Longitudinal analysis of Head Circumference Growth Among Infants with Congenital Zika Virus Exposure

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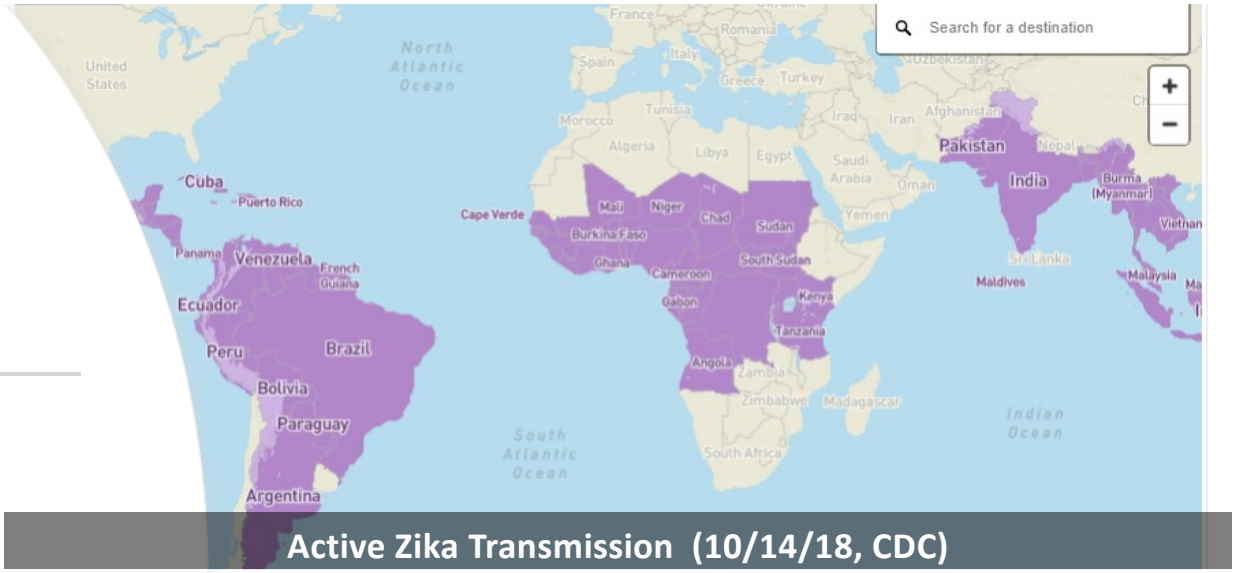
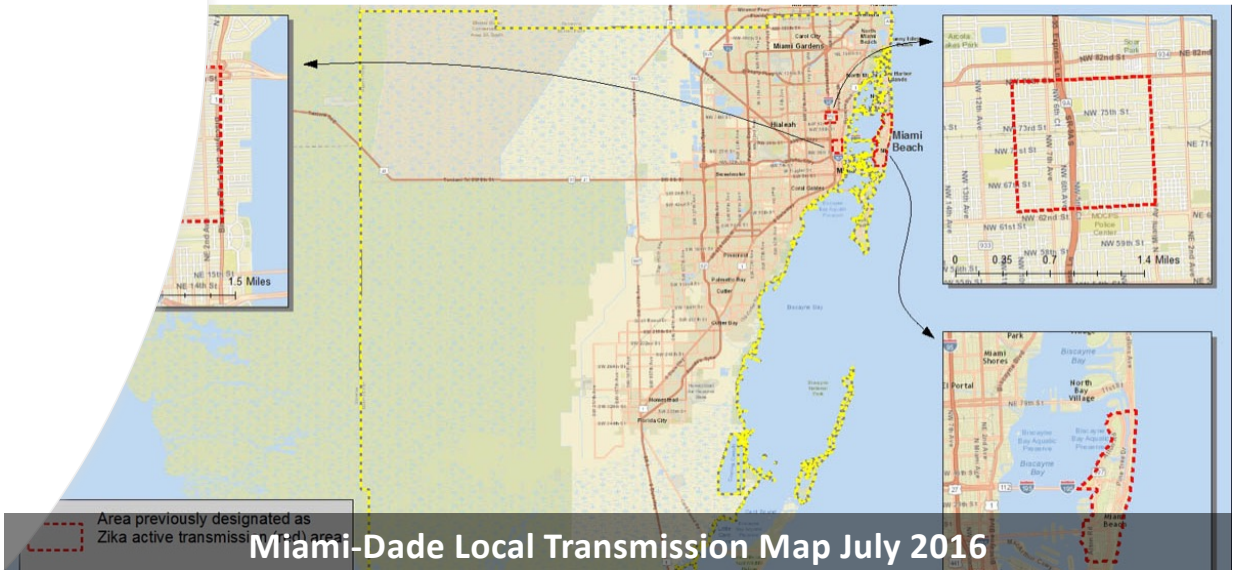
Zika Virus

- Zika virus is a single-stranded RNA flavivirus, closely related to Dengue virus
- 1947- Discovered in a rhesus monkey in the Zika forest of Uganda
- 1952- First human case of Zika virus in Uganda
- 2007- First large Zika outbreak in the Pacific Island of Yap
- Transmission
  - Bite of an infected Aedes aegypti mosquito
  - Sexually
  - Mother to Child
  - Blood Transfusions



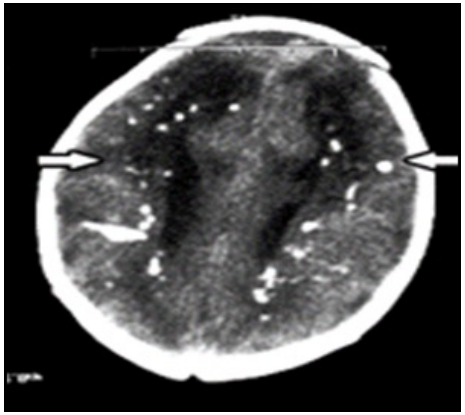
Active Zika Transmission (10/14/18, CDC)



Miami-Dade Local Transmission Map July 2016

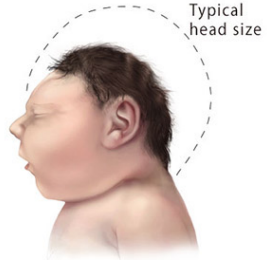
Zika Virus & Pregnancy

- Discovery of Zika Associated Birth Defects
  - January 2016- Researchers in Brazil report the first confirmed diagnosis of in-utero Zika virus transmission among 2 infants with microcephaly
  - January 2016- CDC issues travel notice advising against pregnant women from traveling to areas with Zika virus transmission
  - February 2016- Florida Governor declared a public health emergency
  - January 2017- Data collection begins for the Florida Zika Pregnancy and Infant Registry (FZPIR)
- Zika Associated Birth Defects
  - Microcephaly at birth
  - Brain abnormalities- intracranial calcifications, abnormal cortical gyral patterns, ventriculomegaly
  - Structural eye abnormalities- microphthalmia, coloboma, cataracts, intraocular calcifications
  - Developmental delays
  - Congenital contractures and joint abnormalities



Baby with Typical Head Size

Baby with Microcephaly



Baby with
Severe Microcephaly

FL Zika Pregnancy and Infant Registry (ZPIR) Surveillance Process

CHD Epidemiologist and Pregnancy Registry Coordinator

- Identify cases
- Lead investigation and record collection

MERLIN entry

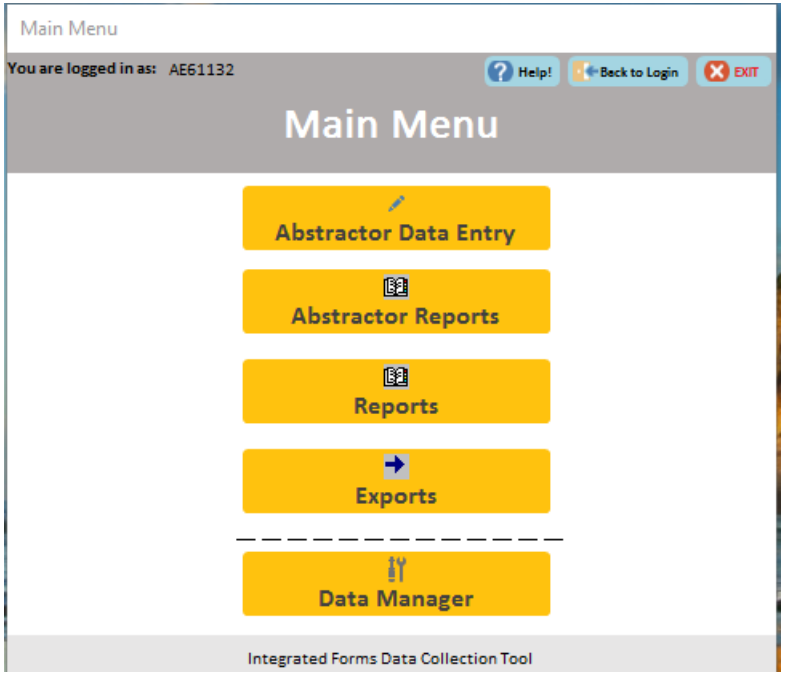
Florida DOH Bureau of Epidemiology

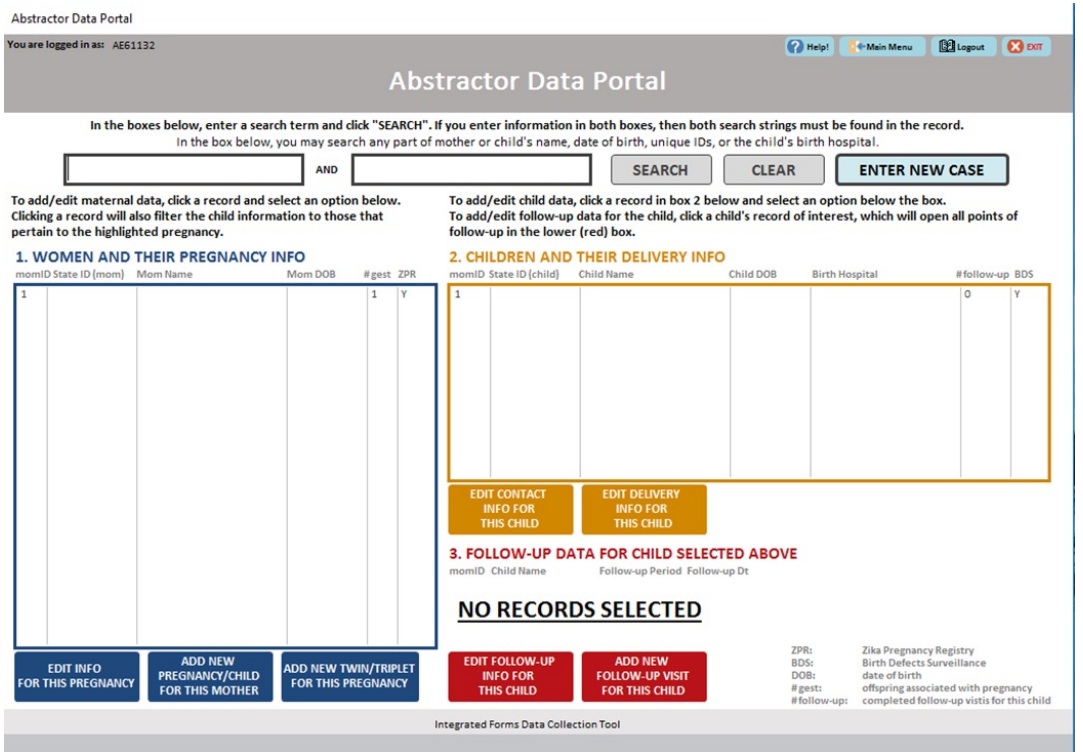
- Case Review
- Final ZPIR Case List Determination

Florida Birth Defects Registry

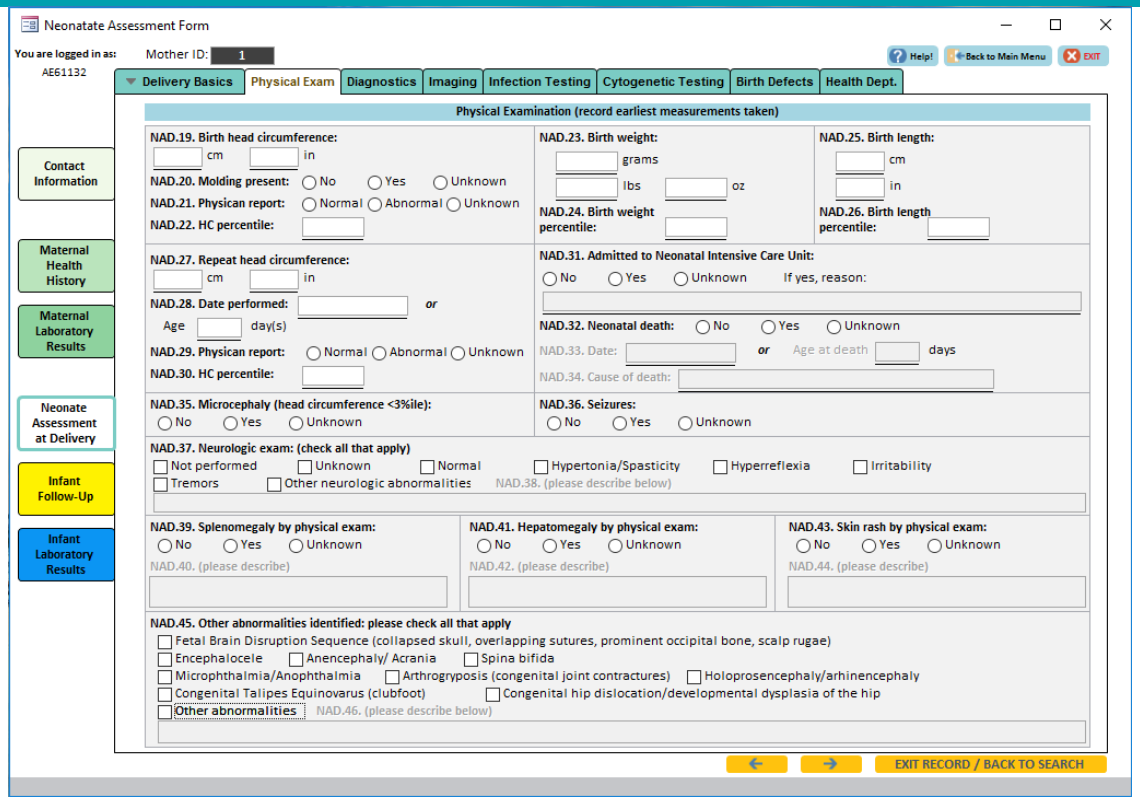
- Abstraction of ZPIR prenatal, birth, 2,6,12,18,24 month records
- Reporting to CDC

Zika Related Birth Defects Database





Data Collection



Study Sample

Florida Zika Pregnancy and Infant Registry (FZPIR)

- Conducts surveillance of all pregnancies with lab evidence of confirmed or probable Zika virus infection (N=535)
- Collect prenatal, birth, and pediatrician visits for 2,6,12,18 and 24 months

Study sample: live births in Florida between 1/1/16-3/31/18

- Inclusion Criteria: baseline HC measure (birth) and at least 1 follow-up measure
- N=319

Analysis Overview

Descriptive statistics

Spaghetti Plots & Time Plots

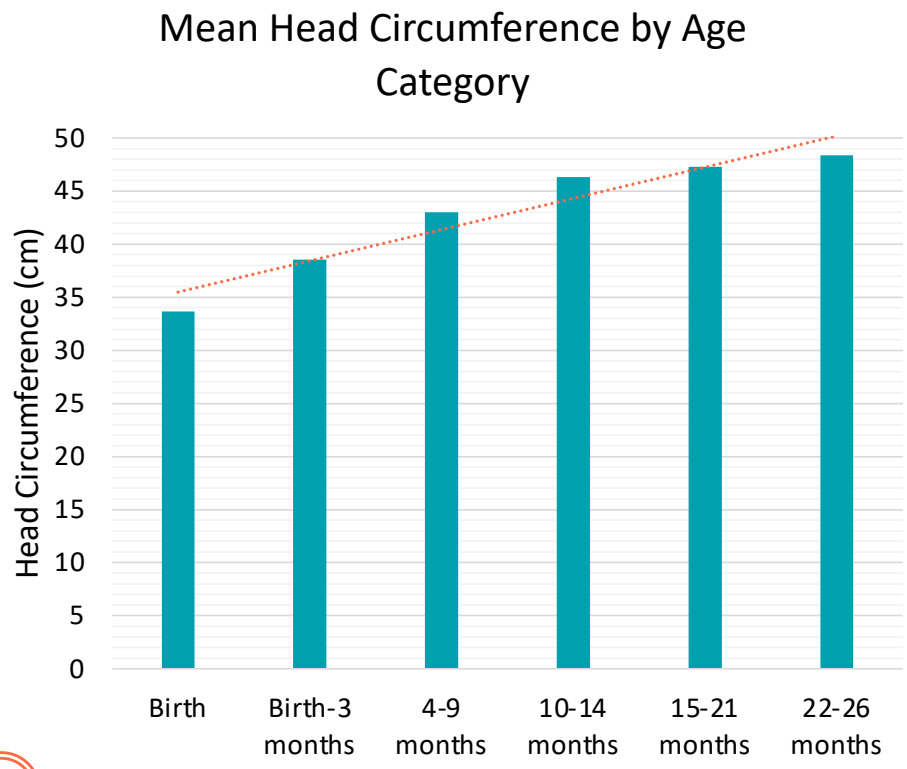
Linear mixed methods approach

1. Mean Structures
2. Variance Structures
3. Mean Parameters
4. Random Variables
5. Influential Data Points

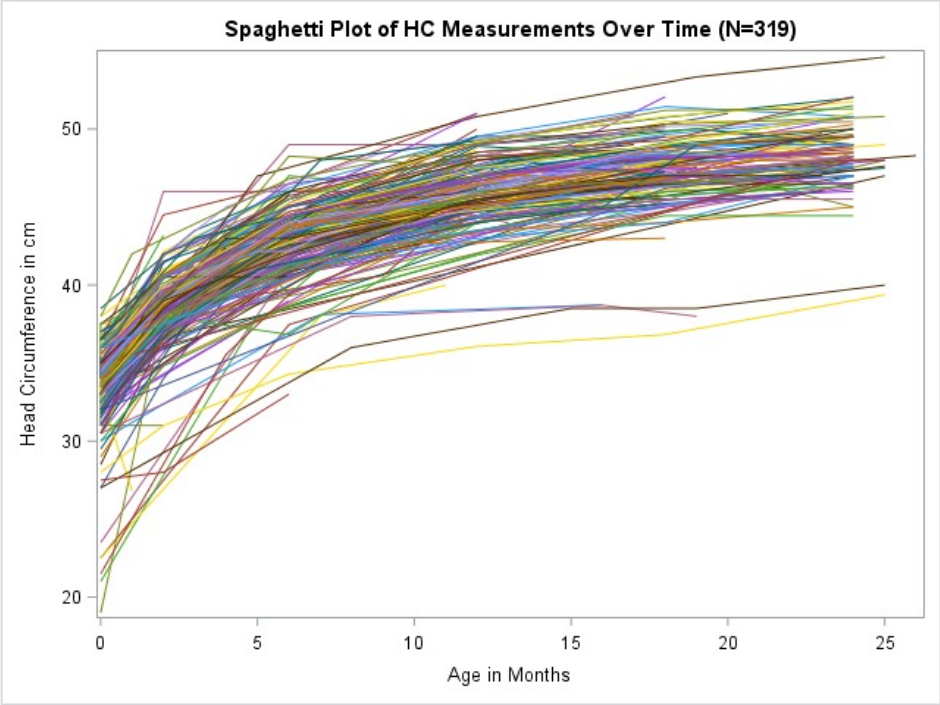
Sample Characteristics (N=319)

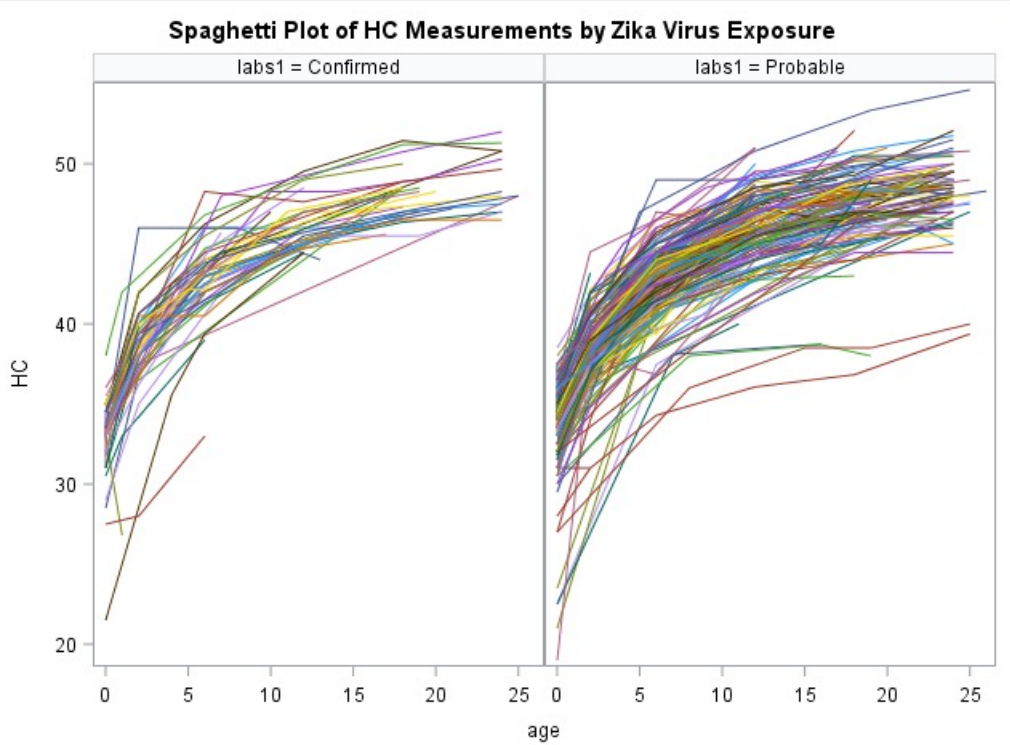
Characteristic	N (%)
Zika Lab Results	
Confirmed	50 (15.7)
Probable	269 (84.3)
Exposure Location	
Florida	27 (8.5)
Travel Related	239 (74.9)
Undetermined	53 (16.6)
Sex	
Male	173 (54.2)
Female	146 (45.8)
Gestational Age (weeks)*	38.3 (23-41)

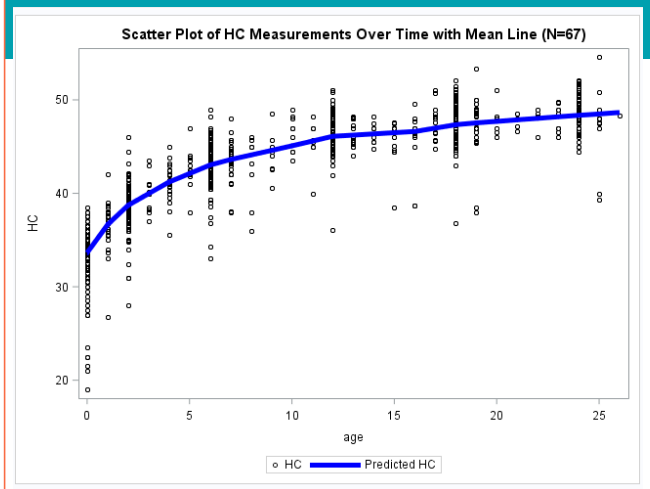
*Mean (min-max)

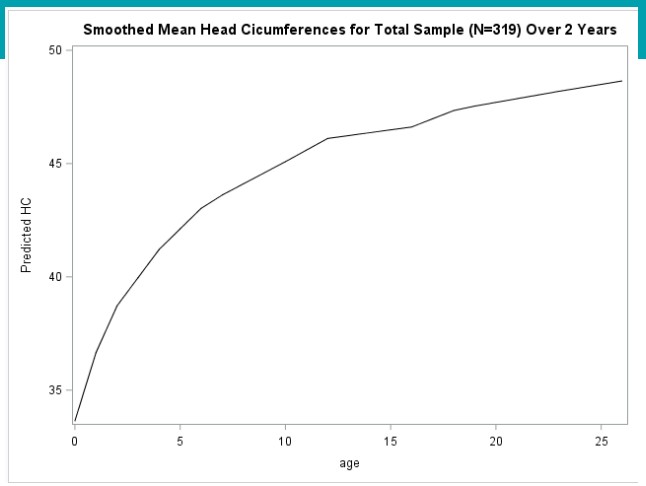


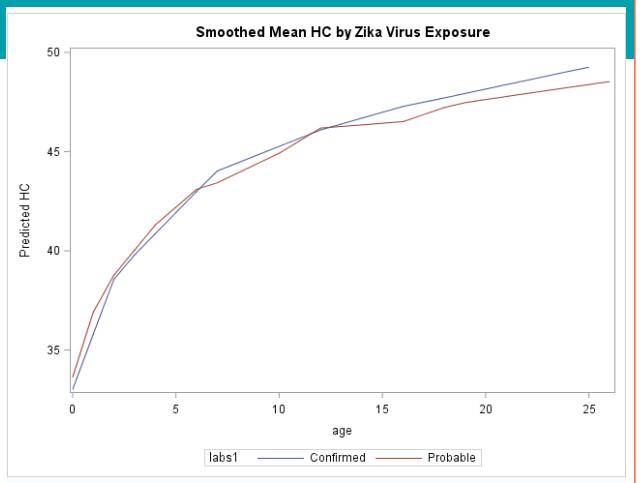
Spaghetti Plots





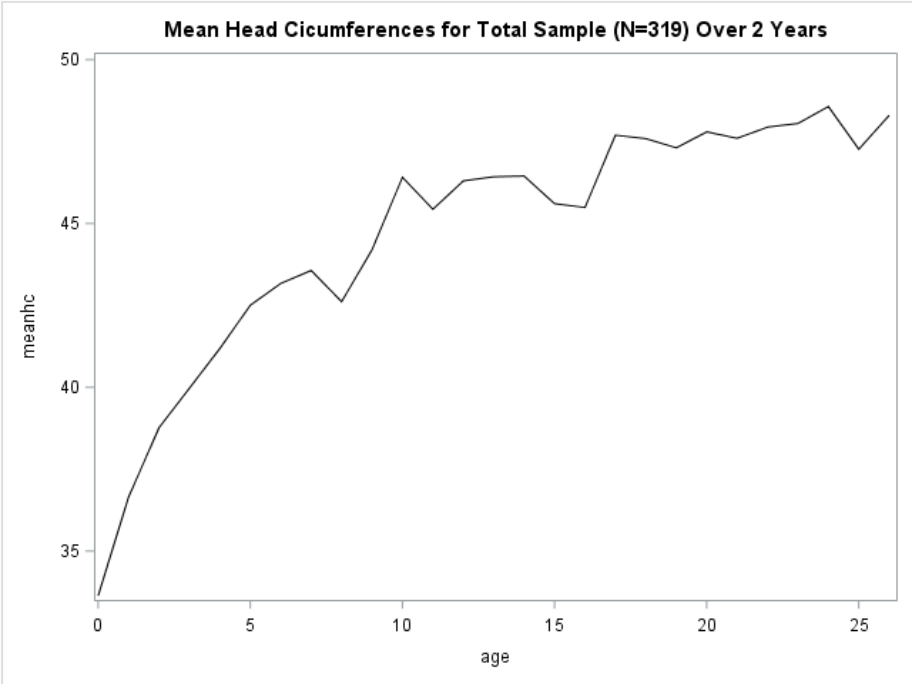


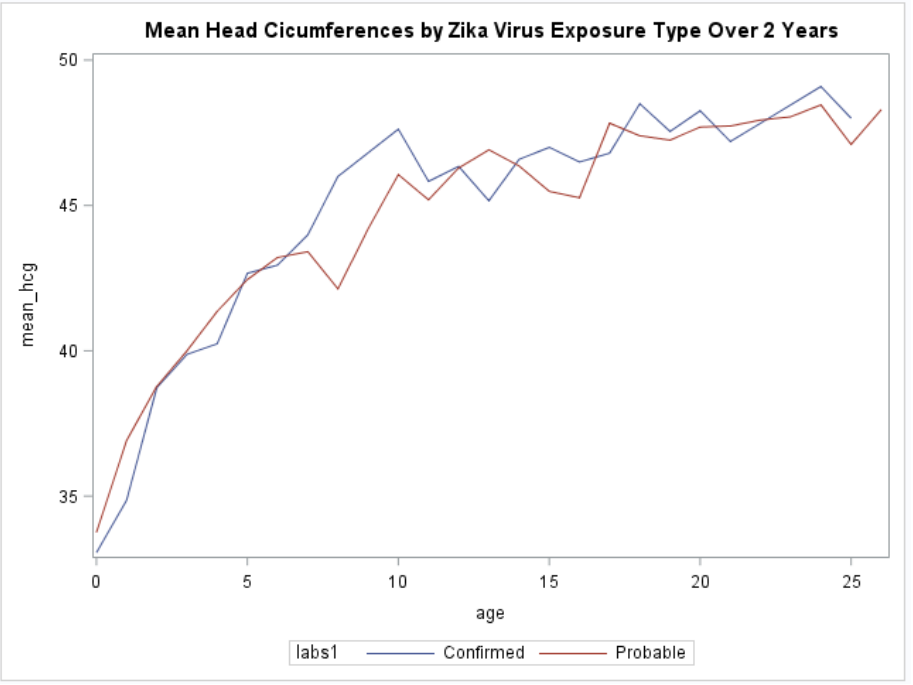




Smoothed means

Un-smoothed means





Model Selection- Step 1 and 2

model HC = age labs
random intercept/ type=UN

Mean Structure		
	AIC	BIC
Linear Age	6676.3	6695.1
Categorical Age	**5235.9**	**5269.8**
Age*Age	5662.3	5684.9

model HC = agecat labs
random intercept/ type=UN

Variance Structure			
	AIC	BIC	Residual Variance
Random Intercept Only	5237.0	5244.6	1.9385
Random Slope Only (age)	5676.3	5683.8	3.6539
Random Intercept and Slope	**5216.1**	**5231.2**	**1.6621**

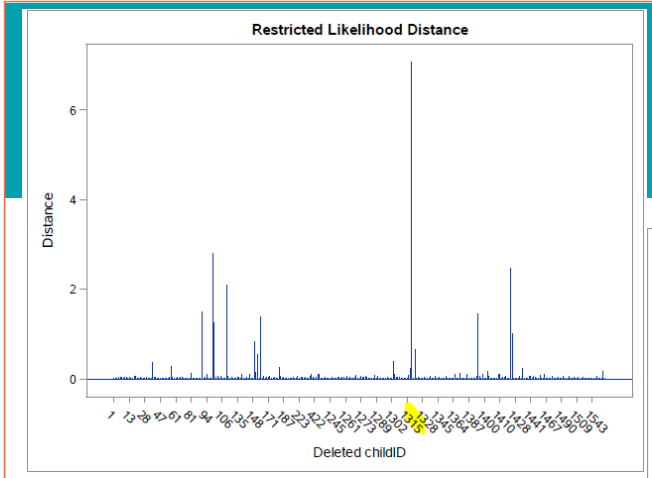
Model Selection- Mean Parameters (Step 3)

	AIC	BIC	Residual Variance	Covariate P-values
Full Model: Age, labs, gestational age, sex, exposure location	5117.4	5173.9	1.6734	Labs: 0.4750 Gestational age: <.0001 Sex M vs. F: <.0001 Exposure- Imported: 0.0332 Undetermined: 0.0321
Reduced Model 1: Age, gestational age, sex, exposure location	**5115.9**	**5168.6**	**1.6735**	**Gestational age: <.0001** **Sex M vs. F: <.0001** **Exposure- Imported: 0.0266** **Undetermined: 0.0252**
Reduced Model 2: Age, labs, gestational age, sex	5118.5	5167.5	1.6716	Labs: 0.3264 Gestational age: <.0001 Sex M vs. F: <.0001
Interaction Model: Age, labs, gestational age, sex, exposure location, age*exposure location	5116.5	5210.6	1.6412	Labs: 0.4851 Gestational age: <.0001 Sex M vs. F: <.0001 Exposure- Imported: 0.008 Undetermined: <.0001 5 interaction terms significant

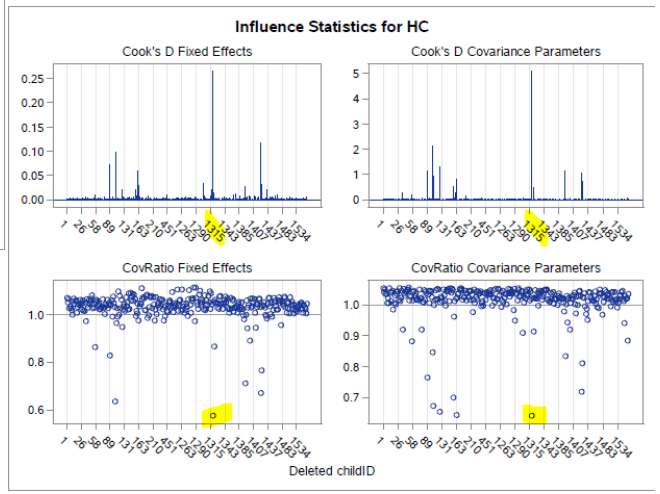
Model Selection- Final Random Effect Variables (Step 4)

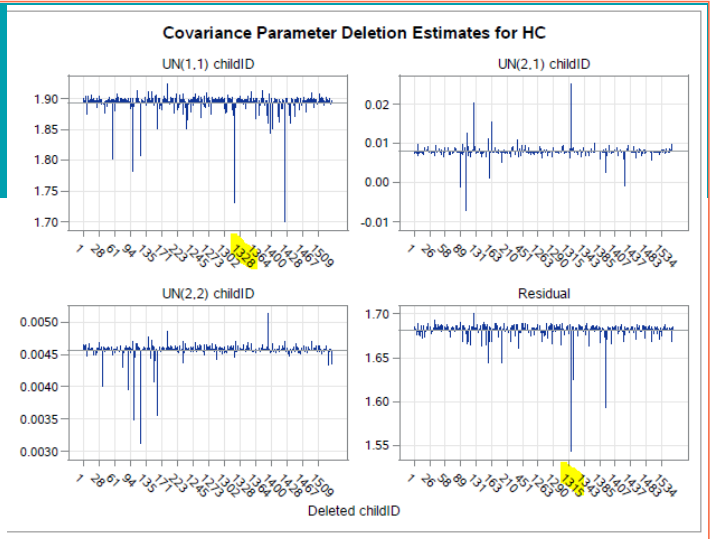
- Reduced Model 1
- model HC = agecat ga sex exp/ s;

	AIC	BIC	Residual Variance
Random Intercept Only	5152.8	5160.3	1.9379
Random Slope Only (age)	5415.0	5422.5	2.8889
Random Intercept and Slope	**5118.4**	**5133.4**	**1.6811**



PRESS statistic: 228.79
Cook's D: 0.26497
COVRATIO: 0.6405
COVTRACE: 0.3304





HC	agecat	exp1	ga1	sex1
19	1	Local	41	2
38	2	Local	41	2
46	4	Local	41	2
.	5	Local	41	2
.	3	Local	41	2
.	3	Local	41	2

1314	1.29772	0.0176
1315	1.29539	0.0180
1317	1.29915	0.0797
1319	1.29936	0.2310
1320	1.24232	7.0789
1321	1.29810	0.0158
1322	1.27464	0.6464

Influential Data Points (Step 5)

Final Model

HC= Age, gestational age, sex, exposure location

Estimated G Matrix

Row	Effect	Subject	Col1	Col2
1	Intercept	1	1.8926	0.007881
2	age	1	0.007881	0.004564

Estimated G Correlation Matrix

Row	Effect	Subject	Col1	Col2
1	Intercept	1	1.0000	0.08480
2	age	1	0.08480	1.0000

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	childID	1.8926
UN(2,1)	childID	0.007881
UN(2,2)	childID	0.004564
Residual		1.6811

Estimated V Matrix for Subject 1

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	3.5737	1.9083	1.9399	1.9872	2.0344	2.0817
2	1.9083	3.6234	2.0104	2.1125	2.2145	2.3166
3	1.9399	2.0104	3.8325	2.3630	2.5746	2.7862
4	1.9872	2.1125	2.3630	4.4200	3.1148	3.4907
5	2.0344	2.2145	2.5746	3.1148	5.3361	4.1952
6	2.0817	2.3166	2.7862	3.4907	4.1952	6.5808

Estimated V Correlation Matrix for Subject 1

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	1.0000	0.5303	0.5242	0.5000	0.4659	0.4293
2	0.5303	1.0000	0.5395	0.5279	0.5036	0.4744
3	0.5242	0.5395	1.0000	0.5741	0.5693	0.5548
4	0.5000	0.5279	0.5741	1.0000	0.6414	0.6472
5	0.4659	0.5036	0.5693	0.6414	1.0000	0.7080
6	0.4293	0.4744	0.5548	0.6472	0.7080	1.0000

Solution for Fixed Effects

Effect	exp1	sex	agecat	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				17.7459	1.4609	314	12.15	<.0001
agecat			1-3 months	4.7747	0.1087	673	43.93	<.0001
agecat			10-14 months	12.4591	0.1319	673	94.47	<.0001
agecat			15-21 months	13.7330	0.1548	673	88.72	<.0001
agecat			22-26 months	14.7630	0.2067	673	71.44	<.0001
agecat			4-9 months	9.3886	0.1141	673	82.27	<.0001
agecat			Birth	0	.	.	.	.
ga1				0.4053	0.03795	673	10.68	<.0001
sex		Female		-0.7189	0.1795	673	-4.00	<.0001
sex		Male		0	.	.	.	.
exp1	Imported			0.7152	0.3246	673	2.20	0.0279
exp1	Undeterm			0.8425	0.3784	673	2.23	0.0263
exp1	Local			0	.	.	.	.

Final Model- Variance

- Estimated variance of random intercepts: 1.8926
- Estimated variance of random slope: 0.004564
- Estimated covariance of intercept and slope: 0.007881

Covariance Parameter Estimates		
Cov Parm	Subject	Estimate
UN(1,1)	childID	1.8926
UN(2,1)	childID	0.007881
UN(2,2)	childID	0.004564
Residual		1.6811

Estimated V Matrix for childID 1						
Row	Col1	Col2	Col3	Col4	Col5	Col6
1	3.5737	1.9083	1.9399	1.9872	2.0344	2.0817
2	1.9083	3.6234	2.0104	2.1125	2.2145	2.3166
3	1.9399	2.0104	3.8325	2.3630	2.5746	2.7862
4	1.9872	2.1125	2.3630	4.4200	3.1148	3.4907
5	2.0344	2.2145	2.5746	3.1148	5.3361	4.1952
6	2.0817	2.3166	2.7862	3.4907	4.1952	6.5808

Estimated G Correlation Matrix				
Row	Effect	childID	Col1	Col2
1	Intercept	1	1.0000	0.08480
2	age	1	0.08480	1.0000

Estimated V Correlation Matrix for childID 1						
Row	Col1	Col2	Col3	Col4	Col5	Col6
1	1.0000	0.5303	0.5242	0.5000	0.4659	0.4293
2	0.5303	1.0000	0.5395	0.5279	0.5036	0.4744
3	0.5242	0.5395	1.0000	0.5741	0.5693	0.5548
4	0.5000	0.5279	0.5741	1.0000	0.6414	0.6472
5	0.4659	0.5036	0.5693	0.6414	1.0000	0.7080
6	0.4293	0.4744	0.5548	0.6472	0.7080	1.0000

Final Model- Correlation

- Estimated correlation between random intercept and slope: 0.08480

Final Model- Inferences

- Compared to birth, HC significantly increases at each age category
- Significant associations between sex and gestational age with HC
- **When controlling for age, gestational age, and sex, exposure location had a significant impact on HC**

Solution for Fixed Effects

Effect	exp1	sex	agecat	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept				17.7459	1.4609	314	12.15	<.0001
agecat			1-3 months	4.7747	0.1087	673	43.93	<.0001
agecat			10-14 months	12.4591	0.1319	673	94.47	<.0001
agecat			15-21 months	13.7330	0.1548	673	88.72	<.0001
agecat			22-26 months	14.7630	0.2067	673	71.44	<.0001
agecat			4-9 months	9.3886	0.1141	673	82.27	<.0001
agecat			Birth	0	.	.	.	.
ga1				0.4053	0.03795	673	10.68	<.0001
sex		Female		-0.7189	0.1795	673	-4.00	<.0001
sex		Male		0	.	.	.	.
exp1	Imported			0.7152	0.3246	673	2.20	0.0279
exp1	Undeterm			0.8425	0.3784	673	2.23	0.0263
exp1	Local			0	.	.	.	.

Conclusion

- Determined it's important to control for gestational age and gender when assessing HC growth
- Did not find a significant association between Zika exposure lab results (confirmed vs. probable) as hypothesized
- Found an association between location of Zika exposure and average HC that prompts some further investigation

References

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