Human Cytomegalovirus Vaccines

by
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Congenital CMV

- 0.5 – 2% of all pregnancies complicated by CMV infection

- After primary infection:
  1. 10% symptomatic infection at birth, causes microcephaly, encephalitis, retinitis, hepatosplenomegaly, purpura
  2. 90% asymptomatic at birth, but about 15% will have deafness or neurologic sequelae
  3. 100% of infected fetuses will excrete CMV at birth in saliva and urine, 50% in blood

- Reinfection occurs in 1-2% of seropositive women
## Burden of Congenital CMV Infection

### Congenital CMV infection rates in live births

- US, Canada, Western Europe, Australia & Japan – 0.5% to 1%
- Latin America, Africa and most Asian countries – 1% to 2%

### Estimated annual live births with congenital CMV

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated Live Births</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>20,000 – 30,000</td>
</tr>
<tr>
<td>Brazil</td>
<td>~35,000</td>
</tr>
<tr>
<td>India</td>
<td>270,000 – 540,000</td>
</tr>
<tr>
<td>Nigeria</td>
<td>65,000 – 130,000</td>
</tr>
</tbody>
</table>
Congenital CMV – an Important Cause of Neurologic Morbidity

- Congenital CMV disease
- Down syndrome
- Fetal alcohol syndrome
- Spina bifida/anencephaly
- Pediatric HIV/AIDS
- Invasive Haemophilus influenzae b
- Congenital Rubella Syndrome

Annual no. U.S. children with long-term sequelae

Cannon 2009
CMV Seroprevalence Rates Among Women of Reproductive Age and Birth Prevalence of Congenital CMV

Manicklal, Clin Microbiol Rev 2013
Cannon, Rev Med Virol 2010
# Prevalence of congenital CMV Infections in Resource Poor Settings

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Week of conception</th>
<th>Specimen</th>
<th>n</th>
<th>Prevalence, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schopfer 1978</td>
<td>Ivory Coast</td>
<td>-</td>
<td>Urine</td>
<td>2032</td>
<td>1.4 (1.0–2.0)</td>
</tr>
<tr>
<td>van der Sande 2007</td>
<td>Gambia</td>
<td>2002–2005</td>
<td>Urine</td>
<td>741</td>
<td>5.4 (4.0–7.3)</td>
</tr>
<tr>
<td>Sohn 1992</td>
<td>Korea</td>
<td>1989–1991</td>
<td>Urine and cord blood</td>
<td>514</td>
<td>1.2 (0.5–2.6)</td>
</tr>
<tr>
<td>Tsai 1996</td>
<td>Taiwan</td>
<td>-</td>
<td>Urine</td>
<td>1000</td>
<td>1.8 (1.1–2.8)</td>
</tr>
<tr>
<td>Dar 2008</td>
<td>India</td>
<td>-</td>
<td>Saliva, urine</td>
<td>423</td>
<td>2.1 (1.1–4.0)</td>
</tr>
<tr>
<td>Luchsinger 1996</td>
<td>Chile</td>
<td>1989–1994</td>
<td>Urine and saliva</td>
<td>658</td>
<td>1.8 (1.0–3.2)</td>
</tr>
<tr>
<td>Weinrich 1997</td>
<td>Brazil</td>
<td>1994–1995</td>
<td>Saliva</td>
<td>663</td>
<td>3.2 (2.1–4.8)</td>
</tr>
<tr>
<td>Yamamoto 2011</td>
<td>Brazil</td>
<td>2003–2009</td>
<td>Urine and/or saliva</td>
<td>12195</td>
<td>1.0 (0.8–1.2)</td>
</tr>
<tr>
<td>Noyola 2003</td>
<td>Mexico</td>
<td>-</td>
<td>Saliva</td>
<td>560</td>
<td>0.9 (0.4–2.1)</td>
</tr>
<tr>
<td>Estripeaut 2007</td>
<td>Panama</td>
<td>2003–2004</td>
<td>Urine</td>
<td>317</td>
<td>0.6 (0.2–2.5)</td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; CI, confidence interval.

- Studies that were conducted in well-baby nurseries or excluded severely ill newborns.
- Mothers tested as part of the study.
- Indicates specimen or method used for confirmation.

Lanzieri, 2014
Birth Prevalence of Congenital CMV infection in Ribeirão Preto, Brazil

7484 mothers

8047 infants

87 (1.08%) infants with congenital CMV (95% CI: 0.86-1.33)

Birth Prevalence of Congenital CMV Infection in Rural North India

- 1720 mothers
- 1720 infants
- 20 (1.2%) infants with congenital CMV (95% CI: 0.85-1.34)

Dar et al., Pediatr Infect Dis J 2016, December 28
Congenital CMV and Hearing Loss
Estimated Number of children with Congenital CMV in the U.S. from Mothers with Primary and Non-primary Infection During Pregnancy

Congenitally infected children born to seronegative mothers in US, per year — 3,722 (4,419 – 16,049)

Congenitally infected children born to seropositive mothers in US, per year — 29,918 (23,508 — 36,830)

Wang, Clin Infect Dis 2011
### Congenital CMV Infection Following Non-primary Maternal Infection in Sweden and England

<table>
<thead>
<tr>
<th>At birth</th>
<th>Sequelae</th>
<th>Mild</th>
<th>Moderate/Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>42% (8/19)</td>
<td>10% (2/19)</td>
<td>32% (6/19)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>14% (19/135)</td>
<td>7% (9/135)</td>
<td>7% (10/135)</td>
</tr>
</tbody>
</table>

- Of the 16 with moderate/severe outcomes, 9 had mothers with confirmed or presumed non-primary infection

Maternal Immunity

- Thought to provide significant protection against intrauterine transmission

- Significantly lower rates of sequelae following non-primary infection (Fowler, NEJM 1992)

- Protects from transfusion acquired CMV disease in premature infants

- Hyperimmune globulin may or may not prevent transmission and improve outcome

- Vaccine strategies have been focused on preventing primary maternal infection during pregnancy
Prevention of Congenital CMV Infection Challenges for Developing Vaccines

• Maternal immunity
  • Protective immune responses have not been defined
  • Preexisting seroimmunity does not provide complete protection
  • Most infants with cCMV in highly seropositive populations including LMIC are born to women with preexisting seroimmunity
• Precise estimates of disease burden in LMIC are limited
Congenital CMV Global Burden

Summary

- Congenital CMV infections are common throughout the world; however, its contribution to developmental disorders in the developing world is not well defined.

- Congenital CMV infections are an important cause of CNS disease and sequelae.

- Congenital infection following non-primary maternal infection represents the major source of infected infants in most of the world.
Why a CMV Vaccine?

- To prevent congenital infection in infants of seronegative women, and if possible seropositive women

- To prevent CMV infection in transplant recipients
  - Seronegative solid organ transplant recipients at high risk of primary infection
  - Seropositive bone marrow transplant patients at high risk of reactivation
Cytomegalovirus

non-structural protein: IE1

pp65, pp150

gB

gH/gL/
UL128-131
Kaplan-Meier Curve of CMV Infections Related to Vaccination with gB

Bernstein, D., Et al, doi: 10.1016/j.vaccine.2015.11.056
Natural infection level of immunity is defined by testing sera from 39 healthy subjects with the same assays.
Importance of Pentamer in Protection Against Intrauterine Infection

- Antibodies block infection of cytотrophoblasts
- Rapid production of antibodies reduces transmission
- Magnitude and kinetics of CD4+ T cells reduces transmission

CMV Vaccine Concept is Based on Replication Defective Virus

- Inclusion of pentameric complex
- T-cells that may contribute to protective immunity
- UL51 and IE1/2 are fused to ddFKBP, which renders the CMV proteins unstable and therefore prevents replication, whereas the addition of Shld-1 stabilizes the ddFKBP and therefore permits replication.

Vaccine production (with Shld-1)

Vaccination (no Shld-1)
Vaccine was administrated at 100 or 10 µg/dose in rhesus macaques (n=5).

Neutralizing Abs against viral epithelial entry are measured at the indicated time points.

Recombinant gB vaccine with an oil-in-water emulsion adjuvant T-cell responses to multiple viral antigens were demonstrated in ELISPOIT assay (Data not shown)
Live CMV Vaccines in Development

<table>
<thead>
<tr>
<th>Attenuated strain (Towne)</th>
<th>Med Coll VA</th>
</tr>
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<tbody>
<tr>
<td>Recombinants with wild virus (Towne-Toledo)</td>
<td>Medimmune</td>
</tr>
<tr>
<td>Replication-defective virus</td>
<td>Merck</td>
</tr>
<tr>
<td>Alphavirus Replicon</td>
<td>Novartis</td>
</tr>
<tr>
<td>Vectored: MVA, adeno, LCMV, VSV</td>
<td>City of Hope Queensland Inst., Hookipa, Yale</td>
</tr>
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</table>
## Non-living CMV Vaccines in Development

<table>
<thead>
<tr>
<th>Non-living CMV Vaccines</th>
<th>Developers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant gB glycoprotein with adjuvant (2)</td>
<td>Sanofi Pasteur, GSK</td>
</tr>
<tr>
<td>DNA plasmids</td>
<td>Astellas, Inovio</td>
</tr>
<tr>
<td>Self-replicating RNA</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Peptides</td>
<td>City of Hope</td>
</tr>
<tr>
<td>Dense bodies</td>
<td>Vaccine Project Management (Germany)</td>
</tr>
<tr>
<td>Virus-like particles</td>
<td>Variations Bio, Redbiotech</td>
</tr>
<tr>
<td>Soluble Pentamers</td>
<td>Humabs</td>
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</table>
**Immune Correlates of Protection Against CMV Transmission to the Fetus**

*(Lilleri, Gerna and the Pavia Team)*

<table>
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<tr>
<th>Higher and faster response to pentamer</th>
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<tbody>
<tr>
<td>Wider and faster response to Nt epitopes on pentamer</td>
</tr>
<tr>
<td>Faster Plaque Formation inhibiting antibody</td>
</tr>
<tr>
<td>IFN(\gamma) + producing CD4+ and CD8+ T cells</td>
</tr>
<tr>
<td>Higher Reverted effector memory cells (T_{EMRA})</td>
</tr>
<tr>
<td>Faster lymphocyte proliferation</td>
</tr>
<tr>
<td>Faster IL-2 production by CD4+ cells</td>
</tr>
<tr>
<td>Higher 1L-7R pos CD4+ T cells</td>
</tr>
</tbody>
</table>

* Rev Med Virol 2017*
Vaccination of Women Intending Pregnancy with Follow-up

- **Endpoint:** Infection of fetus
- **Advantages:**
  - Can demonstrate prevention of transmission to fetus
  - Demonstrates real public health value
- **Disadvantages:**
  - Long study duration
Probable First Targets for CMV Vaccination

- Girls 11-13 yrs. of age (association with HPV, TdAcP, MCV4)
- Seronegative women of child-bearing age
- All infants, to reduce viral circulation
- Solid organ transplant recipients
- Hematogenous stem cell transplant recipients
Chief Unanswered Questions About Prevention of CMV

- Can maternal-fetal transmission in seropositive women be prevented?
- Can maternal-fetal infection in seropositive women be prevented by boosting antibody or CMI to US 2-11 proteins?
- Can protective immune responses be prolonged over age of child-bearing?
At Present

The need for a CMV vaccine in seronegative women to prevent fetal abnormalities is clear.

There are many candidate vaccines, based on gB, pp65 or pentamer.

In clinical trials there has been some evidence of efficacy in the prevention of CMV acquisition by vaccinees.

Seropositive women also transmit CMV to their fetuses, with sequelae that are significant although maybe generally less serious than in fetuses of seronegatives.

However, the immunological deficits that permit CMV infection in seropositive women are undefined and vaccination has not been explored in them.