



# **Burden of Congenital Cytomegalovirus (CMV) Infection and Disease in the United States**

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**The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.**

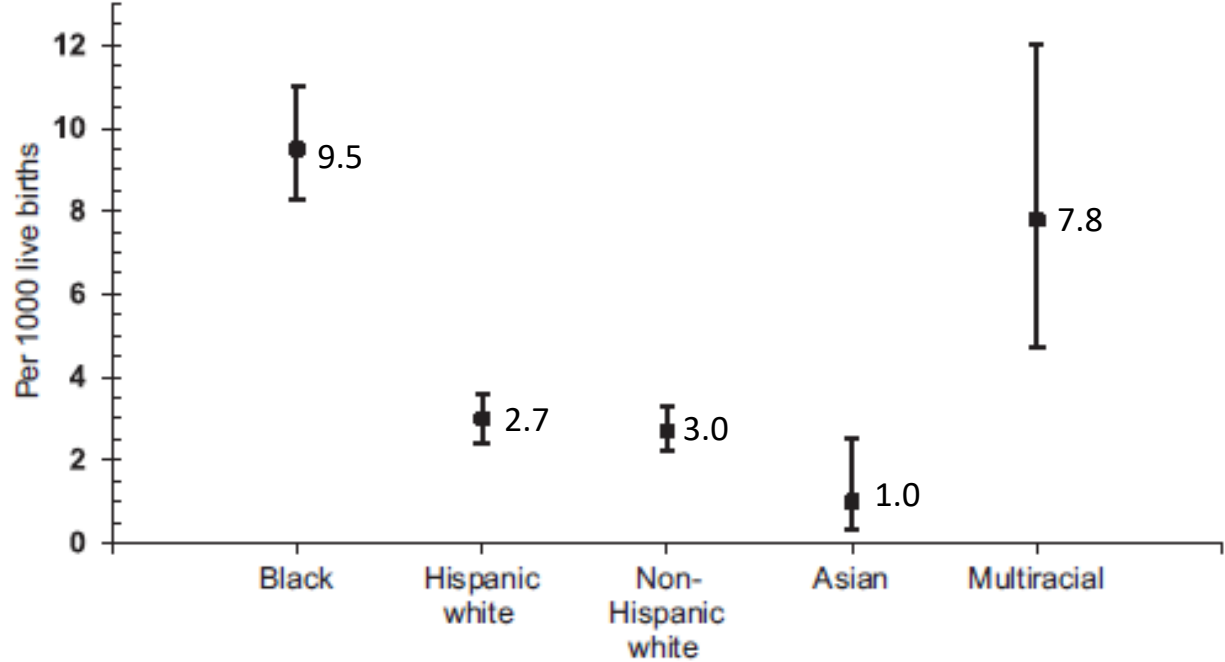
# Outline

- **Burden of congenital CMV infection**
- **Burden and costs of congenital CMV disease and sequelae**
- **Newborn screening for congenital CMV infection**

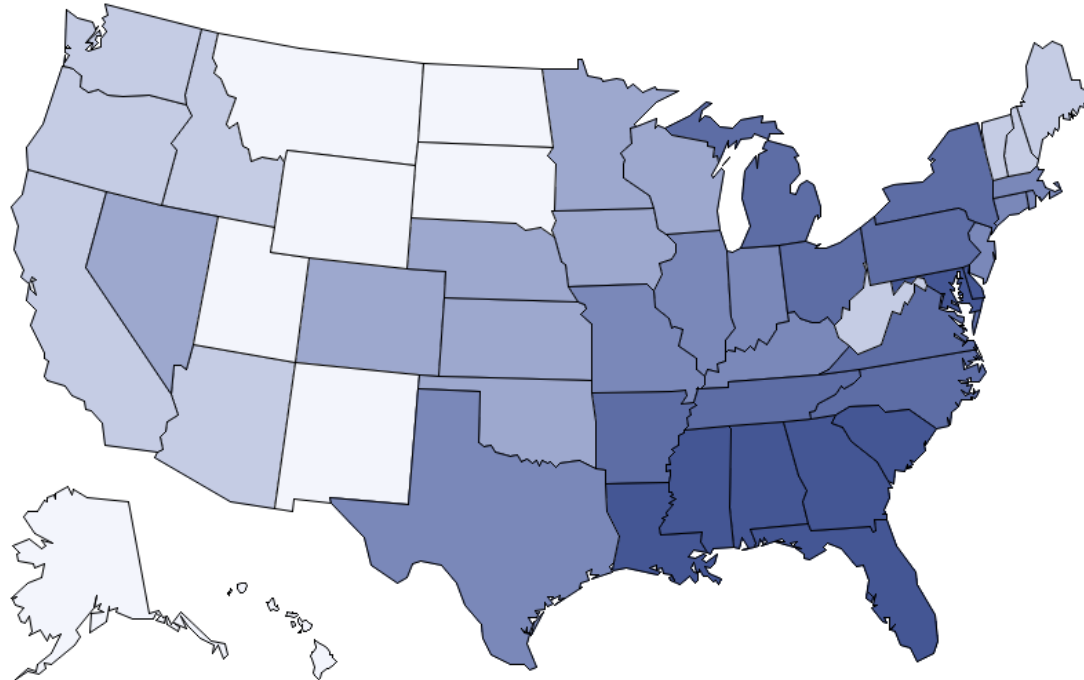
# Burden of Congenital CMV Infection, United States

- **Prevalence: 3-5 per 1,000 live births**
  - **12,000-20,000 infants per year**
  
- **Consensus that prevention of congenital CMV infection would be a feasible, acceptable clinical trial endpoint**

# Prevalence of Congenital CMV Infection by Race/Hispanic Origin, United States, 2007-2012



# Prevalence of Congenital CMV Infection by State, United States, 2007-2012



CMV birth prevalence per 1,000 live births

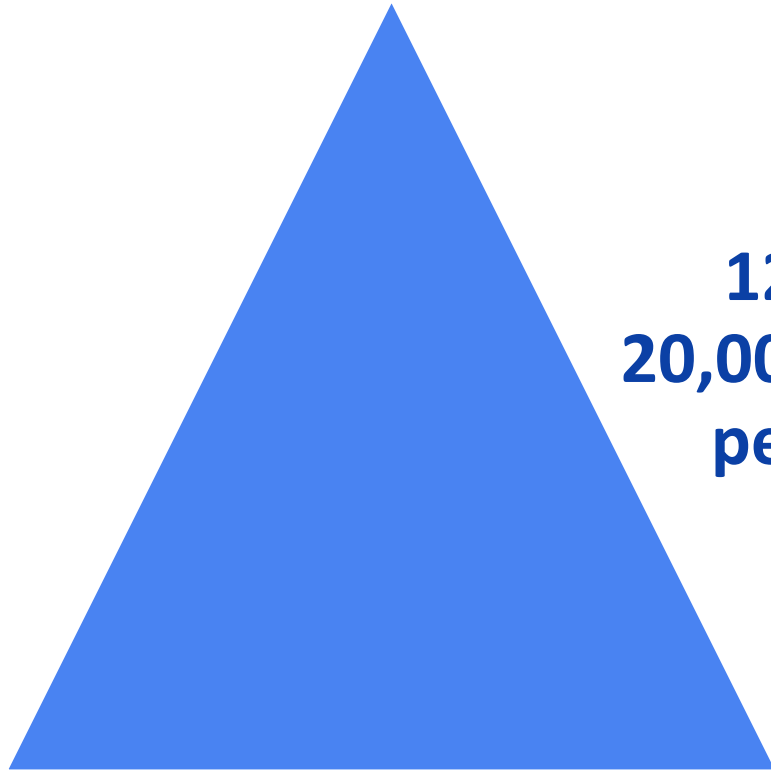
2.4 - 3.0	3.0 - 3.2	3.2 - 3.5
3.6 - 4.0	4.0 - 4.5	4.5 - 6.6

Unpublished. Estimates based on race/Hispanic specific CMV birth prevalence from CHIMES and live birth distribution by state, 2007-2012. Estimates of CMV birth prevalence for Asian or Pacific Islanders, and American Indian or Native Alaskan are lacking, thus Alaska and Hawaii estimates might be underestimated.

# Outline

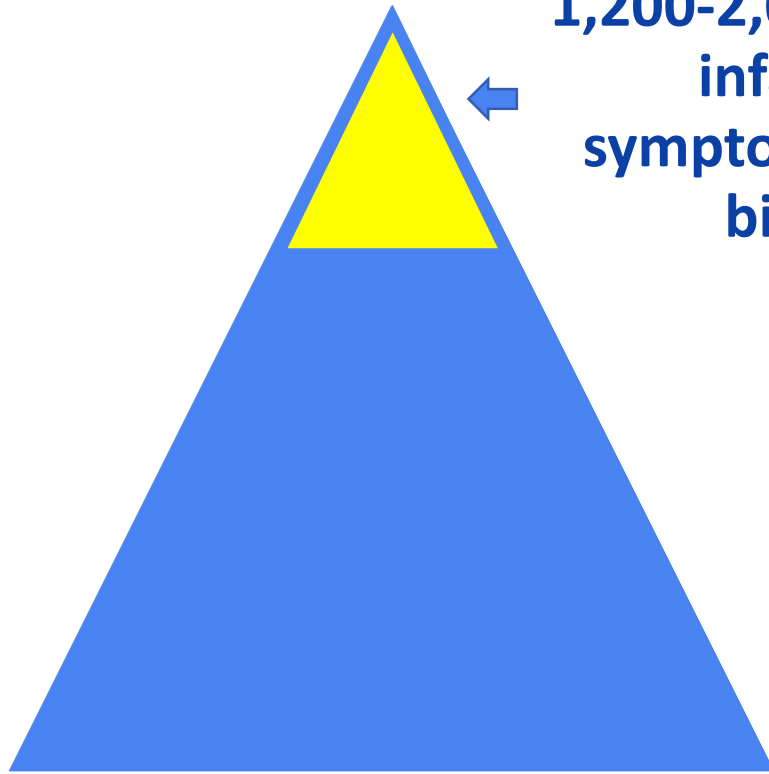
- Burden of congenital CMV infection
- **Burden and costs of congenital CMV disease and sequelae**
- Newborn screening for congenital CMV infection

# Burden of Congenital CMV Infection, United States



**12,000-  
20,000 infants  
per year**

# Burden of Congenital CMV Disease in the Neonatal Period, United States



**1,200-2,000 (10%)  
infants  
symptomatic at  
birth**



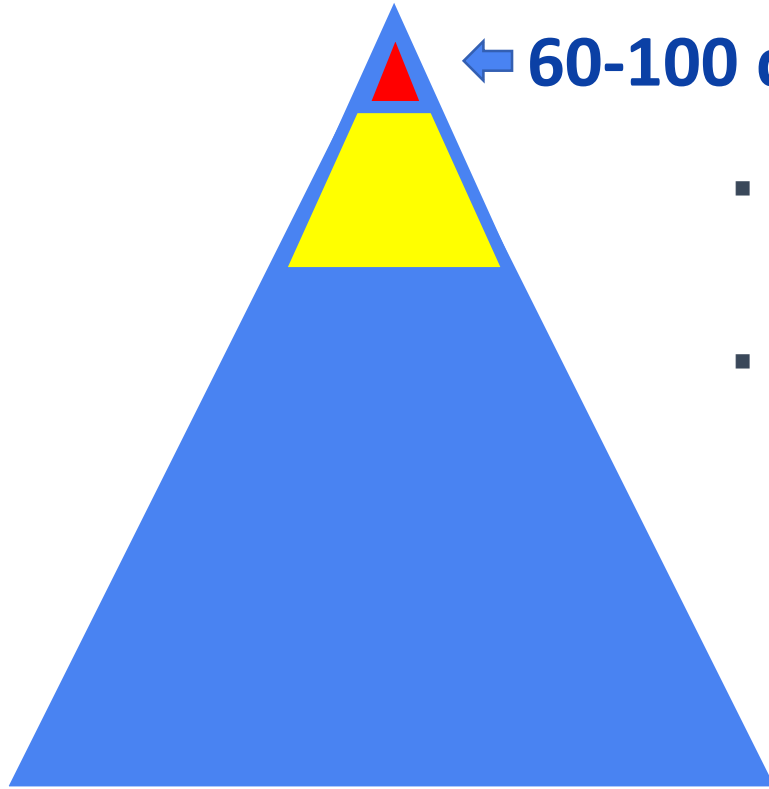
- **Purpura/petechiae**
- **Jaundice**
- **Hepatosplenomegaly**
- **Elevated liver enzymes**
- **Hyperbilirubinemia**
- **Thrombocytopenia**
- **Neurologic disorders**
- **Microcephaly**

Fowler et al. A Targeted Approach for Congenital Cytomegalovirus Screening Within Newborn Hearing Screening. Pediatrics 2017

Goderis et al. Hearing Loss and Congenital CMV Infection: A Systematic Review. Pediatrics 2014



# Congenital CMV Associated Deaths, United States



← 60-100 deaths

- 5% of infants with congenital CMV disease in the neonatal period
- 5 in 1,000 infants with congenital CMV infection

# Congenital CMV Disease with Sequelae, United States 600-1,400

(50-70%) of  
symptomatic  
infants will have  
neurologic  
impairment

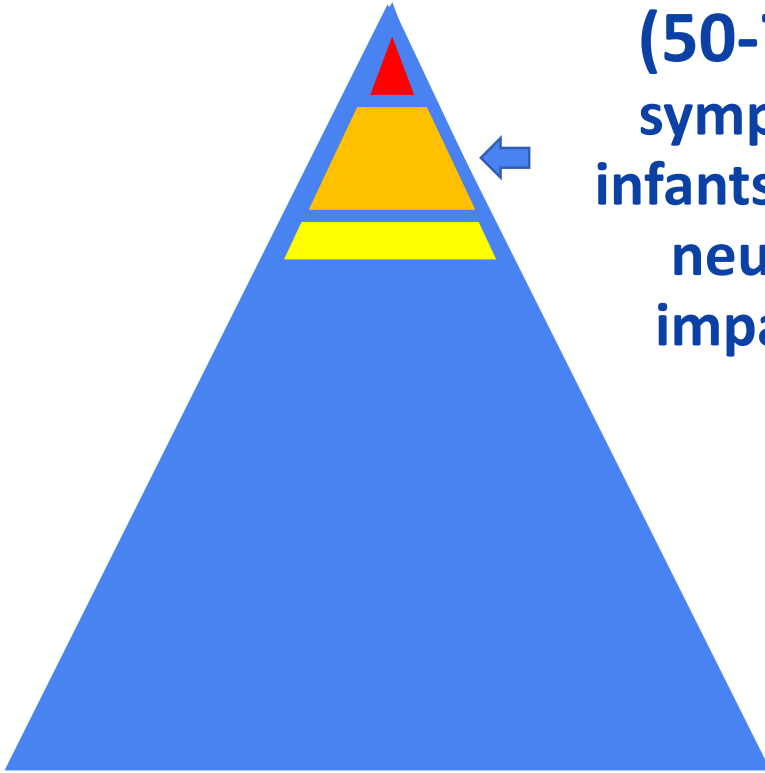


Photo credit: Whitten Sabbatini for The New York Times

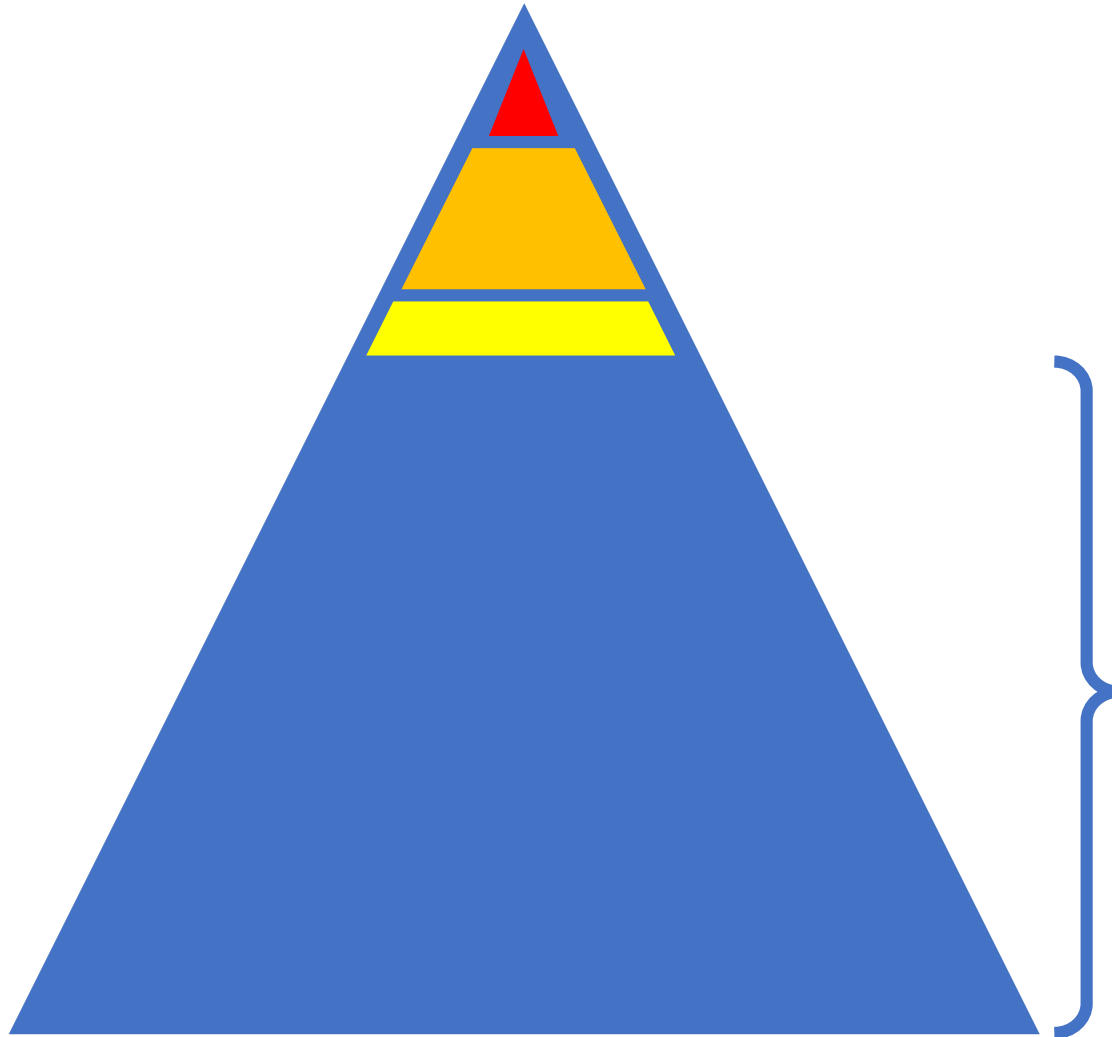
- Intellectual disability
- Cerebral palsy
- Vision loss
- Deafness

Fowler et al. A Targeted Approach for Congenital Cytomegalovirus Screening Within Newborn Hearing Screening. Pediatrics 2017

Goderis et al. Hearing Loss and Congenital CMV Infection: A Systematic Review. Pediatrics 2014

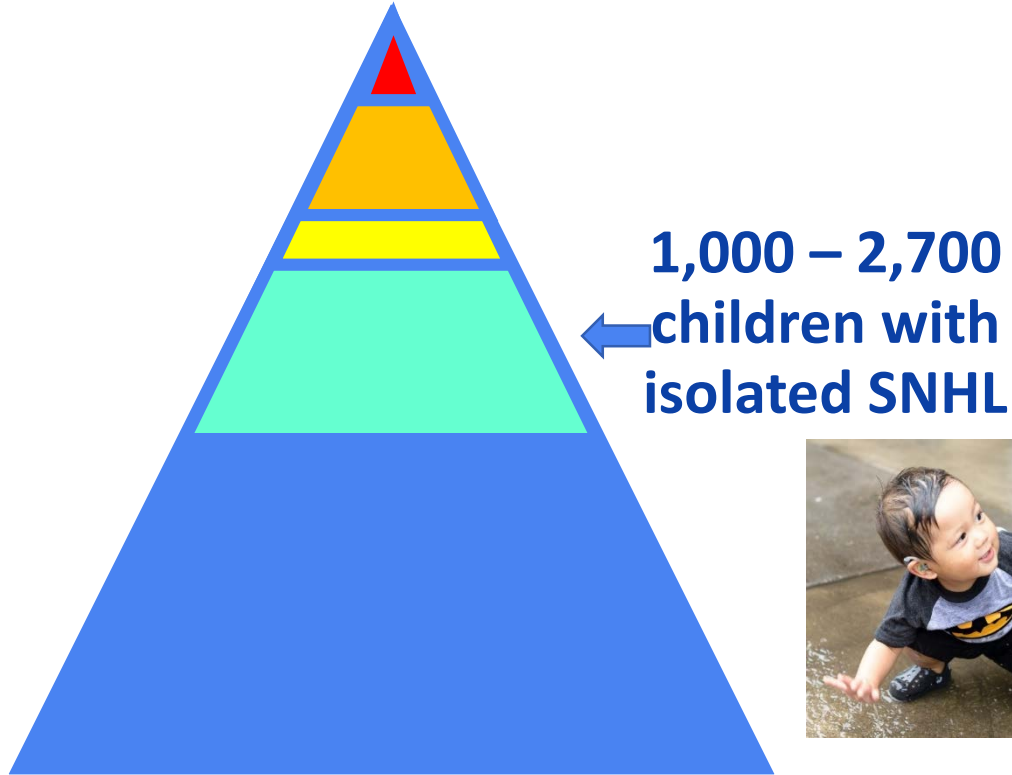
Dollard et al. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol 2007

# Asymptomatic Congenital CMV Infection, United States



**10,000 – 18,000 (90%)  
infants with asymptomatic  
congenital CMV infection**

# Burden of Isolated Sensorineural Hearing Loss (SNHL) with Congenital CMV Infection, United States



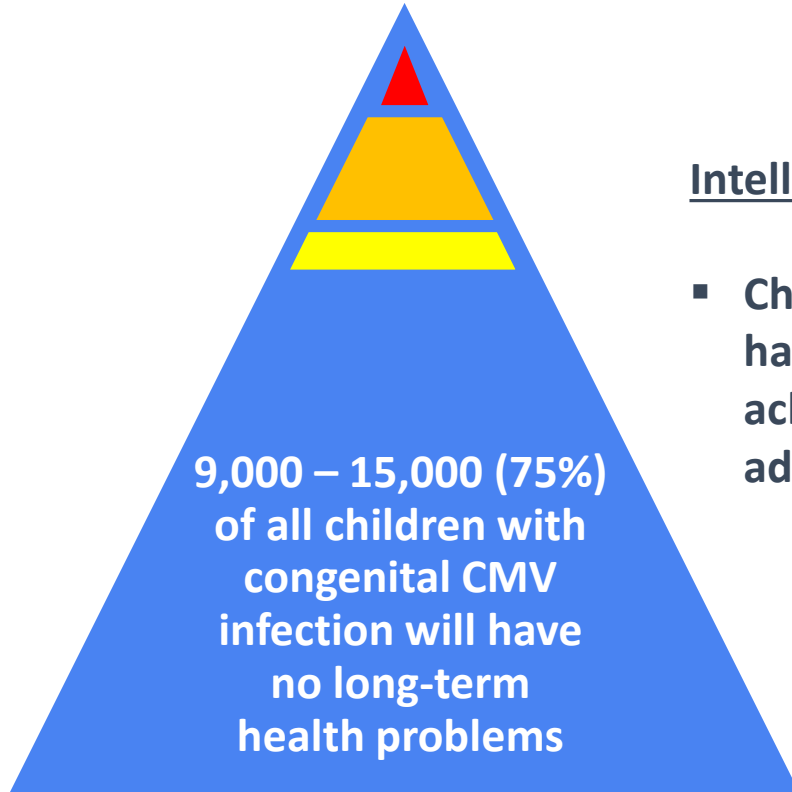
- 10-15% of asymptomatic infants develop SNHL
- 53% missed by newborn hearing screening – delayed-onset SNHL
- By age 2 years, 500-900 children with severe to profound SNHL in at least one ear
- By age 4 years, 200-360 children with bilateral severe to profound SNHL – cochlear implant candidates

Fowler et al. A Targeted Approach for Congenital Cytomegalovirus Screening Within Newborn Hearing Screening. Pediatrics 2017

Goderis et al. Hearing Loss and Congenital CMV Infection: A Systematic Review. Pediatrics 2014

Lanzieri et al. Hearing loss in children with asymptomatic congenital CMV infection. Pediatrics 2017

# Long-Term Outcomes among Children with Asymptomatic Congenital CMV Infection, United States



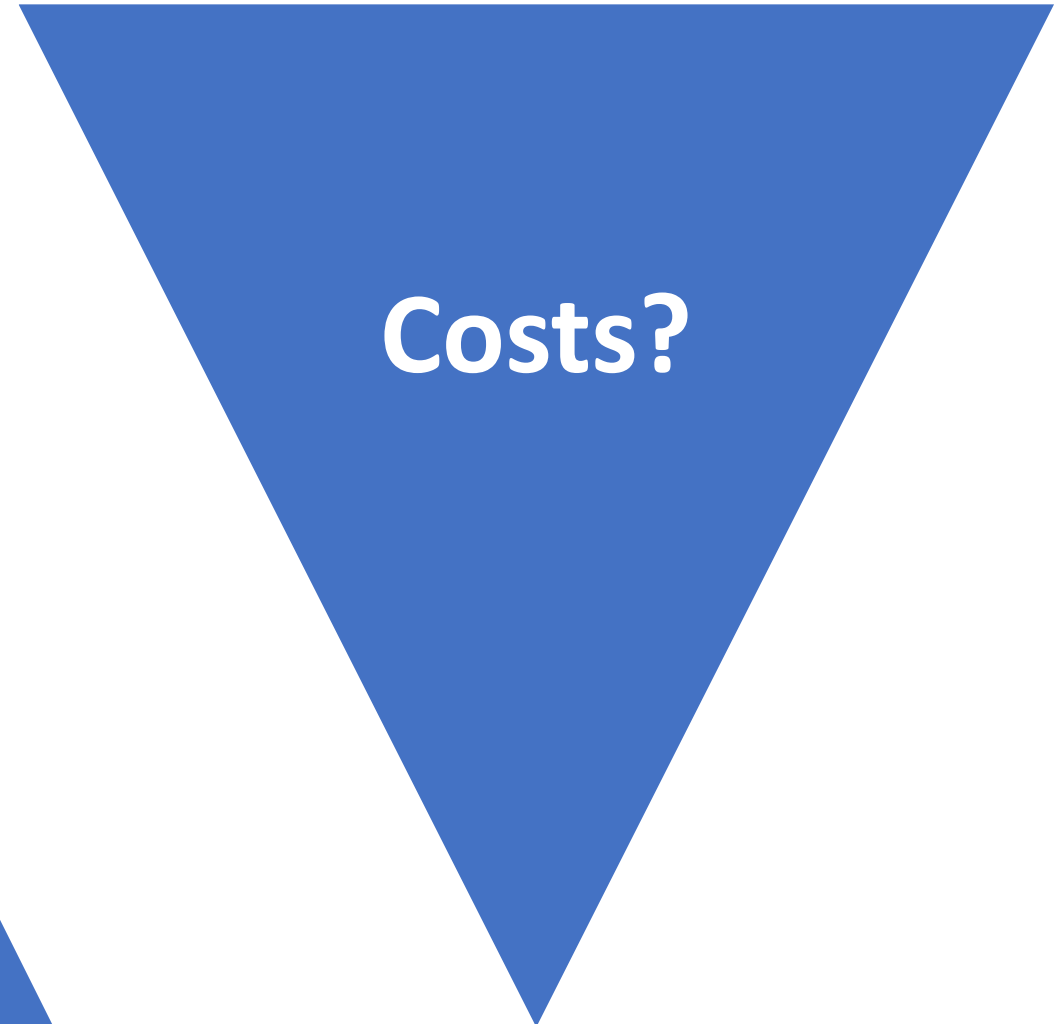
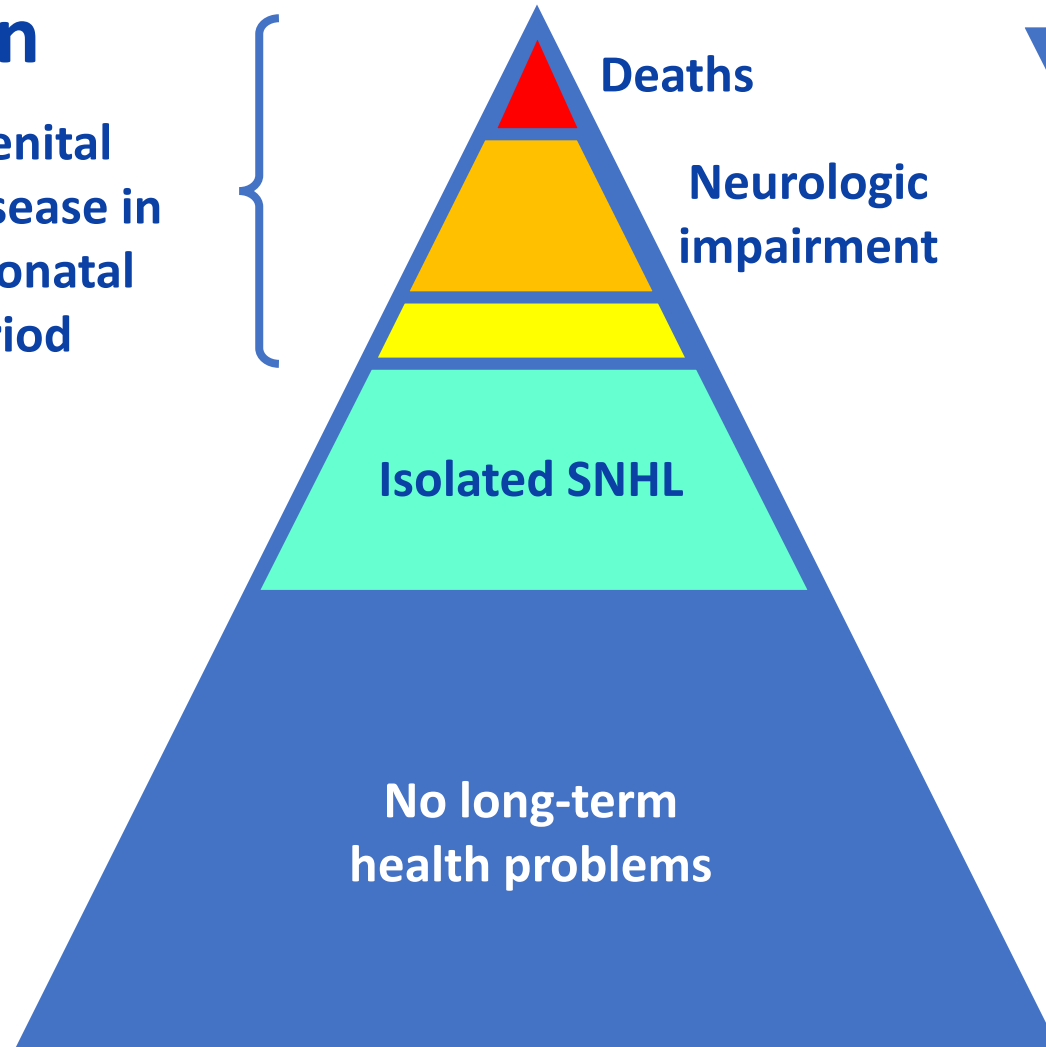
## Intelligence, language and academic achievement

- Children with normal hearing by 2 years of age have no differences in IQ, vocabulary or academic achievement scores during childhood or adolescence, compared to uninfected children

# Congenital CMV Infection, Disease and Sequelae

## Burden

Congenital  
CMV disease in  
the neonatal  
period



# Estimated Costs

Clinical characteristics	Costs per child	Reference
<b>Congenital CMV disease diagnosed in the neonatal period (data from commercial insurance)</b>	<b>\$363,000 average medical expenditure in the first 4 years of life, <u>15-fold</u> compared to other insured children</b>	<b>Grosse et al 2018</b>
<b>Severe neurologic impairment (e.g. microcephaly and cerebral palsy)</b>	<b>\$1 million in excess health care costs in the first 4 years of life, not including supportive care \$3.8 million lifetime cost</b>	<b>Li et al 2017</b>
<b>Sensorineural hearing loss</b>	<b>\$120,000 in additional education costs* \$100,000 unilateral cochlear implantation**</b>	<b>Grosse et al 2007 Trinidad et al 2017</b>

\*2007 dollars \*\*estimated cost for adults

Grosse et al. The Healthcare Cost of Symptomatic Congenital CMV Infection in Privately Insured US Children: Estimates from Administrative Claims Data. Abstract. CMV Public Health and Policy Conference. Vermont 2018

Li et al. Cost-effectiveness of Increasing Access to Contraception during the Zika Virus Outbreak, Puerto Rico, 2016. Emerg Infect Dis 2017

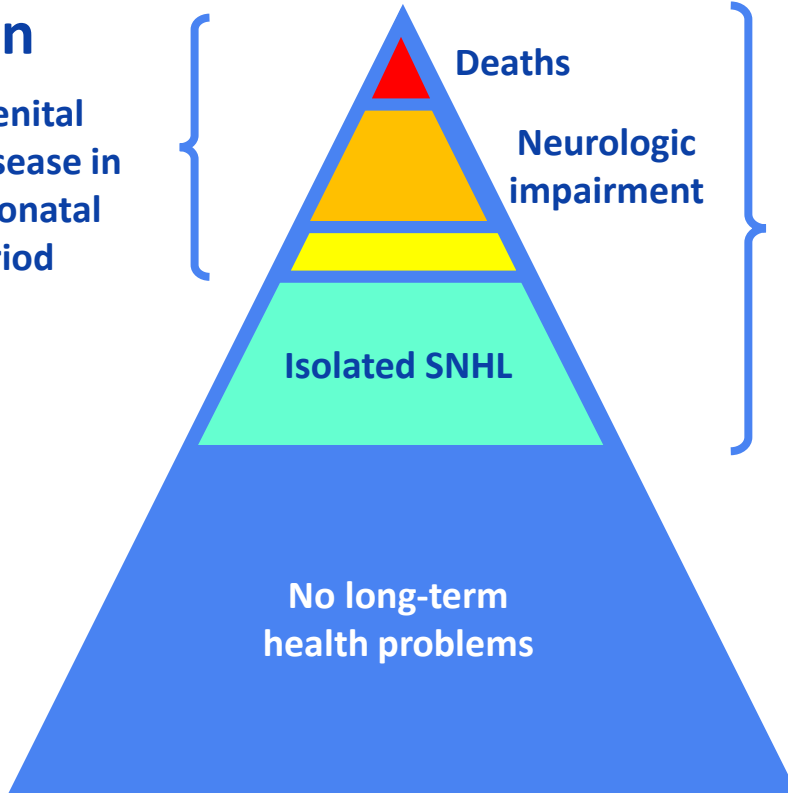
Grosse et al 2007. Education cost savings from early detection of hearing loss: New findings. Volta Voices 2007

Trinidad et al. Simultaneous versus sequential bilateral cochlear implants in adults: cost analysis in a US setting. Laryngoscope 2017

# Newborn Screening for Congenital CMV infection

## Burden

Congenital CMV disease in the neonatal period



Clinical sensitivity



Infants with disease or sequelae

Analytical sensitivity



All infected infants



# Evaluating the Clinical Sensitivity of Dried Blood Spots (DBS) for Newborn CMV Screening, Minnesota

- Funded by CDC and NVPO
- Goal
  - Assess DBS testing method for efficiency and high-throughput capability, thus, suitability for newborn screening and measuring vaccine clinical trial endpoints
- Methods
  - 30,000 newborns screened using saliva swab and DBS, confirmed with urine, PCR testing
  - CMV-positive infants followed from birth through 4 years of age



# Newborn Screening for Congenital CMV Infection

## ■ DBS

Pros: existing public health infrastructure

Cons: lower analytical sensitivity – 28-80%, varies by extraction method

Unknown clinical sensitivity

## ■ Saliva

Pros: high analytical and clinical sensitivity, tested on large scale studies

Cons:

- require new public health infrastructure for collection and testing
- require confirmation with urine
- variable sample quality
- possible false-negatives

# Evaluating the Clinical Sensitivity of DBS for Newborn CMV Screening, MN – Interim Findings

- 8,085 newborns screened over 2 years
- 28 (3.5 per 1,000) confirmed CMV-positive
  - DBS: 75% analytical sensitivity, 9% false-positive rate
  - Saliva: 89% analytical sensitivity, 14% false-positive rate
- Follow-up is ongoing to determine clinical sensitivity



# Conclusions

- **Burden and costs of congenital CMV infection, disease and sequelae are substantial**
- **Newborn screening for congenital CMV infection**
  - **Public health and laboratory challenges to be resolved**
    - **Lack of standardized, high-throughput screening test, for public health labs**
  - **Identification of additional infants that may benefit from early intervention (e.g. isolated delayed-onset SNHL)**
  - **Most infants are not affected, thus, identification of all infected infants might not be required**
  - **Assessing DBS clinical sensitivity will be key for evaluating its suitability for newborn CMV screening and for measuring clinical trial endpoints**

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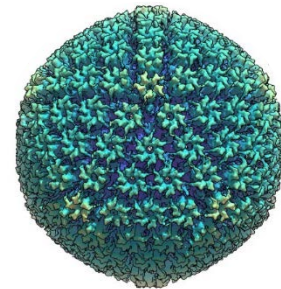
# Thank you!

For more information, contact CDC  
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TTY: 1-888-232-6348 [www.cdc.gov](http://www.cdc.gov)

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# Advances, Gaps, and Challenges in Developing CMV Vaccines

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Sept 13, 2018



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Human Services

# NIAID/NICHD Workshop on CMV

- **Cytomegalovirus Infection: Advancing Strategies for Prevention and Treatment**
  - Sept. 4-6, 2018
  - Goals: review the current state of knowledge of CMV disease and identify knowledge gaps and other barriers to advancement of vaccines, therapeutics and diagnostics for CMV
  - 198 attendees (167 in person) from academia, government and industry
  - Plans to publish a CMV supplement based on this workshop on JID

## ORGANIZING COMMITTEE:

Christopher Beisel, PhD  
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Nahida Chakhtoura, MD  
Paul Griffiths, MD, DSc

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Manisha Patel, MD  
Tatiana Lanzieri, MD

Catherine Laughlin, PhD  
Richard Whitley, MD  
Philip Pellett, PhD  
Philip Krause, PhD  
Uma Reddy, PhD



# Workshop Sessions

- Introduction
  - Virus Biology, disease burden and manifestations
- Therapeutics
- Diagnostics
- Vaccines
  - Vaccines under development
  - Correlates of protection
  - Regulatory considerations
- Gaps/challenges

# Need for a CMV Vaccine

- Safe, durable and broadly protective
- Two main target diseases:
  - Congenital CMV
  - Prevention of transmission and/or reactivation in transplant recipients
    - Solid Organ Transplants (SOT)
    - Hematopoietic Cell Transplant (HCT), e.g., bone marrow transplant for leukemia patients

# A CMV Vaccine Should Be Feasible

- Natural maternal immunity modulates placental CMV transmission risk
  - 40% transmission risk in primary maternal infection
  - ~1-4% transmission risk with reinfection

(Simonazzi, 2017)
- Live-attenuated and gB subunit vaccines have been partially effective in clinical trials (~50% VE)
- Important targets of neut Abs and T cells are known
  - gB glycoprotein- mediates fibroblast entry
  - Pp65- major tegument protein- main target of CD8+Tcells
  - Pentameric complex (gH/gL/UL128/UL130/UL131A) mediated epithelial entry, target of neut Ab and T cells

# CMV Vaccines for Transplant Recipients

- **Astell/Vical**
  - DNA vaccine ASP0113
  - Phase 3 trial in CMV+ HCT patients: safe but failed to demonstrate efficacy
- **City of Hope**
  - MVA recombinant triplex
  - Safe and immunogenic in Phase I trial
  - Ongoing Phase 2 in HCTs
- **Hookipa**
  - LCMV recombinant (gB+pp65) HB-101
  - Safe and immunogenic in Phase I trial ( good Ab and T cell responses)
  - Ongoing Phase 2 in SOT (Kidney)

# CMV Vaccines for Congenital Indication-1

- **Merck**
  - Replication defective V-160
  - Safe and immunogenic in Phase 1 trial- ( CMV+ and -)
  - Ab and T cell levels comparable to natural infection
  - Planning for Phase 2 trial
- **Sanofi Pasteur**
  - Recombinant protein-gB+ MF59
  - 50% efficacy in Phase 2 trials for prevention of primary CMV infection
  - Reformulating vaccine with additional Ags and new Adj
  - Also evaluating vax in transplant patients ( Ph. 1 and 2)
- **GSK**
  - Recombinant protein-gB+ AS01
  - Safe and immunogenic in Phase 1 trial ( CMV-)
  - Reformulating vaccine with additional Ags ( + pentameric complex )

# CMV Vaccines for Congenital Indication-2

- **Pfizer**
  - Recombinant rhesus proteins (pentamer, +/-gB, +/- pp65) + QS-21
  - NHPs studies showed high Neut Abs, good T-cell responses but no protection from viremia upon challenge. Hard to do vertical transmission studies ( most NHPs are CMV+)
  - Halted CMV vaccine program
- **Moderna**
  - mRNA expressing gB+ pentamer and pp65 in lipid nanoparticles
  - Started safety/immunogenicity Phase 1 trial in CMV+ and CMV – in Dec 2017
- **VBI vaccines**
  - VLPs expressing gB +/-Alum
  - Safe and immunogenic in Phase 1 trial ( CMV-)
  - Planning for next stages of development

# Scientific Challenges

- Relevant animal models limited (strict species specificity)
- Unknown immune correlate(s) of protection
  - NHP studies have shown that neut Abs don't correlate with protection
  - Relative role of humoral and cellular immunity in protection unclear
- Primary infection vs. re-infection vs. reactivation
  - What is the relative importance of each in congenital transmission and disease?
  - What are the immune correlates that protect against each?
- Unclear role of anti-gB antibodies in controlling infection
  - Neutralizing? Other functions?
- CMV mostly a cell-associated infection ( not classical viremia)
- Non- standardized immunologic assays and diagnostics
  - Need standards for PCR, serology and T cell assays

# Clinical/Regulatory Challenges

- Epidemiologic unknowns
  - High variability in rate of CMV acquisition
  - CMV sero-prevalence by country, region, and/or ethnicity
- Sample size requirements for cCMV vaccines
- Complicated clinical development path leading to licensure
  - Can vaccine benefit be shown in seropositive women? Can a vaccine boost existing immunity?
- If congenital vaccine is targeted to toddlers ( like rubella) or to adolescents (like HPV), duration of immunity will be critical



# NIH's Contributions to CMV Vaccine Development

- Contemporary epidemiologic data (inform sample size calculations)
  - Leverage existing ongoing studies
    - ZIP
    - NICHD CMV hyperimmune globulin treatment
    - Chimes
    - Several grant funded studies
- Vaccine Treatment and Evaluation Units and grant awards to support Phase I/ Phase II studies
- SBIR contracts to develop Point of care CMV serologic assays
  - Indication: rapidly screen subjects for trials



# Zika in Infants and Pregnancy (ZIP) Study

- Sponsors: NIH & Oswaldo Cruz Foundation (Fiocruz)/Brazil
- Current enrollment as of May 25, 2018 (opened June 2016)
  - 6,212 mothers, 3,518 infants
- Follow women for Zika infection, infants for  $\geq 1$  yr
- Key endpoints: pregnancy outcomes, congenital anomalies, other developmental problems



# ZIP and CMV

- Plans to leverage ZIP to elucidate:
  - Rates of cCMV infection in this cohort
  - Factors associated with cCMV infection in seropositive women
  - Correlates of protection in seropositive women

# Rapid POC Sero-Diagnostic for CMV

Five one-year Phase I contracts awarded by NIAID in August 2017:

- Luna Innovations, Inc. (Roanoke, VA)
- nanoComposix (San Diego, CA)
- Operational Technologies Corp. (San Antonio, TX)
- Qoolabs, Inc. (San Diego, CA)
- Zymeron Corp. (Durham, NC)

4/5 contractors eligible for Phase II contracts



# Questions?



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# Regulatory Considerations for CMV Vaccines

Cytomegalovirus Infection: Advancing Strategies for Prevention and Treatment  
and NVAC

September 5 & 13, 2018

Phil Krause

OVRP/CBER/FDA

# There is general agreement on the “gold standard” for clinical trials

- Randomized, controlled, double-blind trials demonstrating protection against clinical disease are considered the best way to show efficacy
  - Such trials can demonstrate substantial evidence of effectiveness to support “traditional approval” in the U.S.
    - Immunologic response can also be used as an endpoint if there is a scientifically well-established immunologic marker to predict protection that can be reliably measured in a validated assay
  - The study endpoint normally is closely linked to the desired indication

# Alternatives to “traditional approval”

- Reasonable likelihood of clinical benefit standard applies to:
  - Accelerated approval based on a surrogate endpoint (US): Under certain conditions (serious or life threatening illnesses & therapeutic benefit over existing treatments), approval may be based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity
  - Animal rule: Can only be used when “traditional approval” and “accelerated approval” are not feasible
- Similar provisions apply elsewhere:
  - Extraordinary use new drug (Canada)
  - Conditional Marketing Authorization (EU)
  - Approval under Exceptional Circumstances (EU)
- All of these options require post-marketing effectiveness follow-up
  - For accelerated approval, these are “adequate and well-controlled” studies, usually underway at time of approval, that must be conducted with due diligence
  - For animal rule, these may be “field trials”



# Study endpoints for vaccines under “accelerated approval”

- “surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit”
  - For vaccines, this is usually an immunological endpoint measured in an *in vitro* assay
  - Other endpoints may be considered
- “an effect on a clinical endpoint other than survival or irreversible morbidity”

# Proposed endpoints for CMV vaccine studies in the immunocompromised



**Table 2**

Proposed endpoints for CMV vaccine clinical trials in different target populations

Target population	Objectives	Endpoint
Hematopoietic stem cell transplant recipients	Prevent CMV disease by reducing the rate of occurrence of surrogate markers	Prevention of CMV viremia (and associated antiviral use) Composite endpoints including CMV disease
Solid organ transplant recipients	Prevent CMV disease	Prevention of CMV-associated disease (including CMV syndrome) Prevention of CMV viremia (and associated antiviral use)

# Proposed endpoints for CMV vaccine approaches to prevent cCMV

**Table 2**  
Proposed endpoints for CMV vaccine clinical trials in different target populations

Target population	Objectives	Endpoint
Children <2 yrs of age	Prevent maternal and congenital CMV infection by removing an important source of maternal infections	Rate of CMV infection in vaccinees
Adolescent girls	Prevent primary CMV infection which may have long-term deleterious consequences to the host Prevent infection in future mothers and their children (preventing congenital infection)	Rate of CMV infection in vaccinees
Women of childbearing age (women likely to become pregnant)	Prevent primary CMV infection which may have long-term deleterious consequences to the host Prevent maternal and congenital CMV infection	Rate of CMV infection in vaccinees Rate of cCMV infection in their children

# Potential non-cCMVi endpoints to evaluate immunization of women of childbearing age

- Maternal outcomes that may predict cCMV protection
  - Immune markers, if possible to identify
  - Protection against clinical (or lab) findings that predict cCMV risk, if these could be identified
- Less definitive indicators of cCMVi in the presence of maternal infection?
  - e.g., elective or spontaneous terminations with findings suggestive of cCMVi
    - Risks: could potentially reduce power, introduce post-randomization confounding

# Could a maternal infection endpoint support a cCMV indication?

- It may be easier to prevent cCMVi than maternal infection
  - Using maternal infection as an endpoint may thus risk the success of the vaccine trial
- It may be difficult to demonstrate effectiveness against reinfection or reactivation in seropositive mothers, so maternal infection is potentially a more useful endpoint for seronegatives
- A vaccine might also reduce maternal infection without reducing cCMVi, possibly by selectively reducing milder infections that might not transmit cCMV
- These considerations may also apply to Zika vaccines

# Further consideration of maternal infection endpoint

- Concern: vaccine that only prevented mild infection might have effect in mothers but not in infants
  - Note that most vaccines are better at preventing severe than mild infections
    - Could relative effect of a CMV vaccine on milder vs. more severe maternal infections be assessed within a study?
  - Very high vaccine efficacy in pregnant women would increase the likelihood of effectiveness in preventing cCMV
    - A less stringent lower bound could be considered for cCMVi if success criteria for maternal CMVi were more stringent
  - Even if there were no demonstrated benefit for cCMV, a vaccine that reduced CMV infection in mothers would likely lead to reduced elective terminations

# Would vaccine efficacy vs cCMV need to be shown in both seronegatives and seropositives?

- Serostatus may influence both vaccine responses and potential utility of vaccine response against the background of previously existing immunity
- May depend on underlying seropositivity rates at ages proposed for immunization
- How readily can vaccine be evaluated against maternal infection among seropositives (reinfections vs. reactivations)?
- Could effectiveness vs infection in non-pregnant populations be relevant?

# Duration of vaccine effect

- How long does vaccine-induced protection need to last?
- Does a vaccine need to show long-term protection against CMV infection vs. potentially easier endpoints to achieve?



# Could residual doubts be addressed in post-licensure “RWE” observational studies?

- May be difficult (though not impossible) to both identify cCMV in observational studies and link with previous immunization of the mother
- Observational studies have potential for bias
- Evidence from observational studies nonetheless may be considered under certain circumstances
- Higher confidence in observational study results may be associated with certain outcomes/features, e.g.,
  - High efficacy
  - Inclusion of measures to reduce/evaluate potential bias
    - Internal consistency
    - Results consistent with known findings
  - Prospectively written protocol with prespecified endpoints and analysis methods
    - Mitigate concern for data-mining and publication bias
  - More than one study showing similar results

# Summary

- Identifying appropriate endpoints for cCMV vaccine studies is complex and challenging.
- CBER is committed to working with sponsors to identify feasible and scientifically sound approaches to CMV vaccine development.