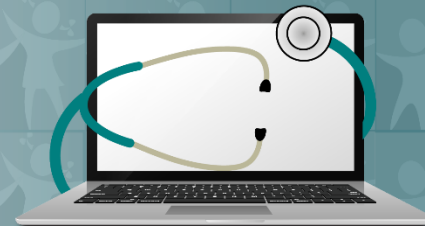




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Topics included:
Air Quality, Pesticides,
Natural Disasters, BPA,
Mold, Lead, Mercury



Insect repellants during pregnancy in the Zika era

Blair Wylie, MD MPH, Maternal-Fetal Medicine, Mass General Hospital
Rose Goldman, MD, Harvard School of Public Health
Region 1 PEHSU

Input/ review of Zika slides: Dr. Andrea Ciarinello, Infectious Disease, Mass General

Dr. Laura Riley, Maternal-Fetal Medicine, Mass General

Input/review of repellent slides: Region 1 PEHSU staff (Goldman, Woolf, Hauptman)

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Conflicts of Interest

No financial conflicts of interest in any topic discussed today.

Funding Information

The New England PEHSU, a Pediatric Environmental Health Specialty Unit, prepared this presentation.

This material was supported by the American Academy of Pediatrics (AAP) and funded (in part) by the cooperative agreement FAIN: **1U61TS000237-02** from the Agency for Toxic Substances and Disease Registry (ATSDR).

Acknowledgement: The U.S. Environmental Protection Agency (EPA) supports the PEHSU by providing partial funding to ATSDR under Inter-Agency Agreement number **DW-75-95877701**. Neither EPA nor ATSDR endorse the purchase of any commercial products or services mentioned in PEHSU publications

Objectives

- Describe the effects of Zika virus during pregnancy
- Examine available toxicity data for the two insect repellants suggested for personal protection against Zika
 - - *N, N*-diethyl-30methylbenzamide (DEET)
 - - Permethrin
- Evaluate epidemiologic data from human pregnancies about the effects of DEET and permethrin during pregnancy



Zika and Microcephaly

Zika Virus Background

- Flavivirus
 - Single-stranded RNA virus
 - Related to dengue, yellow fever, Japanese encephalitis, West Nile virus, St. Louis encephalitis
 - Neurotropic
- Vector borne illness
- Human vectors
 - Anthroponotic (human→vector→ human)
 - Other transmission modes
 - Perinatal
 - Sexual
 - Transfusion
 - Breast milk (theoretical)



Zika Virus

- *Aedes aegypti* – most efficient vector
 - Feeds primarily on humans; often bites multiple humans in single blood meal, hard to appreciate the bite, close contact with humans
 - Daytime feeder
 - Also transmits dengue, chikungunya, yellow fever
- *Aedes albopictus*
 - Feeds primarily on animals
 - Also transmits dengue, chikungunya, yellow fever, WNV, JE, EEE
 - Can survive in more temperate climates, extending potential area for



Aedes aegypti

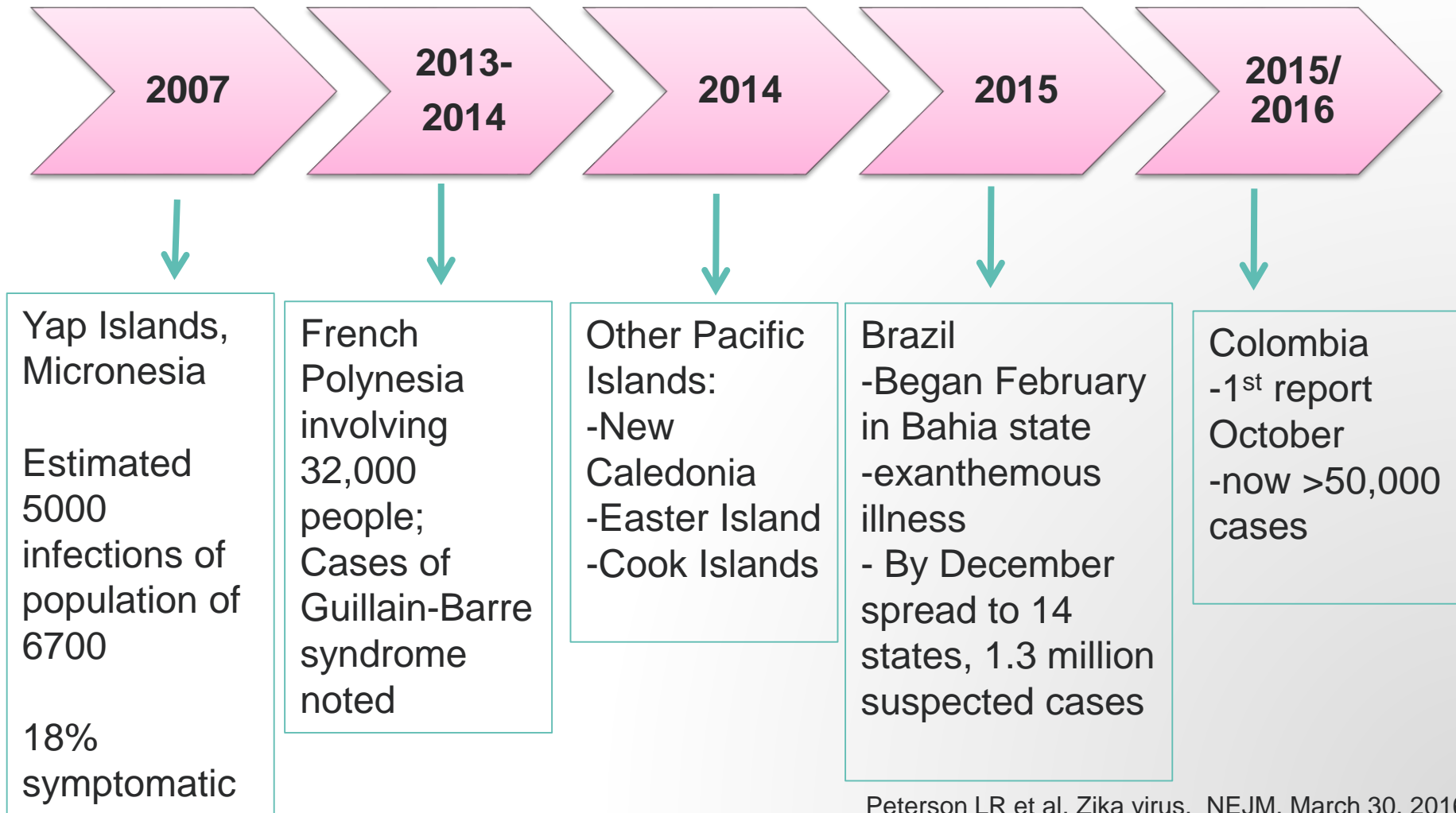


Aedes albopictus

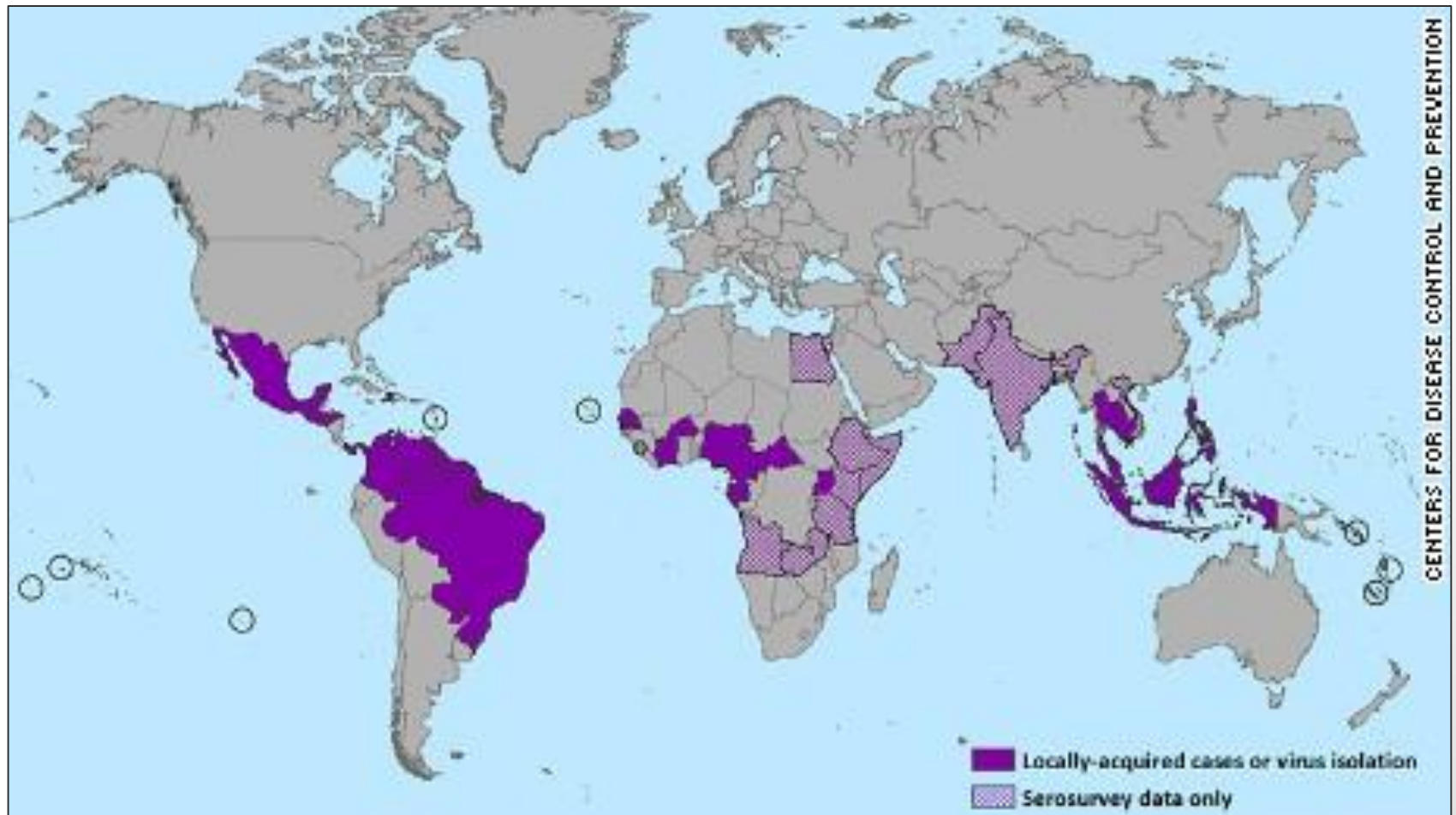
Zika Virus History

- Monkeys in Zika Forest, Uganda (1947)
- Humans in Uganda (1950s)
- Endemic in parts of Africa and Asia (seroprevalence studies)
- Human illness first recognized in Nigeria (1953)
- Sporadic cases until 2007 (Micronesia outbreak)

Zika Virus – More recent outbreaks

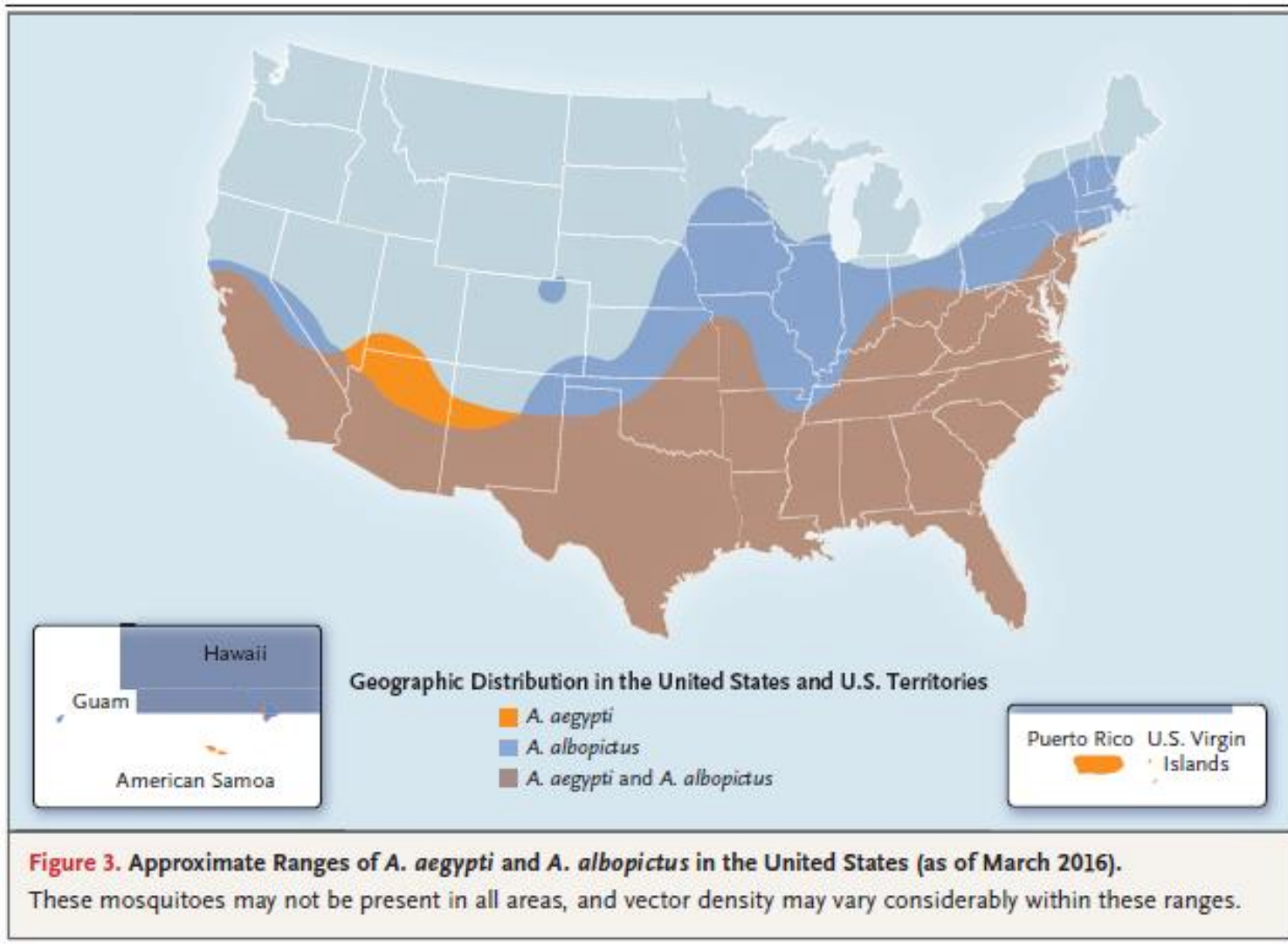


The evolving Zika map



Available online at [cdc.gov](https://www.cdc.gov)

Aedes mosquitoes in the US



Zika Virus - Brazil

- Spring 2015: 1st Zika cases in Brazil reported
- Sept 2015: Increase in infant microcephaly
 - Historical incidence 0.5/100,000 live births
 - Under-reported in past (HC not routinely measured)
 - Europe: 1-2/100,000
- 2015: 20/100,000 live births (>3,000 cases)

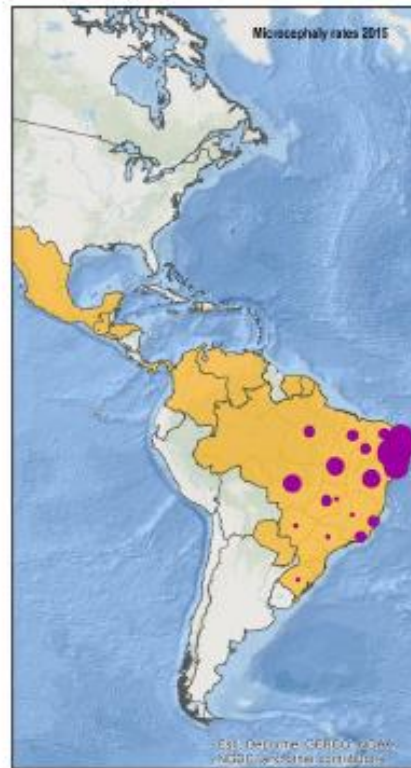
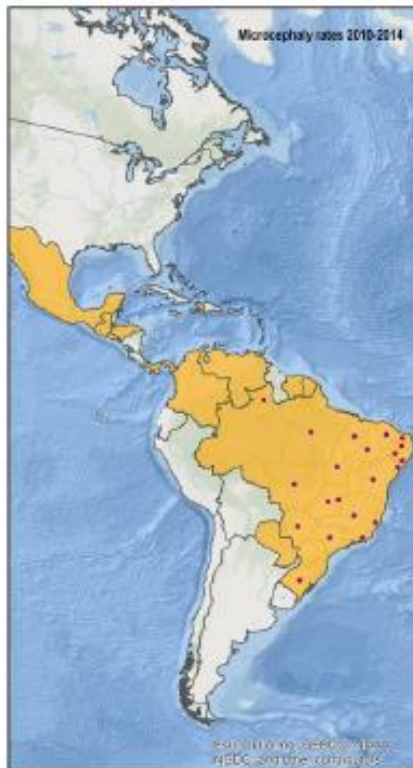
Historic number of cases of Microcephaly in Brasil 2010 - 2015

	2010	2011	2012	2013	2014	2015
Brasil	153	139	175	167	147	3,530

Source: Brasil Health Ministry

Zika Virus - Brazil

Comparison of the rates of microcephaly in the Americas and Caribbean from 2010-2014 and 2015



Updated as of Epidemiological Week 52
(December 27, 2015 – January 2, 2016)

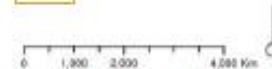
Microcephaly rates by state in Brazil
(cases per 1,000 live births)

- 0.1-1.0
- 1.1-15.0
- 15.1-30.0
- 30.1-45.0
- 45.1-88.6

Countries

Countries with Zika confirmed cases

- Epi Week 52 2015
- Country limits
- Brazil State Boundaries



Data Source:
Reported from the
IHR National Focal
Points and through
the Ministry of
Health websites.

Map Production:
PAHO-WHO AD CHA
IR ARO

Source: Pan American Health Organization, Epidemiological update, 17 January 2016

Microcephaly

- Small head compared to infants of same sex/age
- Implications for cognitive and neurologic function



Baby with Typical Head Size



Baby with Microcephaly



Baby with Severe Microcephaly

April 14, 2016

SPECIAL REPORT

**Zika Virus and Birth Defects — Reviewing the Evidence
for Causality**

Sonja A. Rasmussen, M.D., Denise J. Jamieson, M.D., M.P.H.,
Margaret A. Honein, Ph.D., M.P.H., and Lyle R. Petersen, M.D., M.P.H.

Rasmussen et al. NEJM . April 2016.
Available online at <http://www.nejm.org/doi/full/10.1056/NEJMoa1602412>

Shepard's criteria for proof of teratogenicity in humans

- 1) Proven exposure to the agent at one or more critical times during prenatal development
- 2) Consistent findings by ≥ 2 high-quality epidemiologic studies with:
 - control of confounding factors
 - sufficient numbers
 - exclusion of positive and negative bias factors
 - Prospective studies if possible and relative risk

Shepard's criteria for proof of teratogenicity in humans

- 3) Careful delineation of clinical cases, a specific defect or syndrome is very helpful
- 4) Rare environmental exposure that is associated with rare defect
- 5) Teratogenicity in experimental animals important but not essential
- 6) Association should make biologic sense

Evidence linking microcephaly to maternal Zika

- Temporal association of both Zika and microcephaly epidemics in Brazil *and French Polynesia*
- High rates of microcephaly among infants born to mothers with antecedent acute Zika infection
- Zika RNA in amniotic fluid of microcephalic fetuses
- Zika RNA in brain tissue of microcephalic fetuses/infants (neurotropic)
- Mutation identified in currently circulating virus, distinct from virus circulating previously

Spectrum of Pregnancy/Fetal Outcomes

- Prospectively enrolled pregnant women with rash and tested for Zika by PCR
- 88 women enrolled; 82% tested positive for Zika
- Ultrasound performed in 42 of the Zika+women and all Zika-neg

Spectrum of Pregnancy/Fetal Outcomes

U/S abnormalities in 29% of Zika+ and 0% Zika-neg

- 2 fetal deaths (stillbirth)
- 5 growth restriction
- 4 microcephaly
- 6 with CNS lesions
 - 4 with ventricular calcifications
 - 2 with other- ventriculomegaly
- 7 with abnormal amniotic fluid or umbilical artery Dopplers



Zika Prevention for Pregnant Women

Recommendations for Zika Prevention in Pregnancy

- Avoiding travel to Zika endemic areas if pregnant
- Condoms or abstinence following travel of male partner to Zika endemic areas for remainder of pregnancy
- Family planning- Suggested wait times before attempting conception after possible exposure (travel or sexual)

	Women	Men
Zika symptoms	8 weeks after sx	6 months after sx
No Zika symptoms	8 wks after exposure	8 wks after exposure

<http://www.cdc.gov/zika/prevention/>

ACOG and SMFM joint statement. Practice Advisory: Updated Interim Guidance for Care of Women of Reproductive Age during a Zika outbreak. March 31, 2016.

Vector Control for Zika Prevention in Pregnancy

- Avoiding insect bites
 - Aedes: daytime and indoor/outdoor biters
 - Remove standing water
 - Air conditioning and/or screens; nets
 - Long sleeves and pants
 - Use EPA-registered insect repellants
 - Apply sunscreen first if using both (as repellants decrease SPF)
 - Don't use combination sunscreen/repellent products
 - Treat clothing with permethrin
 - Do not use permethrin directly on skin.

<http://www.cdc.gov/zika/prevention/>

ACOG and SMFM joint statement. Practice Advisory: Updated Interim Guidance for Care of Women of Reproductive Age during a Zika outbreak. March 31, 2016.

N, N-diethyl-3-methylbenzamide (DEET)



DEET

- Insect repellent in use since 1940s
- Now in use by 1/3 US population
- Purported mechanism of action:
 - Disturbs the receptors in the mosquito's antennae that allow it to locate humans
- Effectiveness increases with increasing concentration but plateaus by about 50%
- No evidence of age-dependent differential toxicity



DEET Exposure and Metabolism

- > 200 products with concentrations 4%-100% available in US
 - Above 30-50% not recommended
- Available in combination with sunscreen
 - Combination products not recommended
- Absorption from dermal exposure among non-pregnant human volunteers ranged 5-15%
- Rapid excretion (near complete by 24 hours)
- Does not accumulate in skin



DEET Toxicity- EPA review 1998 & 2014

- Doesn't pose human health concern
- Low acute toxicity
- Adverse effects mostly skin reactions
- Neurologic effects (seizures, encephalopathy) reported but rare
 - secondary to self-poisoning by ingestion or excessive dermal application
- Not a reproductive or developmental toxicant
- Not genotoxic
- Not a carcinogen

RCT of daily DEET application in 2nd/3rd trimester

- 897 pregnant women in malarious area:
- Randomized to:
 - Thanaka alone (local paste), n=448
 - DEET (1.7 g qd) + thanaka, n=449
- Apply nightly to exposed legs/arms
- Outcomes evaluated
 - Birth anthropometrics
 - Newborn neurologic examination
 - Anthropometrics and developmental milestones until 1 year



RCT of daily DEET application in 2nd/3rd trimester

- Exposure
 - 0% (0 of 30) urine samples with detectable DEET (LOD 0.1 ucg/mL)
 - 8% (4 of 50) cord blood samples with detectable DEET (range 1 – 2.44 ucg/mL)
 - can cross placenta
- Side effects
 - Skin warming more frequent with DEET
 - No difference in headache, dizziness, nausea, vomiting



RCT of daily DEET application in 2nd/3rd trimester

No statistically significant differences between groups.

	DEET n=449	Control n=448
Birth weight (g)	2868	2853
Birth length (cm)	48.0	48.5
Head circ (cm)	32.7	32.8
Arm circ (cm)	10.1	10.0
Neurologic exam at birth (optimality score)	18.5	19
Developmental delay at 1 year	2.3%	1%

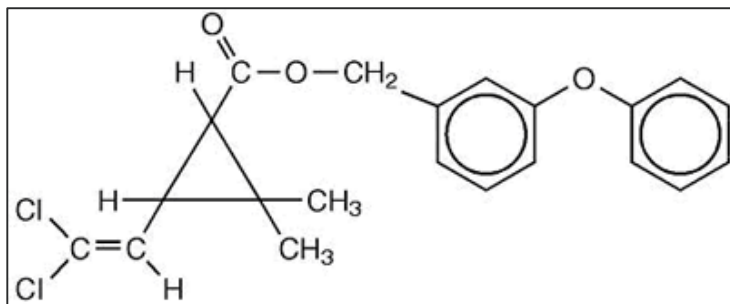


Permethrin



Permethrin Overview

- An insect repellent and insecticide
- Used to treat clothing, bednets
 - Only pesticide currently registered to treat fabric
- Also available as spray



EPA Permethrin Fact Sheet.

https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/fs_PC-109701_1-Jun-06.pdf

Permethrin is a pyrethroid insecticide

- Pyrethrins are insecticides derived from the extract of chrysanthemum flowers
- Pyrethroids are synthetic forms of pyrethrins
- Neurotoxicant to insects
 - Inhibits sodium channels in the nerve cell
 - Highly toxic to fish and bees as action negatively correlated with temperature (worse for) cold-blooded animals



Pyrethroid toxicity to humans

- Poorly absorbed by human GI tract and skin
- Generally quickly metabolized by liver enzymes
- Side effects: occasional numbing, tingling, burning to skin (reversible)
- Active ingredient often dissolved in solvent like carrier, which may have side effects
- Excessive exposure → acute neurotoxicity including n/v, weakness, salivation, shortness of breath, seizures

Dermal exposure to topical permethrin

- Pharmaceutical use: Topically as cream to treat scabies
 - Class B by FDA during pregnancy
 - WHO compatible with breastfeeding
- Absorption $<1\%$ of total dose when applied topically to scalp or to skin (as single exposure)
- Elimination of metabolite near complete by 1 week



Exposure to permethrin from treated fabrics

- Exposure studies conducted in German and US military personnel wearing permethrin-treated uniforms
- Exposure levels measured by urinary metabolites
 - 200 x higher exposures (when comparing median excretion) compared to general population background exposure
 - Exposure corresponded with duration of exposure
 - Calculated daily exposures still 6-7 fold lower than WHO Acceptable Daily Intake for oral ingestion (25 $\mu\text{g}/\text{kg}/\text{day}$)

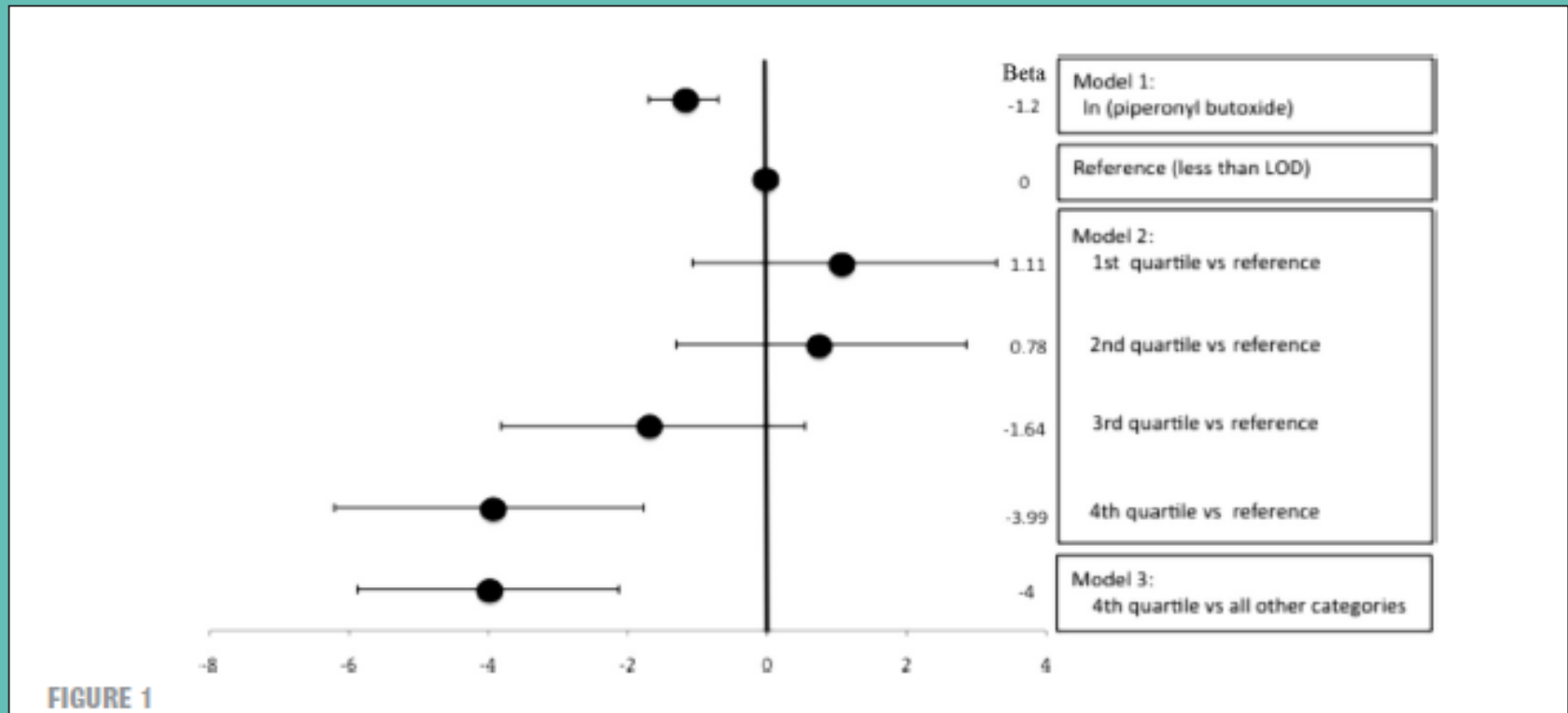
Developmental neurotoxicity of pyrethroids?

- Younger mammals may be more susceptible
 - Mammalian sodium channels have complex regional and temporal ontogeny
- Experimental and preliminary epidemiology suggest prenatal exposure to pyrethroids may adversely effect learning and behavior
 - mostly animal data; very little human data
- Potential for developmental neurotoxicity at low level exposures to developing fetus or newborn not well understood

Risk of delayed mental development in children, age 36 months

Exposure:

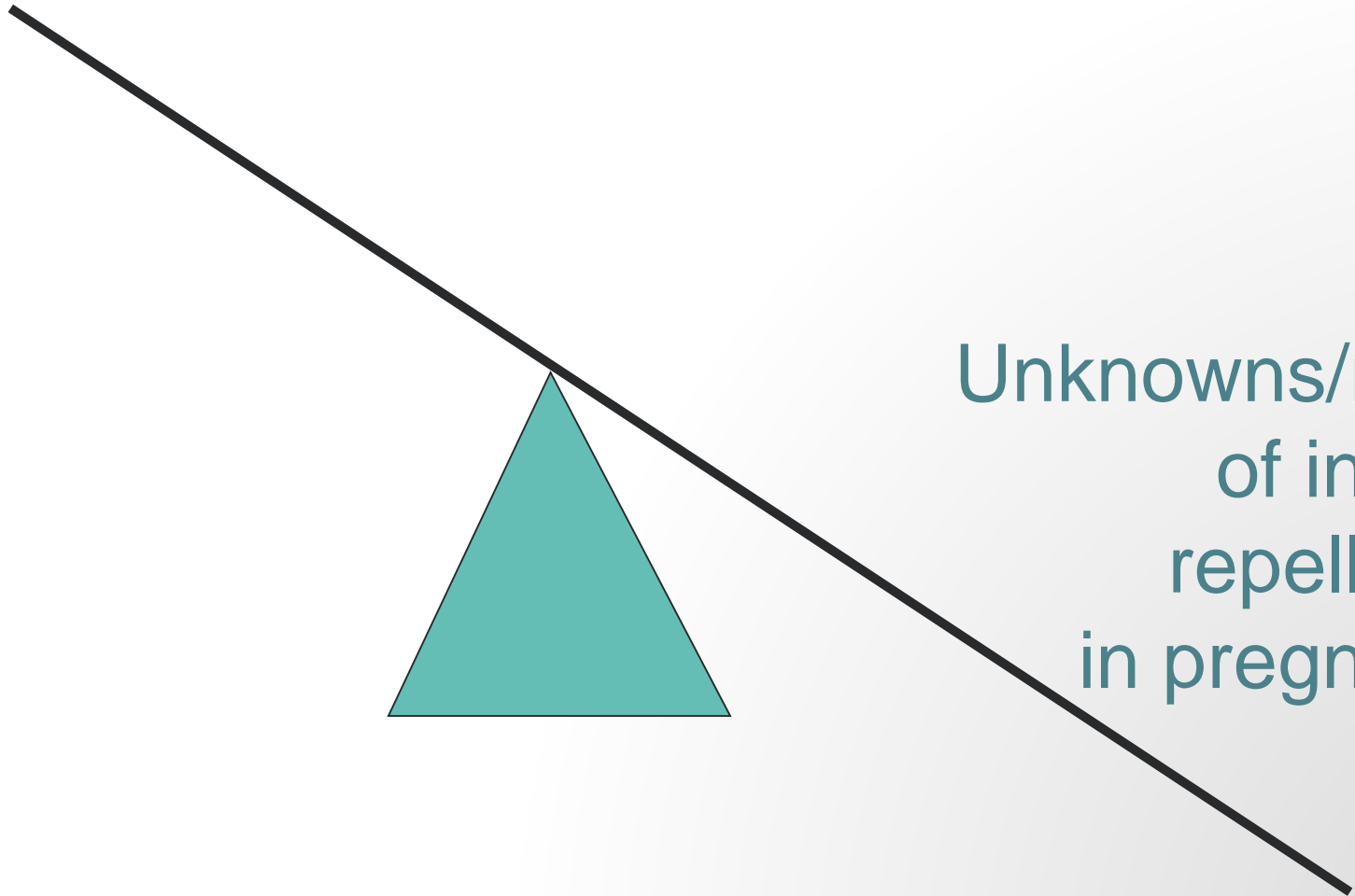
piperonyl butoxide (PBO*) in prenatal personal air samples



*PBO is a nonspecific indicator of pyrethroid use.

Are we sending the right message about DEET/Permethrin for prevention of Zika?

Risks of Zika to fetus



Unknowns/risks
of insect
repellants
in pregnancy

What about wider issues of vector control?

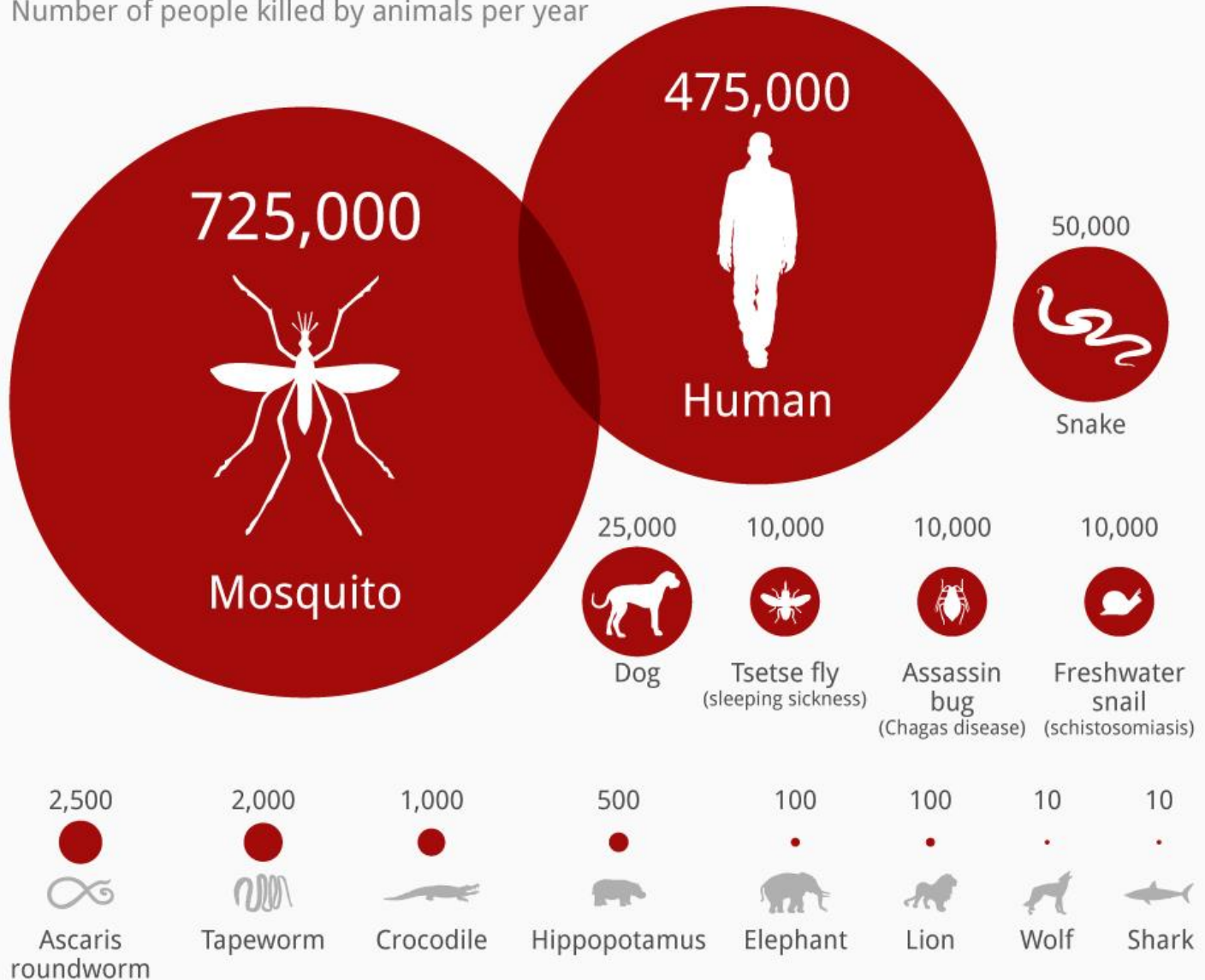
- Climate change and rise of vector borne illness
- Insecticide spraying
 - Malarious areas for years have had to contend with the risks/benefits of spraying
 - Are there alternative applications that minimize exposure to the wider population?
- Insecticide resistance
- Impact of chronic low level exposure to larger population

WHO recommended insecticides for indoor residual spraying against malaria vectors

<i>Insecticide compounds and formulations¹</i>	<i>Class group²</i>	<i>Dosage (g a.i./m²)</i>	<i>Mode of action</i>	<i>Duration of effective action (months)</i>
<i>DDT WP</i>	OC	1-2	contact	>6
<i>Malathion WP</i>	OP	2	contact	2-3
<i>Fenitrothion WP</i>	OP	2	contact & airborne	3-6
<i>Pirimiphos-methyl WP & EC</i>	OP	1-2	contact & airborne	2-3
<i>Pirimiphos-methyl CS</i>	OP	1	contact & airborne	4-6
<i>Bendiocarb WP</i>	C	0.1-0.4	contact & airborne	2-6
<i>Propoxur WP</i>	C	1-2	contact & airborne	3-6
<i>Alpha-cypermethrin WP & SC</i>	PY	0.02-0.03	contact	4-6
<i>Bifenthrin WP</i>	PY	0.025-0.05	contact	3-6
<i>Cyfluthrin WP</i>	PY	0.02-0.05	contact	3-6
<i>Deltamethrin SC-PE</i>	PY	0.02-0.025	contact	6
<i>Deltamethrin WP, WG</i>	PY	0.02-0.025	contact	3-6
<i>Etofenprox WP</i>	PY	0.1-0.3	contact	3-6
<i>Lambda-cyhalothrin WP, CS</i>	PY	0.02-0.03	contact	3-6

The World's Deadliest Animals

Number of people killed by animals per year



Additional Slides:

DEET and children

Children and DEET

- Studies show that products with higher amounts of DEET protect people longer.
 - Concentrations >30% provide no additional protection
- American Academy of Pediatrics (AAP) recommends that repellents should contain no more than 30% DEET when used on children.
 - Insect repellents also are not recommended for children <2 months.

Source: adapted from www.healthychildren.org

Tips for Using Repellents Safely with Kids

- **Dos:**

- Read the label and follow all directions and precautions.
- Only apply insect repellents on the outside of a child's clothing and on exposed skin. *Note: Permethrin-containing products should not be applied to skin.*
- Spray repellents in open areas to avoid breathing them in.
- Use just enough repellent to cover a child's clothing and exposed skin. Using more doesn't make the repellent more effective. Avoid reapplying unless needed.
- Help apply insect repellent on young children. Supervise older children when using these products.
- Wash children's skin with soap and water to remove any repellent when they return indoors, and wash their clothing before they wear it again.

- **Dont's:**

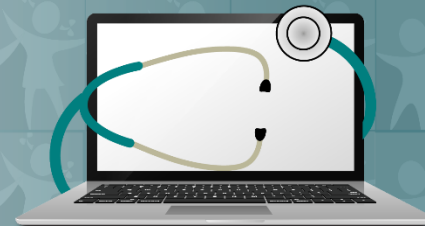
- Never spray insect repellent directly onto a child's face. Avoid the eyes and mouth.
- Do not spray insect repellent on cuts, wounds, or irritated skin.
- Do not use products that combine DEET with sunscreen. The DEET may make the sun protection factor (SPF) less effective. These products can overexpose a child to DEET because the sunscreen needs to be reapplied often.

Source: adapted from www.healthychildren.org



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