

Baseline microcephaly prevalence in rural Guatemala: implications for neonatal screening for congenital Zika virus infection

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Disclosures




- Nothing to Disclose



CONGENITAL MICROCEPHALY



- Disturbance in early brain development
 - Etiologies: Infection, malnutrition, genetic or metabolic disorder, iatrogenic, stroke, idiopathic
 - Definition before Zika: OFC < -3 SD below growth curve
 - 3.30 cases per 10,000 live-births in Latin America prior to Zika epidemic
 - Increased incidence was early sign of Zika epidemic
 - Integral to neonatal screening programs for congenital Zika infection
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MICROCEPHALY CASE DEFINITION




Origin of Case Definition	Microcephaly Case Definition	OFC Cut-Offs (cm)
Brazil's MOH November – December, 2015	Term: $\leq 33\text{cm}$ Preterm: $\leq 3^{\text{rd}}$ %ile Fenton GC	M ≤ 33.0 F ≤ 33.0 Varies by GA & gender
	December 2015 - March, 2016	Term: $\leq 32\text{cm}$ Preterm: $\leq 3^{\text{rd}}$ %ile Fenton GC
PAHO/WHO March – August, 2016	Term: < -2 SD WHO GC Preterm: < -2 SD Fenton GC	M < 31.9 F < 31.5 Varies by GA & gender
	Term: $< 3^{\text{rd}}$ %ile WHO GC Preterm: $< 3^{\text{rd}}$ %ile Fenton GC	M < 32.0 F < 31.6 Varies by GA & gender
WHO – Known Gestational Age August 2016 - current	All: < -2 SD InterGrowth-21 GC	Varies by GA & gender
	All: $< 3^{\text{rd}}$ %ile InterGrowth-21 GC	Varies by GA & gender
WHO – Unknown Gestational Age August 2016 - current	Term: < -2 SD WHO GC	M < 31.9 F < 31.5
	Term: $< 3^{\text{rd}}$ %ile WHO GC	M < 32.0 F < 31.6
	Term: < -3 SD WHO GC	M < 30.7 F < 30.3

MOH: Ministry of Health; PAHO: Pan-American Health Organization; WHO: World Health Organization; OFC: occipital frontal head circumference; GA: gestational age; GC: growth curve; SD: standard deviation




DEFINITION LIMITATIONS



- Limited comparability to pre-Zika microcephaly prevalence
 - Impacts attributable fraction & pre-test probability
 - Unknown gestational age not fully addressed
 - Common in LMIC
 - Guatemala: ~25% of women have no prenatal care
 - WHO guidelines
 - High false positive rate
 - Do not address preterm infants
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OBJECTIVES



- Use different microcephaly case definitions to estimate microcephaly background prevalence in rural Guatemala in a neonatal population of unknown gestational age born primarily before potential Zika virus exposure
 - Propose a new case definition for microcephaly to address infants of unknown gestational age
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METHODS



- Retrospective review of baseline OFCs for infants 0-13 days
 - Enrolled in Creciendo Sanos community health program in rural Southwest Guatemala
 - Born August 1, 2014 to March 31, 2016
 - Anthropometry (OFC, weight, length) prospectively collected by trained community health workers at home visits
 - OFC to nearest 0.1cm (measured at least twice, recorded highest number, used flexible tape measures)
 - Length to nearest 0.1 cm (Seca measuring board for infants)
 - Weight to nearest 0.1 kg (Salter-Brecknell hanging scale)
 - Zika virus was first identified in this area in April 2015
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ESTIMATED GESTATIONAL AGE



- Gestational age by ultrasound or LMP not reliably available
- Two methods for estimating gestational age:
 - *All infants assumed term (≥ 37 weeks gestational age)*
 - Majority home births, no clinical interventions, living at time of enrollment
 - *All infants given estimated gestational age by centering height at a Z-score of zero on gender-adjusted Fenton growth curves*
 - Percentiles and Z-scores for OFC and weight then obtained

Data Entry Cells - Boys					
					(Enter up)
	Gest Age or		Weight	Length	HC
	Postmenstrual Age	Day: 0-6	22.5-50 wks	23.5-50 wks	23.5-50 wks
ID			grams	cm	cm
	38	5	2900	50.0	31.5
	39	2	3600	50.5	34.7
	36	5	3300	48.0	36.0

Calculated Cells - Boys						
z-scores				Percentiles		
SGA, AGA or LGA by weight**	Weight Z	Length Z	Head circumference Z	Weight %	Length %	Head circumference %
AGA	-0.9	0.0	-2.0	18%	51%	2%
AGA	0.4	0.0	0.0	65%	50%	51%
AGA	0.9	0.0	1.9	82%	51%	97%



NEW CASE DEFINITIONS



	Case Definition	OFC Cut-Offs
Fenton for Unknown Gestational Age	All: <-2 SD Fenton GC	Varies by GA & gender
	All: <3 rd %ile Fenton GC	
	All: <-3 SD Fenton GC	



DESCRIPTIVE CHARACTERISTICS

Characteristic	No (%) (n=296)
Gender	
Male	143 (48.3)
Female	153 (51.7)
Birth Year	
2014	20 (6.8)
2015	214 (72.3)
2016	62 (20.9)
Age	
0-6 days	257 (86.8)
7-13 days	39 (13.2)
Weight, g	
1500<2000	2 (0.7)
2000<2500	8 (2.7)
2500<3000	78 (26.4)
≥3000	208 (70.3)
Length, cm	
40<45	4 (1.4)
45<50	139 (47.0)
≥50	153 (51.7)
OFC, cm	
≤30	7 (2.4)
>30≤31	17 (5.7)
>31≤32	48 (16.2)
>32≤33	91 (30.7)
>33	133 (44.9)

- Median estimated GA:
 - 38w5d [32w5d- 44w3d]
- Mean OFC measurement:
 - Male: 33.5cm [30-37cm]
 - Female: 32.9cm [29.5-36.4cm]
- Mean OFC Z-score:
 - -0.68 (^{95%}CI:-0.78 to-0.58)

ESTIMATED MICROCEPHALY




	Origin of Case Definition	Microcephaly Case Definition	Identified Microcephaly No (%)	Microcephaly Background Prevalence per 10,000 Live-Births
Microcephaly	WHO – Unknown Gestational Age	All: <-2 SD WHO GC	36 (12.2)	1,216
		All: <3 rd %ile WHO GC	43 (14.5)	1,453
	Fenton – Unknown Gestational Age	All: <-2 SD Fenton GC	13 (4.4)	439
		All: <3 rd %ile Fenton GC	20 (6.8)	676
Severe Microcephaly	WHO - Unknown Gestational Age	All: <-3 SD WHO GC	9 (3.0)	304
	Fenton – Unknown Gestational Age	All: <-3 SD Fenton GC	1 (0.3)	34




LIMITATIONS



- Definitive gestational age not known
 - Cannot obtain sensitivity/specificity
 - Uncertainty in estimates
 - Population at risk of Zika virus exposure
 - Fenton growth curves
 - Based on children in developed countries
 - Used to assess post-natal growth of preterm infants
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CONCLUSIONS



- Background microcephaly in this community is high
 - Microcephaly: 439 -1,453 per 10,000 live-births
 - Severe Microcephaly: 34 -304 per 10,000 live-births
 - Why?
 - Changes to case definition
 - Under-reporting/Under-recognition
 - Population specific factors
 - Inaccurate measurements
 - Fenton growth curves standardize approach to unknown gestational age
 - May limit false positives compared to WHO
 - Identifies asymmetric growth restriction
 - Can use in infants beyond 24 hours of life
 - InterGrowth-21 growth curves may be other option
 - 22% of infant heights exceeded available late-preterm/term growth curves
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IMPLICATIONS OF HIGH BACKGROUND PREVLANCE



Congenital Zika virus infection screening programs

- Microcephaly as initial screening: High false positives
 - Over-utilization of scarce resources in LMICs
 - Delays in care to children who truly need it
 - Unnecessary emotional and financial burden to families
- Step-wise approach to screening important



Collaborators

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Questions?



COMPARING GROWTH CURVES



Growth Curve	Derived Population	Growth Standard Ages	Interval Cut-offs
WHO	Term infants HIC & LMIC	Term (37 to <42 weeks) to 59 months	Single for birth, then weekly
Fenton	Pre-term infants in HIC	24 to <50 weeks GA	Gestational day
InterGrowth-21	Term & Pre- term infants in LMIC & HIC	Late pre-term to term: 33 to <43 weeks GA Preterm: 27 to <65 weeks GA	Gestational day Gestational week



ESTIMATED MICROCEPHALY



Origin of Case Definition	Microcephaly Case Definition	Identified Microcephaly No (%)	Microcephaly Background Prevalence per 10,000 Live-Births
Brazil's MOH November – December, 2015	Term: $\leq 33\text{cm}$ Preterm: $\leq 3^{\text{rd}}$ %ile Fenton GC	125 (42.2)	4,223
	December 2015 - March, 2016	Term: $\leq 32\text{cm}$ Preterm: $\leq 3^{\text{rd}}$ %ile Fenton GC	48 (16.2)
PAHO/WHO March – August, 2016	Term: < -2 SD WHO GC Preterm: < -2 SD Fenton GC	15 (5.1)	507
	Term: $< 3^{\text{rd}}$ %ile WHO GC Preterm: $< 3^{\text{rd}}$ %ile Fenton GC	20 (6.8)	676
WHO – Unknown Gestational Age August 2016 - current	All: < -2 SD WHO GC	36 (12.2)	1,216
	All: $< 3^{\text{rd}}$ %ile WHO GC	43 (14.5)	1,453
	All: < -3 SD WHO GC	9 (3.0)	304
Fenton – Unknown Gestational Age	All: < -2 SD Fenton GC	13 (4.4)	439
	All: $< 3^{\text{rd}}$ %ile Fenton GC	20 (6.8)	676
	All: < -3 SD Fenton GC	1 (0.3)	34

COMPARING DEFINITIONS



	Fenton GC <-2 SD No (%) (n=13)	Fenton GC <3 rd percentile No (%) (n=20)
Brazil MOH ≤33cm	13 (100.0)	20 (100.0)
Brazil MOH ≤32cm	11 (84.6)	18 (90.0)
PAHO/WHO <-2 SD	5 (38.5)	11 (55.0)
PAHO/WHO <3 rd %ile	6 (46.2)	12 (60.0)
WHO <-2 SD	6 (46.2)	12 (60.0)
WHO <3 rd %ile	7 (53.8)	13 (65.0)
Identified on All Case Definitions	5 (38.5)	11 (55.0)



MICROCEPHALY ASSOCIATIONS



Outcome: Microcephaly defined as <3rd percentile on Fenton growth curve

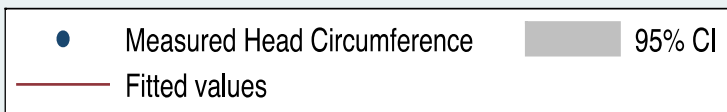
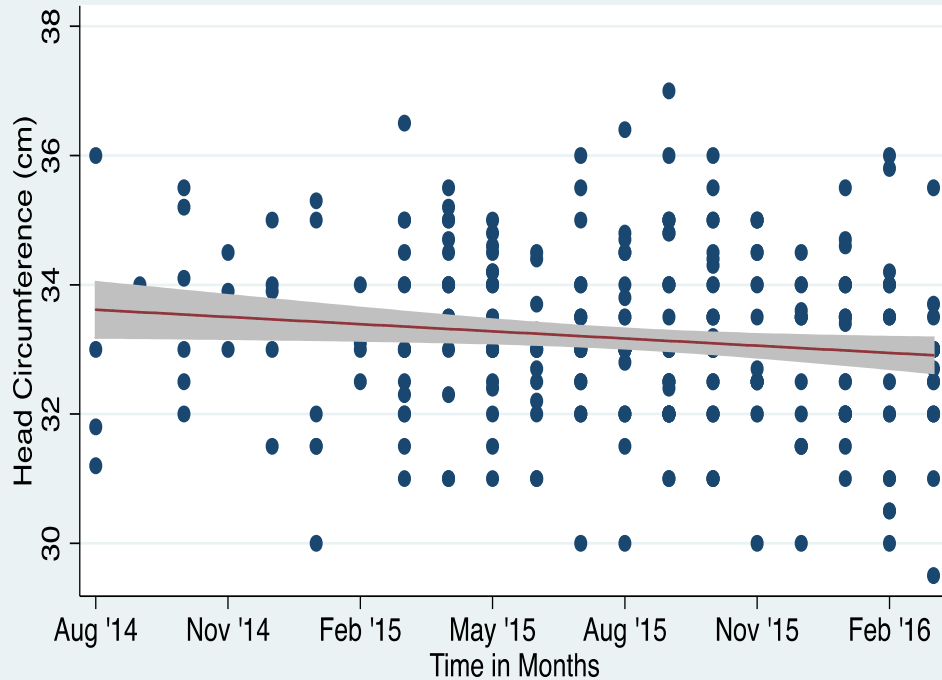
	Prevalence Ratio	95% CI	P-Value
Weight <-1 SD	3.77	1.6-8.8	0.002
Small for Gestational Age (<10 th ile)	4.68	1.8-12.3	0.002
Accounting for Time			
Pre-Post May 1, 2015	0.65	0.3-2.6	0.368
Pre-Post December 1, 2015	0.64	0.2-1.9	0.414
Birthdate	0.998	0.995-1.001	0.249



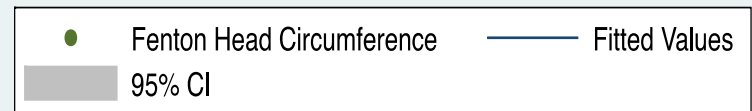
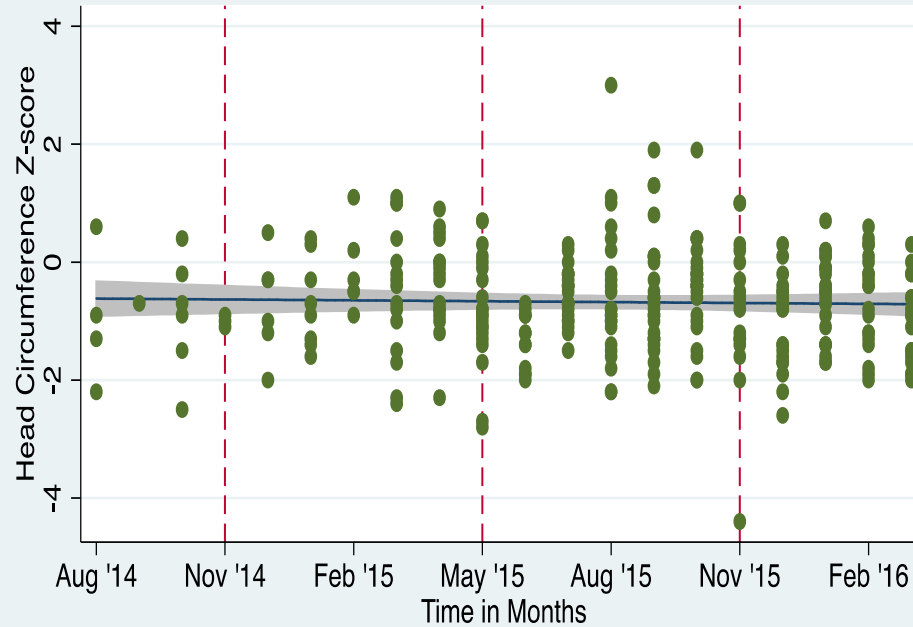
OFC ASSOCIATIONS



Head Circumference Over Time



Head Circumference Z-Score Over Time



Wet (May-Oct) and dry (Nov-Apr) seasons indicated by vertical red lines