Maternal Vaccination to Protect Infants from Herpes Simplex and Cytomegalovirus

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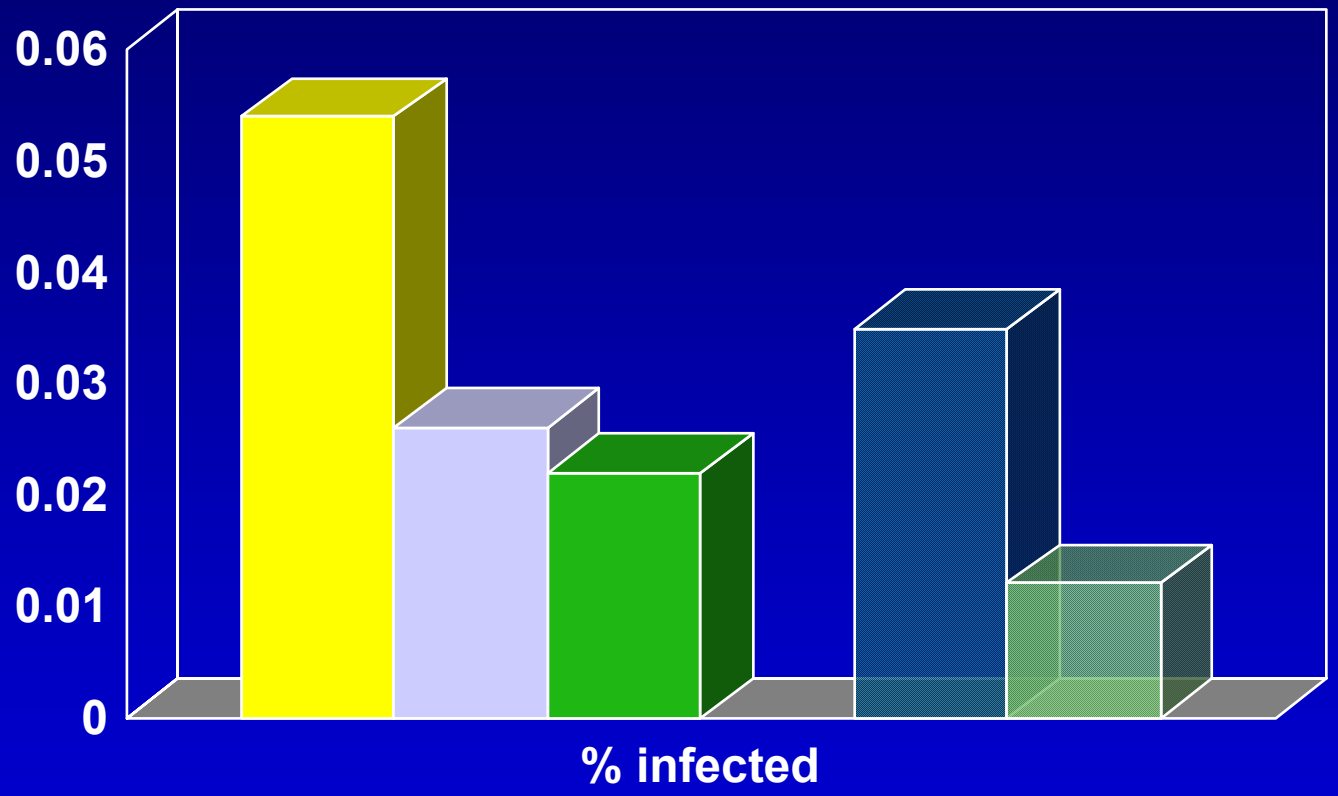
PERINATAL HSV TRANSMISSION

- HSV is usually transmitted from mothers to infants.
- Most mothers of infected infants have
  - No history of genital herpes
  - No known exposure to genital herpes
  - No clinical signs at delivery

PERINATAL HSV INFECTION RATES RELATED TO MATERNAL HSV SEROSTATUS



31,663 women

- Seroneg
- HSV-1 +
- HSV-2+
- HSV-2 only
- HSV-1+/-2+

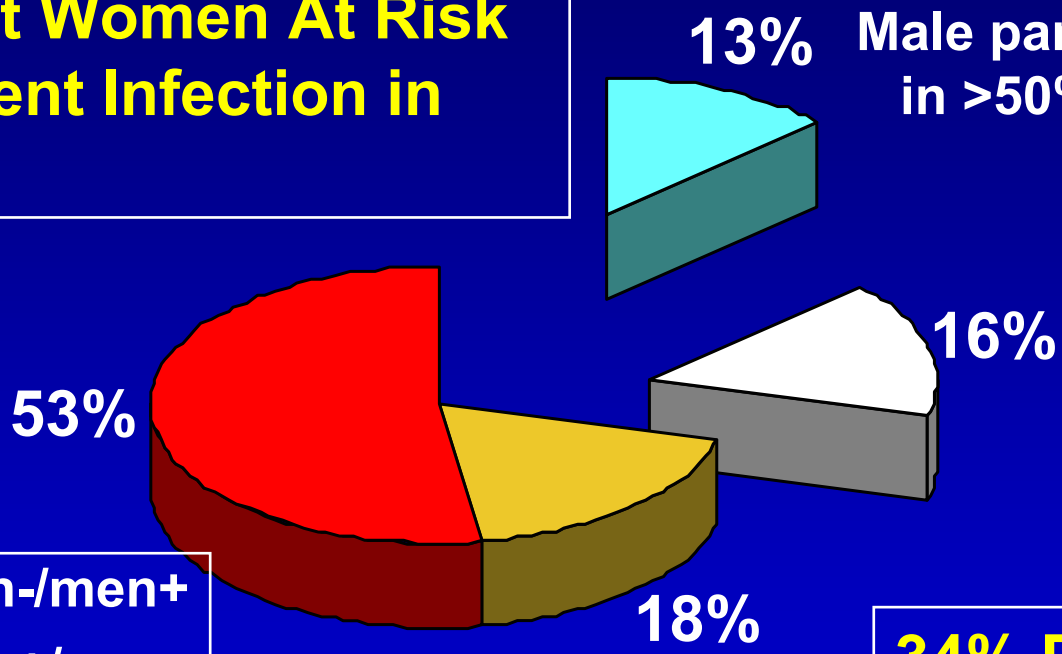
Rate per 100,000 births:

Seronegative	= 54
HSV 1	= 26
HSV 2	= 22

[Brown et al. JAMA, 2003]

HSV-2: ACQUISITION OF OF MATERNAL INFECTION DURING PREGNANCY

13% Pregnant Women At Risk Most with Silent Infection in Partner

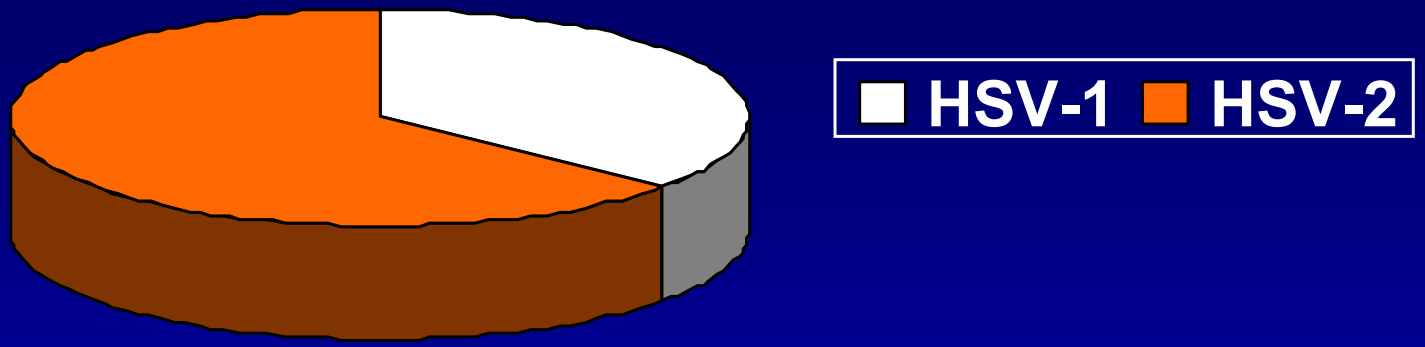


Male partner asymptomatic in >50% of these couples

34% Pregnant Women HSV-2 infected

N Engl J Med 1992;326:16-20

HSV-1 TRANSMISSION TO INFANTS

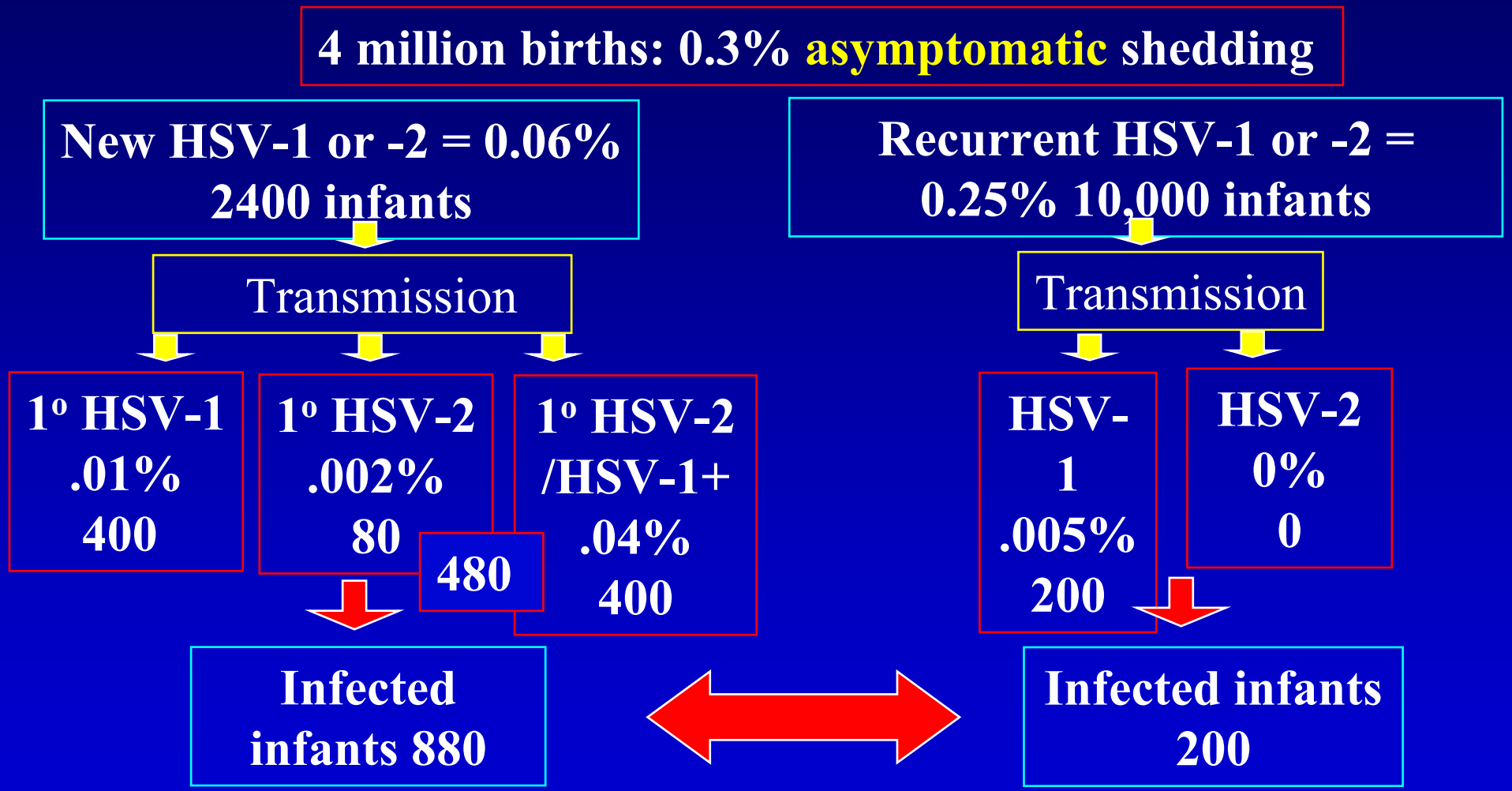


Incidence of Neonatal Herpes: Seattle cohort

HSV-1	45.3 / 100,000 births
HSV-2	80.3 / 100,000 births
HSV-1 or -2	125.6 / 100,000 births

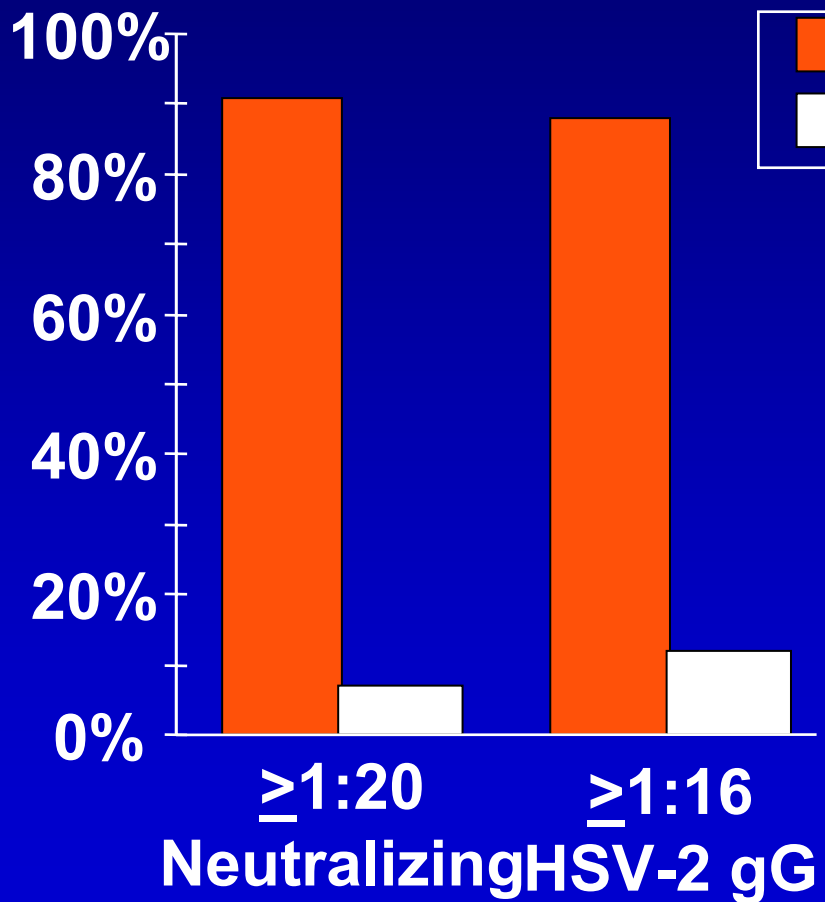
Changing epidemiology: Neonatal HSV is caused by HSV-1 and HSV-2 (Brown, 2001)

HSV TRANSMISSION TO INFANTS



HIGHEST RISK IF MOTHER SUSCEPTIBLE DURING PREGNANCY

PERINATAL INFECTION RISK RELATED TO INFANT PASSIVE ANTIBODY STATUS



Infants with passive antibodies

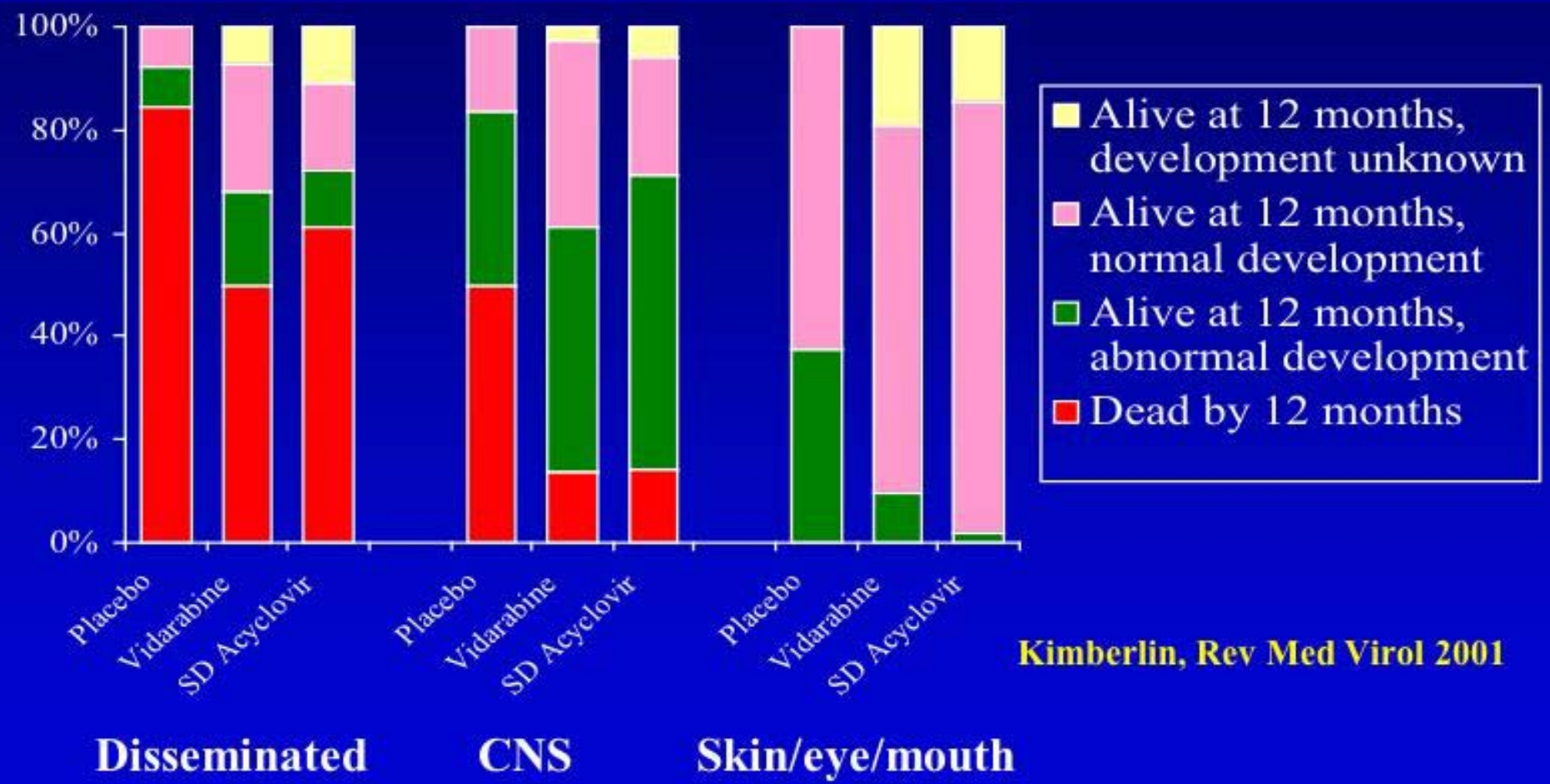
- Born to mothers with recurrent HSV-2 infection

- Exposed to less HSV-2 virus with recurrent shedding

Alternatives to HSV Vaccination

- HSV serologic testing of mothers and partners with new methods for detecting HSV-1 and HSV-2 antibodies to minimize exposure
- Antiviral prophylaxis in late gestation for mothers with HSV-2 antibodies
- Identifying infants exposed to HSV-1 or HSV-2 at delivery and defining useful interventions

Morbidity and Mortality Among 229 Infants with Neonatal HSV Infection, 1974-1998



Kimberlin, Rev Med Virol 2001

HSV Candidate Vaccines

Vaccine: Subunit recombinant glycoprotein gB2/gD2/MF59, 30 ug/dose

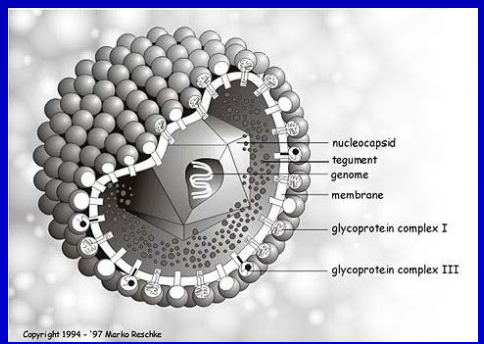
Regimen 0, 1, 6 mo

Study populations

- monogamous HSV-2 seronegative, n = 531
- STD Clinic HSV-2 seronegative, n = 1862

Outcome

Decreased acquisition in women first 150 days after enrollment only



[Corey 1999]

HSV Candidate Vaccines

Vaccine: Subunit recombinant glycoprotein gD2/ASO4 (alum-lipid), 20 ug/dose

Regimen 0, 1, 6 mo

Study populations

- dual HSV-1/HSV-2 seronegative, n = 847
- HSV-1+/HSV-2 seronegative, n = 1862

Outcome

- Decreased genital herpes disease in HSV-1/HSV-2 seronegative women
- Trend towards decreased infection in dual HSV-1/HSV-2 seronegative women [Stanberry 2002]

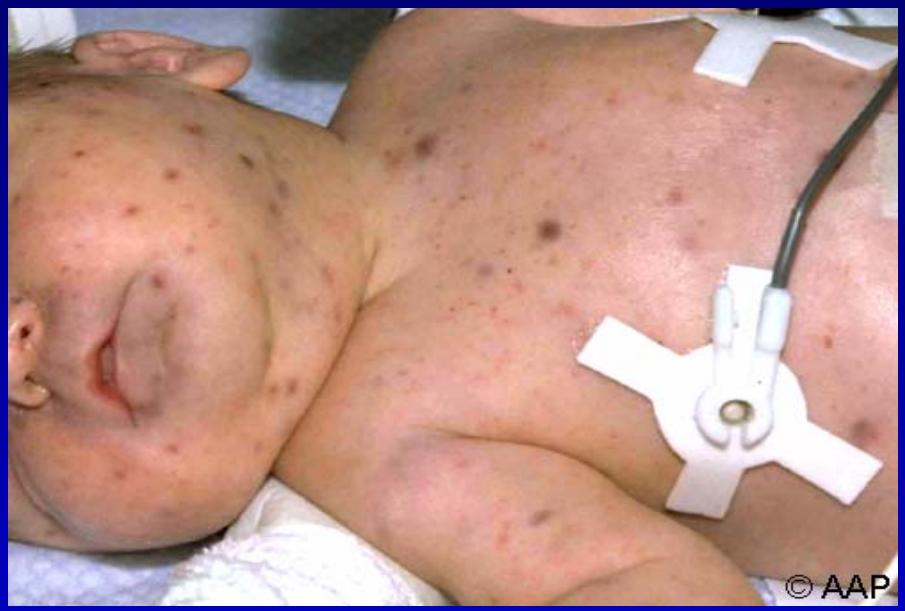
Clinical Trial Endpoints: HSV Vaccines

- Prevention or decrease in maternal infection
  - dual HSV-1/HSV-2 seronegatives
    - HSV-1 as well as HSV-2 protection
  - HSV-1+/HSV-2 negative
    - HSV-2 protection
- Decreased maternal genital disease caused by HSV-1 or HSV-2
- Decreased asymptomatic shedding
- Decreased transmission to infant
- Prevention of HSV disease in infants

HSV Vaccines: Alternatives to Glycoprotein Subunit Vaccines

- Live attenuated HSV-1/HSV-2 recombinants
- Disabled infectious single cycle mutants
  - gH, ICP8, ICP27, ICP10 deletions

Congenital CMV Infection



- Term newborn
- Uncomplicated pregnancy
- Small for gestational age
- Microcephaly
- Hepatosplenomegaly
- Jaundice, petechiae
- Thromobocytopenia/ neutropenia
- Elevated liver function tests

Congenital CMV Infection

- **Consequences of CMV for the infant**

Symptomatic	10%
Mortality 10% / Severe sequelae	
Asymptomatic	90%
Asymptomatic + later detection of hearing loss / neurologic deficits	5 – 15%

- **4,000-8,000 infants/yr with CMV-related retardation and hearing loss in the US**

Maternal Immunity and Protection from Congenital CMV

- **Transmission related to maternal status**

Primary infection	15 – 40%
Reactivation or re-infection	1-2 %

- **Risk of congenital CMV infection**
  - 70-90% decreased risk with pre-existing immunity
  - Significant decreased risk of symptoms at birth or later sequelae

[Adler, 1995;Fowler 2003; Plotkin 2002]

CMV Vaccine Candidates

- Live attenuated Towne - tissue culture passage
- Live attenuated Towne/Toledo chimeras - recombinant viruses
- Non-replicating canarypox (ALVAC) vector with gB or pp65
- Subunit recombinant gB/MR59 or gB/alum
- Peptide (pp65) fusion with T-helper/CTL epitopes and lipid tail
- DNA vaccine
- CMV dense body particles

Candidate CMV Vaccines

	Sponsor	Evaluation
Towne	NIH	Seronegative adults, children,transplant
Towne/Toledo	MedImmune	Seropositive adults
gB/MF59	Chiron	Seronegative adults; toddlers
ALVAC gB/pp65 (pp65) fusion	Aventis City of Hope	Seronegative adults Pep Transplant
DNA vaccine	Vical	Transplant
DB particles	Gutenberg	Seronegative adults

Candidate CMV Vaccines

Towne

Seronegative women, child in daycare
- Phase I: 600 pfu/dose vs. placebo;no protection
- Phase II: 6000 pfu/dose

Phase I: seronegative toddlers

Phase I: seronegative adults, IL12 + Towne [S.Adler]

Towne/Toledo

Safety/immunogenicity in seronegative adults

Recomdinant gB/MF59

Seronegative women, vs. placebo; adolescents

ALVAC gB Seronegative adults - poor immunogenicity

prime + Towne = three doses of gB/MF59

pp65 CD8 CTL induced

Clinical Trial Endpoints: CMV Vaccines

Evaluation of efficacy

- Decreased maternal infection
  - child in day care
- Decreased congenital infection
  - less intrauterine transmission
- Decreased newborn and longterm sequelae

CMV vaccine with 60% efficacy against primary infection could eradicate CMV from a community [Griffiths, 2001]