Reducing infection-caused fetal death: a checklist-enhanced primary prevention approach

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“Equations inside Equations”

Theobold Smith’s Equation

Theobald Smith’s Equation

Inf = inoculum x virulence
Host Defenses

Number x Virulence
Host Defenses (Innate, Acquired)

Theobald Smith’s Equation

Rockefeller University: multiple discoveries in experimental pathology
Factors Supporting Behavior-Based Primary Prevention @ Infection Caused Stillbirth

- **Nature**
  - Doesn’t kill parent
  - Low frequency, low prevalence
- **Social/Epidemiology, Biases**
  - “Other people”
- **Gender Disparity**
  - “Women & Children first”?*
- **Economic**
  - “Willing to pay” “Bauman costs”
  - Bayesian low prevalence → testing challenges
- **Health Policy**
  - “No NIH for women”
- **Advocacy**

Protect yourself and your family using “do it yourself” behaviors

Global report on PTB and Stillbirth (SB): evidence for effectiveness of intervention


- Analyzed 2,000 intervention studies systematically → 2008 → 49 relevant and adequate
- **PTB: 11 intervention**
  - **High** → Medium → Low
- **SB PREVENTION**
  - Screening and treatment SYPHILIS (1940’s)
  - Treatment for malaria (Cochrane)
  - *Insecticide treated mosquito netting (Cochrane RR 0.67), “INTs”*
- **Primary prevention**

New Zika Virus Guidelines @ Asymptomatic Pregnant Women

MMWR 2017

- **Screen for risk of exposure/symptoms: everyone (patient/partner)**
- **“at risk” conduct NAT**
  - Nuclear acid testing at least once per trimester, unless already Positive
  - Consider NAT testing @ amniocentesis
**CHIKUNGUNYA VIRUS (CV): An update on the biology and pathogenesis of this emerging pathogen**

- Outbreaks Africa, Asia, Caribbean, Americas
  - *Aedes aegypti* AND *Aedes albopictus*
    - Subtropics → temperate climate
    - Acute inflammation: fever, rash, joint pain
  - Transmit to baby if mother infected @ birth
  - Miscarriages and SB in Reunion study
  - Avoid being bitten by "mosquitoes"
  - No specific Rx

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**Causes of death among STILLBIRTHs (SBs)**

- SBs @ 1/160 pregnancies in US ≥ 20 weeks
- X = Number of Infant Deaths
- "Systemic Evaluation"
- 663 women enrolled
  - Probable case of death 61%
  - Possible cause >6%
  - Obstetric conditions 29%
  - Placental conditions >3%
  - Structural 14%
  - "Infection" 12.9% (~AA)
  - Umbilical cord 10.4%

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**TORCH → LESS TORCHEZ**

<table>
<thead>
<tr>
<th>1965</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture, serology</td>
<td>Culture, serology</td>
</tr>
<tr>
<td>Animal</td>
<td>X rays, culture</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>Listeriosis</td>
</tr>
<tr>
<td>Others</td>
<td>Enterovirus</td>
</tr>
<tr>
<td>Rubella (measles, varicella)</td>
<td>Syphilis</td>
</tr>
<tr>
<td>Cytomagalovirus, coxsackie</td>
<td>STIs, strep B</td>
</tr>
<tr>
<td>Herpes, hepatitis B</td>
<td>HIV, syphilis, hepatitis B</td>
</tr>
<tr>
<td></td>
<td>Enteric</td>
</tr>
<tr>
<td></td>
<td>Zoonosis: malaria, Q fever (Coxiella burnetii), Lyme, WNV, dengue, yellow fever, arenavirus, leishmaniasis, rickettsia</td>
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Complexity

Complex systems are characterized by many independent components where low level actions produce high level results.

J. Werfel
Science 2014; 343: 754

Occam's Razor

Sir William Hamilton, 9th Baronet, Scottish metaphysical philosopher
Atul Gwande’s Checklist

1° Prevention vs. Infection-caused Fetal Death

1. **Hygiene**
   - Food choice/preparation — avoid deli food stored a long time, under-cooked, cross-contamination (*E. coli, Listeria, Salmonella*)

2. **Respiratory**
   - Enterovirus, hanta virus (aerosolized mouse droppings)

3. **Bites (zoonosis)**
   - Malaria (mosquitos), Rocky Mountain Spotted Fever (ticks), Lyme (ticks), West Nile Virus (mosquitos)

4. **Invasive**
   - Blood transfusion, organ transplant → CMV

**Prevention Strategies**

- Vaccination
  - Childhood, adult, maternal influenza
- Oral hygiene/care
  - Periodontal disease, dental hygiene, root canal
- Screen Reproductive Tract Infections

WE ARE NOT ALONE

- 2013 "top advances" in science
  - Person: 90% microbes, 10% human cells
  - i.e., we are “superorganisms,” multi-chimera
  1. Shared genome “hologenome”
  2. Immune system – intentions
  3. Metabolism
  4. Reproduction (wasps)
  5. Modulate emotions
  6. Brain functioning: autism, schizophrenia
  7. Interactive ↔ “Pregnancy bacteria” (Howerton)
  8. “How to be a good SYMBIOT?”
Human Microbiome

Cervical mucus stratify risk for PTB

Intracellular bacteria in placenta basal plate
Cost-effectiveness of screening and Rx for BV in EARLY PREGNANCY among women at LOW RISK for PTB

- “BV is important risk factor for PTB”
- Detected 10-30% pregnant women, often asymptomatic
- Rx BV in HIGH RISK women reduces risk

<table>
<thead>
<tr>
<th>Study Decision Tree (Prior Study)</th>
<th>Screening + Clinda Rx</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity Analysis</td>
<td>Rate PTB @ 2%</td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>Rx cost saving if PTB is 7.3%</td>
<td></td>
</tr>
</tbody>
</table>

Mosquitos transmit malaria, WNV, Zika
Ticks transmit Lyme disease and RMSF and others

Listeria
Toxoplasmosis

Chorioretinal toxoplasmosis (serologic testing was positive for *Toxoplasma gondii* IgG antibody (low level) and negative for IgM antibody. Hafidi A, Daoudi E. *NEJM* 2014; 370(4): 363

Toxoplasmosis: Mice lose fear of cats

Mechanism of placental viral infection


- Models
  - Adenoviruses
  - HSV
  - AAV
  - CMV
- Efficient transduction
- Apoptosis
- Inflammation
Leonard "Chico" Marx (March 22, 1887 – October 11, 1961)

"I wasn’t kissing her. I was whispering in her mouth.”

CMV
Human CMV infection is detected frequently in SBs and is associated with fetal thrombotic vasculopathy

- Known cause SB
- Evaluated multiple tissues @ 130 SBs, # CMV DNA and protein in routine autopsy
- CMV POS in placenta, kidney, liver → 15% singletons >20 wks
- Fetal thrombotic vasculopathy only abnormality (placenta too)
  - 60% CMV vs. 28 control, p=0.01
- “Molecular testing is important”

CMV-infected lining cells of gastric crypts

A RCT of hyperimmune globulin to prevent congenital CMV
Revello MG, CHIP Study Group. NEJM 2014;370; 1316

- Congenital CMV @ 1% major cause mortality/morbidity
- 2005 uncontrolled study of 1st infection ↓ intrauterine transmission 40→16%
- ∴ RCT 124 pregnant women 5-26 wks
  - Rx placebo vs. HIG-CMB q 4 wk until 36 wks or @ CMV in AF, endpoint congenital infection @ birth or AF

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<thead>
<tr>
<th></th>
<th>HIG</th>
<th>Placebo</th>
<th>P=</th>
</tr>
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<tbody>
<tr>
<td>CMV</td>
<td>33%</td>
<td>44%</td>
<td>0.13</td>
</tr>
<tr>
<td>Clinical/lab-outcomes</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>ND with HIG-CMVg. 1* prevention or infection before pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antenatal interventions for preventing transmission of CMV from mother-to-fetus during pregnancy
McCarthy FP, Rowlands S. Cochrane Database Syst Rev 2011; CD008371

- No RCTs
- Pre-conception immunity
- Chemoprevention

CMV: Prevention, Diagnosis, Therapy
Kotton CN. Am J Transplant 2013; Suppl 3: 24-40

- Most common cause transplant morbidity, childhood deafness
- Prevention
  - Universal prophylaxis
  - Preemptive therapy
- Others
  - Childhood "parties"
  - No blood transfusion, kissing, urine, handwashing

Passive immunization during pregnancy for congenital CMV
Ngure C, et al; Congenital CMV Collaborating Group; NEJM; 2005; 353 (14): 1350-62

- Dx Greek women with evidence 1° CMV <20 wk
- Treatment of CMV hyperimmune globulin is safe
  - congenital infection, aOR 0.32 (0.1 to 0.94); 95% CI, p>0.4
- 2-year follow-up (monthly injection)
Chlamydia

Strategies for Partner Notification for STIs, including HIV

- Enhanced patient referral
- Expedited partner therapy
  - Contact referral
  - Provider referral
- No optimal strategy
CD4+ T lymphocyte infected with HIV

Host cell (green) is infected by and produces HIV particles (red).
Electron micrograph by Dr. David Hockley from an infected culture provided by Dr. Robin Weiss, University College London, London.

He’d make a checklist!

TORCH → LESS TORCHEZ
(1965) (2014)

- Toxoplasmosis
- Listeriosis
- Rubella (measles, varicella)
- Enteroviruses
- Cytomegalovirus, coxsackie
- Syphilis
- Herpes, hepatitis B
- STIs, strep B
- Respiratory: influenza, adenovirus/AAV, H. influenzae, pertussis, rubella
- Occupational: oral, blood
- Enterics
- Zoonosis: malaria, Q fever (Coxiella burnetii), Lyme, WNV, dengue, arena viruses, yellow fever, leishmaniasis, rickettsia
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   Blood transfusion, organ transplant → CMV

Less TORCHEZ

*Infectious diseases cause adverse pregnancy outcomes including stillbirth, perinatal complication and death in childhood,*

  - 12% in US**
  - 7.6 mm worldwide

*Edwards MS (UT) JAMA 2013; 311: 1115-6
*Stillbirth Collaborative Network Writing Group. JAMA 2011; 306: 2459-68

*Can infants be protected by MATERNAL VACCINATION?

- Best example: anti → pertussis, influenza, **H. influenzae B, pneumococcus
- Maternal immunization vs. viral disease
  - England J, Glezen WP (Wyeth) RSV antibody in breast milk
  - GBS???

- **PLoS 2013 Bishchoff SC (may need ↑ dose)
Create your own miracle.

Mikeala Shiffrin. N Y Times 22. 2. 2014, B11

“Flies spread disease. Keep yours zippered.”
Garrison Keillor

Summary

“Don’t let it end like this. Tell them I said something.”
Recognized Sources of Confusion/ Miscommunication and Error @ Infection Caused Stillbirth/Pregnancy Loss

- Leadership
- Cross-Discipline "silos" no woman's NIH
- Definition/chaos
- Epidemiologic e.g., CDC-Preterm/Stillbirths
- Culturally complex
- Neglected
- "Vulnerable underappreciated" guilt
- "Racism" grieving 
- "Failure" parents, providers
- "Unknown" parents, providers
- Inconsistent association, different settings i.e., Chlamydia, IgM+, IgG-
- Economic analytic "willing to pay?"
- "Challenging to make vaccines"
- Reductionist approaches
- Need "RCT" evidence
- "Experiments reluctance vs reductionism"
- Pathophysiology complex
- "Calculous too difficult"
- "Complex diseases Host + environment + agent"
- "Variables in interpretation, recommendation"