Preventing Congenital Zika Syndrome: Lessons Learned from Rubella Elimination

Warkany Lecture
Teratology Society
June 25, 2017
José F. Cordero, MD, MPH
Josef Warkany was an M.D. He was a superb clinician and a very good basic scientist. James Wilson was an embryologist with a Ph.D. degree, who was an impeccable investigator with unquestionable integrity. Clarke Fraser was a geneticist with both an M.D. and a Ph.D. degree. So, thanks to Clarke, the founding members had two Ph.D. degrees and two M.D. degrees among them.

We were in perfect balance from the inception of the Society, at least with regard to the degrees held by the three senior founding members.

Is this diversity an important part of our Society?

Our membership consists of the following:

1. Basic scientists at universities, research institutes, and government laboratories working in the fields of experimental teratology, embryology, toxicology, pharmacology, anatomy, cell biology, physiology, psychology, and molecular biology

2. Basic scientists in industry working in the above-mentioned fields

3. Basic scientists and clinicians working in research, regulatory affairs, or administration at the National Institutes of Health, Environmental Protection Agency, OSHA, Food and Drug Administration, or Centers for Disease Control

4. Physician-scientists, physician-clinicians and adjunct clinicians, which includes pediatricians, obstetricians, pathologists, clinical geneticists, clinical teratologists or dysmorphologists, genetic counselors, and teratology counselors

5. Epidemiologists and statisticians who may be basic scientists or clinically trained. Have we maintained this diversity? It is difficult to say, based on the original earned degree of the members, since medical trainees frequently take up basic science, and sometimes a Ph.D.-trained person deals largely with clinical analysis such as epidemiology. In terms of the interests of the presidents, 23 have been from the basic sciences (Ph.D.), 12 have had medical training; 4 have had MD-Ph.D. degrees, and one had dental training. The total number of disciplines and main research areas of the presidents are given in Table 6.

6. Twenty of the 40 presidents were primarily involved in embryology, which is taken to include experimental teratology. Thought has been given to rotating the type of members of the council and officers in hope of increasing versatility. We suggest that this idea be studied. However, classification of individuals may be indistinct and the availability of good candidates in each category might be limited at times.

We doubt that anyone would argue against diversity, which provides a wide range of expertise necessary to carry out the responsibilities of the Teratology Society to the scientific community, and to the public. The interchange between disciplines has been highly educational to the membership. One of the greatest assets of the Teratology Society is the scientific and clinical diversity of its membership. It is in the best interests of the Society to perpetuate this diversity.

ANTHROPOMORPHIC ANALYSIS OF THE SOCIETY

Comparing the progression of the Teratology Society to human developmental stages may be derided by a few members, but it does serve as a framework for discussion. If this section produces controversy, we hope the result will turn into a constructive influence on the Society. Other societies seem to have a birth, childhood, adolescence, young and middle age and old age and senescence. Since we are a society based on the study of growth and development, there is some merit to this approach. Table 5 charts our membership output of abstracts as well as the types of scientific techniques used in the annual meeting abstracts.

Concept of the Teratology Society occurred in 1959 during a walk on the beach in Florida. The discussion followed a number of birth defects meetings (‘courtship’) which were sponsored by the National Institutes of Health, National Foundation (March of Dimes), Association for

Fig. 1. Founders in the late 1950s. From left to right: James Wilson, F. Clarke Fraser, and Josef Warkany.
Key Points

• Zika is one of many emerging diseases the world would face in this century.
• Preparedness for emerging infections must be a priority
• There are lessons to be learned from Zika emergence and from Rubella elimination
• Control and elimination of Zika to prevent Congenital Zika Syndrome is a complex proposition that would require multiple strategies in order to succeed
Zika: The Road Ahead

• Zika Emergence is a call to:
  • Strengthen public health infrastructure at the local, state, national and global levels
  • Expand and strengthen collaboration between all sectors of community life including inserting public health in social media
  • Connect and speed up basic science, vaccine and product development and its translation to public health practice
Outline

• Emerging infections as a global challenge
• The Case of Zika Emerging in Puerto Rico
• From Rubella Vaccine to an Effective Zika Elimination Strategy
Emerging, Reemerging and Intentional Dispersal of Infectious Diseases: A Global Public Health Challenge

Global Chemical Production, 2000-2050
Another Source of Emerging Diseases

- In the US alone
  - about 83,000 chemical substances on sale since 1979
  - about 62,000 were in commercial use in 1976 when the Toxic Substances Control Act was enacted.
  - Few chemicals have been evaluated for safety or teratogenicity

Source: Environmental Health Perspectives • volume 117 | number 8 | Page 1203 August 2009
The Concept of Emerging Diseases...

Special Issue

Emerging Infectious Diseases: A Brief Biographical Heritage

D. Peter Drotman
Centers for Disease Control and Prevention, Atlanta, Georgia, USA

The concept that infectious (and other) diseases emerge and reemerge is not new, and neither is the search for causes of disease emergence. However, societies frequently overlook or forget that microbes evolve, adapt, and emerge in response to nonmicrobial and even nonbiologic changes in the physical and social environment. Sometimes we need to be rudely reminded of this lesson. Two scientists who have delivered such reminders, both in the vision of these scientists and anthropologist, and Joshua Lederberg, the founder of cellular microbiology, were not well described, he seems to have correctly diagnosed typhus (or possibly relapsing fever) as the cause of the Silesian epidemic (1). Even though Virchow's diagnosis cannot be confirmed, it is consistent with clinical...
Zika: History of Discovery, 1947

• Zika is a virus of the same family as dengue and yellow fever
• Transmitted by mosquitos, *Aedes aegypti*, and other Aedes species, the same vector that also transmits dengue, chikungunya, and yellow fever
• Zika is a flavivirus

FROM:
Accessed March 1, 2016
How has Zika Spread Around the World?

Countries with Active Zika Transmission, CDC, 2017

Clinical Symptoms

- Mild or no symptoms
- Rash, headache, joint pain, red eye (non-purulent conjunctivitis)
- 3-12 days post-infection
- Last for about one week
- Supportive treatment only
- Persistent in semen and eye
- 4 of 5 infected are asymptomatic

Source: CDC, 2016
Characterizing the Pattern of Anomalies in Congenital Zika Syndrome for Pediatric Clinicians

Cynthia A. Moore, MD, PhD; J. Erin Staples, MD, PhD; William B. Dubyns, MD; André Pessoa, MD; Camila V. Ventura, MD; Eduardo Borges da Fonseca, MD, PhD; Erlane Marques Ribeiro, MD, PhD; Liana O. Ventura, MD; Norberto Negreira Neto, MD; J. Fernando Arena, MD, PhD; Sonja A. Rasmussen, MD, MS
Where is Puerto Rico?

- Located in the West Indies, next to Dominican Republic and Haiti
- United States Territory since 1898
- Has a population of about 3.4 million
- Endemic area for dengue, chikungunya, and now Zika
- A major portal of entry for emerging tropical diseases in US soil
Zika Virus Local Transmission, Puerto Rico, 2015-2016

FIGURE 1. Zika virus disease cases* (N = 30), by week of onset of patient's illness — Puerto Rico, November 23, 2015—January 28, 2016

Source: https://www.cdc.gov/mmwr/volumes/65/wr/pdfs/mm6506e2.pdf
Public Health Response to Zika, Puerto Rico, 2016

• Monitoring of Zika
  • Establishing Laboratory capacity
  • Monitoring all Zika-positive pregnant women
  • Monitoring microcephaly & other birth defects
  • Track Guillain-Barré syndrome cases

• Implement Risk Reduction Strategies
  • Community Engagement

• Establish a Vector Control Program
Puerto Rico established an arboviral surveillance with weekly reports of presumptive and confirmed cases of Zika, dengue and chikungunya.

Zika Response, Laboratory Capacity, Puerto Rico 2016

• What was needed?
  • Sufficient capacity to
    • Test Zika samples
      • From 50 to 2000 tests per week
    • Track testing, results, and reporting
  • Trained laboratory and support staff
  • Sufficient laboratory supplies
    • PCR & IgM kits
Puerto Rico: Zika in Pregnancy 2016-2017

- Confirmed Cases: 40,357 → ~200,000 infected
- Pregnant Women: 3,833
  - 1,919 (50%) Symptomatic → ~9,500 infected
  - 1,921 (50%) Asymptomatic → ~20% detected
- Guillain-Barré Cases: 70 (53 confirmed Zika, 17 flavivirus)
  - 2 deaths
- Congenital Defects
  - 42 cases
Zika Response: Protection of Blood Supply
Blood Donors Surveillance for Zika,
Puerto Rico, 2016

Active Infections

<table>
<thead>
<tr>
<th>Month</th>
<th>Estimate</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>April</td>
<td>~10,000</td>
<td>0.3%</td>
</tr>
<tr>
<td>May</td>
<td>~26,000</td>
<td>0.8%</td>
</tr>
<tr>
<td>June</td>
<td>~46,000</td>
<td>1.4%</td>
</tr>
<tr>
<td>July</td>
<td>~60,000</td>
<td>1.8%</td>
</tr>
<tr>
<td>August</td>
<td>~70,000</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

Source: CDC, MMWR, 2016
Public Health Response to Zika, Puerto Rico, 2016

• Monitoring of Zika
  • Establishing Laboratory capacity
    • Need to surge capacity to >2,000 tests per week
  • Monitoring all Zika-positive pregnant women
  • Monitoring microcephaly & other birth defects
  • Track Guillain-Barré syndrome cases

• Implement Risk Reduction Strategies
  • Community Engagement

• Establish a Vector Control Program
Zika Community Education: Puerto Rico, 2016

- Need to convey message of urgency about Zika and particularly for pregnant women
  - How to be protected against mosquito bites?
    - CDC Zika kits
    - Clothing with long sleeves and pants
    - Screens in all doors and windows in the home
    - Use of air-conditioning to sleep
    - Remove mosquito breeding sources

[Image]

CDC’s Response to Zika
PREGNANT AND LIVING IN AN AREA WITH ZIKA?

Zika Prevention Kit for Pregnant Women

Your Zika Prevention Kit contains products to help prevent the spread of Zika. Please use these items to protect yourself against Zika virus. Always follow instructions on the product.

Bed Net
- If your room has mosquitoes in it, sleep under the bed net.
- Mosquitoes can live inside houses and will bite at any time, day or night.

Mosquito Spray
- A mosquito spray, such as the one in the kit, will help keep mosquitoes from biting you.
- Use only EPA registered mosquito spray like the one in the kit.
- Always follow the directions on the bottle.
- For this spray to work well you will need to put it on again as directed.
- Do not spray under your clothing.

Condoms
- During sex, it is possible to get Zika virus from a partner who has Zika. If you have sex during your pregnancy, you should use condoms the right way every time.
- Condoms can also help prevent HIV and other sexually transmitted diseases.

Standing Water Treatment Tablets
- Use water treatment tablets to kill mosquito eggs in standing water around your house, such as in rain barrels. Do not put them in water you drink.
- When used as directed, these tablets will not harm you or your pets (dogs and cats).

Permethrin Spray
- Spray your clothes with the bug spray called permethrin. This will help protect you from mosquito bites.
- Clothes sprayed with permethrin will protect you for 6 months. You can wash your clothes up to 6 times during the 6 weeks and the permethrin will still protect you.
- Make sure to read the directions on the bottle.
- Do not spray permethrin on your skin.

www.cdc.gov/zika
Zika Community Education: Puerto Rico, 2016

Challenges

• CDC Zika kits
  • Condom use
  • Permethrin resistance

• Cost of screens in households and air conditioning

• Public Perception
  • Is there a problem with Zika?
  • Zika is mostly a silent epidemic with 80% asymptomatic

• Impact on Tourism & Economy

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- **When used as directed, these tabs will not harm you or your pets (dogs and cats).**

Permethrin Spray
- Spray your clothes with the bug spray called permethrin. This will help protect you from mosquito bites.
- **Clothes sprayed with permethrin will protect you for 2 months. You can wash your clothes up to 8 times during the 2 weeks and the permethrin will still protect you.**
- Make sure to read the directions on the bottle.
- Do not spray permethrin on your skin.

www.cdc.gov/zika
Public Health Response to Zika, Puerto Rico, 2016

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  • Monitoring all Zika-positive pregnant women
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• Implement Risk Reduction Strategies
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• Establish a Vector Control Program
Major League Baseball Cancels Series In Puerto Rico Due To Zika Concerns

May 7, 2016 - 11:09 AM ET

MERRIT KENNEDY

Impact on Tourism and the Economy

SOURCE:
From Monitoring and Containment to Prevention: Countermeasures
Zika Countermeasures: Research and Development

- Research on biology of Zika infection
- Vaccine development
- Therapeutics
- Diagnostics
- Product development
  - Novel Vector Control Strategies
Rubella infection During Pregnancy causes Congenital Rubella Syndrome

• Rubella
  • A very mild disease in adults
  • First human infection to be recognized as a teratogen
• Congenital Rubella Syndrome
  • Triad of:
    • Sensorineural Deafness
    • Congenital Heart Disease
    • Cataracts


Dr. Norman McAlister Gregg
1892-1966
Congenital Rubella Syndrome
Clinical Findings

• Newborn disease
  • Meningo-encephalitis
  • Jaundice
  • Purpura
  • Thrombocytopenia
  • Hepatosplenomegaly
  • Low birth weight

• Microcephaly
• Glaucoma
• Cataracts
• Pigmentary retinopathy
• Congenital Heart Disease
  • PDA
  • Pulmonic Stenosis
• Radioluscent bone disease

Source: https://www.cdc.gov/rubella/about/photos.html#
Rubella Elimination: From 1963 to 2016


Congenital Rubella Syndrome Elimination, United States, 2005

FIGURE. Number of reported cases of rubella and congenital rubella syndrome (CRS), by year, and chronology of rubella vaccination recommendations by the Advisory Committee on Immunization Practices — United States, 1966–2004

Source: MMWR. March 25, 2005 / Vol. 54 / No. 11

Source: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4946a3.htm
Rubella Elimination, Americas Region, 2015

Americas region is declared the world's first to eliminate rubella

Historic achievement follows similar "firsts" against smallpox in 1971 and polio in 1994

Washington, D.C., 29 April 2015 (PAHO/WHO) — The Americas region has become the first in the world to be declared free of endemic transmission of rubella, a contagious viral disease that can cause multiple birth defects as well as fetal death when contracted by women during pregnancy.

This achievement culminates a 15-year effort that involved widespread administration of the vaccine against measles, mumps and rubella (MMR) throughout the Western Hemisphere. The announcement comes as 45 countries and territories of the Americas are participating in the 13th annual Vaccination Week in the Americas (April 25 to May 2).

WHO News

- Statement from UNICEF Executive Director Anthony Lake and WHO Director-General Margaret Chan on the cholera outbreak in Yemen as suspected cases exceed 200,000
- Abuse of older people on the rise — 1 in 6 affected
- WHO Director-General elect welcomes new funding for polio eradication
Approaches to Zika Elimination
Zika Vaccine:
Research and Development

• Vaccines
  • Zika Purified Inactivated Virus (ZPIV)
    • Inactivated Zika virus with a Japanese encephalitis protein shell
  • Moderna Zika Vaccine
    • lipid nanoparticle (LNP) encapsulated modified mRNA vaccine encoding wild-type or variant ZIKV structural gene
  • GeoVax & UGA
    • VLPs—virus-like particles—mimic a live virus but do not contain genetic material; they cannot replicate or cause infection, yet they elicit a strong immune response in the cells of the person being vaccinated.

• Others
Key Attributes of Candidate Zika Vaccines

- Highly effective > 90% efficacy
- Prevent infection during pregnancy
- Have the potential to control and eliminate Zika
Experience with Dengue Vaccine

**Efficacy by Serotype:**

- **Ranges:**
  - 42.3% to 77.7%
  - 50.2% to 80.9%

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**Table 3. Serotype-Specific Vaccine Efficacy.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vaccine Group</th>
<th>Control Group</th>
<th>Vaccine Efficacy (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>Person-Yr at Risk</td>
<td>Incidence Density (95% CI)</td>
<td>Person-Yr at Risk</td>
</tr>
<tr>
<td>Modified per-protocol analysis*</td>
<td>Cases no.</td>
<td>Cases no.</td>
<td>Cases no.</td>
</tr>
<tr>
<td>Serotype 1</td>
<td>66</td>
<td>66</td>
<td>6,196</td>
</tr>
<tr>
<td>Serotype 2</td>
<td>58</td>
<td>50</td>
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<tr>
<td>Serotype 3</td>
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<tr>
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<td>Intention-to-treat analysis</td>
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<td>Serotype 1</td>
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<td>Serotype 2</td>
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<td>Serotype 3</td>
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<td>Unknown</td>
<td>15</td>
<td>14</td>
<td>13,514</td>
</tr>
</tbody>
</table>

* The modified per-protocol analysis was performed at least 28 days after the third injection in all participants who had received three doses, regardless of protocol deviations.
**Aedes Aegypti** elimination in the Americas

- *Aedes aegypti* have been eliminated in the Americas at least three times, even before availability of DDT

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**FRED SOPER (1893 – 1977)**

Lead elimination of *Aedes aegypti* in the Americas during the first half of the 20th Century. Many of his approaches in vector control are used today.

Hawaii is planning to eliminate *Aedes aegypti*

**Source:** Wikipedia, 2017
Zika Response: Vector Control, Puerto Rico, 2016-2017

• There is a need to address vector control as a strategy to reduce transmission of Zika, dengue, and chikungunya

• Strategies should include:
  • Source reduction
  • Integrated control management
  • Novel approaches
  • All based on strong and well organized community engagement
Screwworm elimination in the Americas, 2016

Source:
https://www.ars.usda.gov/oc/timeline/worm/
Sterile Insect Techniques (SIT) for targeted mosquito elimination

Boy meets girl -----> no offspring

Irradiation -> random DNA changes -> Dominant Lethal Mutations

Genetic Engineering -> engineered DNA changes -> Dominant Lethal Mutations

Wolbachia -> Bacterial Infection -> Cytoplasmic Incompatibility
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- Control and elimination of Zika to prevent Congenital Zika Syndrome is a complex proposition that would require multiple strategies.
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  • Expand and strengthen collaboration between all sectors of community life including inserting public health in social media
  • Connect and speed up basic science, vaccine and product development and its translation to public health practice
It was once said that the moral test of government is how that government treats those who are in the dawn of life, the children; those who are in the twilight of life, the elderly; and those who are in the shadows of life, the sick, the needy and the handicapped.

https://www.brainyquote.com/quotes/quotes/h/huberthhu163688.html
Thank you!

¡Gracias!