

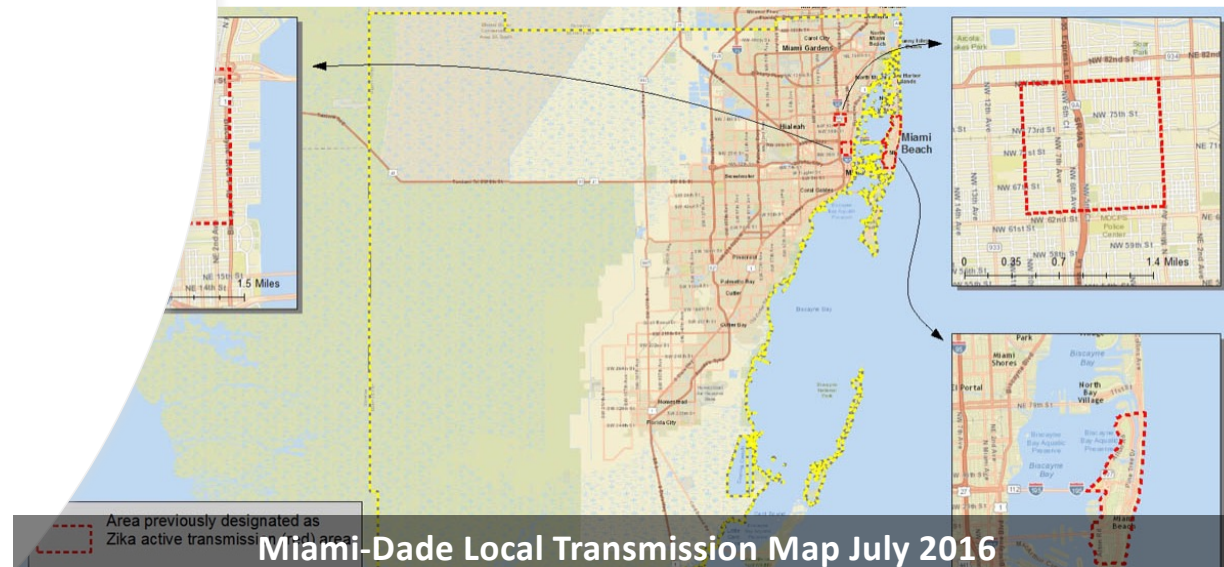
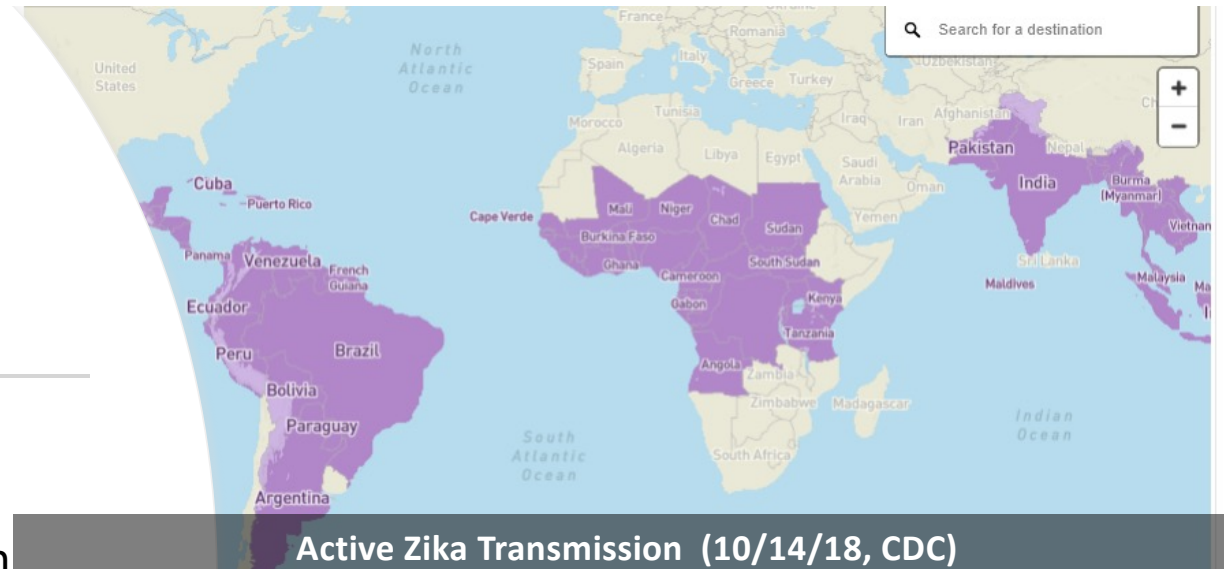
Longitudinal analysis of Head Circumference Growth Among Infants with Congenital Zika Virus Exposure



Amanda L. Elmore

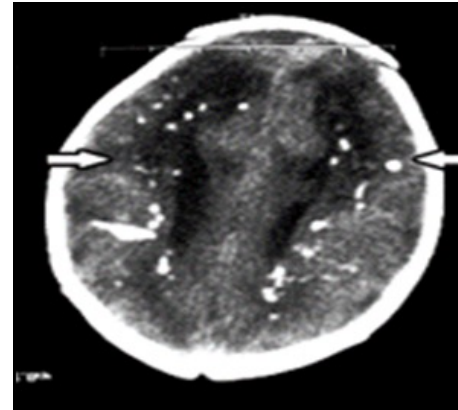
Zika Virus

- 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



Zika Virus & Pregnancy

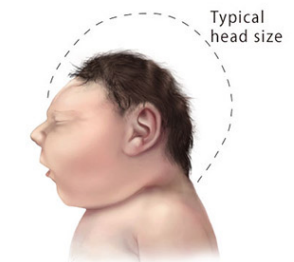
- Discovery of Zika Associated Birth Defects
 - January 2016- Researchers in Brazil report the first confirmed diagnosis of in-utero Zika virus transmission among 2 infants with microcephaly
 - January 2016- CDC issues travel notice advising against pregnant women from traveling to areas with Zika virus 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



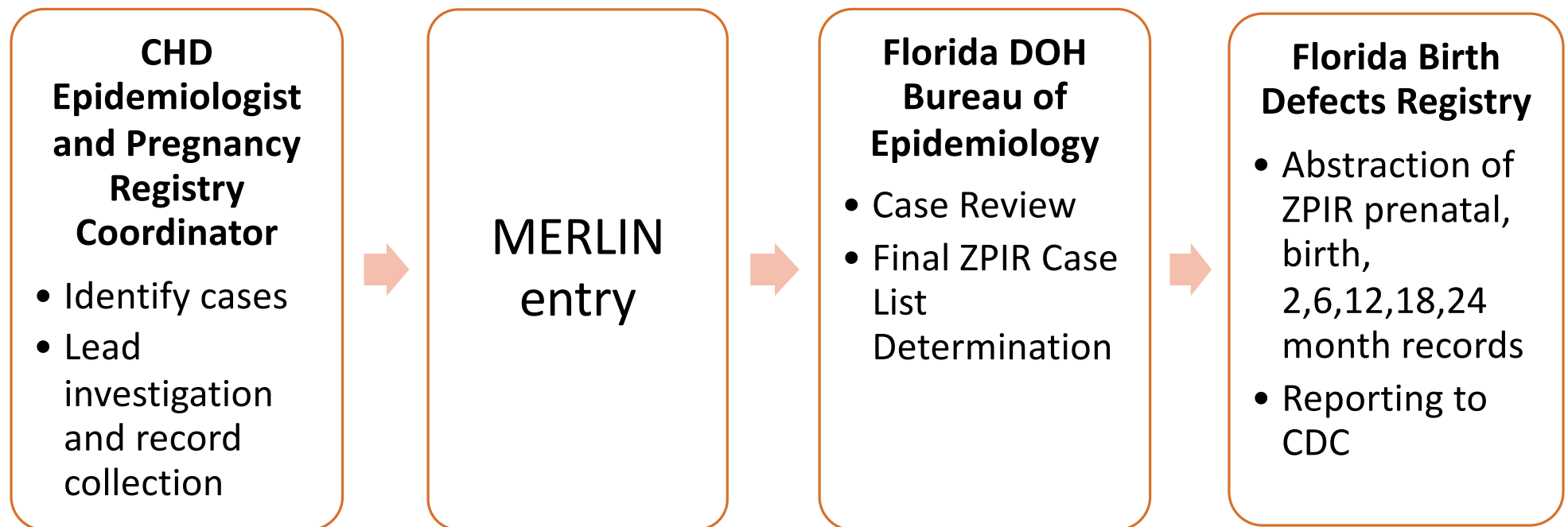
Baby with Microcephaly



Baby with Severe Microcephaly



FL Zika Pregnancy and Infant Registry (ZPIR) Surveillance Process



Zika Related Birth Defects Database

The screenshot displays the 'Main Menu' of the 'Integrated Forms Data Collection Tool'. At the top, a grey header bar contains the title 'Main Menu' and the user login information 'You are logged in as: AE61132'. To the right of the login text are three buttons: 'Help!' with a question mark icon, 'Back to Login' with a left-pointing arrow icon, and 'EXIT' with a red 'X' icon. Below the header, the main menu items are presented as yellow buttons with black text and icons. The items are: 'Abstractor Data Entry' (pencil icon), 'Abstractor Reports' (book icon), 'Reports' (book icon), 'Exports' (blue arrow icon), and 'Data Manager' (fork icon). A horizontal dashed line is positioned between the 'Exports' and 'Data Manager' buttons. The footer of the page is a grey bar with the text 'Integrated Forms Data Collection Tool'.

Abstractor Data Portal

You are logged in as: AEG1132

Help! Main Menu Logout EXIT

Abstractor Data Portal

In the boxes below, enter a search term and click "SEARCH". If you enter information in both boxes, then both search strings must be found in the record.
In the box below, you may search any part of mother or child's name, date of birth, unique IDs, or the child's birth hospital.

AND

SEARCH CLEAR ENTER NEW CASE

To add/edit maternal data, click a record and select an option below.
Clicking a record will also filter the child information to those that pertain to the highlighted pregnancy.

1. WOMEN AND THEIR PREGNANCY INFO

momID State ID (mom)	Mom Name	Mom DOB	# gest	ZPR
1			1	Y

EDIT INFO FOR THIS PREGNANCY ADD NEW PREGNANCY/CHILD FOR THIS MOTHER ADD NEW TWIN/TRIPLET FOR THIS PREGNANCY

To add/edit child data, click a record in box 2 below and select an option below the box.
To add/edit follow-up data for the child, click a child's record of interest, which will open all points of follow-up in the lower (red) box.

2. CHILDREN AND THEIR DELIVERY INFO

momID State ID (child)	Child Name	Child DOB	Birth Hospital	# follow-up BDS
1				0 Y

EDIT CONTACT INFO FOR THIS CHILD EDIT DELIVERY INFO FOR THIS CHILD

3. FOLLOW-UP DATA FOR CHILD SELECTED ABOVE

momID	Child Name	Follow-up Period	Follow-up Dt
-------	------------	------------------	--------------

NO RECORDS SELECTED

EDIT FOLLOW-UP INFO FOR THIS CHILD ADD NEW FOLLOW-UP VISIT FOR THIS CHILD

ZPR:
BDS:
DOB:
gest:
follow-up:

Zika Pregnancy Registry
Birth Defects Surveillance
date of birth
offspring associated with pregnancy
completed follow-up visits for this child

Integrated Forms Data Collection Tool

Data Collection

Neonate Assessment Form

You are logged in as: Mother ID: 1
AE61132

Help Back to Main Menu EXIT

Delivery Basics Physical Exam Diagnostics Imaging Infection Testing Cytogenetic Testing Birth Defects Health Dept.

Physical Examination (record earliest measurements taken)

NAD.19. Birth head circumference: cm in
 NAD.20. Molding present: ☐ No ☐ Yes ☐ Unknown
 NAD.21. Physican report: ☐ Normal ☐ Abnormal ☐ Unknown
 NAD.22. HC percentile:

NAD.23. Birth weight: grams lbs oz
 NAD.24. Birth weight percentile:

NAD.25. Birth length: cm in
 NAD.26. Birth length percentile:

NAD.27. Repeat head circumference: cm in
 NAD.28. Date performed: or Age day(s)
 NAD.29. Physican report: ☐ Normal ☐ Abnormal ☐ Unknown
 NAD.30. HC percentile:

NAD.31. Admitted to Neonatal Intensive Care Unit: ☐ No ☐ Yes ☐ Unknown If yes, reason:
 NAD.32. Neonatal death: ☐ No ☐ Yes ☐ Unknown
 NAD.33. Date: or Age at death days
 NAD.34. Cause of death:

NAD.35. Microcephaly (head circumference <3%ile): ☐ No ☐ Yes ☐ Unknown
 NAD.36. Seizures: ☐ No ☐ Yes ☐ Unknown

NAD.37. Neurologic exam: (check all that apply)
☐ Not performed ☐ Unknown ☐ Normal ☐ Hypertonia/Spasticity ☐ Hyperreflexia ☐ Irritability
☐ Tremors ☐ Other neurologic abnormalities NAD.38. (please describe below)

NAD.39. Splenomegaly by physical exam: ☐ No ☐ Yes ☐ Unknown
 NAD.40. (please describe)

NAD.41. Hepatomegaly by physical exam: ☐ No ☐ Yes ☐ Unknown
 NAD.42. (please describe)

NAD.43. Skin rash by physical exam: ☐ No ☐ Yes ☐ Unknown
 NAD.44. (please describe)

NAD.45. Other abnormalities identified: please check all that apply
☐ Fetal Brain Disruption Sequence (collapsed skull, overlapping sutures, prominent occipital bone, scalp rugae)
☐ Encephalocele ☐ Anencephaly/ Acrania ☐ Spina bifida
☐ Microphthalmia/Anophthalmia ☐ Arthrogryposis (congenital joint contractures) ☐ Holoprosencephaly/arhinencephaly
☐ Congenital Talipes Equinovarus (clubfoot) ☐ Congenital hip dislocation/developmental dysplasia of the hip
☐ Other abnormalities NAD.46. (please describe below)

EXIT RECORD / BACK TO SEARCH



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

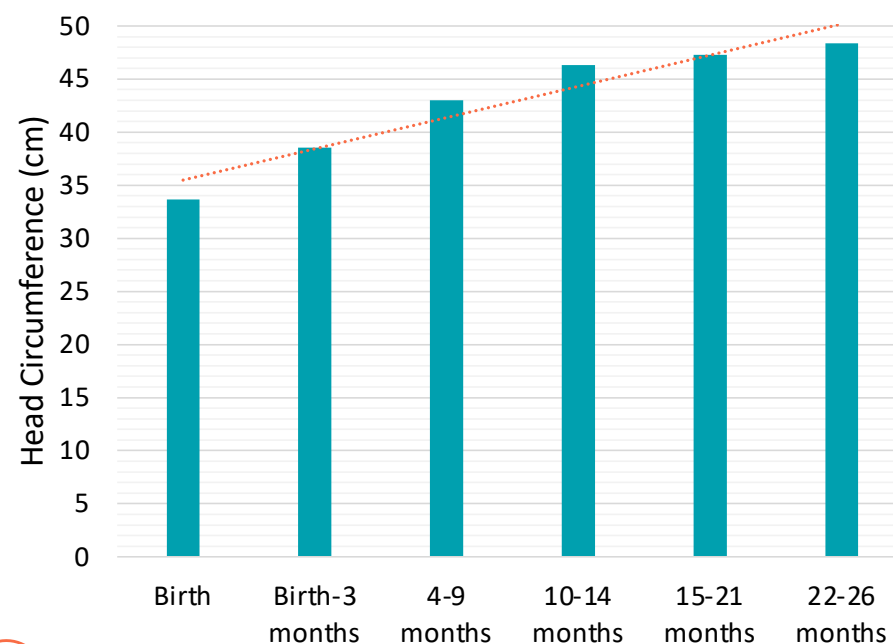
Linear mixed methods approach

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

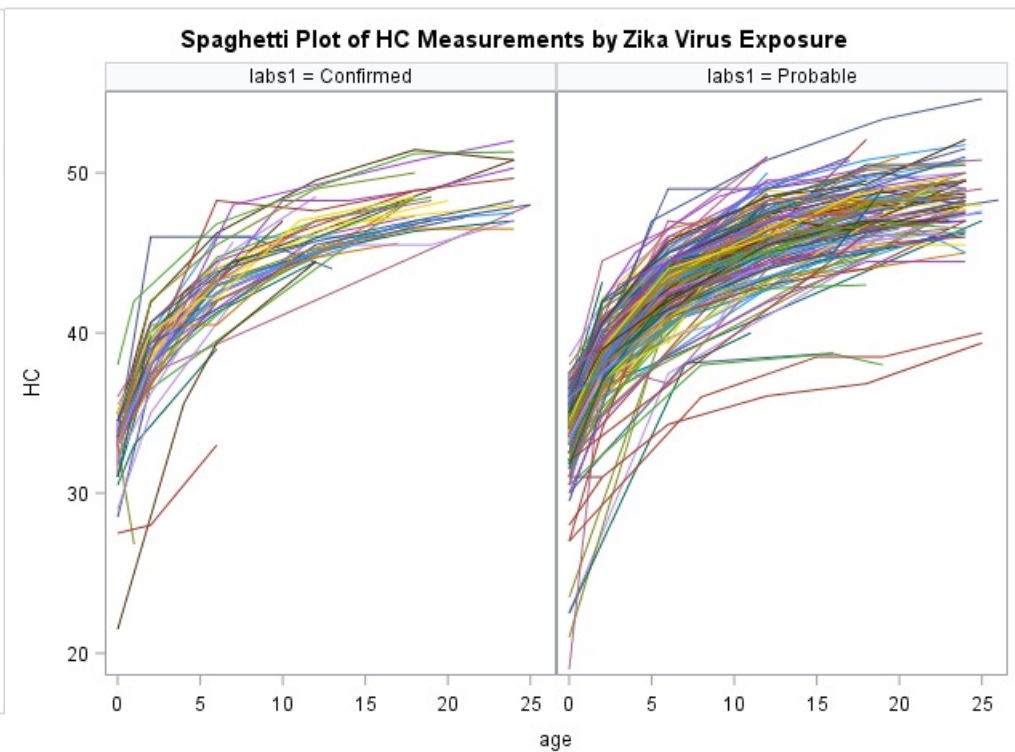
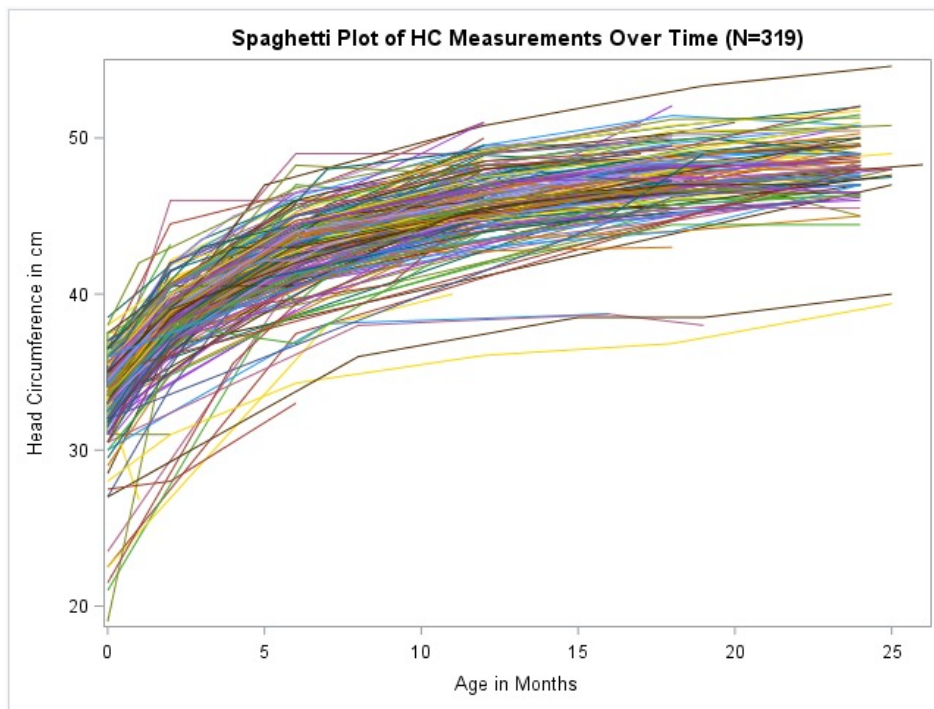
Sample Characteristics (N=319)

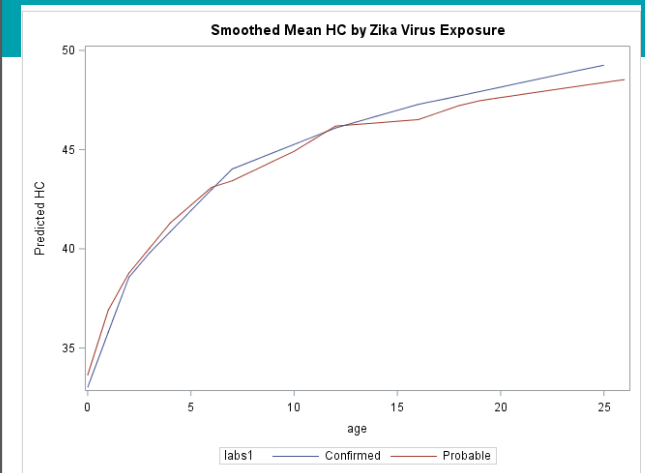
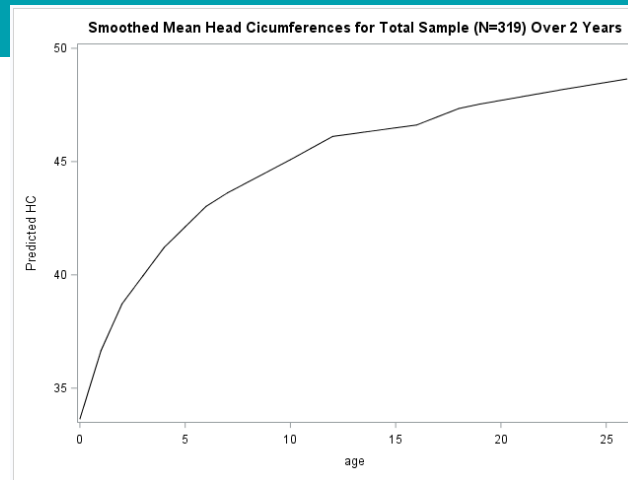
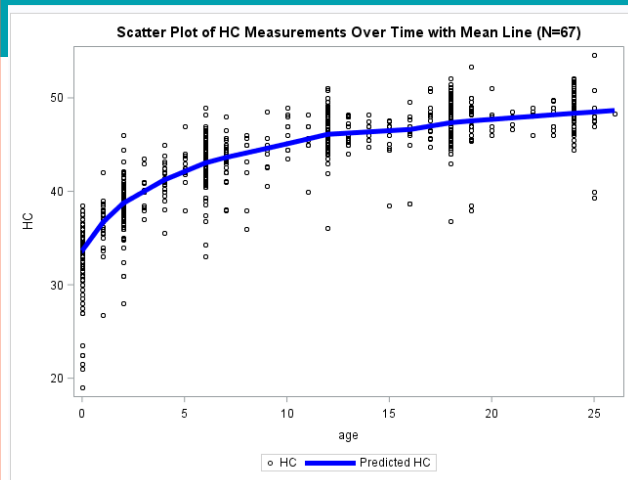
Characteristic	N (%)
Zika Lab Results	
Confirmed	50 (15.7)
Probable	269 (84.3)
Exposure Location	
Florida	27 (8.5)
Travel Related	239 (74.9)
Undetermined	53 (16.6)
Sex	
Male	173 (54.2)
Female	146 (45.8)
Gestational Age (weeks)*	38.3 (23-41)
*Mean (min-max)	

Mean Head Circumference by Age Category



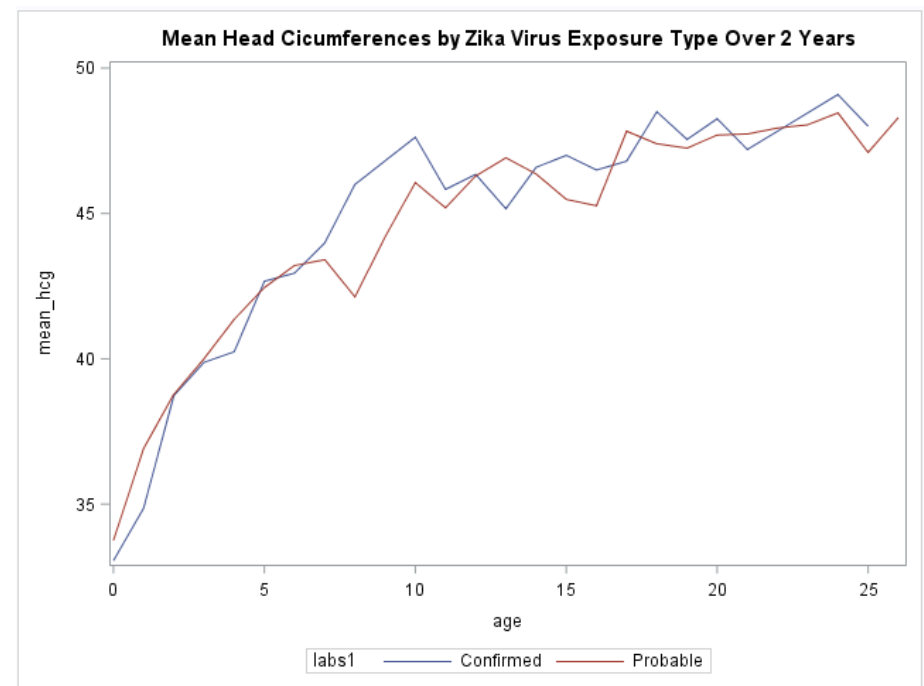
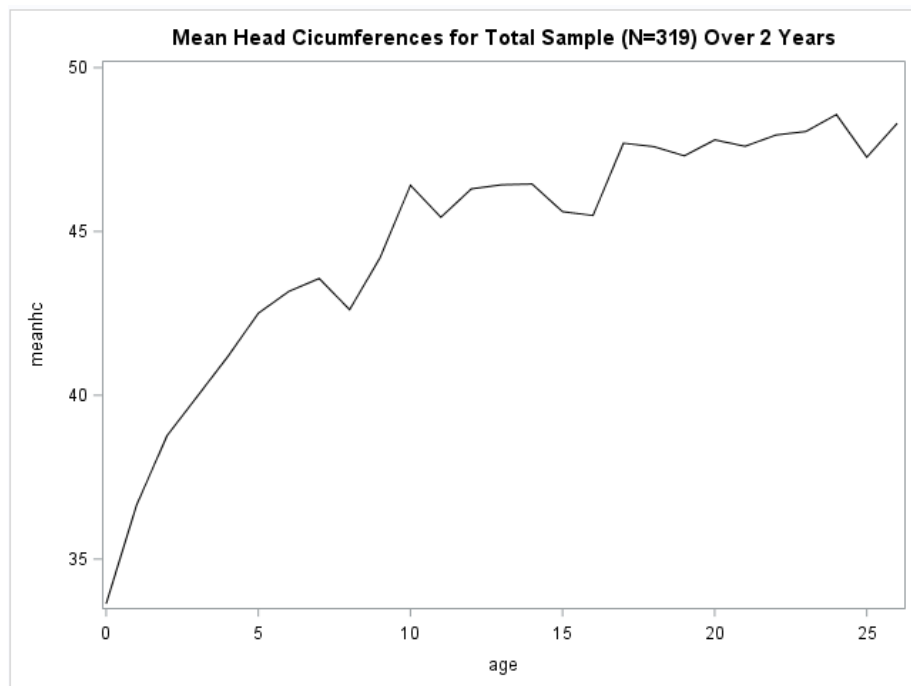
Spaghetti Plots





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

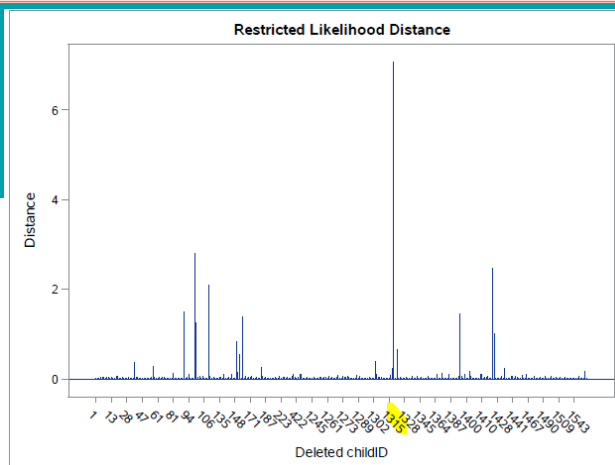
Model Selection- Mean Parameters (Step 3)

	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

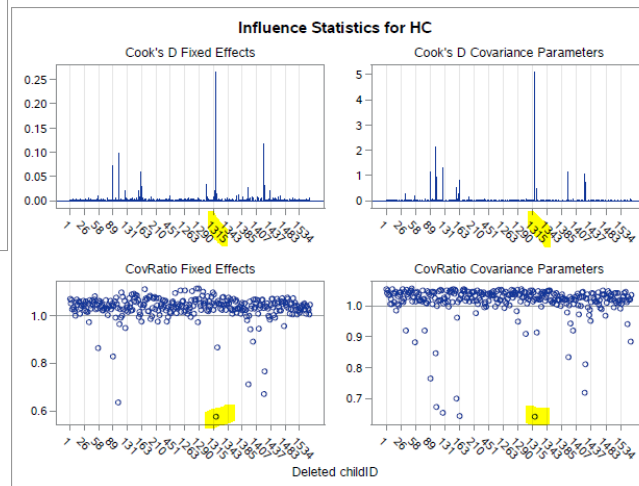
Model Selection- Final Random Effect Variables (Step 4)

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

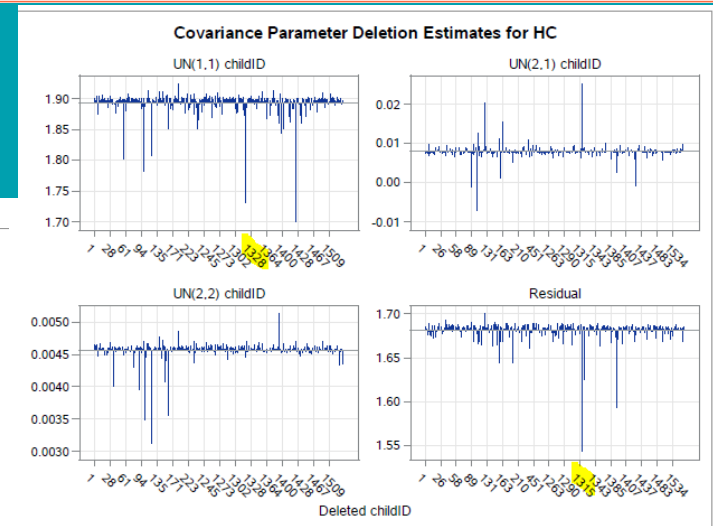
	AIC	BIC	Residual Variance
Random Intercept Only	5152.8	5160.3	1.9379
Random Slope Only (age)	5415.0	5422.5	2.8889
Random Intercept and Slope	5118.4	5133.4	1.6811



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

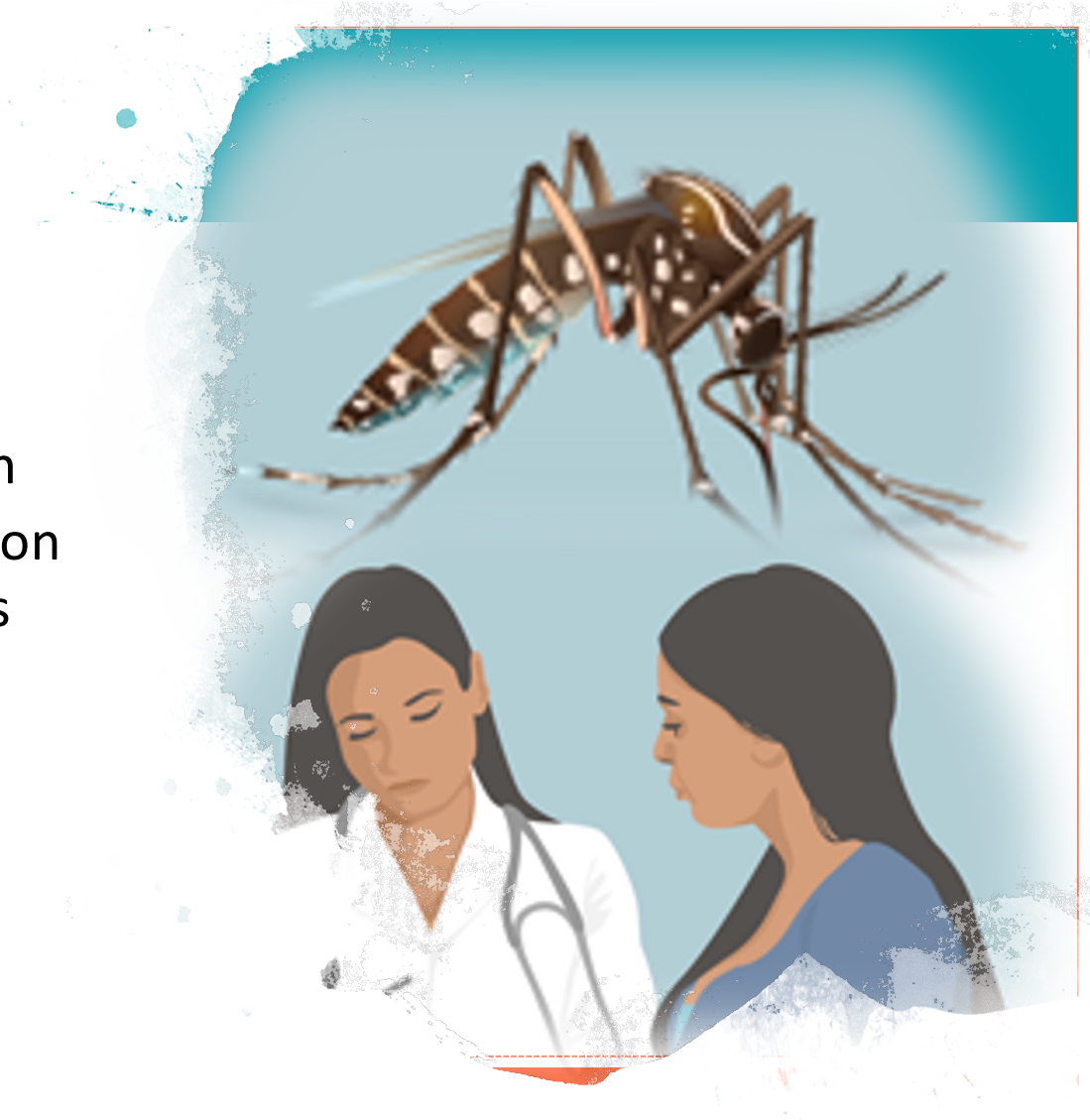
Final Model- Inferences

- 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



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8. Likos A, Griffin I, Bingham AM, et al. Local Mosquito-Borne Transmission of Zika Virus - Miami-Dade and Broward Counties, Florida, June-August 2016. *MMWR Morb Mortal Wkly Rep*. 2016;65(38):1032-1038.