Identification of Birth Defects in Michigan Infants with Sickle Cell Disease and Sickle Cell Trait: MI NBS and MBDR Data, 2004-2006

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Outline

- Background
- Research Questions
- Methods
- Results
- Discussion and Future Directions
- Public Health Implications

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Background

- MI Birth Defects Registry (MBDR)
  - Passive surveillance system
  - Case sharing with other programs
- MI Newborn Screening (NBS)
  - Screens all newborns for 49 diseases and hearing loss
- Little research has been done to assess anomalies associated with sickle cell disease (SCD) or sickle cell trait (SCT).
- NBS program reports all positive SCD cases to MBDR but we never conducted joint analyses for:
  - Validation and quality improvement purposes
  - Comprehensive health status assessment

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Research Questions

- How many children with SCD are missing or misclassified in MBDR compared to NBS records?
- What birth defects are reported in children with SCD or SCT?

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Methods

- Study Design
  - 'capture – recapture' type method with NBS as gold standard
  - Retrospective cross-sectional study

- Study Population
  - Resident infants born in Michigan from 2004 to 2006
  - Diagnosed with SCD or SCT by newborn screening.
    - **SCD**: Inherited blood disorder; sickle-shaped red blood cells; anemia characterized by periodic episodes of pain, acute abdominal discomfort, skin ulcerations of the legs, increased infections.[1]
    - **SCT**: Heterozygous genetic makeup characterized by one gene for normal hemoglobin and one for sickle-cell hemoglobin; clinical disease rarely present.[1]

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[1]Hart AC, Stegman MS, Ford B, eds. International Classification of Diseases 9th Revision Clinical Modification, 6th Edition. Ingenix 2009.

Methods

- Data Sources
  - NBS
  - MBDR
    - Both data sources are routinely linked to live birth records (probabilistic linkage)
    - Electronic Birth Certificate (EBC) records were used as intermediate files – the birth certificate number served as the unique identifier (deterministic linkage)
- Statistical Analysis
  - Relative risk calculated with SAS v. 9.1

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Results – Case Validation

- 186 SCD cases identified by NBS and 100% were linked to live birth records
- 8728 SCT cases identified by NBS and 8446 (96.8%) were linked to live birth records

Table 1: ICD-9-CM codes included in analysis for SCD and SCT cases.

ICD 9 CM	Diagnosis
282.6	Sickle-cell disease
282.60	Sickle-cell disease, unspecified
282.61	Hb-SS disease without crisis
282.62	Hb-SS disease with crisis
282.63	Sickle-cell/Hb-C disease without crisis
282.64	Sickle-cell/Hb-C disease with crisis
282.68	Other sickle-cell disease without crisis
282.69	Other sickle-cell disease with crisis
282.5	Sickle-cell Trait

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Results – Case Validation

Table 2: SCD case classification with NBS as the gold standard (true diagnosis).

MBDR	NBS (Gold Standard)		Total
	Case (SCD)	**Non Case (No SCD)**	
Case (SCD)	166 True Positives (TP)	97 False Positives (FP)	263
Non Case (No SCD)	20 False Negatives (FN)	NA True Negatives (TN)	20
Total	186	97	283

Positive Predictive Value = 0.63

Sensitivity = 0.89

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Results – Case Validation

- Medical Chart Reviews of False Positives
  - 60 (70.1%) charts reviewed to date:
    - **2 true SCD cases,** both had been diagnosed with SCT by NBS
    - 29 normal NBS
    - 5 positive NBS, no additional diagnostic information in charts, but all had been diagnosed with SCT by NBS.
    - 2 inconclusive NBS
    - 14 no NBS or SCD information
    - 8 other diagnoses:
      - 4 other thalassemia,
      - 1 severe anemia,
      - 1 iron deficiency,
      - 2 sickle cell trait

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Results – Additional Anomalies

Table 3: Estimated effect of SCD on the risk of having a birth defect: Michigan MBDR-NBS Data, 2004-2006

Defect Category	Rate in Michigan†	Rate in SCD Population†	Crude	
			RR	95% Confidence Interval
Any Defect	740.9	1190.5	**1.7**	**(1.1, 2.7)**
CNS	47.6	*		
Eye	33.0	*		
Ear/Face/ Neck	18.4	*		
Heart	205.4	357.1	1.8	(0.8, 4.0)
Respiratory	65.1	*		
Cleft Palate, Lip	16.0	*		
Alimentary Canal/Digestive	57.1	*		
Genital/Urinary	162.5	*		
Musculoskeletal	187.9	*		
Integument	51.8	357.1	**7.1**	**(3.2, 16.1)**
Chromosomal	22.5	*		
Other/Unspecified	44.8	*		

†Rates are per 10,000 live births

*Indicates less than 5 cases

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Results – Additional Anomalies

- 2009 Prevalence of SCD in blacks is 1:368 live births
- Stratified analysis by race:
  - 161 (95.8%) of the SCD population were black
  - 20 (12.4%) cases had an additional birth defect
- There were no significant results when stratified by race

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Results – Additional Anomalies

Table 4: Estimated effect of SCT on the risk of having a birth defect: Michigan MBDR-NBS Data, 2004-2006

Defect Category	Rate in Michigan†	Rate in SCT Population†	Crude	
			RR	95% Confidence Interval
Any Defect	740.9	1056.4	**1.5**	**(1.4, 1.6)**
CNS	47.6	68.7	**1.4**	**(1.1, 1.9)**
Eye	33.0	22.5	0.68	(0.44, 1.1)
Ear/Face/ Neck	18.4	17.8	0.97	(0.59, 1.6)
Heart	205.4	303.2	**1.5**	**(1.3, 1.7)**
Respiratory	65.1	88.8	**1.4**	**(1.1, 1.7)**
Cleft Palate, Lip	16.0	13.0	0.81	(0.45, 1.5)
Alimentary Canal/Digestive	57.1	78.2	**1.4**	**(1.1, 1.7)**
Genital/Urinary	162.5	149.2	0.92	(0.77, 1.1)
Musculoskeletal	187.9	279.5	**1.5**	**(1.3, 1.7)**
Integument	51.8	163.4	**3.2**	**(2.7, 3.8)**
Chromosomal	22.5	16.6	0.74	(0.44, 1.2)
Other/Unspecified	44.8	46.2	1.0	(0.76, 1.4)

†Rates are per 10,000 live births

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Results – Additional Anomalies

Table 5: Estimated effect of SCT on the risk of having a birth defect for those who are black: Michigan MBDR-NBS Data, 2004-2006.

Defect Category	Rate in Michigan†	Rate in SCT Population†	Crude	
			RR	95% Confidence Interval
Any Defect	1078.1	1152.8	**1.1**	**(1.0, 1.2)**
CNS	62.2	78.1	1.3	(0.97, 1.6)
Eye	27.9	26.0	0.93	(0.59, 1.5)
Ear/Face/ Neck	19.9	18.4	0.92	0.54, 1.6)
Heart	342.9	342.9	1.0	(0.88, 1.1)
Respiratory	88.7	94.9	1.1	(0.84, 1.4)
Cleft Palate, Lip	12.7	12.2	0.96	(0.50, 1.9)
Alimentary Canal/Digestive	56.4	88.8	**1.6**	**(1.2, 2.0)**
Genital/Urinary	146.3	139.3	0.95	(0.78, 1.2)
Musculoskeletal	266.5	289.3	1.1	(0.95, 1.2)
Integument	182.4	200.6	1.1	(0.93, 1.3)
Chromosomal	22.6	18.4	0.81	(0.47, 1.4)
Other/Unspecified	43.4	42.9	0.99	(0.69, 1.4)

†Rates are per 10,000 live births

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Results – Additional Anomalies

Table 6: Estimated effect of SCT on the risk of having a birth defect for those who are white: Michigan MBDR-NBS Data, 2004-2006.

Defect Category	Rate in Michigan†	Rate in SCT Population†	Crude	
			RR	95% Confidence Interval
Any Defect	662.4	815.4	**1.3**	**(1.0, 1.5)**
CNS	44.1	40.4	0.92	(0.41, 2.0)
Eye	34.1	*	0.39	(0.10, 1.6)
Ear/Face/ Neck	17.8	*	1.1	(0.37, 3.5)
Heart	176.4	208.9	1.2	(0.83, 1.7)
Respiratory	58.5	74.1	1.3	(0.70, 2.3)
Cleft Palate, Lip	16.5	*	1.2	(0.40, 3.8)
Alimentary Canal/Digestive	58.2	47.2	0.81	(0.39, 1.7)
Genital/Urinary	164.5	215.6	1.3	(0.93, 1.9)
Musculoskeletal	171.1	289.8	**1.7**	**(1.3, 2.3)**
Integument	20.7	*	0.98	(0.32, 3.0)
Chromosomal	22.4	*	0.60	(0.15, 2.4)
Other/Unspecified	43.7	60.6	1.4	(0.72, 2.7)

†Rates are per 10,000 live births

*Indicates less than 5 cases

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Discussion

- The linkage between MBDR and NBS identified a few reporting issues between the NBS Follow-up Program and the MBDR.

- Infants with sickle cell trait may have increased risk of having additional birth defects. Further analyses are needed.

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Future Directions

- Conclude the chart reviews and use the findings to correct the information captured in both files.
- Conduct more analyses and control for additional factors such as maternal age, prematurity, and birth weight.
- Expand validation between MBDR and NBS to other disorders on the NBS panel.
- Use the findings to improve the MBDR reporting.

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Public Health Implications

- Through identification of missing and misclassified cases, the MBDR-NBS linkage can help improve program efforts in reporting and follow-up processes.

- Additional research is needed to expand knowledge of birth defects associated with SCD and SCT and may have implications for future studies.

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Thank You!

- Any Questions/Comments?
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