Congenital Infections in Pregnancy

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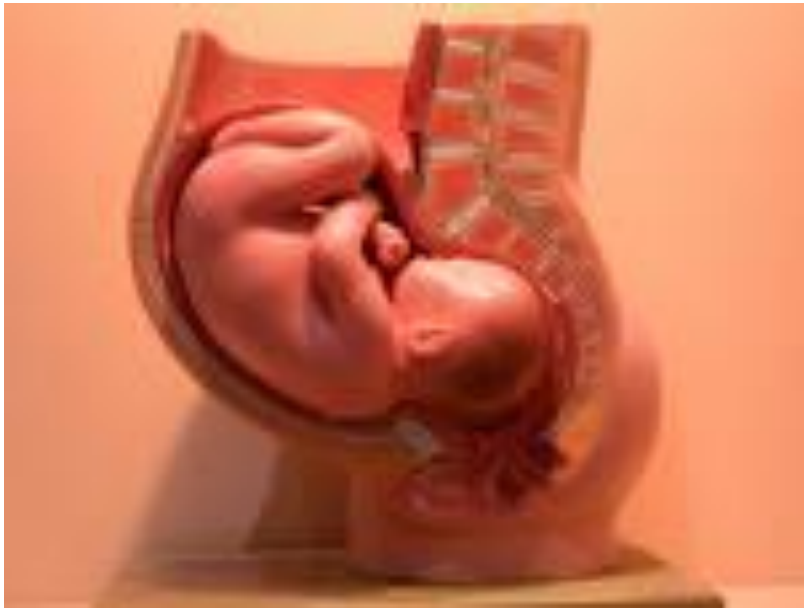


Antenatal Screening at Rotunda Hospital

(Unlinked) anonymous HIV testing – the Rotunda July 1991

Pilot study of unlinked (anonymous) hepatitis B antigen testing July 1996 – December 1997

Routine linked HIV and hepatitis B testing January 1998

Dedicated DOVE clinic

Mother to Child Transmission of Infections

Mother to baby transmission of infections can occur :

- In Utero (congenital)
- During Delivery (perinatal)
- During Breastfeeding (postnatal)

Route of transmission Maternal infections can spread to the embryo and foetus by:

- Infections ascending from the upper vagina via the uterine cervix to the amniotic fluid.
- Hematogenous spread as a result of maternal viremia, bacteremia or parasitemia.

Effect of maternal infections on fetus and newborn

Maternal infections (depending on the causative agent) may have the following effects in fetus and newborn:

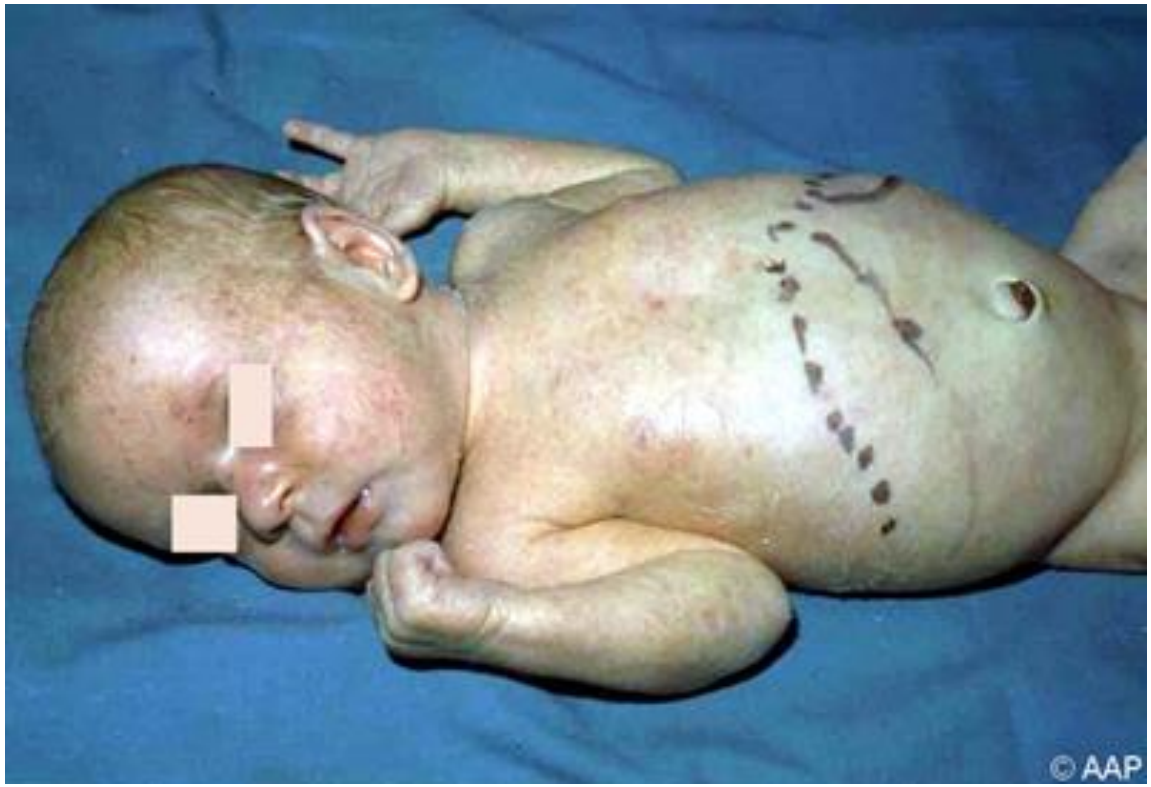
- **Low birth weight**, is defined as birth weight of a live born infant of less than 2500 g (5 pounds 8 ounce) regardless of gestational age (ICD -10).
- **Preterm birth**, defined as the birth of a live infant at less than 37 weeks' gestation, which may happen with several viral, bacterial and some protozoan infections.
- **Abortion and stillbirth**, which may happen with infections crossing the placenta, such as rubella, mumps, smallpox, syphilis, malaria, toxoplasmosis, cytomegalovirus, herpes simplex virus.
- **Development anomalies**, such as central nervous system CNS cardiovascular abnormalities, deafness, and mental retardation may happen with some infections such as rubella and cytomegalovirus.
- **Congenital diseases** may occur with most infections that cross the placenta (CNS, cardiovascular, hepatic and etc) eg rubella and syphilis .
- **Post-natal persistence of infections**, as some infections like Mycobacterium tuberculosis, treponema pallidum, malaria may survive for months and years in infants and may result in disease.

TORCH

- o Toxoplasmosis
- o Other (syphilis, Borrelia)
- o Rubella
- o Cytomegalovirus (CMV)
- o Herpes simplex virus (HSV)

CMV

Blueberry muffin rash
(intredermal hematopoesis)

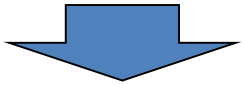


Anemia
Leukopenia
Tromocytopenia

- mortality 10%

Asymptomatic infection

- 90% asymptomatic on birth



- but ~ 10% of them develop:
  - sensorineural hearing loss (SNHL)
  - chorioretinits
  - later in childhood: disorders of psychomotor development

The so-called “asymptomatic" infections:

- Chorioretinitis
- Hearing loss

May be the only consequences!

Screening is required!

- They may affect the child’s development

Syphilis: Pathogenesis

- Mode of transmission

1. Sexual intercourse
2. Blood transfusion
3. Contaminated needles
4. Vertical transmission
5. To hospital personnel by indiscriminate handling of infected lesions

Pathogenesis (2)

- ATTACHMENT, INVASION AND DISSEMINATION
- INNATE HOST RESPONSE – TLR2
- ACQUIRED IMMUNITY - clinical manifestations caused by inflammatory and immune responses rather than by any direct cytotoxic effect of T. pallidum
- BACTERIAL CLEARANCE- phagocytosis of treponemes by macrophages • Predominant cytokine –Th1 • Predominant mediator- IFN-γ 5.
- INVASION OF HOST IMMUNITY AND ESTABLISHMENT OF LATENT INFECTION
- PROTECTIVE AND LONG-LASTING IMMUNITY

Timing of symptomatic disease

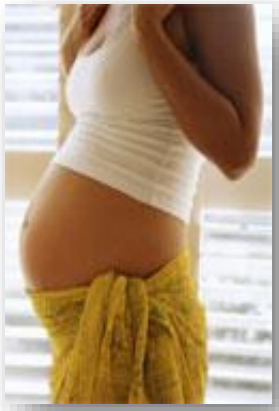
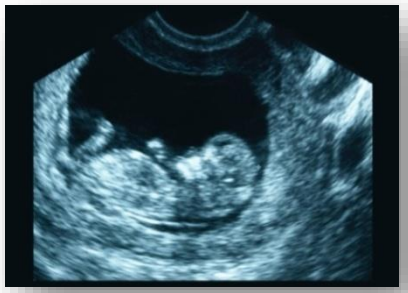
- Symptomatic at birth
- Late neonatal onest
  - Within 5 weeks postpartum
- Late onset
  - After 2 years of age

Symptomatic infection at birth

- Stillbirth
- Generalised neonatal disease
  - Low birth weight, hepato-splenomegaly
  - Nonimmune hydrops + hemolytic anemia
  - Neutropenia and thrombocytopenia

Late neonatal onset

- Osteochondritis (metaphysitis), periostitis (new bone)
- Rash: maculopapular desquamtive
- Syphilitic rhinitis (hemorrhagic)
- Hepatitis, lymphocytosis
- Keratitis
- CSF: pleocytosis + proteinorachia

Pediatric HIV Infection - From Epidemic to Elimination

Brief History of the Evolution of the Pediatric HIV Epidemic

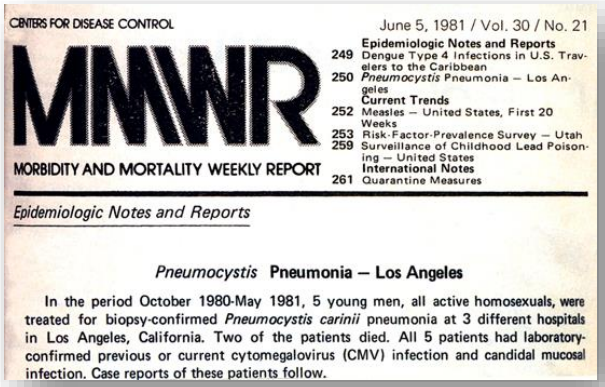
–The beginning

Jim Oleske and Long-Term Survivors
UMDNJ Newark 2003

–The middle

–The end?

GLOBAL PLAN TOWARDS THE ELIMINATION OF NEW HIV INFECTIONS AMONG CHILDREN BY 2015 AND KEEPING THEIR MOTHERS ALIVE



CENTERS FOR DISEASE CONTROL

June 5, 1981 / Vol. 30 / No. 21

MMWR

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Epidemiologic Notes and Reports

Pneumocystis Pneumonia — Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

1982: Recognition of an Epidemic

The NEW ENGLAND JOURNAL of MEDICINE

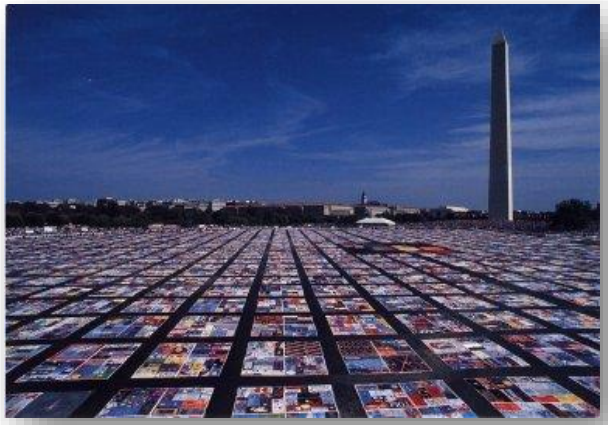
January 12, 1984 Vol. 310 No. 2

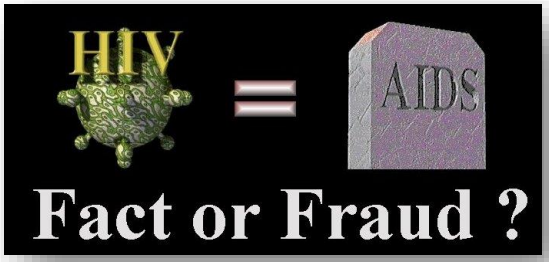
Acquired Immunodeficiency Syndrome in Infants

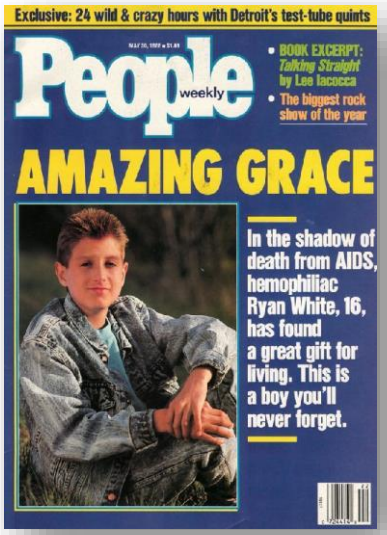
Gwendolyn B. Scott, M.D., Billy E. Buck, M.D., Joni G. Leterman, M.D., Frederick L. Bloom, M.D., and Wade P. Parks, Ph.D., M.D.

N Engl J Med 1984; 310:76-81 | January 12, 1984 | DOI: 10.1056/NEJM198401123100202

The Beginning







Boston Children's Hospital
Until every child is well

November 1977 – Boston Children's Hospital

- 2 year old male
- Severe malnutrition
- Developmental delay
- Thrush
- Recurrent infections/fevers unresponsive to antibiotics
- Persistent diarrhea without etiology
- Parents alcohol, drug abuse, social problems
- Admitting dx: "Psychosocial failure to thrive"

- Anemia/leukopenia
- Low T-cell (then called e-rosette forming cells) number and function
- Hypergammaglobulinemia

→ after a month on hyperal, extensive negative work-up but persistent severe disease

- Developed hypoxia
- Diffuse infiltrates & acidosis
- Pneumococcal bacteremia
- Despite broad spectrum antibiotics, he died.

Autopsy Performed at The Children's Hospital Medical Center
on November 7, 1977 at 3:00 P.M.
by Doctors Bernardo Adolfo & Dorothy Vatner

Microscopic Description and Final Summary
by Gordon F. Vawter, M.D.

Age: 2 years

White, Male
Division 39
#86-95-30

HOURS POSTMORTEM: 3 hours

RESTRICTIONS: None

CLINICAL DIAGNOSIS: Failure to thrive.
T-cell deficiency.
Pneumonia.

FINAL DIAGNOSIS:
Agranulocytosis, chronic, cause undetermined.
Relative myeloid hypoplasia of marrow.
Agnogenic myeloid metaplasia of lymph nodes.
Pneumococcal bacteremia (clinical).
Pneumococcal emphysema (right).
Otitis media, left (gross).
Suspected immune deficiency
(in complete severe combined immunodeficiency).
Suspected thymic dysplasia with secondary atrophy.
Plasma cells in bowel, spleen and lymph nodes.
Deficiency of lymphoid follicles in spleen, lymph nodes and colon.
Underweight spleen.
Chronic ulcers of esophagus and cardia with peptic change and meager superficial monilial growth.

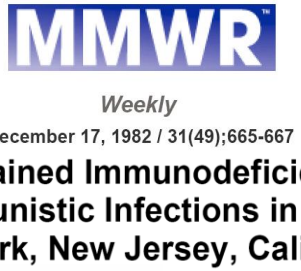
Autopsy showed

- Chronic esophageal ulcers, candida
- Myeloid hypoplasia
- Deficiency lymphoid follicles in spleen, lymph nodes, thymus
- Thymic dysplasia with secondary atrophy/fibrosis
- Blood, pleural fluid grew pneumococci

→

- T-cell deficiency unknown etiology

Pediatric HIV Infection



JAMA 1983;249(17)

Immune Deficiency Syndrome in Children. James Oleske et al. *JAMA.* 983;249(17): 2345-2349.

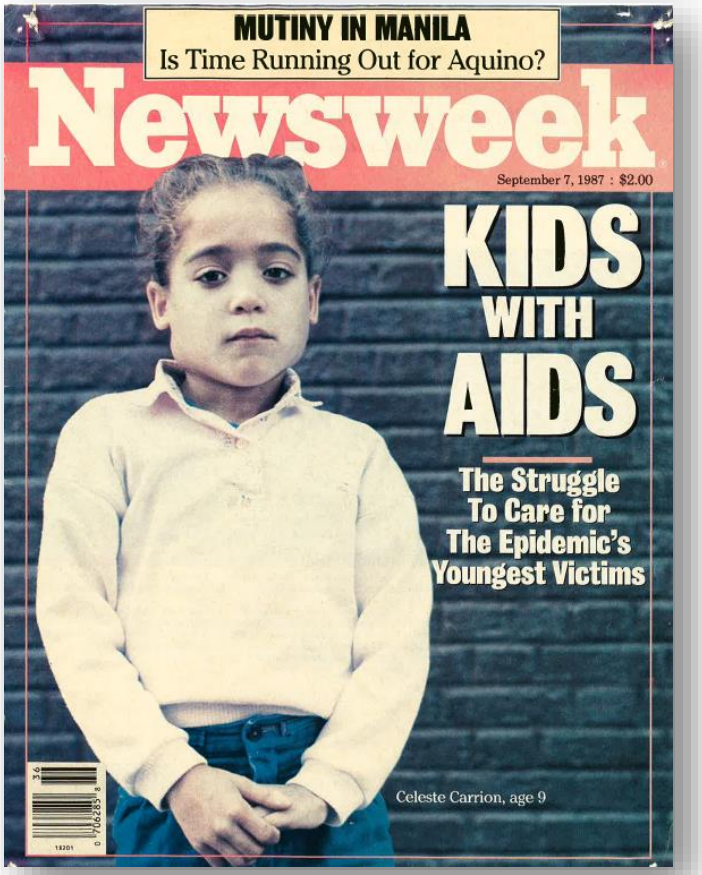
Acquired Immuno-deficiency With Reversed T4/T8 Ratios in Infants Born to Promiscuous and Drug-Addicted Mothers . Arye Rubinsteinet al. *JAMA.* 1983;249(17):2350-2356.

- The first case of pediatric AIDS reported to CDC in 1982, 18 months after 1st report in adults.
- By 1983, reports of AIDS among children of parents with recognized risk factors were published.

"…since 1979…children with an otherwise unexplained immune deficiency syndrome and infections of the type found in adults with AIDS….. 8 children from the Newark, NJ…born into families with recognized risks for AIDS. These patients have had recurrent febrile illnesses, failure to thrive, hypergammaglobulinemia, and depressed CMI. Four of these children have died."

Late 1980's: Mother-to-Child Transmission in the U.S.

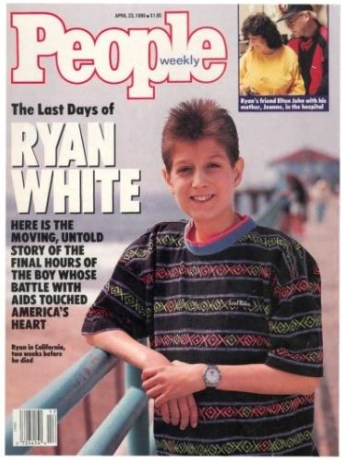
- It was recognized that most pediatric HIV infection occurred through transmission from mother-to-child, although timing of transmission unclear.
- One in four HIV-infected mothers transmitted HIV to their infant.
- By the early 1990s, >16,000 perinatally-infected children had been born in the U.S., with a critical need for prevention.



Timing of HIV transmission

- In utero (cord blood or baby blood positive at birth)
- Intrapartum (cord blood or baby blood negative at birth and positive beyond 72 hours)
- Bryson et al Lancet
- Post partum transmission (studies done by Jackson in Uganda, where mothers breast fed and risk factors for transmission)
- These studies have not been done for Lyme

Hemophilac Children: First “Public” Face of Pediatric HIV
The “Bad Old Days” - AIDS Fears and Hysteria

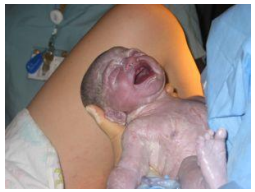


- In 1985 at 13, Ryan White, a hemophiliac, was barred from school in IN. After a court battle, he is finally allowed to attend classes, but after a bullet is fired into his home, his family is moves to nearby town.

- The 3 Ray brothers with hemophilia were barred from public school in FL because of HIV infection. The parents went to federal court to allow their children to attend school. While the Rays won their legal battle, their home was burned down a week after the 1987 decision.

PACTG 076: AZT Regimen Was Designed to Target Multiple Potential Time Points of Transmission

CD4 >200

Pregnancy	Labor/Delivery	Infant
		
AZT 100 mg 5 times daily	AZT IV 2 mg/kg 1 mg/kg/hr	AZT 2 mg/kg q 6 hr x 6 weeks
TARGET: *In Utero* (after 1st trimester)	TARGET: Intrapartum	TARGET: Postpartum
	Pre-Exposure Prophylaxis (PrEP)	**Post-Exposure Prophylaxis (PEP)**

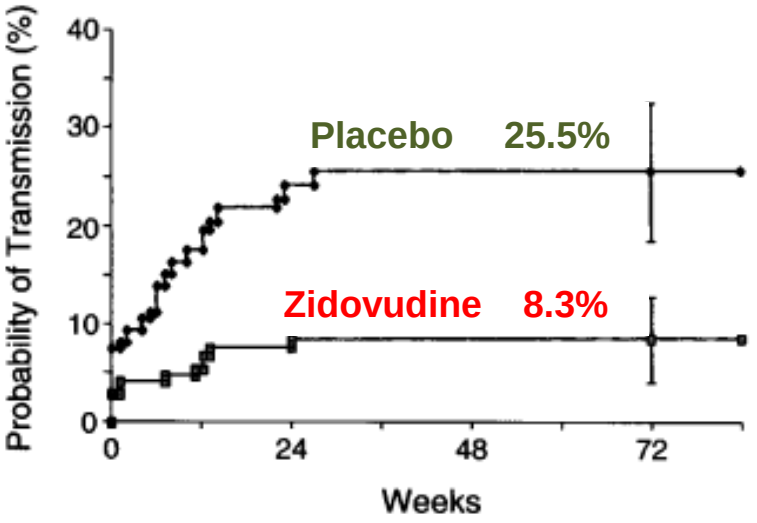
DSMB halted trial Feb 1994

The New England Journal of Medicine

Volume 331 NOVEMBER 3, 1994 Number 18

REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

Edward M. Connor, M.D., Rhoda S. Sperling, M.D., Richard Gelber, Ph.D., Pavel Kiselev, Ph.D., Gwendolyn Scott, M.D., Mary Jo O'Sullivan, M.D., Russell VanDyke, M.D., Mohammed Bey, M.D., William Shearer, M.D., Ph.D., Robert L. Jacobson, M.D., Eleanor Jimenez, M.D., Edward O'Neill, M.D., Brigitte Bazin, M.D., Jean-François Delfraissy, M.D., Mary Culnane, M.S., Robert Coombs, M.D., Ph.D., Mary Elkins, M.S., Jack Moye, M.D., Pamela Stratton, M.D., and James Balsley, M.D., Ph.D., for the Pediatric AIDS Clinical Trials Group Protocol 076 Study Group*

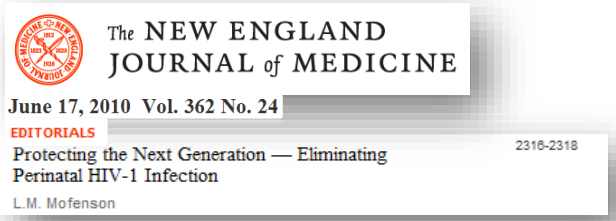


First demonstration of treatment as prevention!

Determinants of Transmission of HIV

- Undetectable HIV VL at delivery means no transmission from mother to child
- NEJM 1999 ACTG 185 study, Mofenson, Lambert et al
- NEJM 1999, WITS Study, Garcia et al

2010: Potential Elimination



The End?

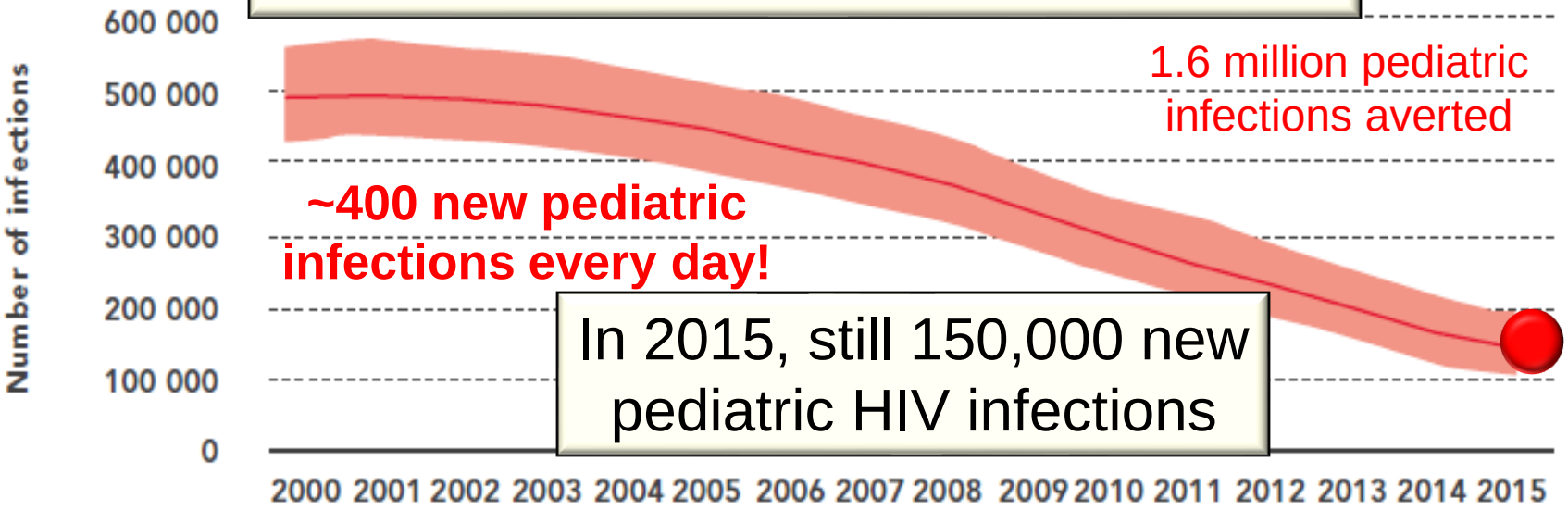
Elimination?

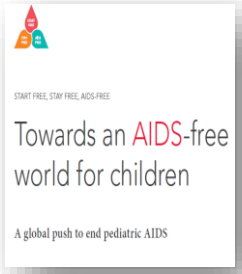
Cure?

Where are We in the Plan to Eliminate New Pediatric HIV Infection?

Major Progress in Preventing Perinatal Infection in Past Decade

But we have not yet reached the goal of global elimination of MTCT





70% decrease in new pediatric infections since 2000

Complications of Pregnancy and Transplacental Transmission of Relapsing Fever Borreliosis

- Larsson et al, JID 2006;194: 1367-74
- Borrelia duttonii is a common cause of complications of pregnancy, miscarriage and neonatal death in sub-Saharan Africa.
- Up to 6.4% of pg women in DRC have dx of RF; with complications of LBW, Preterm delivery, spontaneous abortion, and neonatal death.
- Murine model presented: non-pregnant more severely affected than pregnant mice

RF Borreliosis

- B duttoni in the murine model demonstrates IUGR, placental damage and inflammation, impaired fetal and placental circulation, and decreased maternal Hb levels.
- B duttoni can traverse the maternal-fetal barrier, causing congenital infection. Observed a correlation between spirochete exposure and Low Gestational Weight. Inflammation of placenta, RBC depletion, and haemorrhaging, resulting in nutrient and oxygen depletion to fetus

RF Borreliosis (3)

- Congenital infection was confirmed by microscopy. RF both resides in the placenta and infects the fetus. Trans-placental transmission occurs in up to 72%.
- There was a 12.5 fold decrease in total spirochetal burden and less pronounced signs of illness in pregnant than non pregnant mice, as well as less severe anemia.
- Hypothesised to be Th2 shift or related to hormonal fluctuations.
- The bacteria spreads to and damages the maternal/fetal unit, higher bacterial load is bad, earlier gestational infection is bad

Congenital Borreliosis (Lyme)

- Infants can be infected with Borrelia transplacentally in any stage of pregnancy and/or via mother's breast milk.
- The co-infections: Babesia, Bartonella, Mycoplasma and perhaps even the Ehrlichias may be transmitted transplacentally to the developing fetus

Congenital Lyme

- Gestational Borreliosis can be associated with repeated miscarriages, fetal death in utero, fetal death at term (stillbirths), hydrocephalus, cardiovascular anomalies, intrauterine growth retardation, neonatal respiratory distress, “sepsis” and death, neonatal hyperbilirubinemia, cortical blindness, sudden infant death syndrome and maternal toxemia of pregnancy.

Congenital Lyme

- Borrelia spirochetes have been found at autopsy in fetal brain, liver, adrenal glands, spleen, bone marrow, heart and placenta
- None of the infected tissues showed any sign of inflammation
- Maternal antibiotic treatment during pregnancy does not guarantee that the fetus will be free of infection but lessens risk of complications
- Recommended treatments/duration varies. Avoid doxycycline, usually amoxacillin? For longer periods

Maternal-Fetal Transmission of the Lyme Disease Spirochoete, Borrelia Burgdorferi ACP 1985

Schlesinger et al

- Case of woman who developed Lyme in 1st trimester (annular rash and symptoms), did not receive treatment, and symptoms settled; infant born at 35 weeks gestation, died of congenital cardiac disease (respiratory distress, dilated LV, aortic valvular stenosis, PDA, CofA; pathology revealed LD spirochetes in spleen, kidneys, and bone marrow (not found in heart; no evidence of 'inflammation' on pathology exam); five days post partum mother developed recurrent arthritis, tested Lyme positive, treated with tetracycline with resolution of arthritis.
- Primary infection occurred at the time of organogenesis; thus 'a teratogenetic effect cannot be ruled out'. ? Placental insufficiency?

Case Report: Lyme disease in Pregnancy

- Walsh et al Ob/Gyn Survey 2006
- 42 yo woman, 34 wk gestation L knee pain for one week. From NYC, no rash. Previous summer in Hamptons and LI. History of knee and hip pain at 32yo, investigated with negative work up.
- Arthrocentesis, WBC 44,000, culture negative. Lyme antibody test positive. Given po amox. One week later R knee swollen, fluid removed. Culture negative. Placenta all normal. One week post partum flare up of L knee; this time positive for Bb by PCR. Given additional 2 weeks of amoxacillin.
- Standard treatment does not always cure

Gestational Lyme Borreliosis

- Alan MacDonald, Rheum Ds Clinics N.A.,1989
- 9 year retrospective study of 19 cases of clinically active Lyme disease in pregnant women, 17 women with EM, 1 with facial palsy/arthritis, 1 with arthritis and positive Ab.
- Autopsy and clinical studies have associated gestational Lyme with fetal death, hydrocephalus, cardiovascular abnormalities, neonatal respiratory distress, hyperbilirubinemia, IUGR, cortical blindness, SIDS and maternal toxaemia in pregnancy.
- Spirochetes were identified in histopathological specimens

Lyme Disease During Pregnancy

- Markowitz et al JAMA 255 (24) 3394-6, 1986
- Identified 19 cases of congenital LD, eight in 1st trimester, seven second trimester, two third trimester (2 unknown). 13 received appropriate antibiotic therapy.
- Of 19 pregnancies, 5 had adverse outcomes, including syndactyly, cortical blindness, IU fetal death, prematurity, and rash.
- 'The frequency of such outcomes warrants further surveillance and studies of pregnant women with Lyme disease'.

A systematic review on the impact of gestational Lyme disease in humans on the fetus and newborn

- PLOS One 2018 Lisa Waddell, Public Health Canada
- Systematic review was conducted to summarise the global literature on adverse birth outcomes associated with gestational LD in humans.
- SR identified 45 studies, 29 describing 59 cases reported as gestational LD.
- Adverse outcomes included spontaneous miscarriage or fetal death (n=12), newborn death (n=8), and newborns with abnormal outcomes (n=16).
- ‘Only one case provided some evidence of vertical transmission of Bb that had negative consequences for the fetus’.

Waddell (continued)

- The results of 17 epidemiological studies were reviewed
- No difference in adverse birth outcomes found in exposed population compared to unexposed populations (based on history of bite, antibody test)
- Meta-analysis of nine studies showed significantly higher adverse birth outcomes in women reported to have been treated for gestational LD (11%) compared to those who were not treated during pregnancy (50%).
- ‘The global evidence does not fully characterise the potential impact of gestational LD, and future research that addresses the knowledge gaps may change the findings in this SR’.
- These authors downplay risk of early infection/late infection, role of maternal factors/fetal factors.

Lactation and Lyme Transmission

- Schmidt et al. Detection of Bb DNA by PCR in the urine and breast milk of patients with Lyme Borreliosis, Diagn Micro Infect Diseases 1995. 21 (3); 121-6.
- In addition to urine, breast milk from two lactating women with EM rash were tested and also found reactive

Does Lyme Spread from Mother to Child?

- Yes, it is transplacentally transmitted and it may cause adverse outcomes.
- We have only small studies but it is clear that the bacteria can spread to the placenta and to the baby.
- It is likely that early in utero infection causes more severe damage ? Placental insufficiency, large volume bacteremia may be important factors.
- Lack of ‘inflammation’ in baby does not mean infection is not significant (inflammation comes later)
- Having an ICD 11 code for congenital Lyme would facilitate recognition and better prospective studies and encourage future research

Next Steps

- We need to stop downplaying the extent of Borrelia infection worldwide
- There is no doubt Lyme spreads from a pregnant women to her unborn child; and we can learn from other diseases (HIV, RF, TORCH)
- Prospective studies are needed
- Of course better knowledge of the factors involved in Congenital Lyme/Co-infections is needed, but Lyme research is blocked (Why?)

What studies need to be done to further understand MTCT of Borrelia?

- Prospective studies of pregnant women infected with Borrelia
- Quantitative measures of ‘spirochetemia’ in different trimesters, and measurement of birth outcomes
- Studies of placenta pathology
- Measurement of infection/disease in newborns
- Characterisation of early, birth, post-partum infection and symptomatology in newborns
- Well chosen matched controls, better measures of ‘infection’ than just ‘antibody’