Resurgence of Congenital Syphilis: Enduring Pandemic

Juan C Salazar, MD, MPH, FAAP
Professor and Chair, Dept of Pediatrics
UConn School of Medicine
Physician in Chief, Connecticut Children's
September 24, 2024

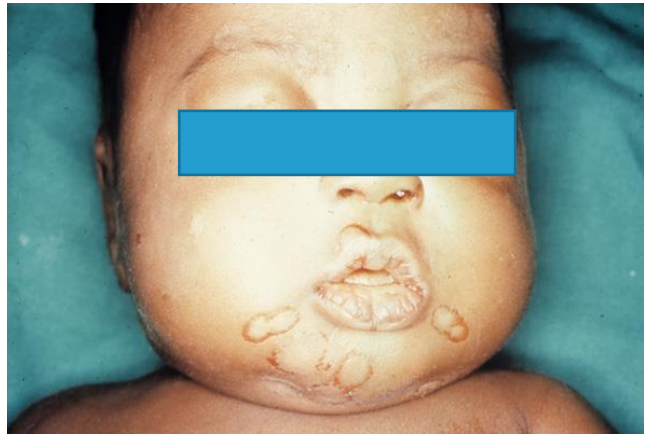
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

ANNUAL MEETING
2024

Key Objectives

- Review the worldwide resurgence of congenital syphilis.
- Describe the variable clinical presentations of congenital syphilis.
- Summarize treatment guidelines for congenital syphilis.
- Review the value of point of care testing for CS prevention.
- Update on recent efforts towards Syphilis Vaccine Development

CS: Perinatal Death - 1969



Photographs courtesy of Dr. Leon Chameides, Hartford Hospital

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Congenital syphilis
Confirmed or Highly Probable - 2015

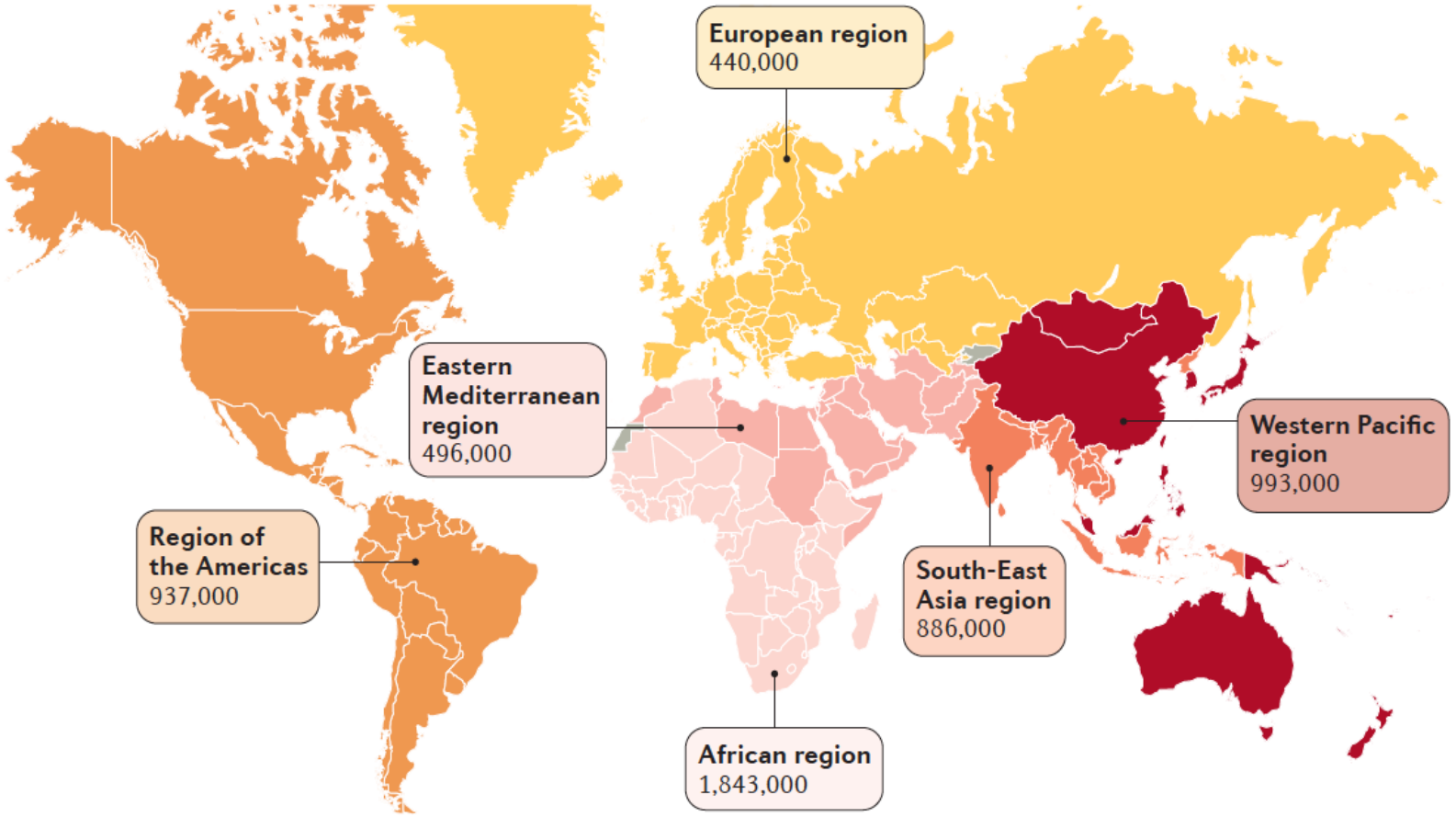
- 34-week gestation, weight 2.2 kg. Three prenatal visits, RPR ordered but not done. Maternal RPR 1:32. 1-2 cm bullous skin lesions. Right periorbital ulceration. Similar lesions in trunk and abdomen. Desquamation of both feet and both hands. Serology de 1:128. CSF normal with negative VDRL. Long bone films abnormal.
- **Images courtesy of Dr. Adriana Cruz and Dr. Silvana Castillo, Cali, Colombia**.

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Epidemiology

The Syphilis Epidemic is Global!

According to the most recent estimate by the WHO, ~18 million individuals 15–49 years of age had syphilis, with an estimated 6 - 8 million new cases every year.



Peeling *et al.* Syphilis Nat Rev Dis Primers, 2017

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Buenaventura, Colombia - 2011

- **Population: 369,753 (2011)**
- **Large numbers of refugees**
- **High maternal mortality rate and high incidence of low-birth weight newborns**
- **Highly endemic for malaria, dengue, leishmaniasis, MDR MTB**
- **2011: 196 CS cases, 12 perinatal deaths**

Gestational and Congenital Syphilis Epidemic in the Colombian Pacific Coast
Cruz, AR, Castrillón, MA, Minotta, AY, Rubiano LC. Castaño, MC, Salazar, JC

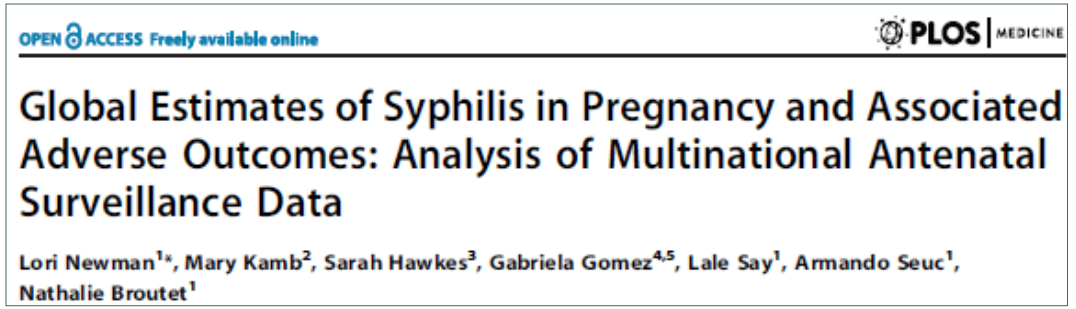
Sexually Transmitted Diseases:
October 2013 - Volume 40 - Issue 10 - p 813-818

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Gestational syphilis and Congenital syphilis Worldwide Epidemiology: 2013-2020

World Health Organization

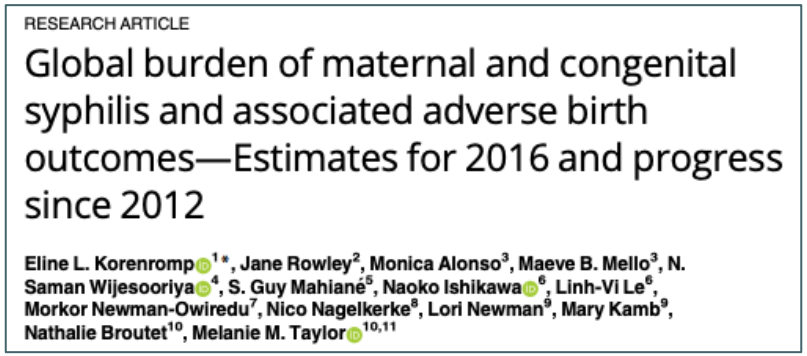
- Gestational Syphilis:
  - 1.3 million cases/yr. (WHO)
- Congenital Syphilis:
  - 700,000 cases/2022 (WHO)
  - 420,000- 600,000 abortions, stillbirths and perinatal deaths
  - 270,000 Dx with CS at birth
  - Global rate – **425 x 100k**
- 90% in the developing world



OPEN ACCESS Freely available online PLOS | MEDICINE

Global Estimates of Syphilis in Pregnancy and Associated Adverse Outcomes: Analysis of Multinational Antenatal Surveillance Data

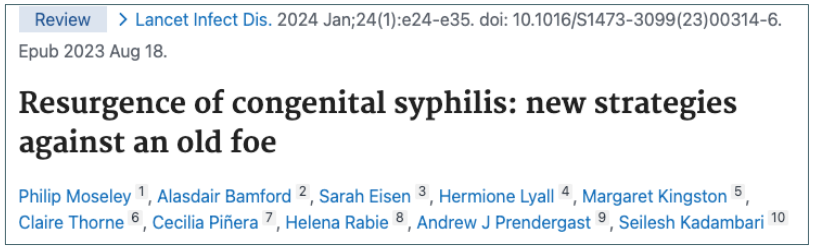
Lori Newman[1]*, Mary Kamb[2], Sarah Hawkes[3], Gabriela Gomez[4,5], Lale Say[1], Armando Seuc[1], Nathalie Broutet[1]



RESEARCH ARTICLE

Global burden of maternal and congenital syphilis and associated adverse birth outcomes—Estimates for 2016 and progress since 2012

Eline L. Korenromp[1]*, Jane Rowley[2], Monica Alonso[3], Maeve B. Mello[3], N. Saman Wijesooriya[4], S. Guy Mahiané[5], Naoko Ishikawa[6], Linh-Vi Le[6], Morkor Newman-Owiredu[7], Nico Nagelkerke[8], Lori Newman[9], Mary Kamb[9], Nathalie Broutet[10], Melanie M. Taylor[10,11]



Review > Lancet Infect Dis. 2024 Jan;24(1):e24-e35. doi: 10.1016/S1473-3099(23)00314-6. Epub 2023 Aug 18.

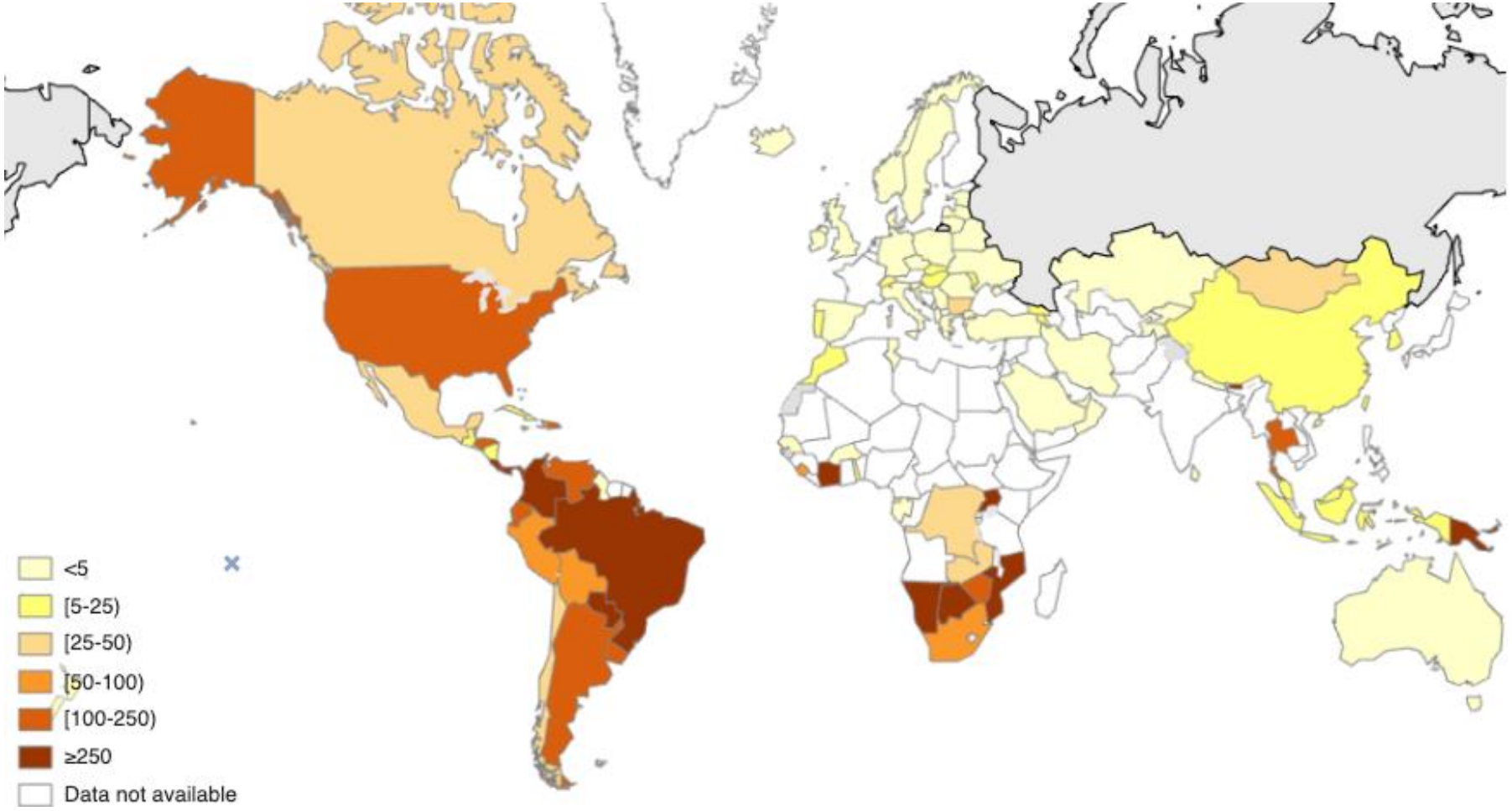
Resurgence of congenital syphilis: new strategies against an old foe

Philip Moseley [1], Alasdair Bamford [2], Sarah Eisen [3], Hermione Lyall [4], Margaret Kingston [5], Claire Thorne [6], Cecilia Piñera [7], Helena Rabie [8], Andrew J Prendergast [9], Seilesh Kadambari [10]

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

CS Rate per 100,000 live births reported - 2022

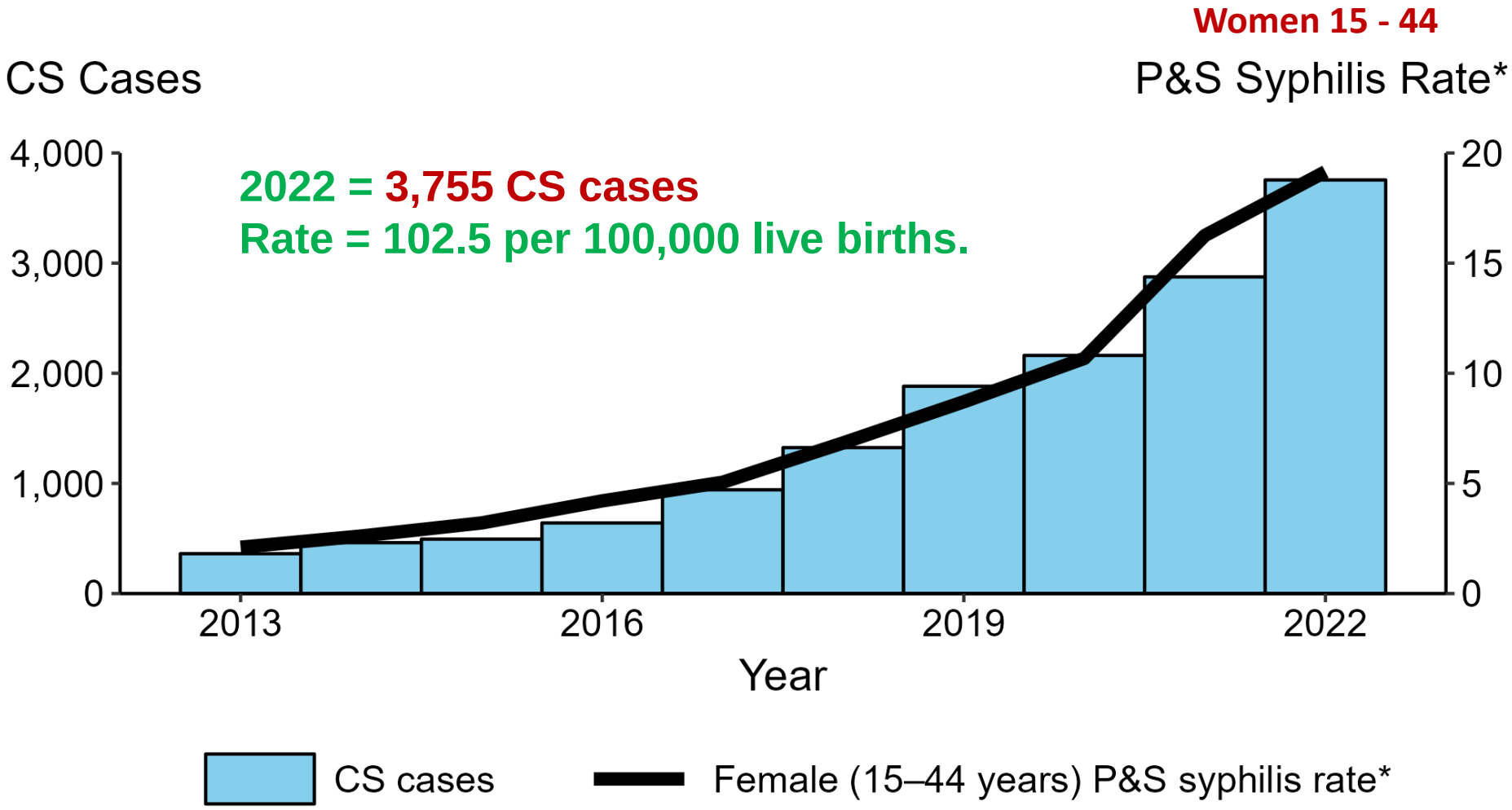
World Health Organization



https://www.who.int/data/gho/data/indicators/indicator-details/GHO/congenital-syphilis-rate-per-100-000-live-births

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

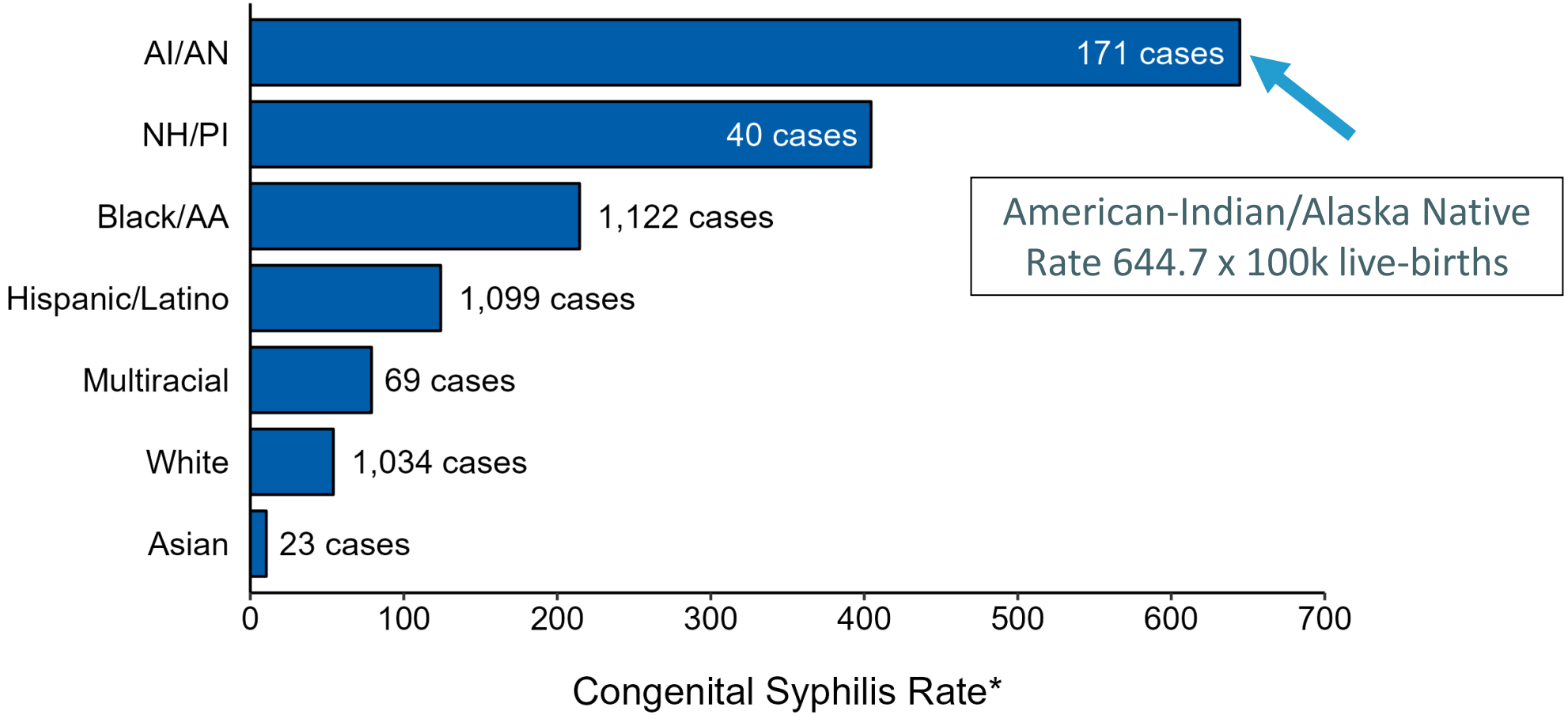
Congenital Syphilis: CDC Reported Cases by Year of Birth and Rates of Reported Cases of Primary and Secondary Syphilis Among Women Aged 15–44 Years, USA 2013-2022



ACRONYMS: CS = Congenital syphilis; P&S = Primary and secondary syphilis.

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Congenital Syphilis: Case Counts and Rates of Reported Cases by Race/Hispanic Ethnicity of Mother, USA, 2022

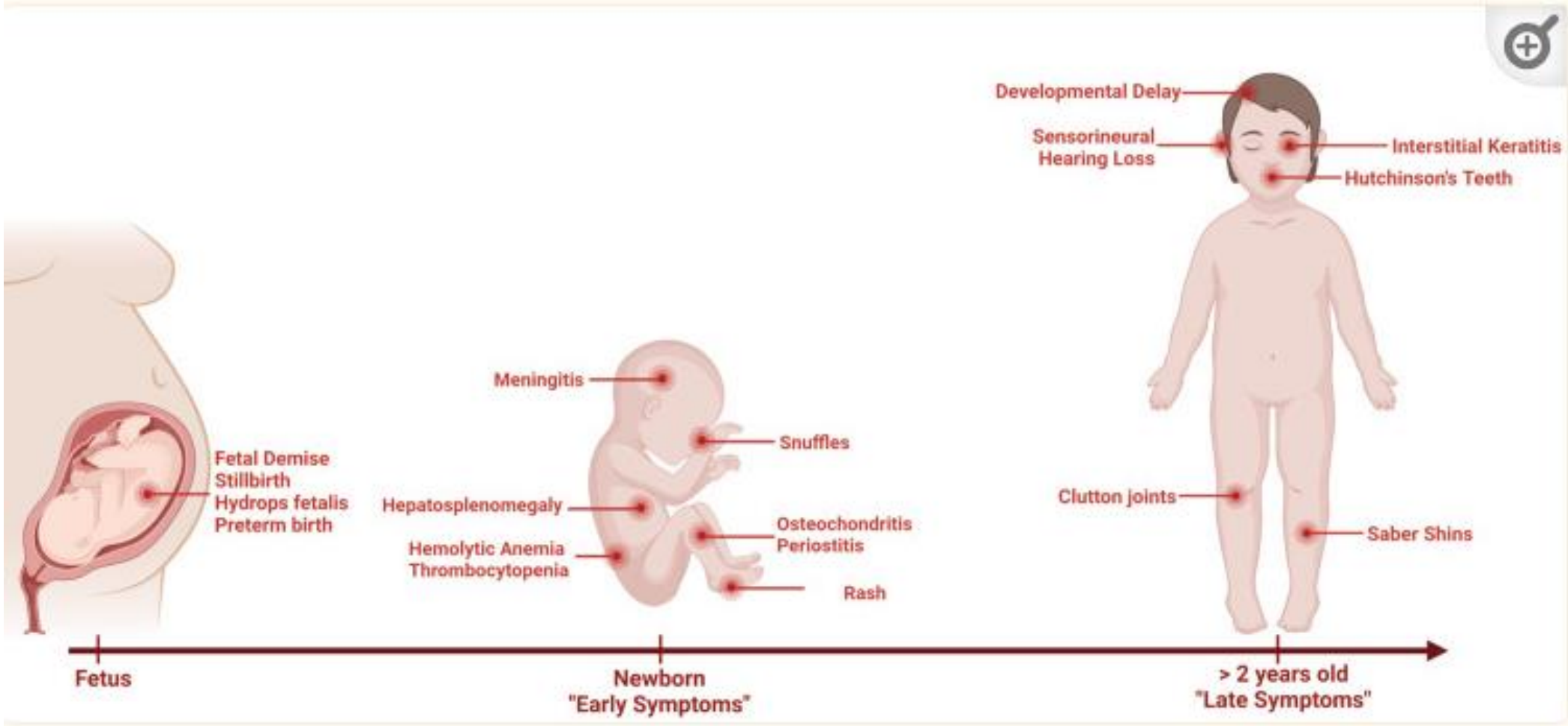


- Center for Disease Control and Prevention
- * Per 100,000 live births
- **NOTE:** In 2022, a total of 197 congenital syphilis cases (5.2%) had missing, unknown, or other race and were not reported to be of Hispanic ethnicity.
- **ACRONYMS:** AI/AN = American Indian or Alaska Native; Black/AA = Black or African American; NH/PI = Native Hawaiian or other Pacific Islander

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Pathogenesis

Congenital Syphilis - Pathogenesis



Cureus. 2022 Dec; 14(12): e33009.
Published online 2022 Dec 27. doi: 10.7759/cureus.33009

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Congenital Syphilis — Pathogenesis

- Early CS manifestations:
  - Due to hematogenous spread of organism and resultant inflammatory response in various organs and tissues
  - Extramedullary hematopoiesis
  - Immune-mediated
- Late CS manifestations:
  - Scarring or stigmata from early disease
  - Reaction to persistent inflammation
  - Noninfectious

Congenital Syphilis - Vertical Transmission

- *In utero*: transplacental route
- Intrapartum: contact with genital lesion
- Increases as stage of pregnancy advances but can occur at any time in gestation
- Related to stage of maternal syphilis

  > during secondary syphilis

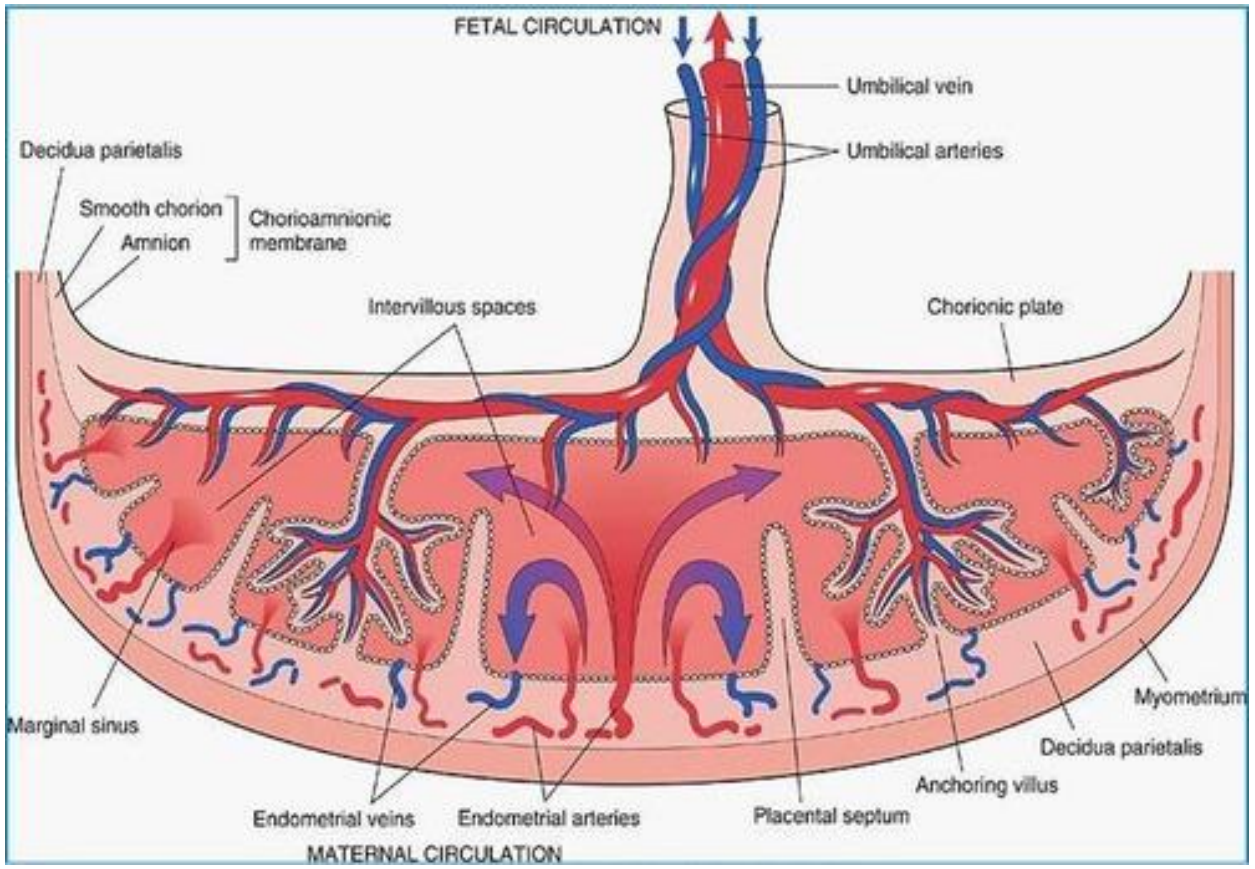
Congenital Syphilis - Outcome according to maternal venereal syphilis clinical stage at diagnosis

	1°	2°	Early Latent	Late Latent
Number of Mothers	26	53	145	27
Results (%):				
Perinatal death	1 (4)	14 (26)	31 (21)	1 (4)
Congenital syphilis	5 (19)	18 (34)	21 (14)	1 (4)
Total	6 (23%)	**32 (60%)**	52 (36%)	2 (7%)

The Parkland Experience (Dallas 1988-1998) – Courtesy of Pablo Sanchez, MD

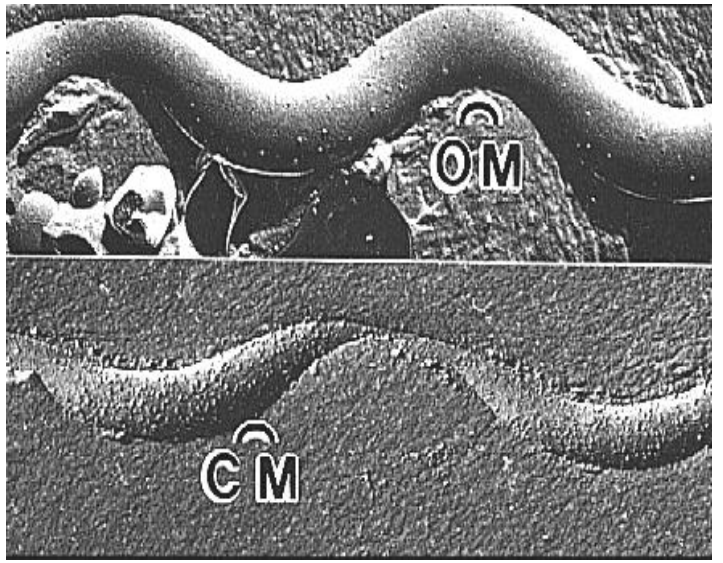
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Congenital Syphilis - Why does the maternal fetal interface fail in preventing transmission?



T. pallidum's Unique Molecular Architecture is a key Determinant of the Spirochete's Immuno-evasiveness

- Lacks LPS
- Rich in lipoproteins: not accessible to host pattern recognition receptors (PRRs)
- Almost denuded outer membrane (rare OMPs)
- Behaves as a stealth pathogen
  - Highly invasive
  - Avoids innate immune recognition
  - Escapes opsonization
  - Low antigenicity and high antigenic variability



Radolf JR et al, PNAS 1989

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Evaluation and treatment of Infants with confirmed, probable or suspected congenital syphilis

It is Difficult to Confirm a Diagnosis of Congenital Syphilis!

- Difficulty in detecting or culturing *T. pallidum* in neonatal clinical specimens
- Difficulty with the interpretation of serologic tests due to transplacentally acquired maternal anti-treponemal IgG
- Lack of sensitive and specific commercially available IgM serologic tests
- Difficulty in the identification of infants with CNS invasion by *T. pallidum*

CDC Case Definition: Congenital Syphilis

- **Confirmed case:** Demonstration of *Treponema pallidum* by darkfield microscopy, fluorescent antibody, or other specific stains in specimens from lesions, placenta, umbilical cord, or autopsy material

- **Probable case:**
  - Infant whose mother had untreated or inadequately treated syphilis at the time of delivery (>30 days prior)
  - Reactive treponemal test and abnormal physical exam, long bone x-rays, reactive CSF VDRL, elevated CSF cell count or protein, or reactive IgM test

- **Syphilitic stillbirth:** fetal death at >20 wks. gestation or BW >500 g and mother with untreated or inadequately treated syphilis

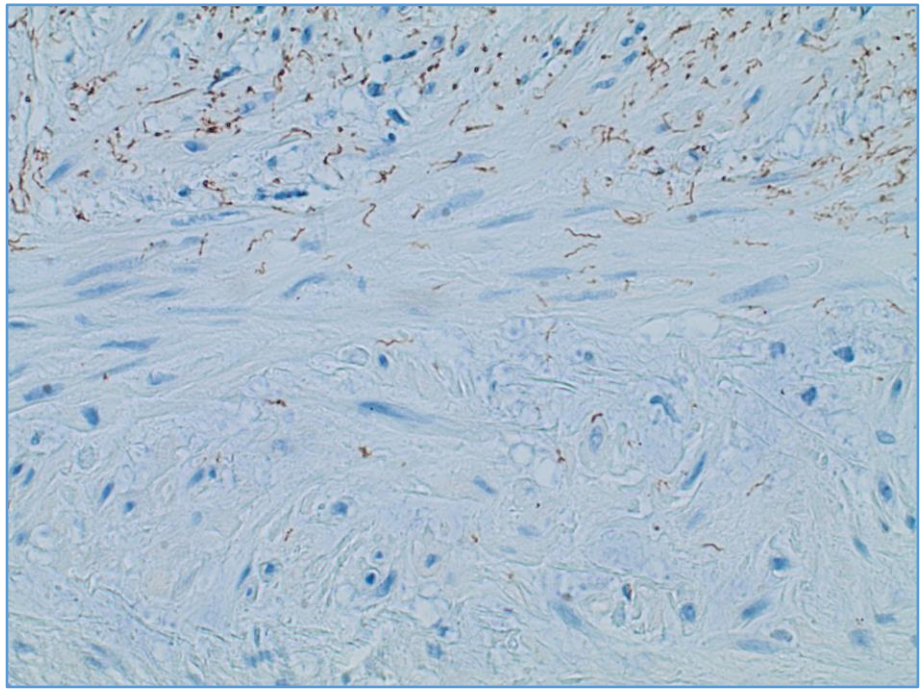
Scenario 1: Proven or Highly Probable CS

- Infant physical exam abnormal and c/w CS
- Positive darkfield or fluorescent antibody test of body fluid(s)
- Positive PCR for *Tp* from bodily fluid or lesion
- Positive rabbit infectivity test (RIT)

A recent case of congenital syphilis – Hartford, CT (2022)

33 weeks with proven Congenital Syphilis

T. pallidum



Materials kindly provided by Drs. Laura Kvenvold, Ian Michelow, & Mary Fiel-Gan

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

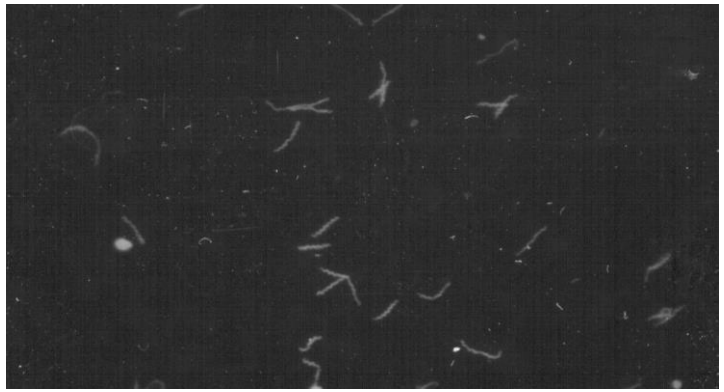
CS: Clinical Manifestations

- Hepatosplenomegaly
- Rash
- Condyloma lata
- Snuffles
- Jaundice
- Pseudoparalysis
- Edema (Hydrops)

CS: Clinical Manifestations

Syphilitic Rhinitis “Snuffles”

Broken vesicles, desquamation



CS: Papulo-squamous plaques

Proven or Highly Probable CS: Evaluation

- Lumbar puncture, CBC / platelet count
- Bone X-rays:
  - CDC: as clinically indicated
  - AAP: unless the diagnosis has been otherwise established
- Other tests (eye exam, LFTs, HUS, ABR, CXR) as clinically indicated

CNS Infection in Congenital Syphilis

- ✓41% of those with abnormal clinical, laboratory, or radiographic evaluation had confirmed CNS disease
- ✓60% of those with abnormal PE findings
- ✓3 infants: + CSF Rabbit Infectivity Test, normal CSF indices
  - ✓(2 abnormal lab evaluation, 1 pos IgM)

Ian Michelow et al. NEJM, 2002

CS: Long Bone X-rays

- Periostitis
- Osteochondritis
- Frequently abnormal: 65% (Houston/Dallas)
- Abnormal findings do not change therapy

Congenital Syphilis: Treatment in Scenario 1

- Confirmed or probable case per CDC guidelines:
  - Aqueous PCN G 50,000 U/kg IV q 8-12 hrs. x 10 d, or
  - Procaine PCN G 50,000 U/kg IM q day x 10 d
- Penicillin dosed missed > 1 day, restart course
- Alternative therapy: On going clinical trials – NIAID presentation
  - Ampicillin
  - Ceftriaxone

Scenario 2: The "ASYMPTOMATIC" infant born to a mom with untreated or inappropriately treated venereal syphilis

What is the likelihood that an infant like this one has congenital syphilis?

Congenital Syphilis: Why evaluate and treat Asymptomatic Infants Born to Mothers With Untreated Syphilis?

	Serum/Blood (n=86)	CSF (n=68)
POS IgM	16%	3% (2/62)
POS RIT	7%	2% (1/62)

Courtesy of Pablo Sanchez, MD

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Congenital Syphilis: Why treat or evaluate Asymptomatic Infants Born to Mothers Treated ≤ 4 Weeks Before Delivery?

	Blood	CSF
No. of Infants:	23*	21*
⊕ IgM	30%	5%
⊕ RIT	5%	0/19

Courtesy of Pablo Sanchez, MD

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

"Asymptomatic scenario 2" INFANT continued

- Evaluation: CBC, platelets, LP, bone X-rays
- Treatment: options
  - Penicillin G (aqueous/procaine) x 10d
  - Benzathine PCN G 50,000 u/kg IM: normal CBC, platelet, lumbar puncture, bone x-rays and follow-up is certain

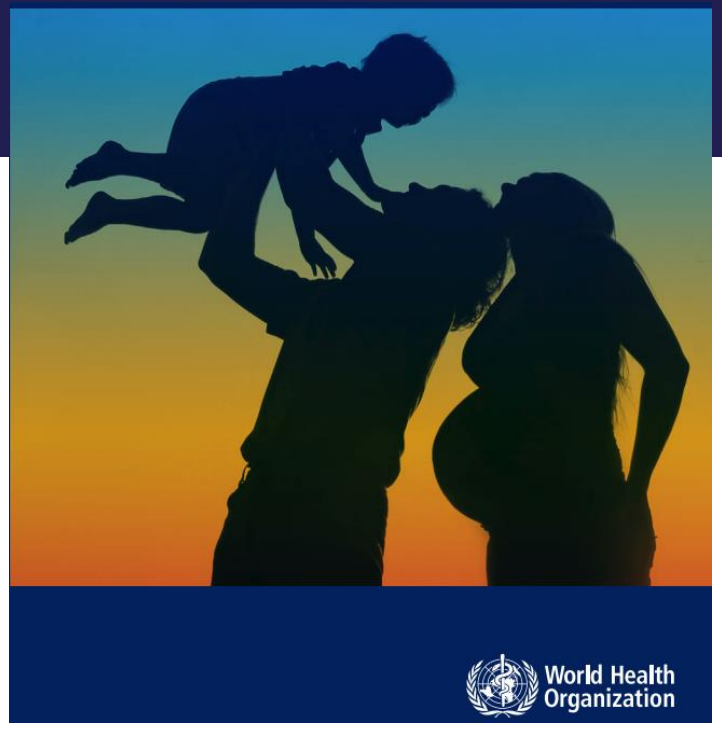
Special Considerations

- Penicillin allergy: desensitize, data insufficient to recommend other agents, but if nonpenicillin agent used, close serologic and CSF follow-up
- HIV infection: infants born to mothers coinfected with HIV do not require different evaluation, therapy, or follow-up for syphilis
- Penicillin shortage: penicillin G, procaine penicillin, benzathine penicillin, ceftriaxone.
  www.cdc.gov.nchstp/dstd/penicillinG.htm/

Prevention

Introducing a framework for implementing triple elimination of mother-to-child transmission of HIV, syphilis and hepatitis B virus

https://iris.who.int/bitstream/handle/10665/375893/9789240086784-eng.pdf?sequence=1



Connecticut Children's

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Prevention

- Ensure adequate universal prenatal care
- Serologic screening (RPR) at 1st prenatal visit; repeat at 28 weeks, and at delivery in high-risk areas
- ? initial screening mothers with treponemal tests
- Do not discharge infant without maternal serologic status documented at least once during pregnancy
- Report all cases to local Health Dept. for contact tracing and identification of core populations and environments

Point of care testing for timely treatment of gestational syphilis and Prevention of Mother to Child Transmission (PMTC) of congenital syphilis

PAHO Bulletin, 2009

Investigación original / Original research

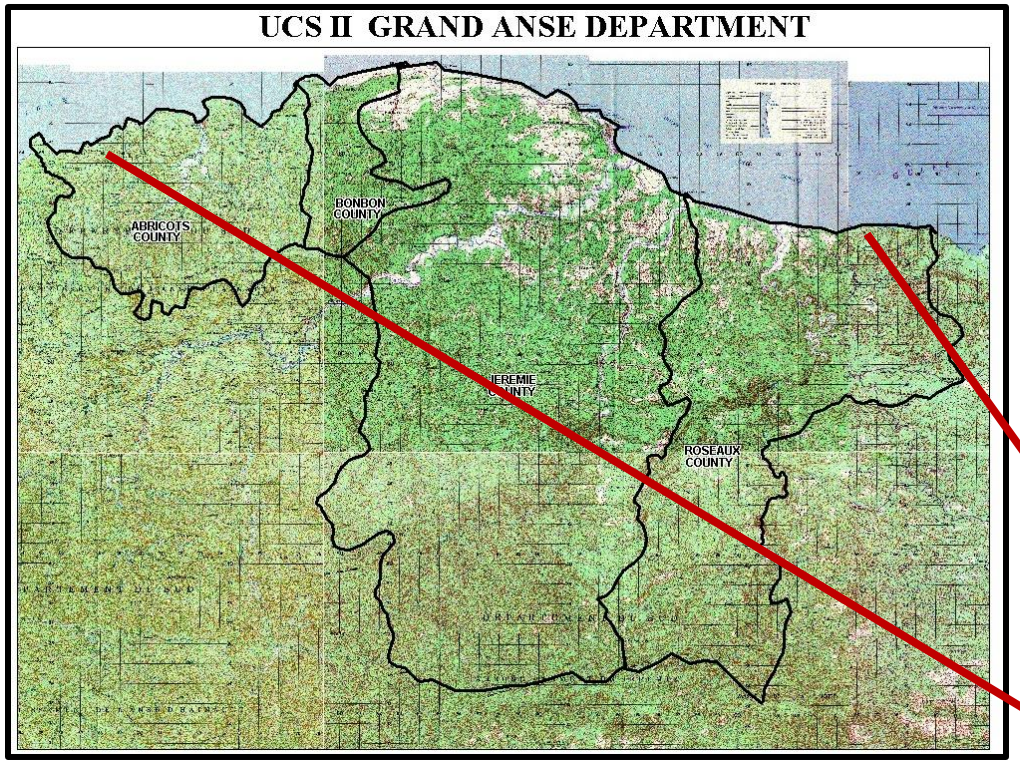
Maternal and congenital syphilis in rural Haiti

Chaylah J. Lomotey,[1,2] *Judy Lewis,*[1,2,3,4] *Bette Gebrian,*[1,5]
Royneld Bourdeau,[5] *Kevin Dieckhaus,*[2,6] *and Juan C. Salazar*[1,2,4]

Suggested citation Lomotey CJ, Lewis J, Gebrian B, Bourdeau R, Dieckhaus K, Salazar JC. Maternal and congenital syphilis in rural Haiti. Rev Panam Salud Publica. 2009;26(3):197–202.

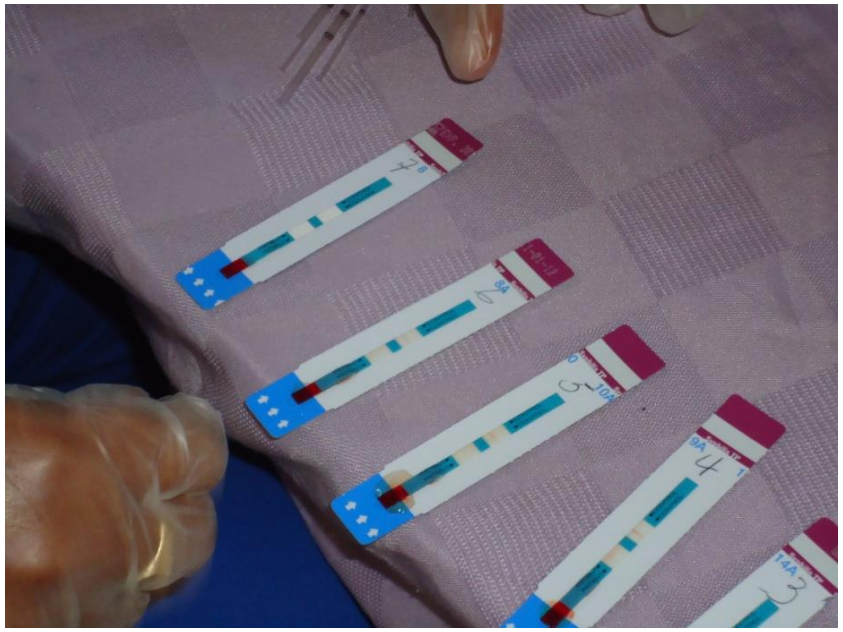
- 410 pregnant women tested (Jeremie)
- 31 (7.6% reactive treponemal rapid test)
- Estimated CS rate: 767 x 100,000

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network



Haitian Health Foundation Jeremie, South-Western Region (Grand Anse Dept)

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network



IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

PMTCT using rapid syphilis testing

CLOSING U.S. PREVENTION GAPS IS CRITICAL TO REDUCE SYPHILIS IN NEWBORNS

IN 2018, **NEARLY 9 IN 10** newborn syphilis cases in the U.S. were in the **South and West**

IN THE WEST

Lack of timely prenatal care was the most common missed opportunity

41%

34%

IN THE SOUTH

Lack of adequate treatment* was the most common missed opportunity

TEST & TREAT TO PREVENT SYPHILIS IN NEWBORNS

HEALTHCARE PROVIDERS SHOULD:

TEST

Test all pregnant women for syphilis at their first prenatal visit

RE-TEST

Re-test women at risk or living in high-burden areas at 28 weeks & again at delivery

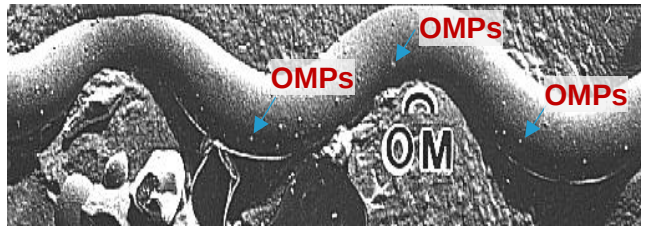
TREAT

Treat* all women with diagnosed or suspected syphilis **immediately** using long-acting benzathine penicillin G; test & treat sex partner(s)

CDC. Missed Opportunities for Prevention of Congenital Syphilis — United States, 2018. MMWR Morb Mortal Wkly Rep. ePub: 4 June 2020.

Progress on Vaccine Development for Syphilis

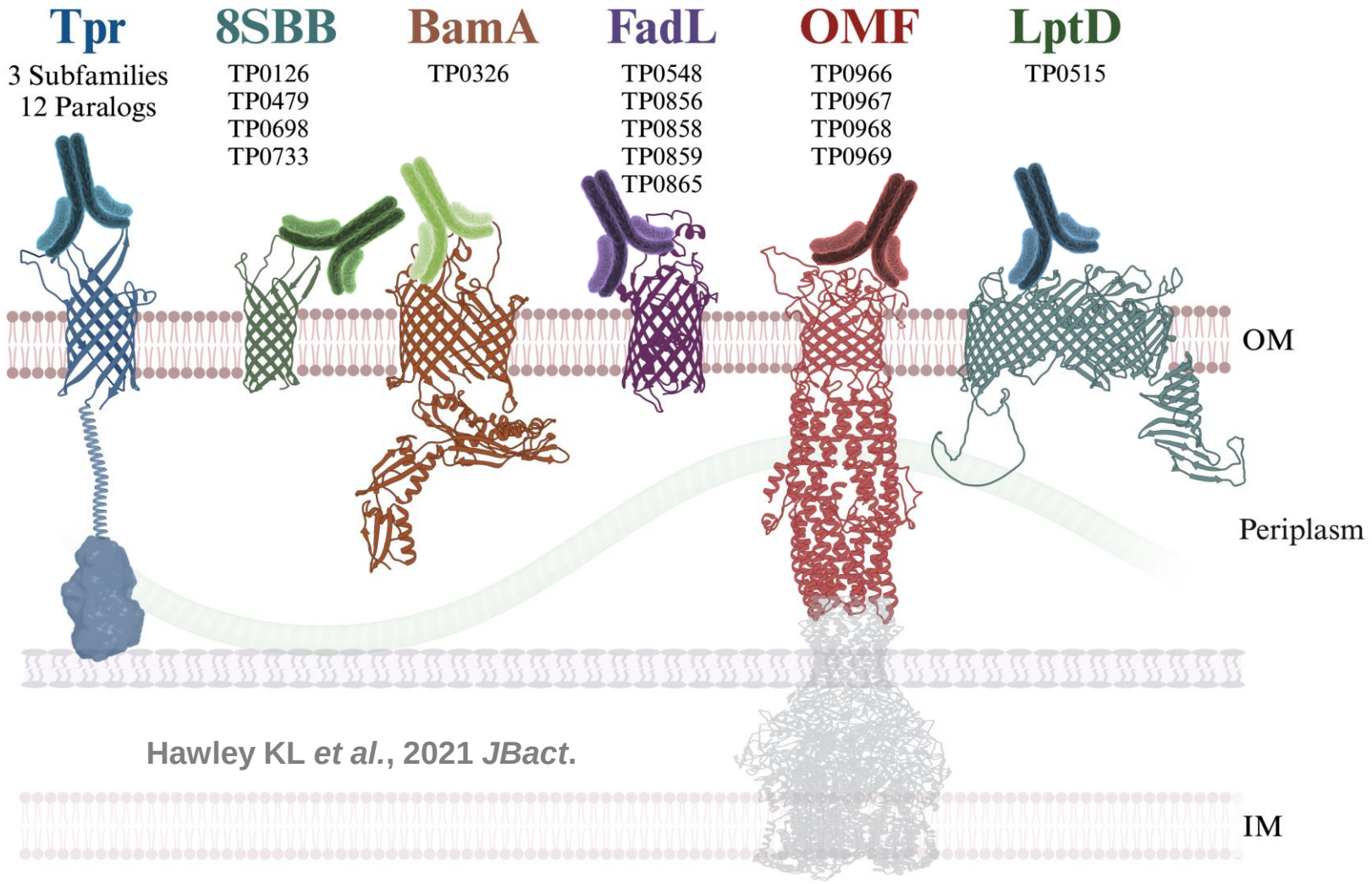
Rational vaccine design requires a detailed understanding of *TPA* outer membrane molecular architecture



The Nichols OMPeome

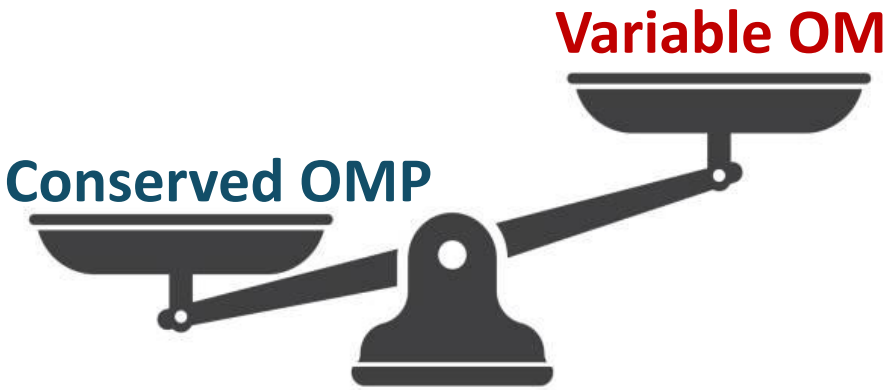
Protective antibodies must be directed against the extracellular loops of OMPs

Do the ECLs undergo variation?



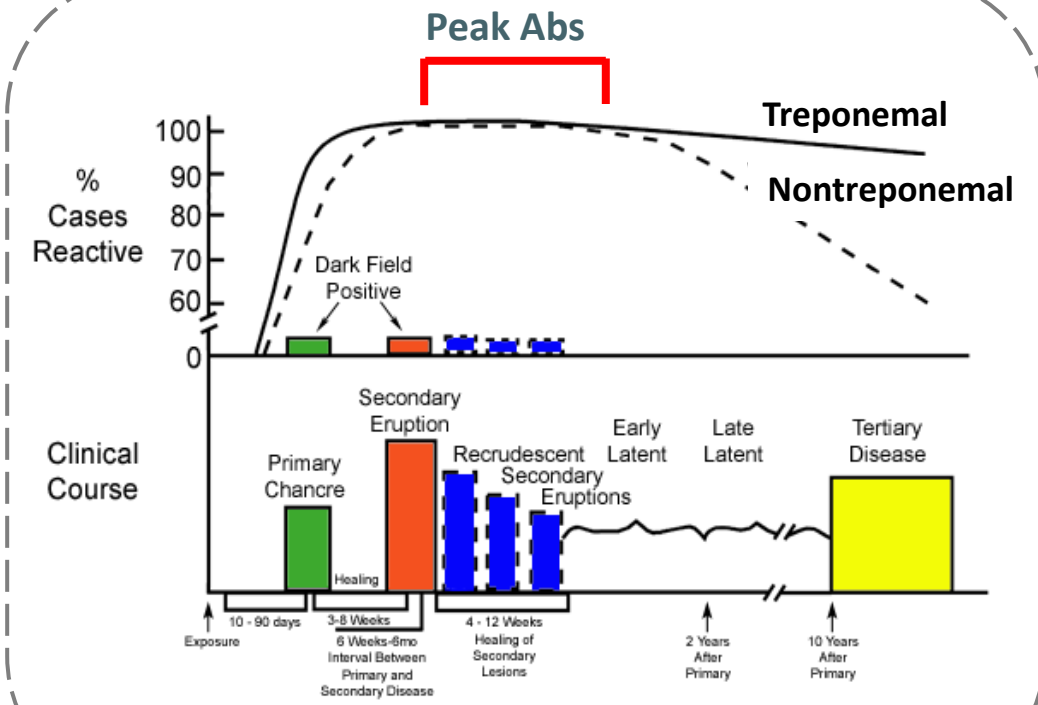
Hawley KL *et al.*, 2021 *JBact*.

The importance of OMP variability and antigenicity in selection of vaccinogens



Vaccine cocktail

Learning from nature



Zinsser's Microbiology 1992, Treponema

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Clinical and genomic diversity of *Treponema pallidum* subspecies *pallidum* to inform vaccine research: an international, molecular epidemiology study

Arlene C Seña, Mitch M Matoga*, Ligang Yang*, Eduardo Lopez-Medina*, Farhang Aghakhanian*, Jane S Chen*, Everton B Bettin, Melissa J Caimano, Wentao Chen, Jonny A Garcia-Luna, Christopher M Hennelly, Edward Jere, Yinbo Jiang, Jonathan J Juliano, Petra Pospíšilová, Lady Ramirez, David Šmajs, Joseph D Tucker, Fabio Vargas Cely, Heping Zheng, Irving F Hoffman, Bin Yang, M Anthony Moody, Kelly L Hawley, Juan C Salazar, Justin D Radolf†, Jonathan B Parr†

A starting point: build a syphilis clinical research consortium

Lancet Microbe 2024;
5: 100871

Published Online August 22, 2024
https://doi.org/10.1016/
S2666-5247(24)00087-9

A global syphilis team targeting outer membrane proteins of *Treponema pallidum*

NIAID U19 AI144177

Connecticut Children's

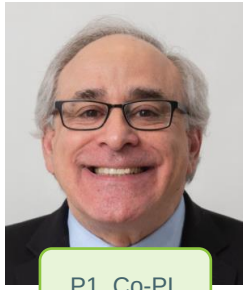
UCONN HEALTH

Spirochete Research Labs

UCONN HEALTH

Duke Human Vaccine Institute
Duke University School of Medicine

Justin D. Radolf, MD



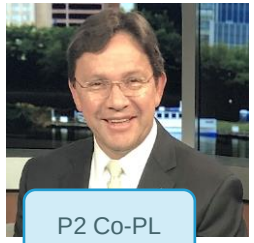
P1 Co-PL

M. Anthony Moody, MD

P3 PL

CRC Principal Investigators

Juan C. Salazar, MD MPH



P2 Co-PL

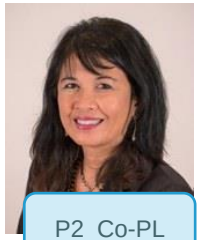
Melissa J. Caimano, PhD

P1 Co-PL

Kelly L. Hawley, PhD

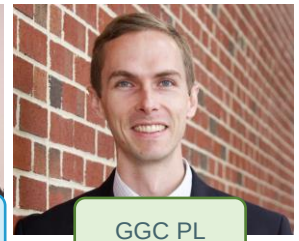
P2 Co-PL

Arlene Seña, MD MPH



P2 Co-PL

Jonathan Parr, MD MPH



GGC PL

Joseph Tucker, MD MPH

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Lilongwe, Malawi

Irving Hoffman, PA

Mitch Matoga, MD

Amit Luthra, PhD

Mauricio Montezuma, MD MPH

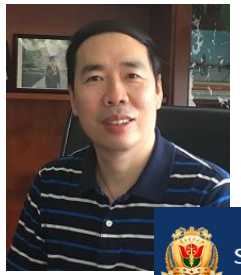
Eduardo Lopez, MD

CIDEIM

Lady G. Ramirez MS

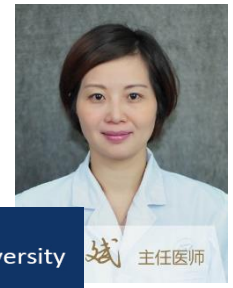
David Šmajs, PhD

Zheng Heping, PhD



Yang Ligang, MD MsC

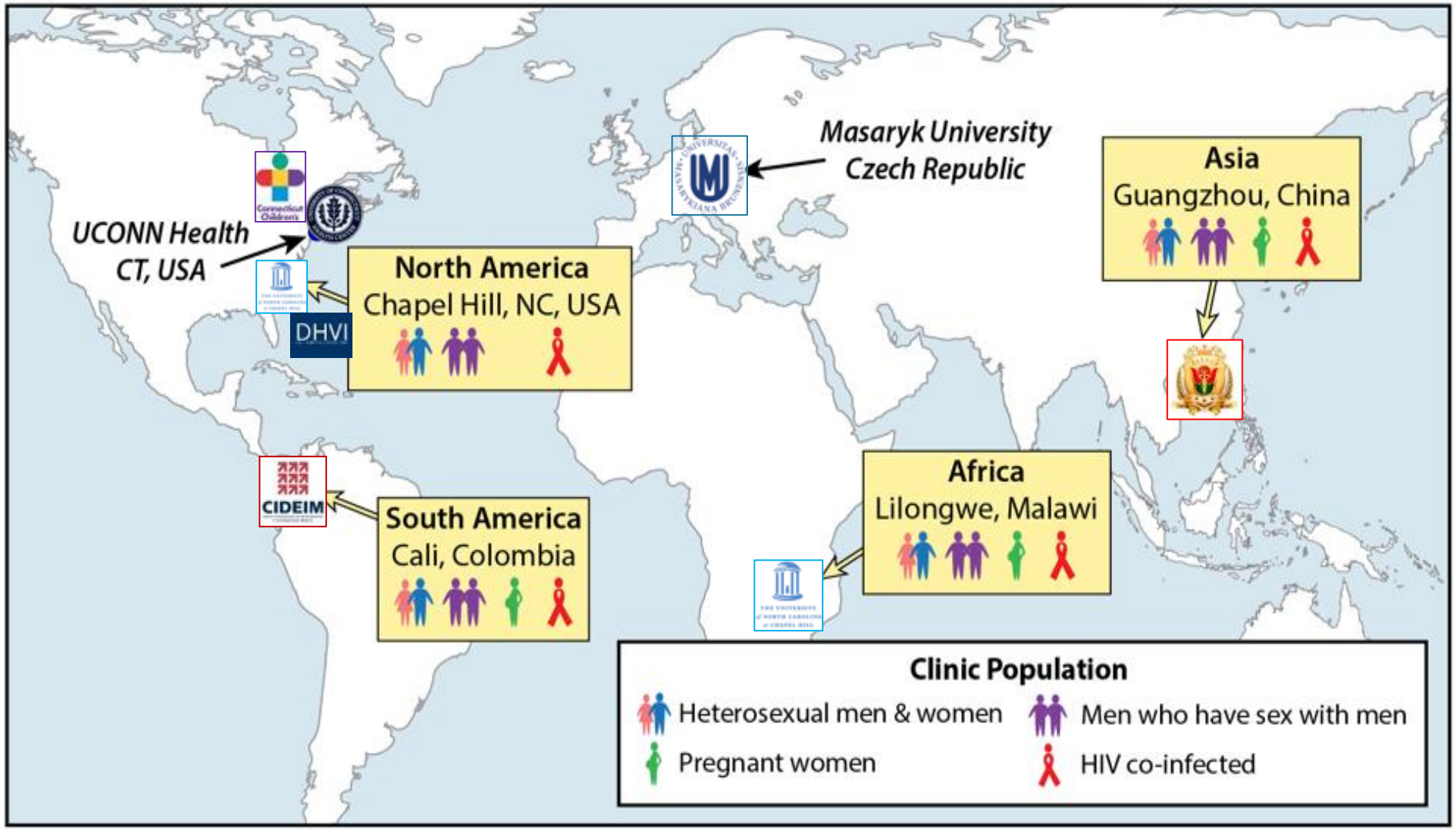
Yang Bin, MD PhD



Southern Medical University

★ Mrs. Julie Vigil (photo not shown)

Our Clinical Research Consortium addresses OMP variability and antigenicity



IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

The Journal of Infectious Diseases

MAJOR ARTICLE

Treponema pallidum Periplasmic and Membrane Proteins Are Recognized by Circulating and Skin CD4$^+$ T Cells

Tara B. Reid,[1] Charmie Godornes,[1] Victoria L. Campbell,[1] Kerry J. Laing,[1] Lauren C. Tantalo,[1] Alloysius Gomez,[2] Thepthara N. Pholsena,[1] Nicole A. P. Lieberman,[3] Taylor M. Krause,[1] Victoria I. Cegielski,[4] Lauren A. Culver,[1] Nhi Nguyen,[1] Denise Q. Tong,[1] Kelly L. Hawley,[5,6] Alexander L. Greninger,[3,7] Lorenzo Giacani,[1,8] Caroline E. Cameron,[1,2] Julia C. Dombrowski,[1,9] Anna Wald,[1,7,8,9] and David M. Koelle[1,3,7,8,10]

[1]Department of Medicine, University of Washington School of Medicine, Seattle, Washington, USA; [2]Department of Biochemistry and Microbiology, University of Victoria, Victoria, British Columbia, Canada; [3]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington, USA; [4]Department of Medicine, University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, USA; [5]Department of Medicine and Pediatrics, UConn Health, Farmington, Connecticut, USA; [6]Division of Infectious Diseases, Connecticut Children's, Hartford, Connecticut, USA; [7]Vaccine and Infectious Diseases Division, Fred Hutchinson Cancer Center, Seattle, Washington, USA; [8]Department of Global Health, University of Washington, Seattle, Washington, USA; [9]Department of Epidemiology, University of Washington School of Medicine, Seattle, Washington, USA; and [10]Center for Translational Immunology, Benaroya Research Institute,

The Journal of Infectious Diseases

EDITORIAL COMMENTARY

T-Cell Responses to *Treponema pallidum* Proteins in Blood and Skin to Advance Syphilis Vaccine Design: Learning From Nature

Juan C. Salazar[1,2,3] and Justin D. Radolf[1,2,4,5,6]

[1]Departments of Pediatrics; [2]Immunology, University of Connecticut School of Medicine, Farmington; [3]Division of Pediatric Infectious Diseases and Immunology, Connecticut Children's, Hartford; Departments of [4]Medicine; [5]Genetics and Genome Sciences; and [6]Molecular Biology and Biophysics, University of Connecticut School of Medicine, Farmington

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Gracias! 致谢!

CIDEIM team
Eduardo Lopez, MD
Nancy Saravia, PhD
Lady G. Ramirez. MS
Jonny Garcia, MD, MS
Adriana R. Cruz, MD

Spirochetal Research Labs - UCHC
Justin Radolf, M.D.
Kelly Hawley, PhD
Melissa Caimano PhD
Carson Karanian

Hartford Hospital
Richard Cartun, PhD
Mary Field Gan, MD

CDC
Alan Pillay, PhD,
David Cox, PhD - retired

Walter Reed
Linda Jagodzinsky, PhD
Nelson Michael, MD, PhD

Cali Health Dept.
Gloria Aristizabal, SPPM
Jorge Duque, MD, MPH

Funding
NIH-K23 AI62439, NIH-5R03TW008023
AI-26756, AI-38894, U19 AI144177,
CCMC, COLCIENCIAS 222940820554
Bill and Melinda Gates Foundation

You can find me at
@DrJuanSalaz
Salazar@uchc.edu

Connecticut Children's

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network