Friends of NICHD

Supporting the Eunice Kennedy Shriver
National Institute of Child Health and Human Development

Research From A to Zika: How What Happens During Pregnancy Influences Child Health

The Role of NICHD in Investigating the Impact of Maternal Exposures on Child Development

Hosted by the Friends of NICHD and in cooperation with

Representatives Jaime Herrera Beutler and Lucille Roybal-Allard
Co-Chairs, Congressional Caucus on Maternity Care

Pregnancy as a Key to Future Health: An Overview

Catherine Y. Spong, M.D.

Acting Director, NICHD

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

NICHD

- Established in 1962 to support and conduct research and training on:
  - Human development across the lifespan
  - Intellectual and developmental disabilities
  - Key processes during pregnancy
- Branched into additional areas of scientific inquiry to improve health of children, women, families, and communities

Developmental Origins of Health and Disease

- Early life affects health outcomes
- Optimizing a woman's health (and in turn the fetus) during pregnancy, future health can be improved for mother and child, thus leading to a healthier population

Dr. David Barker's research led to the concept of DOHaD

Preterm Birth

Leading Cause of Neonatal Mortality

Accounts for

- 1 out of 5 children with mental retardation
- 1 out of 3 children with vision impairment
- Almost half of children with cerebral palsy

Long term implications

For the baby:

Increased risk for cardiovascular disease (MI, stroke, HTN) as an adult

For the mom:

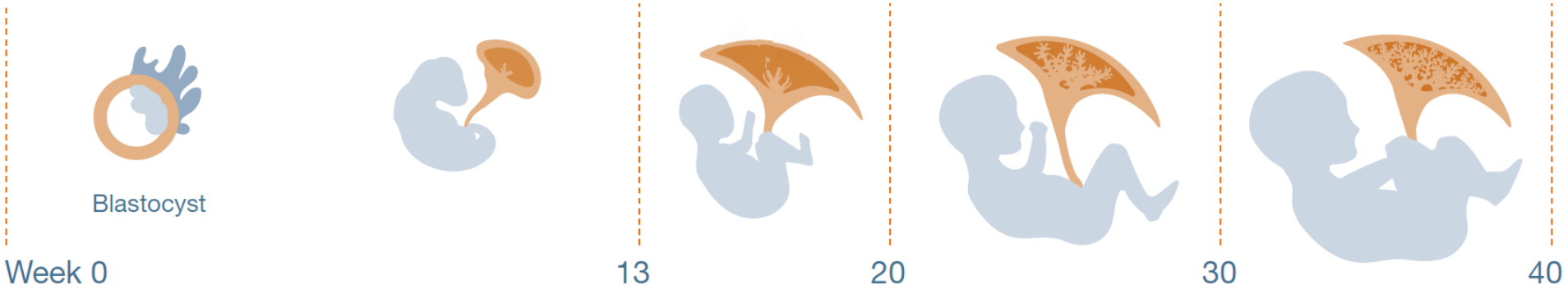
Risk of PTB, heart disease

HPP

Human Placenta Project

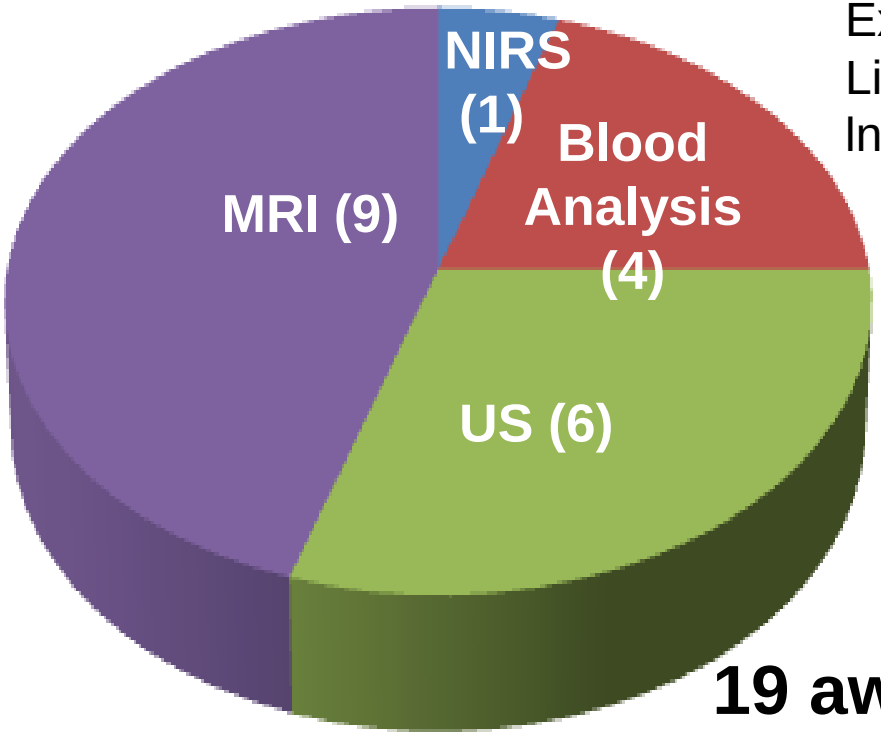
Overarching goal:

Understand human placental development, structure, and function in real time


Blastocyst
Week 0
13
20
30
40

Human Placenta Projects

Near Infrared Resonance Spectroscopy
(assessment of hemodynamic alterations)



Exosomes,
Lipids,miRNA,
lncRNA

19 awards totaling ~$46M

Focus on collaboration across disciplines and development of synergy

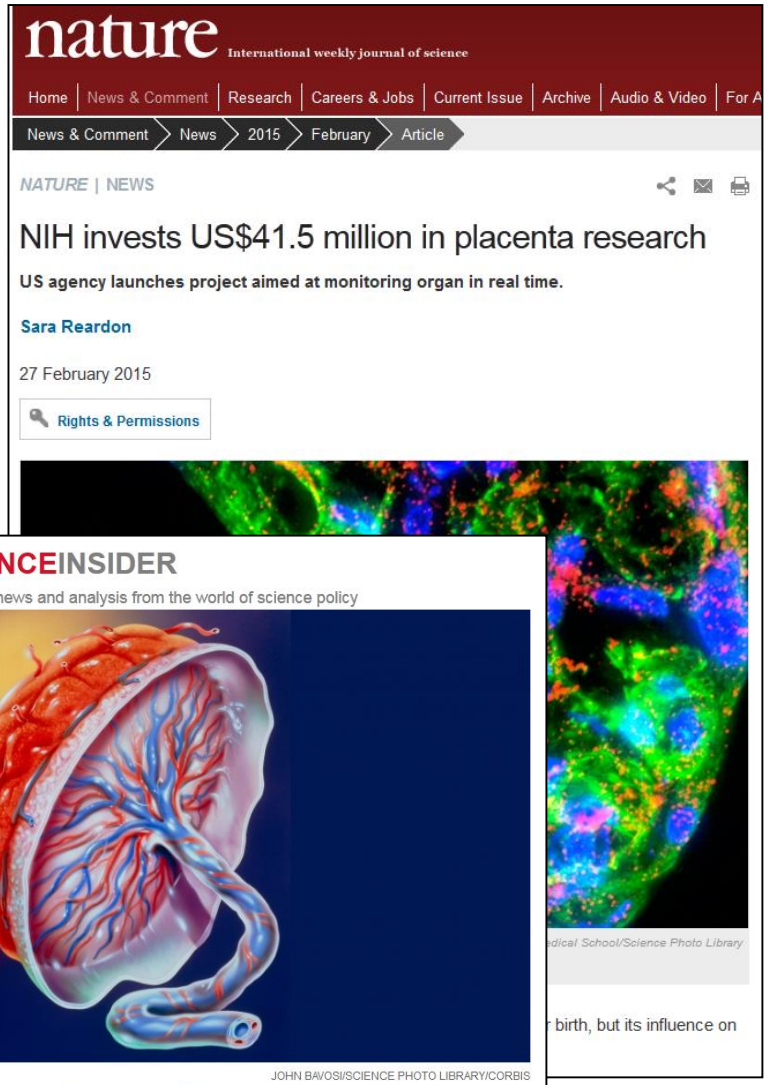
HPP Widespread Interest

Sept 11-13, 2015 Guangzhou, China

THE INTERNATIONAL SYMPOSIUM OF MATERNAL AND FETAL MEDICINE

CHINA HUMAN PLACENTA PROJECT

Dec 1-2, 2015 India



What can HPP provide if goals achieved?

- Novel technologies to monitor an organ - any organ
- A better understanding of disease processes
- Opportunity to improve the health of the world by optimizing health for moms, babies, and families

PregSource™

Crowdsourcing to Understand Pregnancy

PregSource™
Crowdsourcing to Understand Pregnancy

PregSource™

- A crowd-sourced, interactive, mobile app to:
  - Detail the natural history – and variations - of human pregnancy
  - Provide accurate info about pregnancy from trusted sources
  - Let pregnant women know about opportunities to participate in targeted research
- 20 partner organizations

PregSource™
Crowdsourcing to Understand Pregnancy

PregSource™ Partners

NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

Society for Women's Health Research

NIH National Center for Complementary and Integrative Health

CDC Centers for Disease Control and Prevention

NIH National Institutes of Health Office of Research on Women's Health

march of dimes

NIH National Heart, Lung, and Blood Institute

Society for Maternal-Fetal Medicine

Lamaze International

NIH National Institute on Minority Health and Health Disparities

The American Academy of Pediatrics

Preeclampsia Foundation

NIH National Institute of Environmental Health Sciences

AWHONN Promoting the Health of Women and Newborns

Genetic Alliance

NIH National Institute of Nursing Research

NIH National Institutes of Health Office of Behavioral and Social Sciences Research

U.S. Department of Health and Human Services HRSA Health Resources and Services Administration

American College of Nurse-Midwives

The American College of Obstetricians and Gynecologists 1951 Women's Health Care Physicians

American Society for Reproductive Medicine 1944

Scientific Rationale: Defining Normal Pregnancy

PregSource™
Crowdsourcing to Understand Pregnancy

- Women will provide information about common pregnancy experiences in near-real-time:
  - Sleep
  - Nausea
  - Exercise
  - Weight
  - Medication use
- Answers to these topics will help researchers build a more complete picture of normal pregnancy and develop strategies for improving maternal care

Questionnaires

PregSource™
Crowdsourcing to Understand Pregnancy

- Weekly educational updates and appropriate reminders to complete questionnaires
- Woman can see aggregate data showing how her responses compare to other participants'
- Pregnancy-related educational information from our Partners will be available in an online Resource Library
- Plan to follow through 6-12 months after delivery

Zika Virus

NICHD is working on a number of initiatives to understand Zika Virus in pregnancy and pregnancy outcomes

PAR-16-106 - Rapid Assessment of Zika Virus Complications

Zika in Infants and Pregnancy (ZIP) Cohort Study

- Multi-site, multi-country prospective observational cohort
- To determine the risks of Zika infection during pregnancy on maternal and fetal outcomes while controlling for potential confounders
- 10,000 women
- 4 current sites: Brazil, Colombia and Puerto Rico, additional sites planned
- Standardized protocol, data collection
- Supported by NICHD, NIAID, NIEHS and Fundacao Oswaldo Cruz-Fiocruz

ZIP Cohort Study

<13 wks gestation
Offered enrollment into cohort study

Followed through pregnancy

- Zika infection - symptomatic
- Zika infection - asymptomatic
- No Zika infection

All children followed: those with and without anomalies

Cofactors:
- environmental exposures
- co/prior infections
- toxins

Workshop Focused on the Children

- September 22-23, 2016 in Bethesda, Maryland
- Define the evidence to understand how prenatal Zika virus infection affects child development and to identify strategies for evaluation, management, and treatment

Photo attribution: Agência Brasil

NICHD

Improving child health through pregnancy and childhood will result in healthier babies, and improved health of the nation: less heart disease, diabetes and potentially even cancer as these children grow

Questions?

Zika Virus and the Pregnant Woman

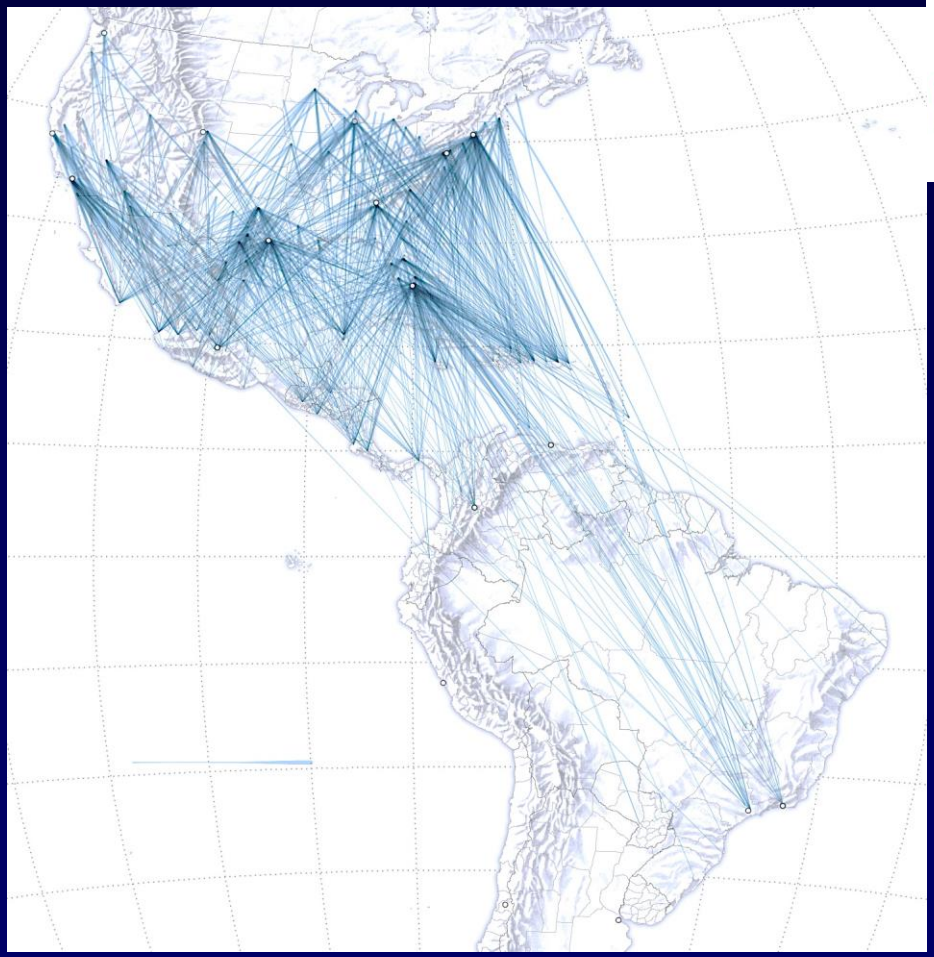
Jeanne S. Sheffield, MD
Maternal-Fetal Medicine
Johns Hopkins Medical Center

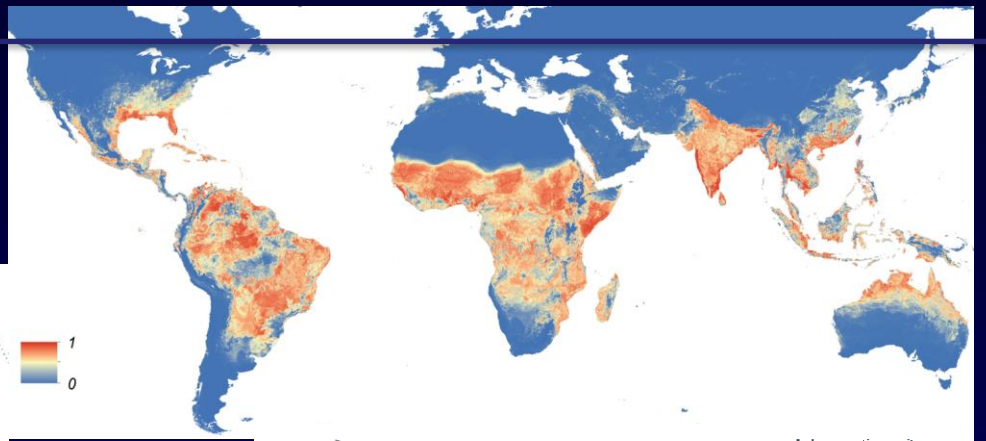
History of Zika Virus

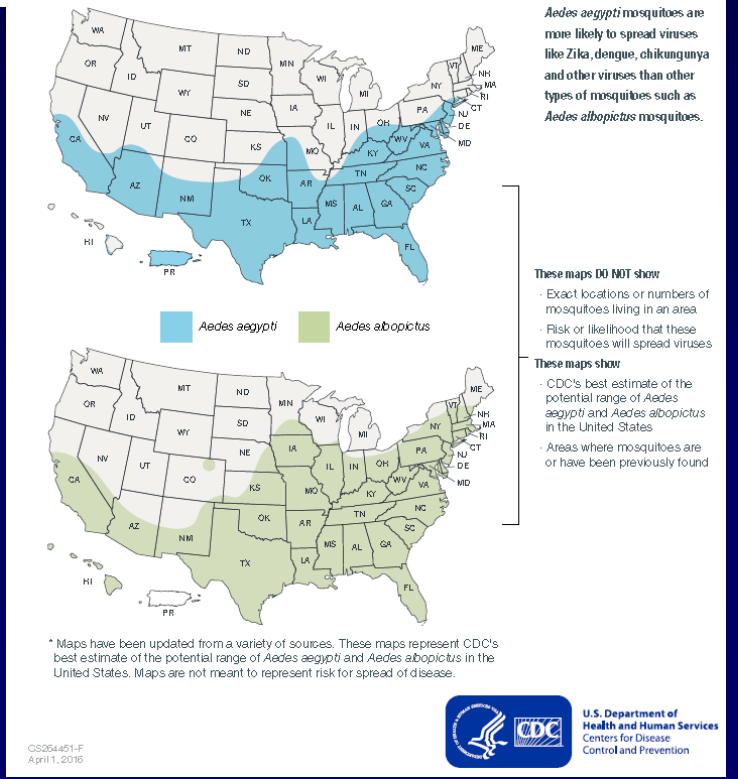
- Initially identified in 1947 in a rhesus monkey in the Zika Valley in Uganda through a yellow fever surveillance program
- First human case reported in Uganda in the 1950s
- Spread from Northern Africa to South East Asia
  - Limited to small-scale epidemics until 2007 when it hit the Yap Islands

Global *Aedes aegypti* Distribution Predicted the Spread of Zika Virus

Courtesy Dr. Thomas Quinn
Director, Center for Global Health
JHU







Brazil 2015

- Northeastern Brazil May 2015 first reported at the same time Dengue was circulating
- September, 2015 an increase in microcephaly cases reported in the same areas as the Zika epidemic (20 cases per 10,000 live births – 20 fold increase)

ZIKV Transmission

- *Aedes* genus of mosquito is the common vector (*Aedes aegypti* and *Aedes albopictus)*
- Vertical transmission
  - Antepartum
  - ?Intrapartum
  - ?Breastfeeding – no cases but ZIKV RNA is found in breast milk. Official recommendation is to allow breastfeeding
- Sexual transmission
- Blood bank
- Laboratory exposure

Zika Virus Infection

- Incubation ~3-12 days
- Viremia ~7 days but now reports out >60 days in a GBS patient
- Only 20% of infected individuals develop symptoms
  - Acute onset fever, maculapapular rash, arthralgias and conjunctivitis are the big 4
  - Myalgias, headache, retroorbital pain, pruritis and vomiting
  - Usually last up to 7 days

Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?

1.A. S. Oliveira Melo[1],
2.G. Malinger[2,*],
3.R. Ximenes[3],
4.P. O. Szejnfeld[4],
5.S. Alves Sampaio[5] and
6.A. M. Bispo de Filippis[5]

ULTRASOUND in Obstetrics & Gynecology

January, 2016

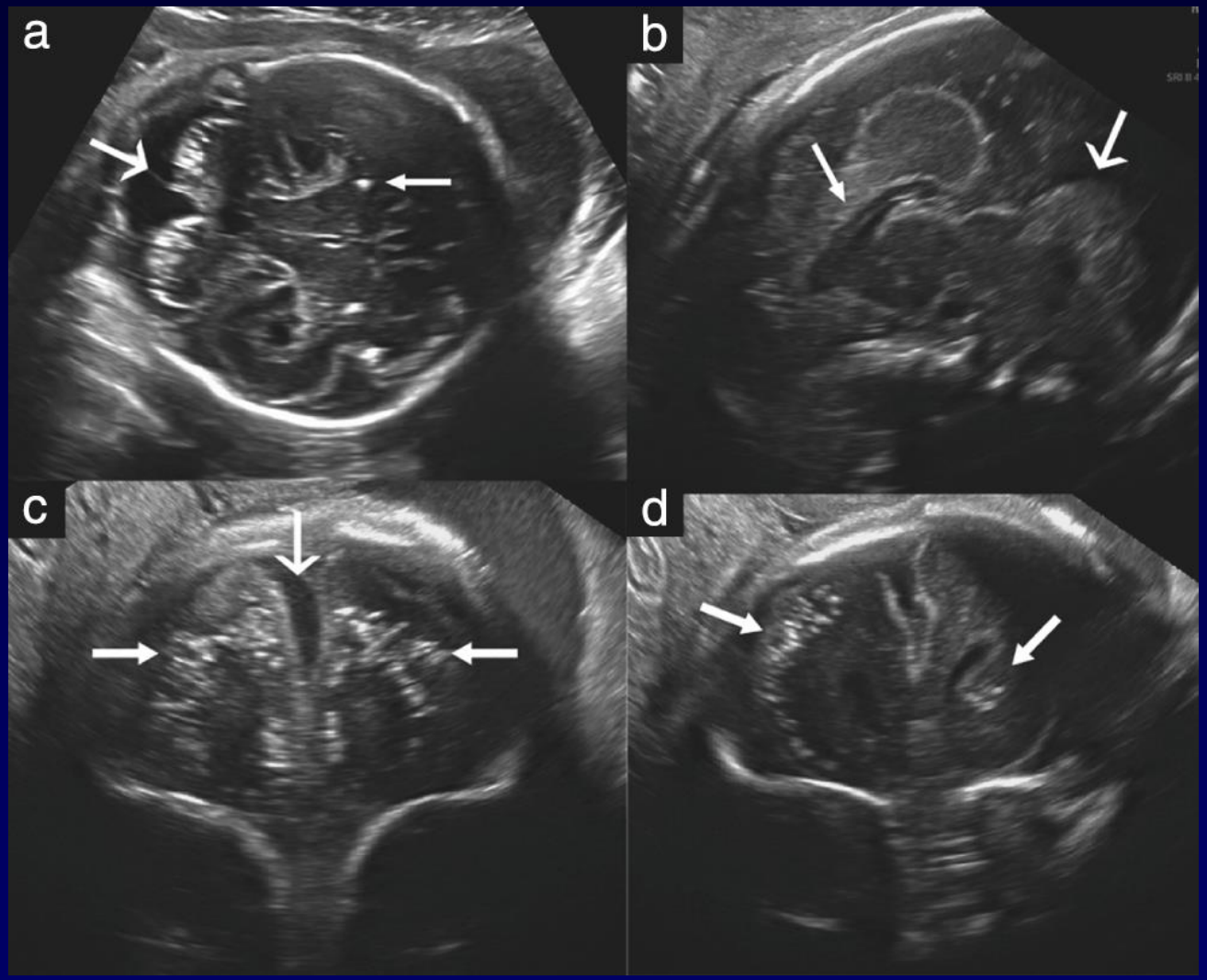
2 Pregnant women diagnosed with fetal microcephaly

- Blood test for Zika negative
- RT-PCR of the amniotic fluid positive

Case 1 at 30 weeks gestation

Case 2 at 29 weeks gestation

Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg?



Intracranial calcifications
Absent normal vermis
Dysgenesis of the corpus callosum
Brain atrophy

Ultrasound in Obstetrics & Gynecology
Volume 47, Issue 1, pages 6-7, 5 JAN 2016 DOI: 10.1002/uog.15831
http://onlinelibrary.wiley.com/doi/10.1002/uog.15831/full#uog15831-fig-0001

Brazilian Ministry of Health Task Force Findings

- The initial 35 infant cohort (≤ 2 SD)
  - All mothers lived in or traveled to endemic areas
    - 74% had a rash in first or second trimester
  - 71% severe microcephaly ≥ 3 SD
  - 49% had at least one neurologic abnormality
  - 27/35 infants had neuroimaging and 100% were abnormal
    - Brain calcifications, cell migration abnormalities, cortical/subcortical atrophy

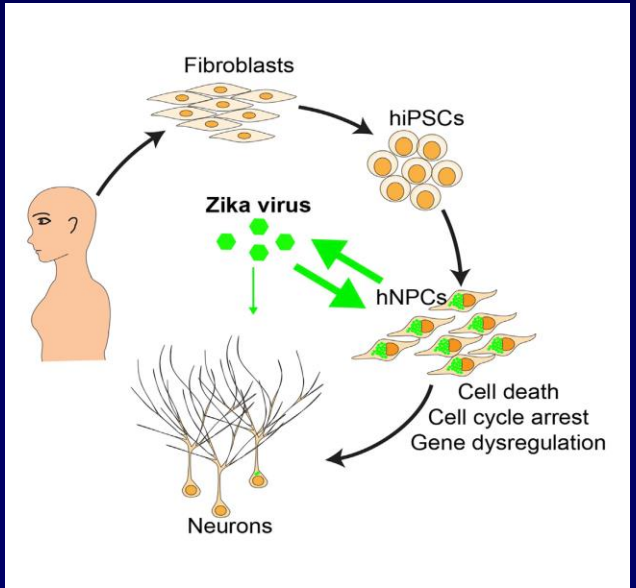
CDC MMWR 1/22/2016

What is Microcephaly….

- Head significantly smaller than would be expected at a specific gestational age and sex
- Associated with
  - Genetic disorders (Chromosomal and single gene disorders)
  - Environmental
    - Perinatal infections
    - Prenatal exposure to drugs or chemicals
    - Perinatal hypoxia or trauma

Biologic Link between Zika and Microcephaly

- Ming, G et al Johns Hopkins March 2016 *Cell Stem Cell*
  - The Zika virus selectively infects cells from the brain cortex resulting in cell destruction or at least disrupted growth by cell cycle dysregulation
    - Cortical neural progenitor cells



Zika model in mice: Miner JJ et al Cell 2016

- 2 mouse models of placental and fetal disease
  - ZIKV infects both the placenta and the mouse fetal brain, often leading to fetal death
    - Trophoblast infection e.g. transplacental infection
  - Model for facilitating pathogenesis, transmission and therapeutics testing

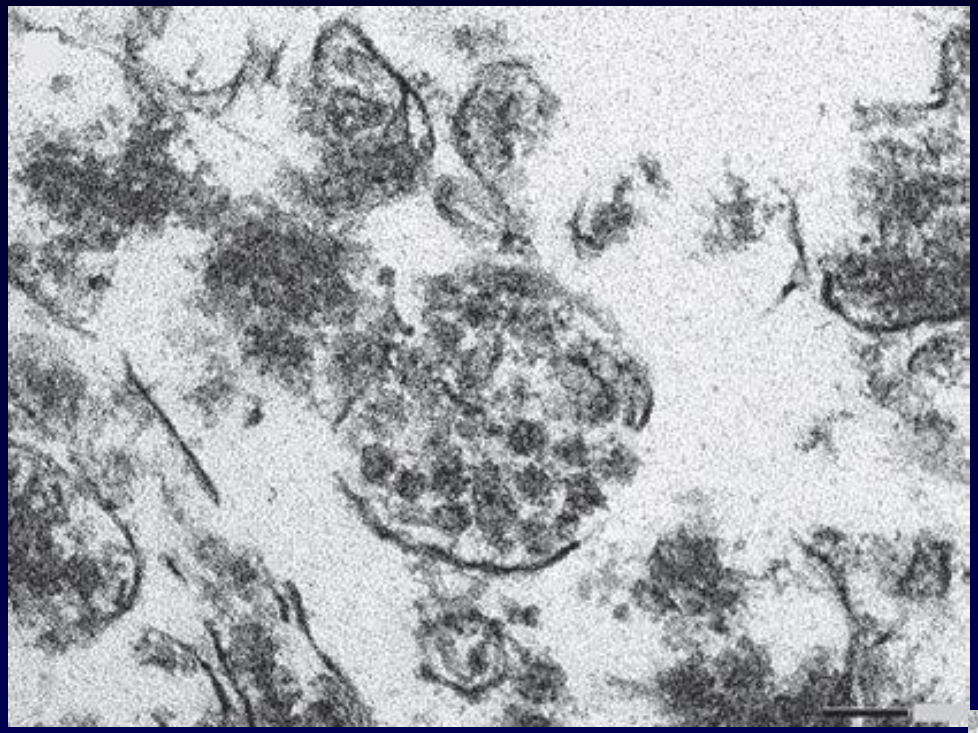
Mlakar et al NEJM 2/10/2016

Mlakar et al NEJM
2/10/2016

Fetal/Neonatal effects

- Eye abnormalities
  - 29 infants with microcephaly in Brazil
    - 35% had ocular abnormalities (chorioretinal atrophy and focal pigment mottling)

Freitas and Colleagues JAMA Ophthal February 9, 2016 Online



Mlakar et al NEJM 2/10/2016

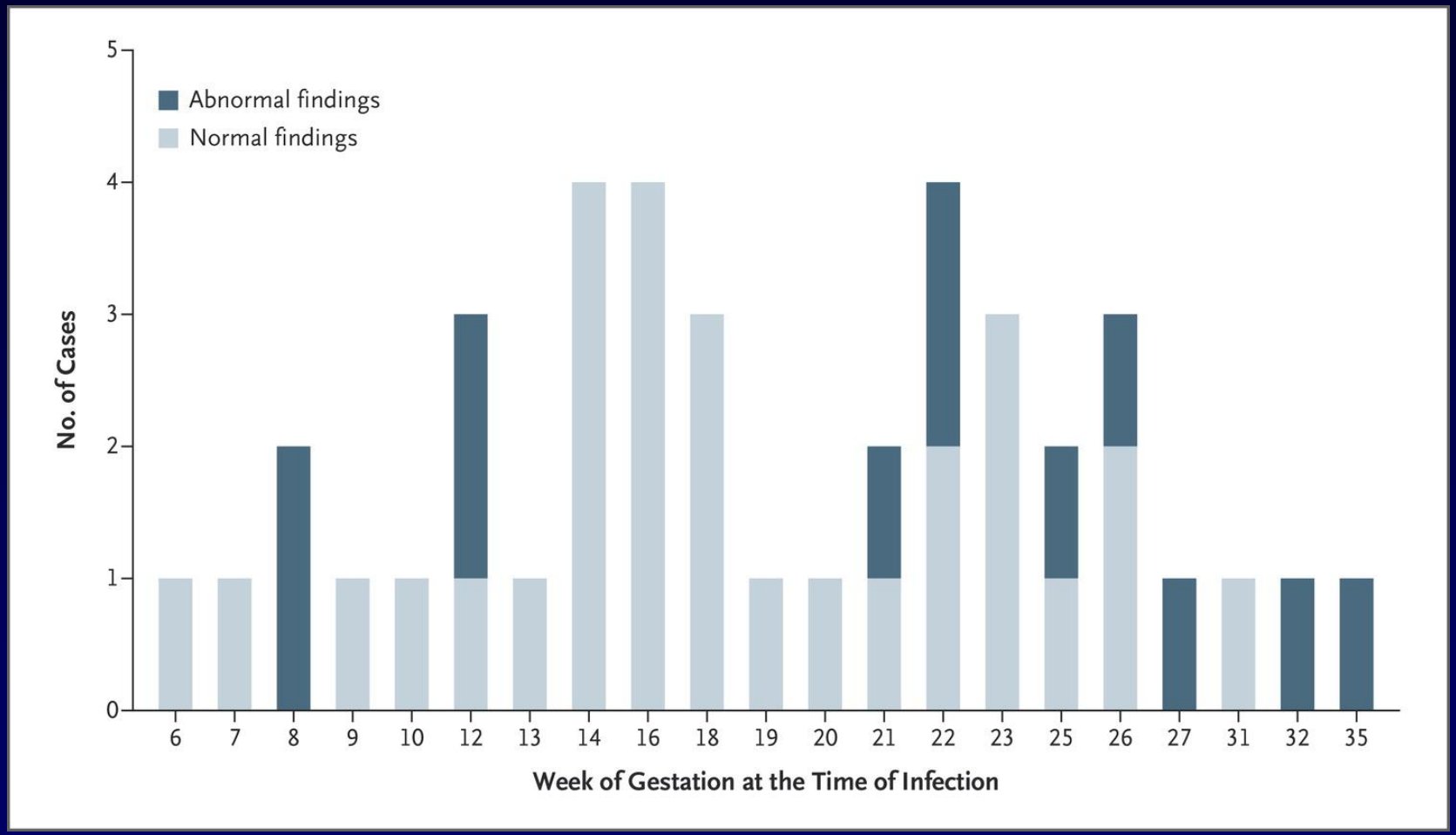
NEJM 3/4/2016
Brasil et al Rio de Janeiro Report

- 88 pregnant women with a concerning rash
  - 72% positive for Zika in blood and or urine
    - Rash was mainly pruritic and maculopapular
    - 65% arthralgias
    - 58% conjunctival injection
    - LAD 41%
    - Fever <1/3 acute infection – mainly low grade and short lived

NEJM 3/4/2016
Brasil et al Rio de Janeiro Report

- Of the 72 Zika positive pregnant women
  - 2 miscarriages in first trimester
  - 42 women (60%) had an ultrasound
    - 12 (29%) abnormal
      - 5 IUGR
      - 4 cerebral calcifications
      - 2 other CNS abnormalities
      - 2 Oligohydramnios/anhydramnios
      - 4 Abnormal dopplers
  - 2 fetal deaths

Week of Gestation at the Time of ZIKV Infection and Abnormal Ultrasonographic and Doppler Findings.

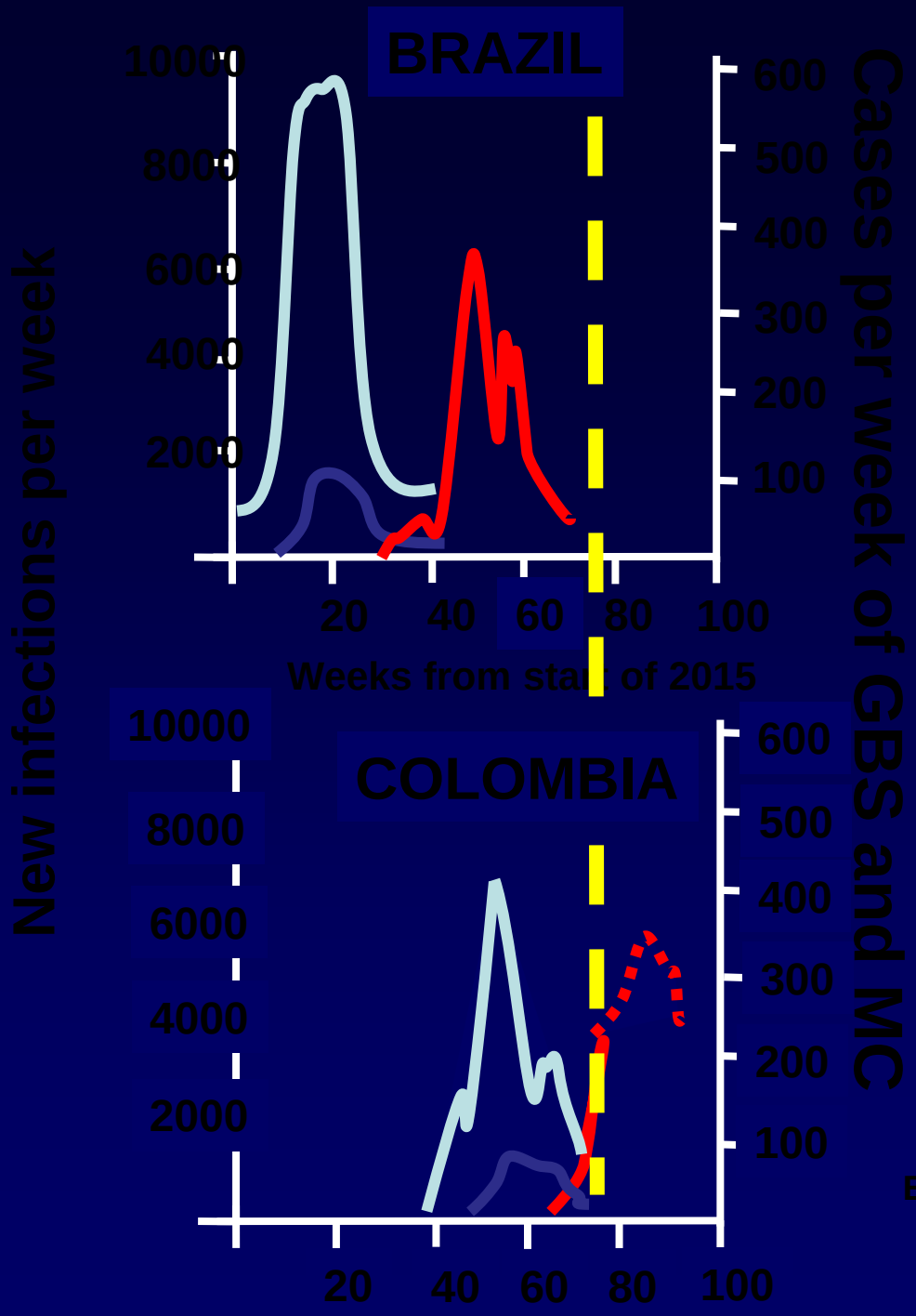


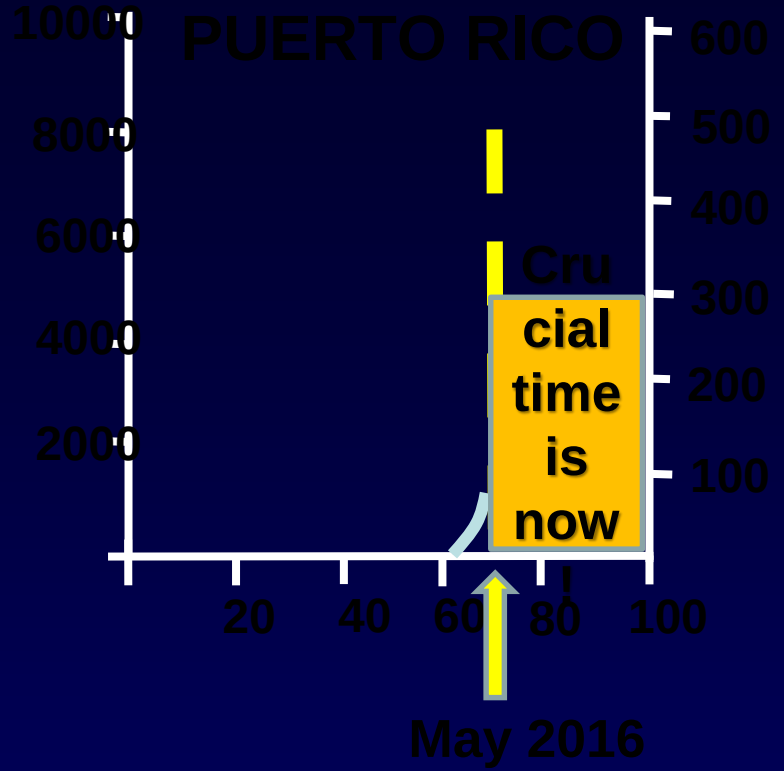
Brasil P et al. N Engl J Med 2016. DOI: 10.1056/NEJMoa1602412

The NEW ENGLAND JOURNAL of MEDICINE

Pregnancy Effects

- Unknown if pregnant women are more susceptible
- Disease does not appear to be any worse in pregnancy
- Transmission to the fetus has been documented in all trimesters though first and second trimester probably highest risk
  - Zika RNA in abortus tissues, AF, placenta and term neonates





Yellow = Current time
Blue = cases reported
Purple= Guillian Barré
Red = microcephaly

Brazil/Columbia: WHO and Pan American Health Organization, May 2016
Puerto Health Dept via Nabal Bracero

At a Glance – Zika in the US June 16, 2016

- **US States**
  - Travel-associated cases reported: 618
  - Locally acquired vector-borne cases reported: 0
  - Total: 618
    - Sexually transmitted: 11
    - Guillain-Barré syndrome: 1
- **US Territories**
  - Travel-associated cases reported: 4
  - Locally acquired cases reported: 1110
  - Total: 1114
    - Guillain-Barré syndrome: 8

Affected Pregnant Women June 16th, 2016

- 481Laboratory Evidence Zika infections in pregnant women
  - 265 in the United States
  - 216 in the U.S. territories
- 55% had clinical symptoms
- Outcomes
  - 4 Liveborn infants with birth defects
  - 5 pregnancy losses with birth defects

The Black Box of “Unknowns”

- True incidence among pregnant women
- Rate of vertical transmission
- Rate of clinical manifestations if the fetus is infected

Vaccination research funding is a vital need to help deal with this potential epidemic.

Maternal Origins of Early Cognitive Development

Prenatal Nutrition and Perinatal/Postnatal Risk

John Colombo, PhD
Professor of Psychology
Director, Schiefelbusch Institute for Life Span Studies
Director, Kansas Intellectual and Developmental Disabilities Research Center
University of Kansas
Lawrence, KS 66045 USA

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Prenatal Nutritional Supplementation and Perinatal/Postnatal Outcomes

- *DHA supplementation and pregnancy outcome* (Susan Carlson/John Colombo), NICHD R01HD047315.
- *The effects of DHA on fetal heart rate and development (*Kathleen Gustafson/John Colombo/Susan Carlson), NICHD HD059019
- *The Kansas Intellectual and Developmental Disabilities Research Center* (John Colombo), NICHD P30 HD002528
- *Docosahexaenoic Acid (DHA) Supplementation in Pregnancy to Reduce Early Preterm Birth* (Susan Carlson), NICHD 1 R01 HD083292
- *Translational Research in Intellectual and Developmental Disabilities* (Kathryn Saunders/John Colombo), NICHD T32 HD007525

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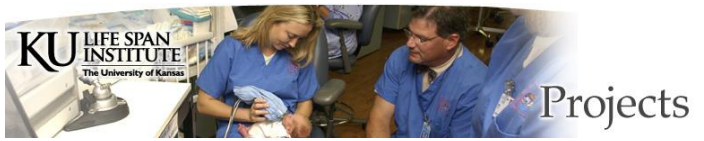
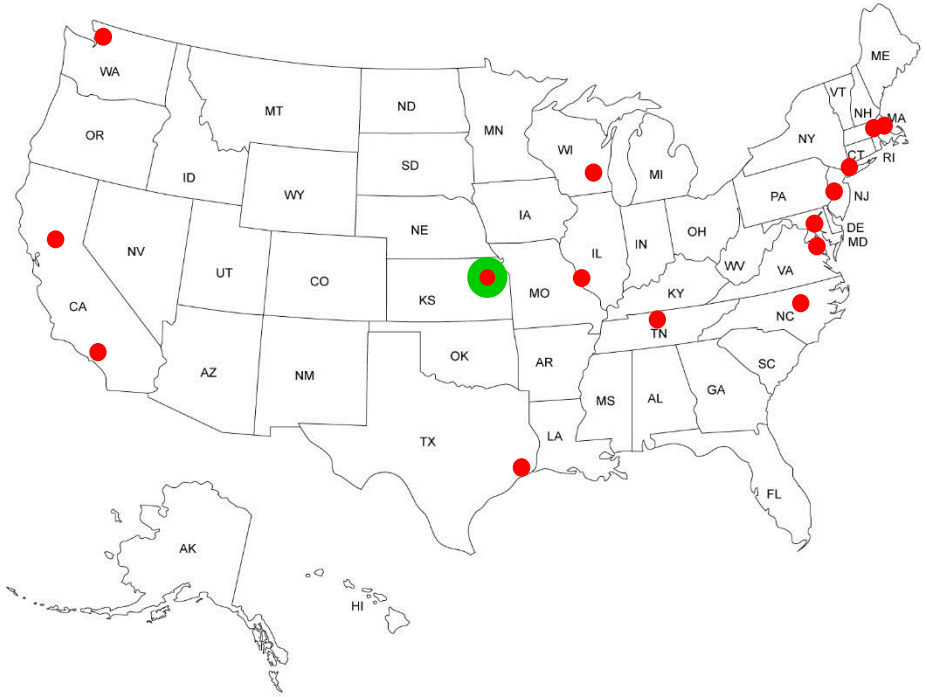


Kansas Intellectual and Developmental Disabilities Research Center, one of 14 IDDRCs in NICHD's network



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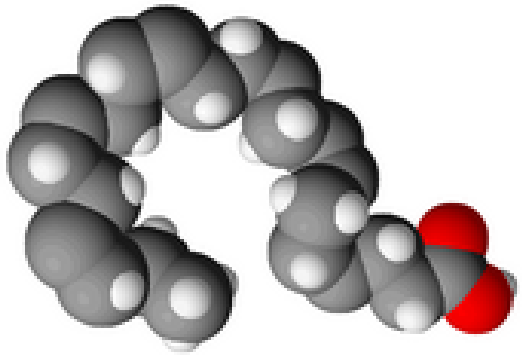
Docosahexaenoic Acid (DHA)

- An essential omega-3 long-chain polyunsaturated fatty acid (LCPUFA)
- Humans *must* get DHA from diet (coldwater fish)
- DHA accumulates in the brain -- contributes to structure and function of neural systems involved in learning and development. It is also has anti-inflammatory properties
- It accumulates most rapidly during early life, *especially during pregnancy*



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Prenatal Nutritional Supplementation:

The Kansas University DHA Outcomes Study (KUDOS)

Two Randomized Groups

Mothers assigned to take either 600 mg/day of DHA or a 0 mg placebo

Pregnancy Outcomes

Gestational age/prematurity

Birthweight

Perinatal Hospitalization

Carlson SE, Colombo J, Gajewski BJ, Gustafson KM et al. (2013). *Am J Clin Nutr*, *97*(4), 808-815.

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KUDOS: Pregnancy Outcomes

Outcomes	Prenatal DHA Supplementation:
Gestational Age	Increased overall pregnancy length
Birthweight	Increased birthweight
Birth Size	Increased infant length and head circumference
Birthweight < 1500g	Reduced the number of infants born at under 1500g
Gestation < 34 wks	Reduced the number of infants born at less than 34 wks
NICU stay	For infants admitted to NICU, DHA reduced the number of days in the NICU
Preterm hospitalization	For infants hospitalized for prematurity, reduced the number of days to discharge

Carlson SE, Colombo J, Gajewski BJ, Gustafson KM et al. (2013).
Am J Clin Nutr, *97*(4), 808-815.

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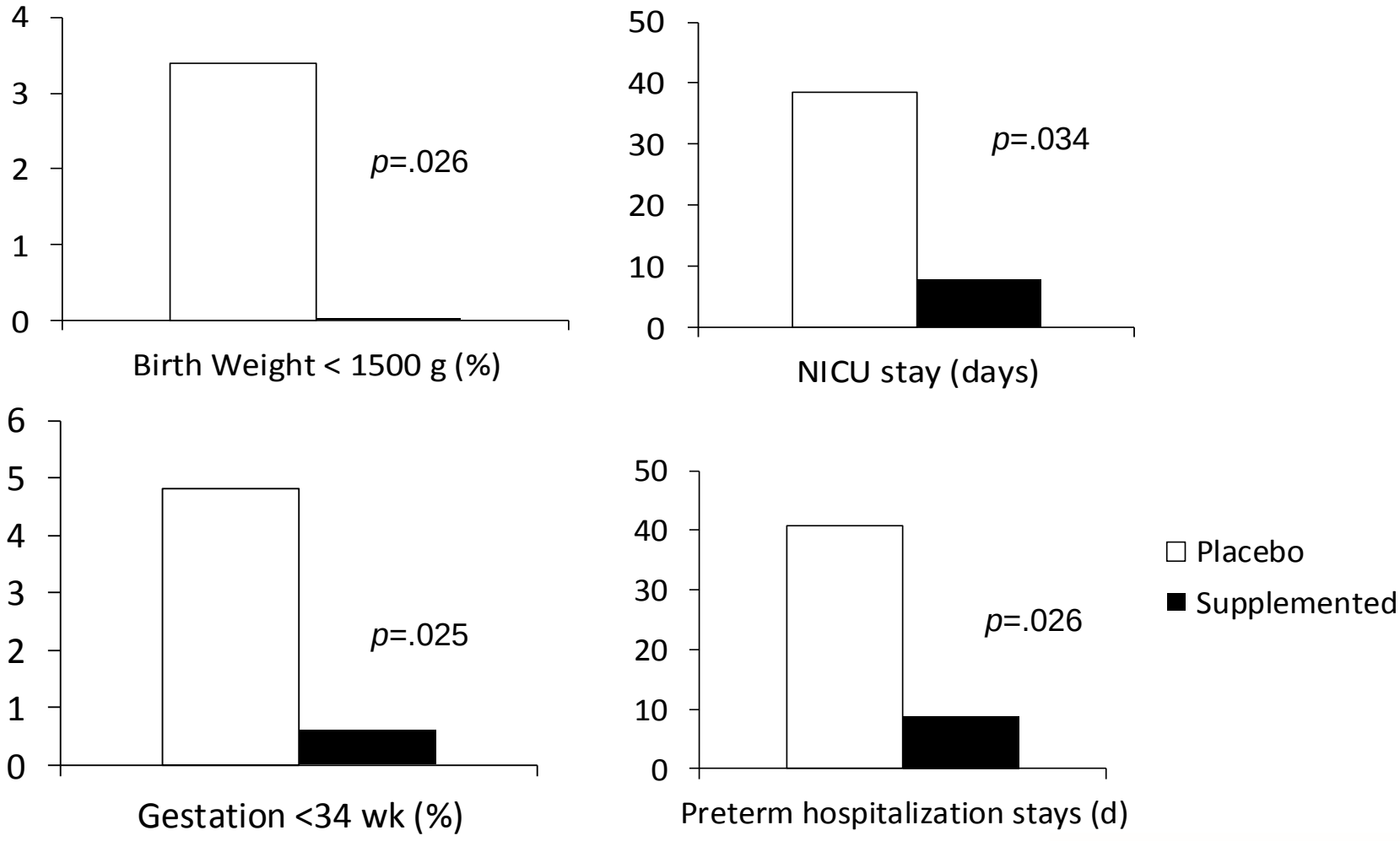
KUDOS: Pregnancy Outcomes



Carlson SE, Colombo J, Gajewski BJ, Gustafson KM et al. (2013). *Am J Clin Nutr*, *97*(4), 808-815.

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Docosahexaenoic acid supplementation (DHA) and the return on investment for pregnancy outcomes ☆, ☆☆

T.I. Shireman [b,1], E.H. Kerling [a], B.J. Gajewski [c], J. Colombo [d], S.E. Carlson [a,*]

[a] The Department of Dietetics and Nutrition, University of Kansas Medical Center, Kansas City, KS, USA
[b] The Department of Preventive Medicine, University of Kansas Medical Center, Kansas City, KS, USA
[c] The Depart
[d] The Depart

ARTIC

Article histo
Received 5
Received in
11 May 201
Accepted 12

Keywords:
Docosahexa
Pregnancy
Hospital cos
Preterm bir

Health care savings: $1678 per infant

Cost of supplement: $ 193 per infant

Net savings: $1485 per infant

"Extrapolating this to the nearly 4 million US deliveries per year suggests universal supplementation with 600 mg/d during the last 2 trimesters of pregnancy **could save the US health care system up to USD $6 billion**."

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Shireman et al. (2016). *PLEFA, 111*, 8-10

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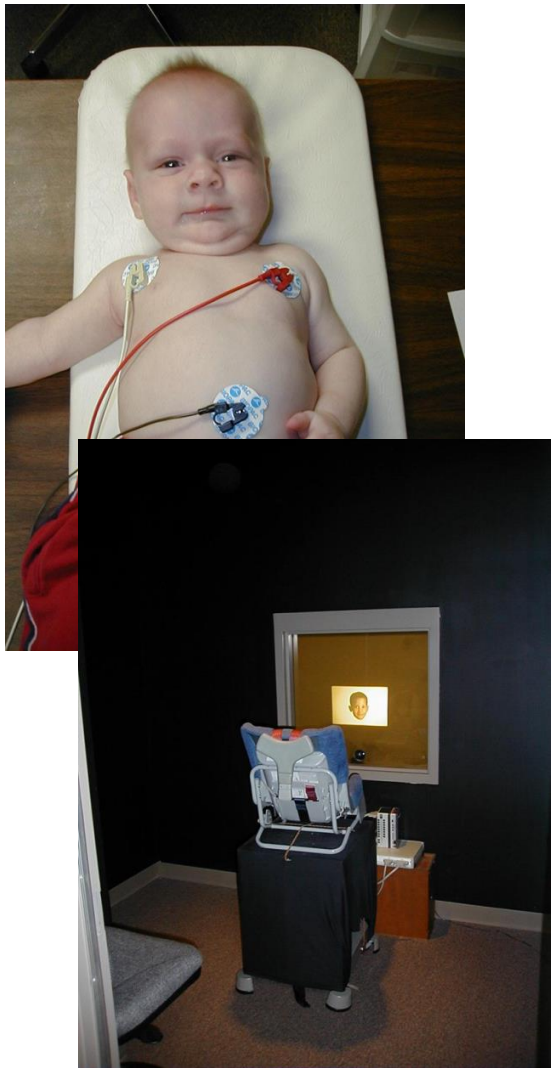
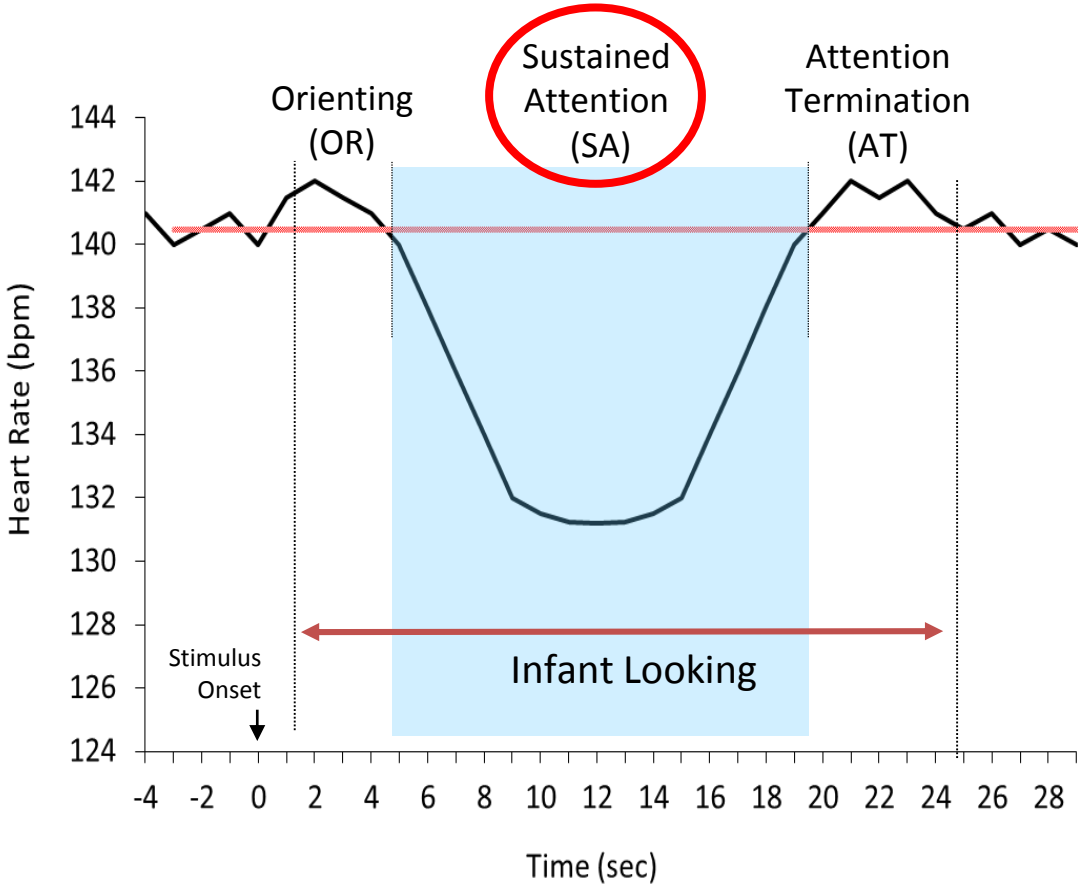
Cognitive Outcomes: Visual Attention in Infancy





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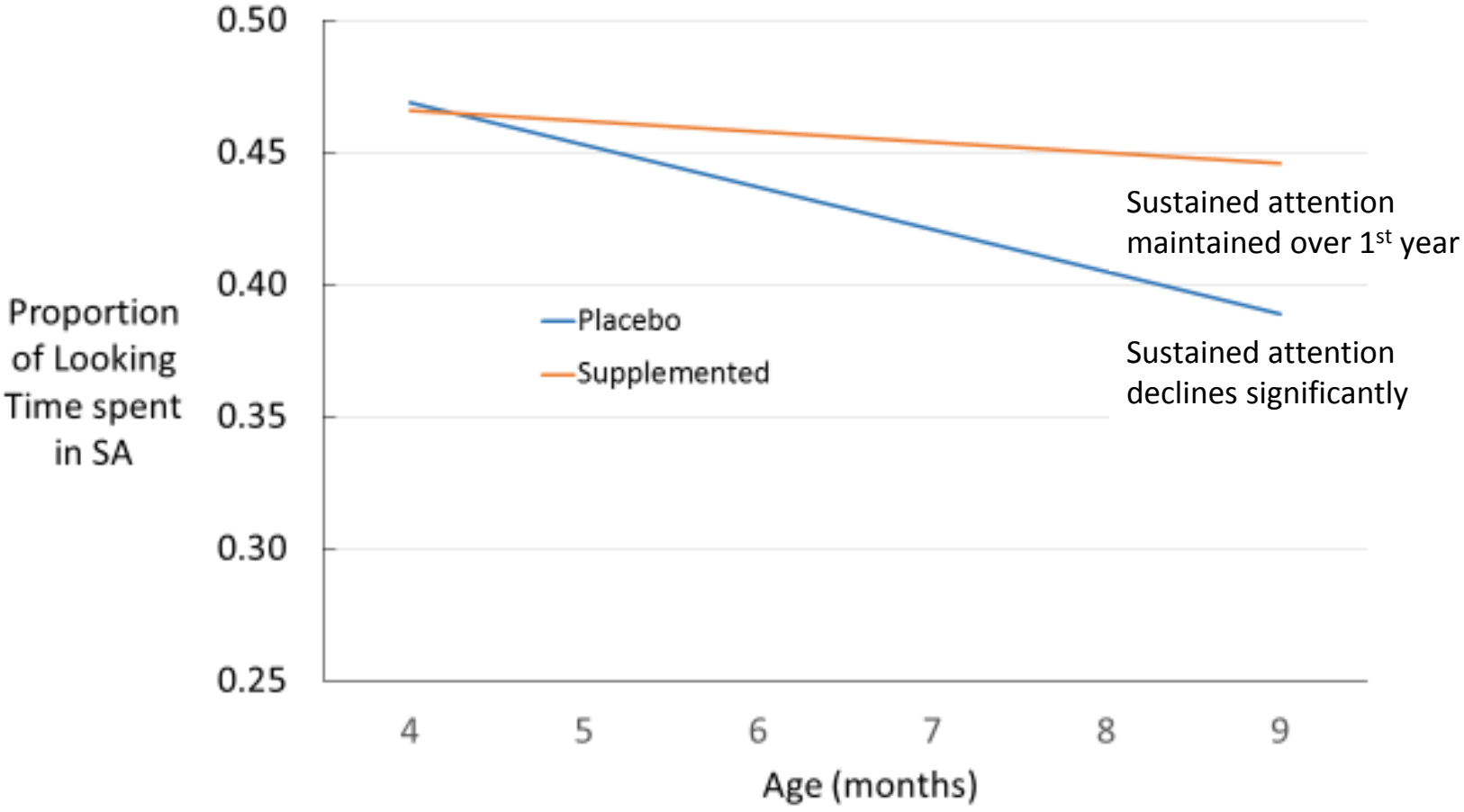
Cognitive Outcomes: Visual Attention in Infancy



Colombo J, Gustafson KM, Gajewski BJ et al. (2016). *Pediatr Res*, in press.

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RESEARCH ARTICLES

The Developmental Course of Habituation in Infancy and Preschool Outcome

John Colombo
Department of I
Schiefelbusch Institute
University

D. Jill S
Department o
University

W. Allen
Schiefelbusch Institute
University

Julie M. I
Clinical Child Psychol
University

Otilia M
Department o
University

9

Early Attentional Predictors of Vocabulary in Childhood

JOHN COLOMBO, D. JILL SHADDY, OTILIA M. BLAGA, CHRISTA J. ANDERSON, KATHLEEN N. KANNASS, AND W. ALLEN RICHMAN

Intelligence 37 (2009) 106–113

Contents lists available at ScienceDirect

Intelligence

ELSEVIER

Structure and continuity of intellectual development in early childhood ☆

Otilia M. Blaga [a], D. Jill Shaddy [a], Christa J. Anderson [a], Kathleen N. Kannass [b], Todd D. Little [a], John Colombo [a,*]

[a] *The University of Kansas, USA*
[b] *Loyola University of Chicago, USA*

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Prenatal Supplementation with DHA

- ***Dramatically Improved Pregnancy Outcomes***
  - Economization of findings show enormous potential savings for US health care system
- ***Long-Term Consequences for Cognitive Development***
  - Findings consistent with improved cognition and IQ seen in previous studies
  - Longitudinal tracking and assessment can be useful in documenting, assessing, and economizing the results of other prenatal risks (e.g., Zika).

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Thank you

Research-based solutions for the challenges of human health and development.

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Cerebral Palsy: Prenatal risk factors and rehabilitation opportunities

Alison Cernich, Ph.D., ABPP-Cn

Director, National Center for Medical Rehabilitation Research

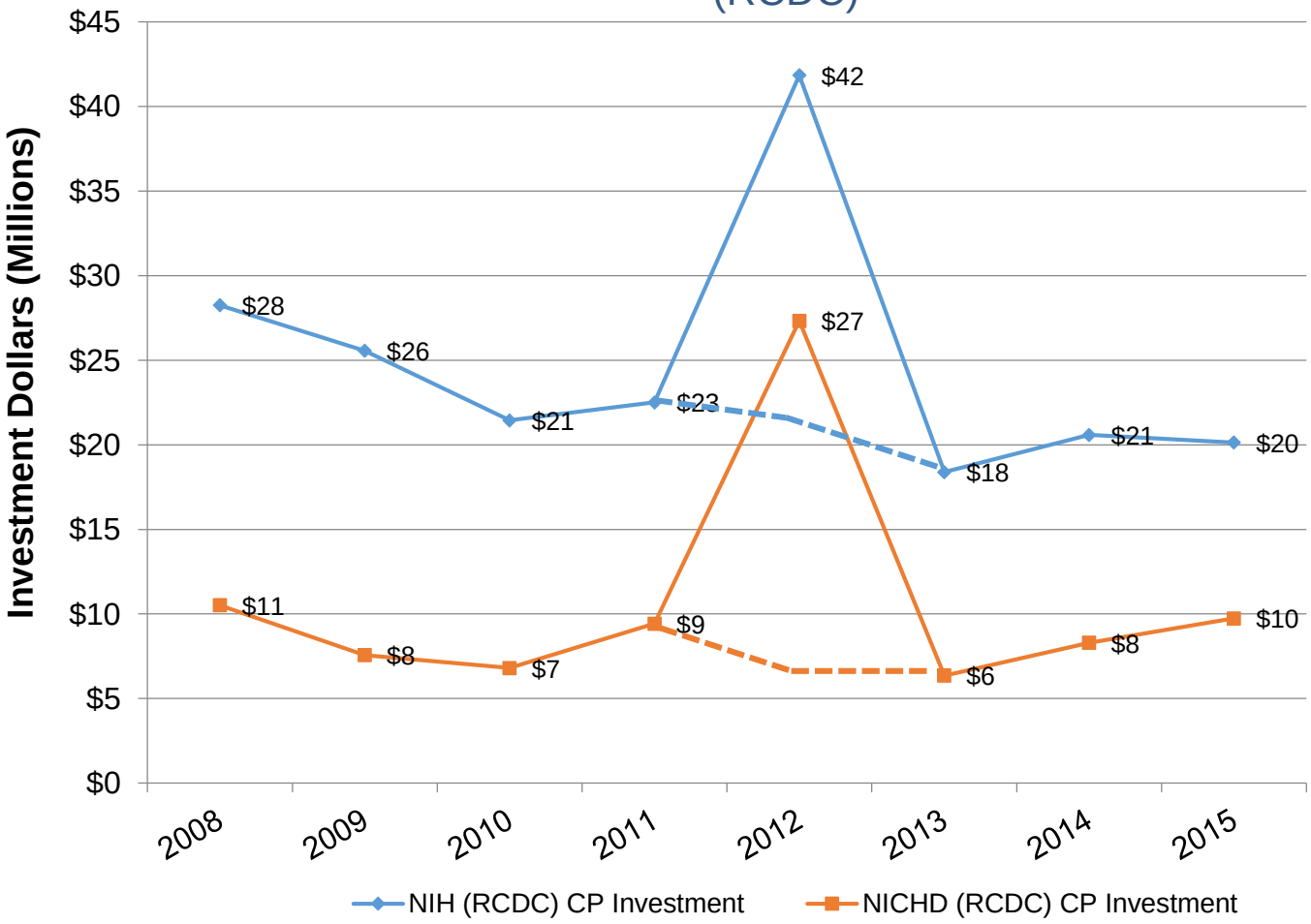
NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

Cerebral Palsy: Description

- A neurodevelopmental disorder that affects movement, muscle tone, posture
  - Can impact cognition, sensation, perception, and behavior
  - Secondary issues include muscle contractures and joint and musculoskeletal problems
- Results from prenatal, perinatal, and early postnatal events that affect primary motor pathways
  - Risk factors include low birth weight, premature birth, gestational infections, perinatal loss of oxygen or blockage of blood vessels in the brain, asphyxia at birth, early childhood brain trauma
- CP cannot be conclusively diagnosed until age 2.
- Incidence is 2-4 individuals per 1,000 live births; affects 17 million people worldwide
- Few, if any, treatments with strong and consistent affects to improve functioning; early therapy and assistive technology can treat impairments and reduce secondary conditions

NIH and NICHD Cerebral Palsy Investment Dollars, FYs 2008 – 2015

(RCDC)



Note: in 2012 a large intramural lab reported a pilot project in CP, and because RCDC does not prorate $, a large increase was shown. The dashed lines show what the CP reported $ would have been if this large lab had not been included.

NICHD: Prevention of Cerebral Palsy

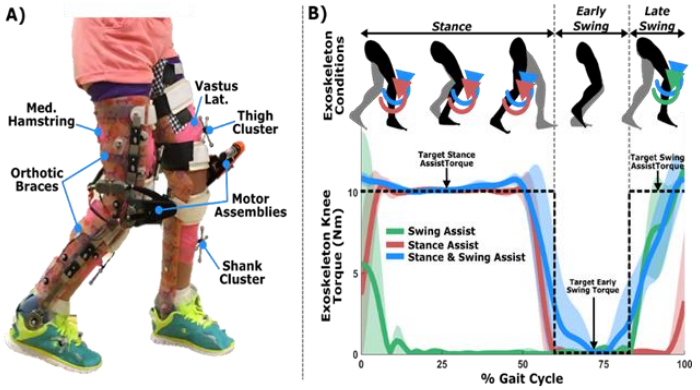
- Investigators in the Maternal Fetal Medicine Units Network of NICHD conducted a large clinical trial to determine the effectiveness of maternal antenatal magnesium sulfate ($MgSO_4$) to prevent neonatal cranial ultrasound abnormalities and cerebral palsy (CP)
- $MgSO_4$ was associated with reduction in CP in children at 2 years of age (Rouse, 2009); decreased cranial ultrasound abnormalities partially explain the decrease in CP in infants born at less than 32 weeks (Hirtz et al., 2015)

NICHD: Rehabilitation for Cerebral Palsy

- The National Center for Medical Rehabilitation Research is funding six clinical trials involving approaches including
  - constraint-induced movement therapies (1R01HD068345, 1R01HD081120)
  - neurorehabilitation therapies (1R01 HD074574)
  - intense physiotherapies (1R01HD079498)
  - daily versus weekly rehabilitation delivery for young children with cerebral palsy (1R01HD083384)
- Additional studies that focus specific impairments such as: devices to help with walking, fine motor movement of the hand, use of neuromodulation techniques to improve motor function, and basic understanding of muscle function and motor learning

Cerebral Palsy: NIH Intramural Research

- Diane Damiano, PhD PT is Chief of a laboratory in the Rehabilitation Medicine Department, NIH Clinical Center that conducts clinical research in Cerebral Palsy (damianod@cc.nih.gov)
- Dr. Damiano's lab works closely with NICHD and NINDS on workshops and conferences and helps to inform extramural on state of the science research.
- Recent and current projects include:
  - Device-augmented locomotor training in children with spastic diplegia
  - Mobile brain imaging technologies (EEG and Near-infrared Spectroscopy) to study cortical control during functional motor tasks in CP
  - Wearable robotic exoskeleton with motor and FES-assist for crouch gait in CP
  - Role of dopamine transmission genes in motor learning
  - Investigation of muscle synergies in CP

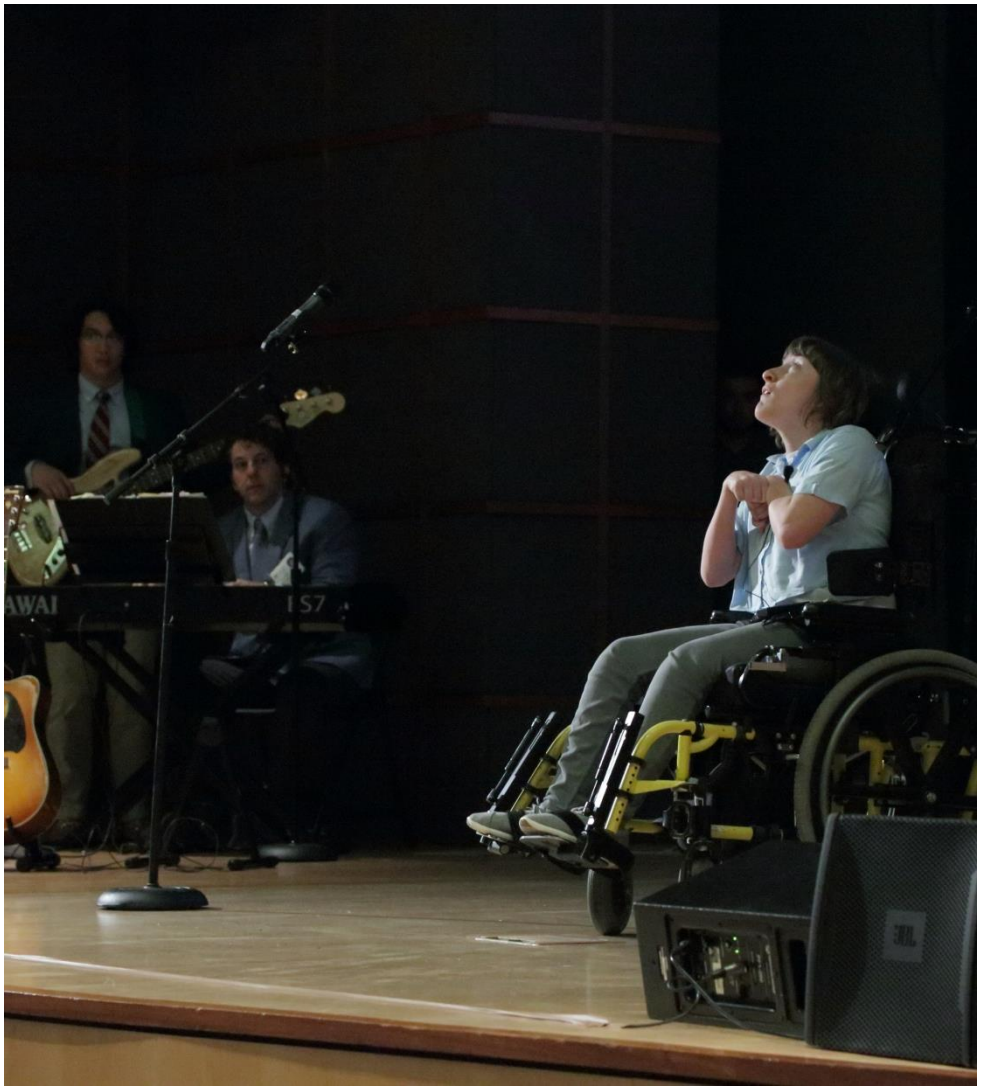


Cerebral Palsy: NIH Efforts

- Development of Common Data Elements for Cerebral Palsy Research (NINDS program; NICHD collaborating)
- Recent Workshops
  - November 2014 – NICHD and NINDS along with American Academy for Cerebral Palsy and Developmental Medicine (AACPDM), the Cerebral Palsy International Research Foundation (CPIRF) and Reaching for the Stars hosted a Workshop on Research Gaps in the Treatment of Cerebral Palsy
  - March 2016 – NICHD, NINDS along with AACPDM, CPIRF and Reaching for the Stars hosted a Cerebral Palsy Workshop on Basic and Translational Research
- Currently 634 CP trials listed in ClinicalTrials.gov

Rehabilitation Research Plan & Conference

- May 2016 – Rehabilitation Research at NIH: Moving the Field Forward
- September 2016 - NIH to submit the Rehabilitation Research Plan to HELP Committee



Same Sky Project, Amy