.g. certain congenital heart defects, chromosomal abnormalities)

3) Missing data for individual cases
   - Race/ethnicity and sex are often missing
   - Occurs most often for miscarriages and terminations in comparison to stillbirths

4) Missing BD cases among non-live births (incomplete ascertainment)
   - Fetuses with certain BDs are more likely to undergo elective terminations early on, so may not have any record of the terminations

(NBDPN Guidelines, 2012)

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Addressing Challenges of Using Non-Live Birth Data

1) Classification/categories for non-live birth outcomes

- Ideally categorizing cases as
  - Stillbirths (i.e. fetal deaths)
  - Spontaneous abortion (i.e. miscarriages)
  - Elective terminations
  - Unknown/unspecified non-live births
- Alternate option for state &/or program restrictions - "other pregnancy loss"
- At minimum, report any non-live birth case
  - Unknown/unspecified non-live birth
  - NBDPN guidelines: important for accurately estimating birth defect prevalence

Table T.1. Prevalence of Birth Defects, Massachusetts: 2013-2014

Defect[1]	Live Birth Count	Stillbirth Count	Other Pregnancy Loss Count	Total Count	Rate per 10,000 Live Births	95% Confidence Interval
Total Cases with a Reportable Birth Defect	3015	68	811	3894	271.0	262.7-279.6
Central Nervous System						
Anencephaly	1	1	29	31	2.16	1.47-3.06

(MCBDRP, 2019)

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Addressing Challenges of Using Non-Live Birth Data

2) Inflation of prevalence estimates

- Gold standard: using only cases with confirmed BD
  - Confirmed through postnatal records (e.g. pathology, autopsy, lab records) whenever needed & possible
- Lack of postnatal confirmation
  - Develop consistent criteria reflecting certainty of prenatal findings (e.g. precision codes used)
  - Review of prenatal findings by consultants knowledgeable about specific birth defects (e.g. clinical geneticist, pediatric cardiologist, etc.)
- NBDPN Guidelines Appendix 12.2

Appendix 12.2

Suggested List of Prenatal Diagnoses That Can Be Included in Prevalence Estimates Without a Clinician's Review of the Defect Certainty

It is recommended that programs engage the services of a clinical geneticist or other consultant knowledgeable about birth defects, fetal development, and prenatal diagnosis to review case information and assess the certainty of all prenatal diagnoses.

If the services of a knowledgeable clinician are not available, it is suggested that inclusion of prenatal diagnoses in prevalence estimates be restricted to the defects on this list, and that prenatal diagnoses not on this list should not be included in defect prevalence estimates.

DEFECT	COMMENT
Abnormal Number of Chromosomes	Karyotype required for diagnosis. Examples include trisomies 13, 18, 21, triploidy, Turner syndrome, Klinefelter syndrome, …

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Addressing Challenges of Using Non-Live Birth Data

3) Missing data for individual cases

- Various data sources
  - Vital records, multiple surveillance sources (healthcare clinics, administrative databases)
- Limiting case ascertainment to non-live birth outcomes with low rates of missing data
  - Arizona: Fetal deaths and vital records fetal death certificates
- Displaying data for presentation
  - Breakdown of count data by birth outcome
  - When calculating stratum-specific prevalence estimates, exclude cases with missing values
  - Texas example…

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Addressing Challenges of Using Non-Live Birth Data

3) Missing data for individual cases (continued)

- Texas example
- Table 6. Case breakdown by birth outcome per BD
- Table 4. Stratum-specific prevalence estimates – exclude cases with missing data

Texas Birth Defects Registry, Report of Birth Defects Among 1999-2016 Deliveries
Table 6. Pregnancy Outcome Distribution for Selected Birth Defects, Texas, 1999-2016

Birth Defect	Live Birth Cases	Live Birth %*	Spontaneous Fetal Death Cases	Spontaneous Fetal Death %*	Induced Pregnancy Termination Cases	Induced Pregnancy Termination %*	Unspecified Fetal Death / Termination Cases	Unspecified Fetal Death / Termination %*
Central Nervous System								
Anencephaly	641	38.42	528	30.00	564	32.05	27	1.53
Spina bifida without anencephaly	2362	90.92	99	3.81	132	5.08	5	0.19

N=1,760

Texas Birth Defects Registry, Report of Birth Defects Among 1999-2016 Deliveries
Table 4. Prevalence of Selected Birth Defects by Mother's Race/Ethnicity, Texas, 1999-2016

Birth Defect	Mother's Race/Ethnicity	Cases	Prevalence†	95% Confidence Interval for Prevalence	
Central Nervous System					
Anencephaly * (p<0.0001)	White non-Hispanic	509	2.07	1.89 -	2.25
	Black non-Hispanic	139	1.77	1.47 -	2.06
	Hispanic	1031	3.07	2.89 -	3.26

N=1,679

(Texas Birth Defects Registry, 2020)

Addressing Challenges of Using Non-Live Birth Data

4) Missing BD cases among non-live births (incomplete ascertainment)

- Very difficult to assess or measure
- Awareness of the BD cases that are likely to result in elective terminations or miscarriages is crucial
  - Abdominal wall defects can be diagnosed 15-18 weeks (can be detected earlier)
  - Screening between 11-13 weeks of pregnancy: some heart defects, NTDs, and chromosomal disorders
- Further individual research through state reports, peer-reviewed articles, etc.
- NBDPN guideline: include as many confirmed non-live birth cases as possible in order to avoid under-reporting

(Diagnosis of Birth Defects, 2004)

Gold Standard vs. Reality

- Limited permissions and/or ability to obtain non-live birth cases
- Difficult to predict the:
  - Amount of missing data (or missing cases)
  - Variations in birth outcomes (especially elective terminations)
- Consistency within program data collection
  - Strengthens individual state BD analysis
  - Explain changes in processes within write-ups as needed
- Report and assess available BD data
  - Include descriptive information when possible (i.e. proportions of birth outcomes)
  - Exclude cases with missing information for specific analysis (stratum-specific prevalence calculations, etc.)

THANK YOU!

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