WASHINGTON STATE BOARD OF HEALTH

Washington State Department of Health

NOTICE OF PUBLIC MEETING

Wednesday, September 21, 2022
9:00 a.m. – 4:00 p.m.

Please Note
This is a virtual meeting held via Zoom. Meeting access and instructions are provided below.

Newborn Screening Technical Advisory Committee (TAC) Agenda
Congenital Cytomegalovirus (cCMV)

Time	Agenda Topic	Speaker
9:00 a.m.	1. Welcome & Introductions	Kaitlyn Donahoe, State Board of Health Allegra Calder, BERK Consulting
9:20 a.m.	2. TAC Expectations & Meeting Norms	Tao Sheng Kwan-Gett, TAC Co-Chair Kelly Oshiro, TAC Co-Chair Allegra Calder, BERK Consulting
9:35 a.m.	3. Overview: Newborn Screening Program & Early Hearing Detection, Diagnosis, and Intervention (EHDDI) Program	John Thompson, Department of Health Marcie Rider, Department of Health
10:00 a.m.	4. Criteria Review	Kaitlyn Donahoe, State Board of Health
10:15 a.m.	Break	
10:20 a.m.	5. Natural History of cCMV; Diagnostic Testing & Available Treatment	Dr. Joseph Bocchini, Willis-Knighton Health System
11:05 a.m.	6. Family Perspective	Melissa Moxley
11:20 a.m.	7. Available Screening Technology	John Thompson, Department of Health Marcie Rider, Department of Health
11:50 a.m.	Lunch	
12:35 p.m.	8. Cost-Benefit Analysis	Caitlin Maloney, Department of Health
1:35 p.m.	9. Application of Criteria & Discussion	Allegra Calder, BERK Consulting
2:45 p.m.	10. Vote #1 - Criteria	Allegra Calder, BERK Consulting
2:55 p.m.	Break	
3:00 p.m.	11. Vote #1 Results & Discussion	Tao Sheng Kwan-Gett, TAC Co-Chair Kelly Oshiro, TAC Co-Chair

(Continued on next page)

Time	Agenda Topic	Speaker
		Allegra Calder, BERK Consulting
3:30 p.m.	12. Vote #2 – TAC Recommendation	Allegra Calder, BERK Consulting
3:40 p.m.	Break	
3:45 p.m.	13. Vote #2 Results & Next Steps	Tao Sheng Kwan-Gett, TAC Co-Chair Kelly Oshiro, TAC Co-Chair Kaitlyn Donahoe, State Board of Health
4:00 p.m.	Adjournment	

Zoom Meeting Information:

To access the meeting online, please click:

- https://us02web.zoom.us/j/82929917674?pwd=dHJVVUlnbU9uMHJNM09wN1BxQ3Judz09

You can also dial in using your phone:

- Call in: +1 (253) 215-8782
- Meeting ID: 829 2991 7674, Passcode: 292431

Important Information to Know:

- This meeting is open to the public. The public can observe the meeting online.
- The Technical Advisory Committee will not take formal action or receive public comment. If you have comments or materials you would like to share with the full Board, please send your copies to wsboh@sboh.wa.gov.
- Times are estimates only. We reserve the right to alter the order of the agenda.
- If you have any technical difficulties accessing the meeting via Zoom, please contact Jo-Ann Huynh, State Board of Health Administrative Assistant, at (360) 236-4110 or by email at jo-ann.huynh@sboh.wa.gov.
- If you need special accommodation, please contact Melanie Hisaw, State Board of Health Executive Assistant, at (360) 236-4110 or by email at melanie.hisaw@sboh.wa.gov by September 16, 2022.

To request this document in an alternate format or a different language, please contact Kelie Kahler, State Board of Health Communication Manager, at 360-236-4102 or by email kelie.kahler@sboh.wa.gov

WASHINGTON STATE BOARD OF HEALTH

Washington State Department of Health

WELCOME

Newborn Screening Technical Advisory Committee: Congenital Cytomegalovirus (cCMV)

September 21, 2022

Meeting Begins at 9:00 a.m.

1. Notice of this meeting and materials were posted to the Board's website in advance of the meeting.
2. The TAC will not take formal action or receive public comment. If you have comments or materials you would like to share with the Board, please send your copies to wsboh@sboh.wa.gov

cCMV Technical Advisory Committee

Welcome, Expectations, Meeting Norms

September 21, 2022

Introductions

Zoom Functions

Zoom technical assistance:
Jo-Ann Huynh, Board Staff
(360) 236-4110
jo-ann.huynh@sboh.wa.gov

Mute/
unmute mic

View participants,
change your name

Turn webcam
on/off

Leave
meeting

Note: Depending on your role, you may not have access to all functions identified on this slide.

Meeting Purpose

Determine whether congenital cytomegalovirus (cCMV) meets the Washington State Board of Health's criteria for inclusion in the list of conditions for which all Washington-born newborns must be screened.

Plan for the Day

- Presentations from Board Staff, Department Staff, subject matter experts, and an impacted family.
- Discussion and evaluation of cCMV against the Board's 5 criteria.
- Vote #1: Criteria
- Additional Discussion
- Vote #2: TAC Recommendation
- Next Steps

Meeting Norms

- Stay engaged; participate with intention
- Listen for understanding; seek clarification and resist assumptions
- Appreciate the diversity of perspectives
- Maintain a respectful space; listen to and respect other points of view
- Participate as fully as you feel comfortable/are able
- Stay on topic; keep our purpose in the forefront of our minds
- Assume positive and good intent

QUESTIONS?

Washington State Board of Health

PROCESS TO EVALUATE CONDITIONS FOR INCLUSION IN THE REQUIRED NEWBORN SCREENING PANEL

The Washington State Board of Health has the duty under RCW 70.83.050 to define and adopt rules for screening Washington-born infants for heritable conditions. Chapter 246-650-020 WAC lists conditions for which all newborns must be screened. Members of the public, staff at Department of Health, and/or Board members can request that the Board review a particular condition for possible inclusion in the NBS panel. In order to determine which conditions to include in the newborn screening panel, the Board convenes an advisory committee to evaluate candidate conditions using guiding principles and an established set of criteria.

The following is a description of the Qualifying Assumption, Guiding Principles, and Criteria which the Board has approved in order to evaluate conditions for possible inclusion in the newborn screening panel. The Washington State Board of Health and Department of Health apply the qualifying assumption. The Board appointed Advisory Committee applies the following three guiding principles and evaluates the five criteria in order to make recommendations to the Board on which condition(s) to include in the state's required NBS panel.

QUALIFYING ASSUMPTION

Before an advisory committee is convened to review a candidate condition against the Board's five newborn screening requirements, a preliminary review should be done to determine whether there is sufficient scientific evidence available to apply the criteria for inclusion.

THREE GUIDING PRINCIPLES

Three guiding principles govern all aspects of the evaluation of a candidate condition for possible inclusion in the NBS panel.

- Decision to add a screening test should be driven by evidence. For example, test reliability and available treatment have been scientifically evaluated, and those treatments can improve health outcomes for affected children.
- All children who screen positive should have reasonable access to diagnostic and treatment services.
- Benefits of screening for the disease/condition should outweigh harm to families, children and society.

CRITERIA

1. **Available Screening Technology:** Sensitive, specific and timely tests are available that can be adapted to mass screening.
2. **Diagnostic Testing and Treatment Available:** Accurate diagnostic tests, medical expertise, and effective treatment are available for evaluation and care of all infants identified with the condition.
3. **Prevention Potential and Medical Rationale:** The newborn identification of the condition allows early diagnosis and intervention. Important considerations:
    - There is sufficient time between birth and onset of irreversible harm to allow for diagnosis and intervention.
    - The benefits of detecting and treating early onset forms of the condition (within one year of life) balance the impact of detecting late onset forms of the condition.
    - Newborn screening is not appropriate for conditions that only present in adulthood.
4. **Public Health Rationale:** Nature of the condition justifies population-based screening rather than risk-based screening or other approaches.
5. **Cost-benefit/Cost-effectiveness:** The outcomes outweigh the costs of screening. All outcomes, both positive and negative, need to be considered in the analysis. Important considerations to be included in economic analyses include:
    - The prevalence of the condition among newborns.
    - The positive and negative predictive values of the screening and diagnostic tests.
    - Variability of clinical presentation by those who have the condition.
    - The impact of ambiguous results. For example the emotional and economic impact on the family and medical system.
    - Adverse effects or unintended consequences of screening.

WASHINGTON STATE
BOARD OF HEALTH

Congenital Cytomegalovirus (cCMV) Overview

Newborn Screening Technical Advisory Committee
September 21, 2022

CLINICAL INFORMATION

- Congenital CMV (cCMV) is different from acquired CMV – acquired CMV results in mild to no symptoms
- cCMV occurs when the infection is passed from a pregnant individual to the unborn baby and may cause health problems — classification groups include:
    - Symptomatic: symptoms present at birth and can include a small head, rash on the face, hearing loss, jaundice, and enlarged liver and spleen; additional long-term health problems can include vision loss and intellectual disabilities — accounts for ~12% of cases
    - Asymptomatic with hearing loss: hearing loss can be present at birth or develop later in childhood; other health problems are not expected — accounts for ~11% of cases
    - Asymptomatic: no health problems — accounts for ~77% of cases
- Screening/testing cannot predict classification groups

TREATMENT/INTERVENTION

- Infants suspected of having cCMV should have a diagnostic evaluation within the first three weeks of life. The testing often includes physical examination, urine or saliva CMV DNA analysis, hearing evaluation, head ultrasound, and eye exam
- Medical management depends on symptoms present:
    - Asymptomatic (with or without hearing loss), regular audiologic evaluations are warranted
    - Symptomatic children would likely be offered off-label antiviral medication (valganciclovir) and supportive therapies. Valganciclovir can have serious side effects and has only been studied in babies with moderate to severe symptoms of congenital CMV infection within the first month of life. There is limited information on the effectiveness of valganciclovir to treat asymptomatic infants with or without hearing loss.

To request this document in an alternate format or a different language, please contact Kelie Kahler, State Board of Health Communication Manager, at 360-236-4102 or by email kelie.kahler@sboh.wa.gov

PO Box 47990, Olympia, WA 98504-7990
(360) 236-4110 • wsboh@sboh.wa.gov • sboh.wa.gov

SAVING LIVES WITH A SIMPLE BLOOD SPOT

NEWBORN SCREENING

Washington State Department of Health

What is Newborn Screening?

Newborn screening is a public health system that detects infants with serious but treatable conditions that may not be apparent at birth.

There are 3 types of newborn screening programs:

1

Blood-spot

2

Hearing

3

Pulse Oximetry

Why is Newborn Screening Important?

- It prevents death and disability for **thousands** of infants every year in the USA by providing early treatment
- The public benefits through savings in health care and disability support costs

Two 6 year old girls with Congenital Hypothyroidism
Healthy 18 year old with CH, detected through Washington Newborn Screening as a baby

Washington Screens for... 32 disorders!

Amino Acid Disorders (6)	Fatty Acid Oxidation Disorders (5)	Organic Acid Disorders (8)
Phenylketonuria	Medium-chain acyl-CoA dehydrogenase deficiency	Isovaleric acidemia
Homocystinuria	Long-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency	Glutaric acidemia type I
Maple syrup urine disease	Trifunction[illegible]ency	Methylmalonic acidemias (CblA/B and MUT)
Citrullinemia type I	Very long-chain acyl-Co[illegible]e deficiency	Propionic acidemia
Argininosuccinic acidemia	Carnitine [illegible]ct	Multiple carboxylase deficiency
Tyrosinemia type I		Beta-ketothiolase deficiency
		3-hydroxy-3-methylglutaric aciduria

32 Disorders

Endocrine Disorders (2)	Lysosomal Storage Disorders (2)	Other Disorders (10)
Congenital hypothyroidism	Mucopolysaccharidosis type I	Galactosemia
Congenital adrenal hyperplasia	Glycogen storage disorder type II (Pompe)	Biotinidase deficiency
		Cystic fibrosis
		Sickle Cell Diseases & Hemoglobinopathies
		Severe combined immunodeficiency
		X-linked adrenoleukodystrophy
		Spinal muscular atrophy

Immediately Life Threatening Conditions

Amino Acid Disorders (6)	Fatty Acid Oxidation Disorders (5)	Organic Acid Disorders (8)
Phenylketonuria	Medium-chain acyl-CoA dehydrogenase deficiency	Isovaleric acidemia
Homocystinuria	Long-chain L-3-hydroxy acyl-CoA dehydrogenase deficiency	Glutaric acidemia type I
Maple syrup urine disease	Trifunctional protein deficiency	Methylmalonic acidemias (CblA/B and MUT)
Citrullinemia type I	Very long-chain acyl-CoA dehydrogenase deficiency	Propionic acidemia
Argininosuccinic acidemia	Carnitine uptake defect	Multiple carboxylase deficiency
Tyrosinemia type I		Beta-ketothiolase deficiency
		3-hydroxy-3-methylglutaric aciduria

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		Cystic fibrosis
		Sickle Cell Diseases & Hemoglobinopathies
		Severe combined immunodeficiency
		X-linked adrenoleukodystrophy
		Spinal muscular atrophy

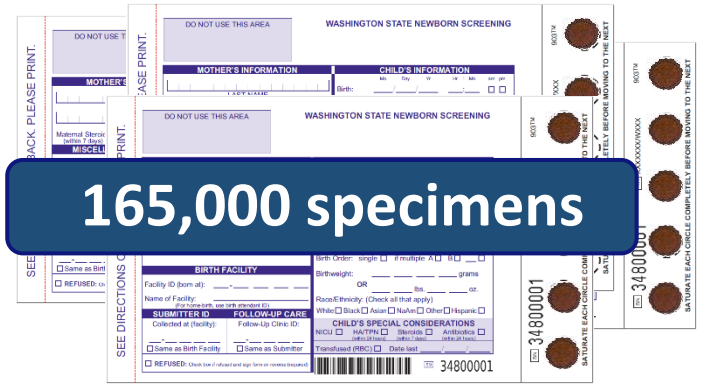
Coming Soon!

Screening for Ornithine Transcarbamylase Deficiency (OTCD)

Anticipate starting screening in Summer 2023
(pending budget approval)

Washington State Numbers

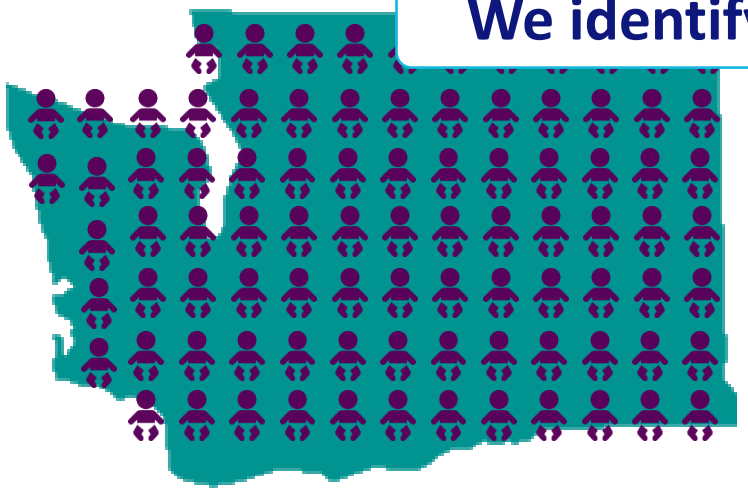
84,000 newborns



165,000 specimens

12 million tests

We identify:



200 infants

every year who benefit from early diagnosis and treatment

1,300 infants with a hemoglobin trait (not disease)

WA Newborn Screening Process

BABY IS BORN!

18-48
HOURS AFTER BIRTH

Collect first specimen

Dry specimen
for 3 hours

Transport specimen
to the State Lab
ASAP!

BEST PRACTICE
24
HOUR TRANSIT

At the Lab, punches are taken from the dried blood spots to test for each of the disorders

Same day/next day results

Results are mailed back to who submitted the specimen

What happens when a baby has abnormal results?

Dedicated team ensures the baby gets the care they need

- Depends on what the results are and which condition is suspected

Can include:

- Ensure repeat specimen is submitted to resolve borderline results
- Facilitate prompt diagnostic testing and treatment for non life-threatening conditions
- Call baby's health care provider to check clinical status, recommend immediate evaluation and diagnostics for life-threatening conditions
- After confirmed diagnoses, ensure baby is linked into specialty care

Specialty Care Partners

Consultants:

- Seattle Children's Hospital
  - Endocrinologist
  - Pediatric Hematologist
  - Biochemical Geneticists
  - Immunologists
  - Pulmonologists
- Mary Bridge Children's
  - Biochemical Geneticists

Community:

- Northwest Sickle Cell Collaborative

Specialty Care Clinics:

- University of Washington
  - PKU Clinic
  - Congenital Hypothyroidism Developmental Evaluation Clinic
  - Neuropsych Evaluation Program
  - Biochemical Genetics Clinic
- Seattle Children's Hospital
  - Biochemical Genetics Clinic
  - Odessa Brown Sickle Cell Clinic
- Mary Bridge Sickle Cell Clinic

Mary Bridge Children's Hospital · Clinics · Foundation
1955 · CELEBRATING 60 YEARS · 2015

UW Medicine
DEPARTMENT OF MEDICINE
DEPARTMENT OF PEDIATRICS
UNIVERSITY of WASHINGTON

Seattle Children's
HOSPITAL · RESEARCH · FOUNDATION

northwest sickle cell COLLABORATIVE

ODESSA BROWN CHILDREN'S CLINIC

Cristine M. Trahms Program for Phenylketonuria
ΦKU Seattle
A Member Forever

How Much Does Screening Cost?

- Fee for screening: $119.30 as of August 7, 2020
- This one-time fee covers all newborn screens an infant receives in WA

  (No additional charge for 2nd or 3rd screens!)

- The Department of Health bills the facility that collected the baby's initial specimen
- The facility then bills the patient's insurance

Quality Assurance & Development

Surveillance

- Ensure every baby in the state receives a valid newborn screen

Education & Outreach

- Provide assistance to health care facilities
- Create educational materials
- Promote newborn screening in the community

Tracking & Reporting

- Send quarterly reports to each facility about their performance in meeting newborn screening guidelines
  - Specimen Collection and Transit Timing Compliance
  - Specimen Quality
  - Demographic Errors

2020 WA State Disorder Summary

General	
Hospital, Birth Center & Home Births	84,529
Specimens Tested	159,922
Infants Diagnosed	
Amino Acid Disorders	9
Biotinidase Deficiency	2
Congenital Adrenal Hyperlasia	6
Congenital Hypothyroidism	108
Cystic Fibrosis	14
Fatty Acid Oxidation Disorders	7
Galactosemia	3
Organic Acid Disorders	0
Severe Combined Immunodeficiency	5
Sickle Cell Disease and Other Clinically Significant Hemoglobinopathies	14
X-linked Adrenoleukodystrophy	13
Lysosomal Storage Disorders	4
Spinal Muscular Atrophy	1
TOTAL	**186**

~Thank you~

Together we protect the lives of
Washington's youngest citizens.

Washington State Department of Health

Washington State Department of Health

EARLY HEARING DETECTION, DIAGNOSIS, AND INTERVENTION PROGRAM

EHDDI Program Overview

Early

Hearing

Detection

Diagnosis

Intervention

EHDDI Program Goals

National 1-3-6 Goals for all state EHDDI Programs

1 All infants receive a hearing screen before they are **one** month old.

3 Infants who do not pass two hearing screens have a diagnostic evaluation before they are **three** months old.

6 Infants who are deaf or hard of hearing start early intervention (EI) services before they are **six** months old.

What's The Rush?

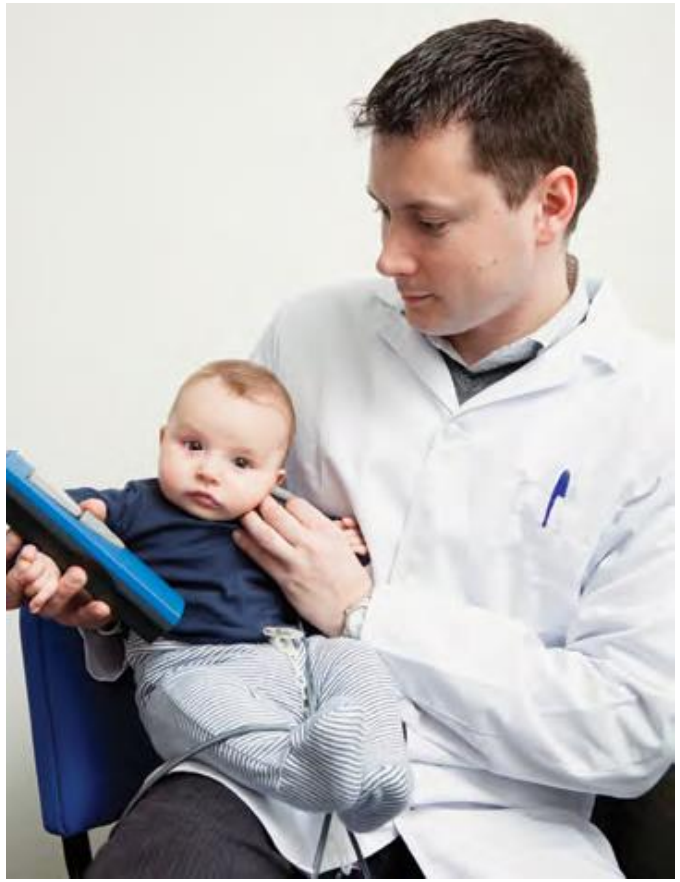
- The first months of an infant's life are a critical time for developing language.
- Delays in identification can lead to developmental delays.
- Research shows that children who are deaf or hard of hearing have better outcomes when they receive early intervention prior to 6 months of age.

Why Screen all infants?

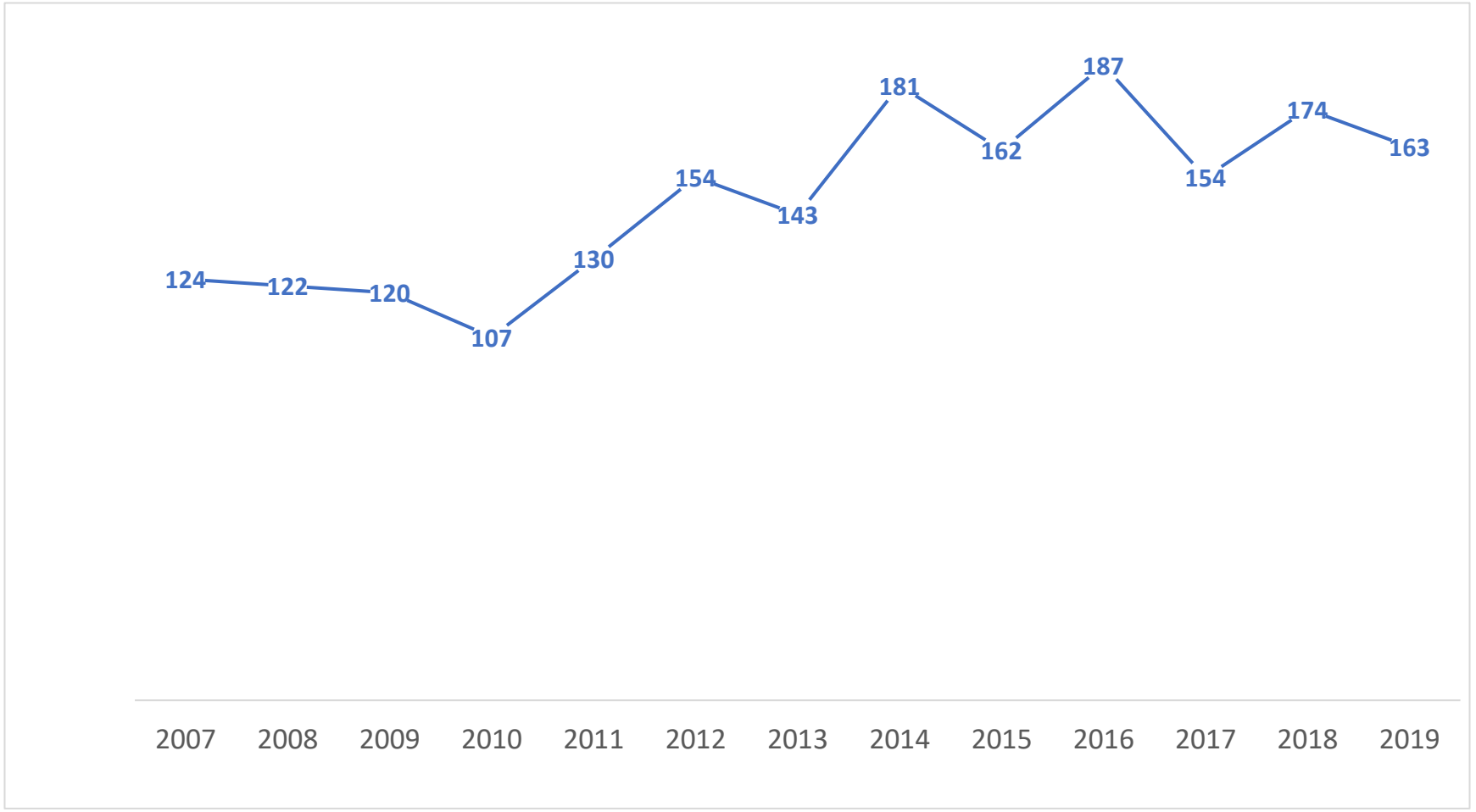
Hearing loss is a common condition present at birth

1-3 per 1000 births

It’s invisible



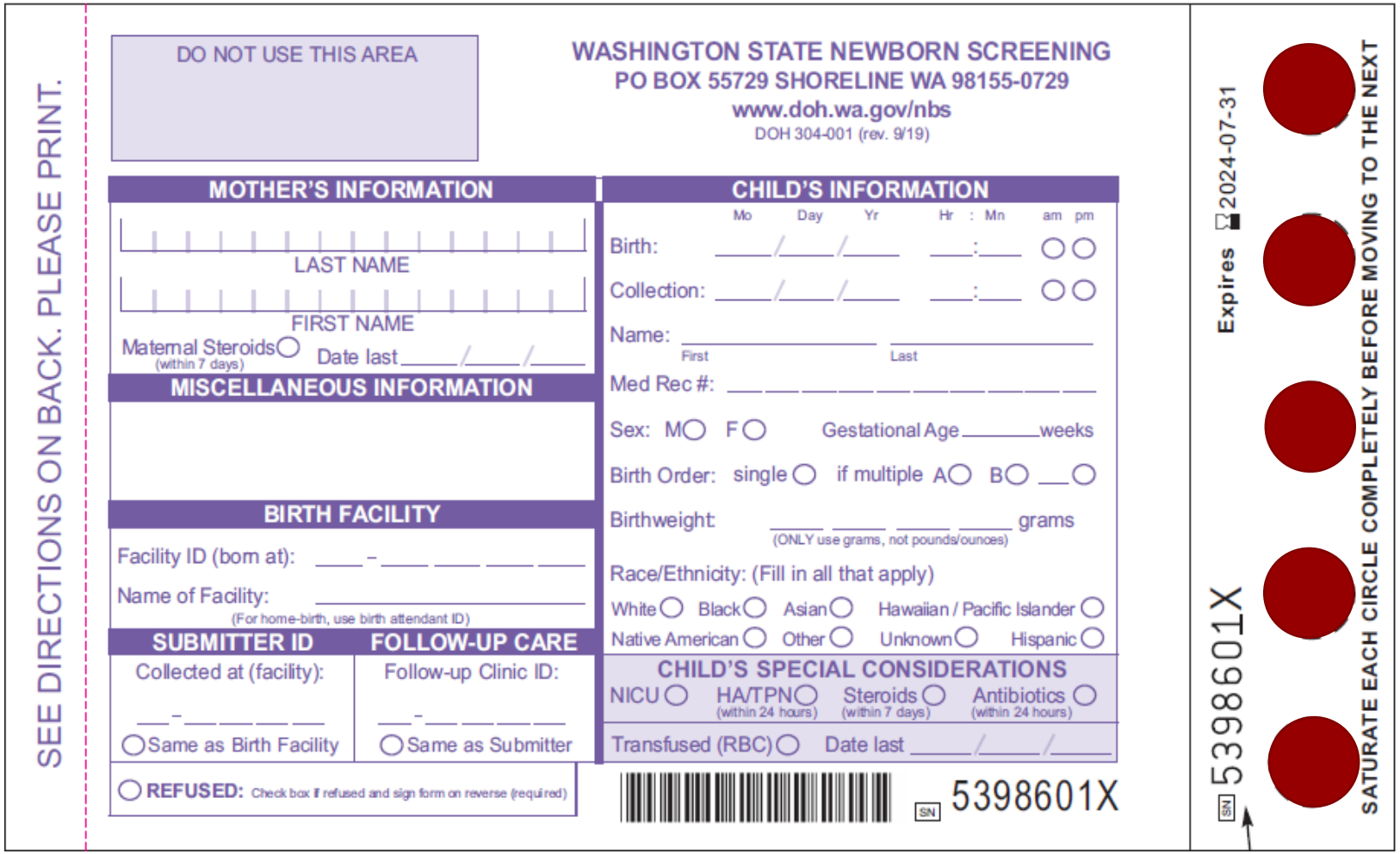
Number of newborns identified as deaf or hard of hearing by year of birth

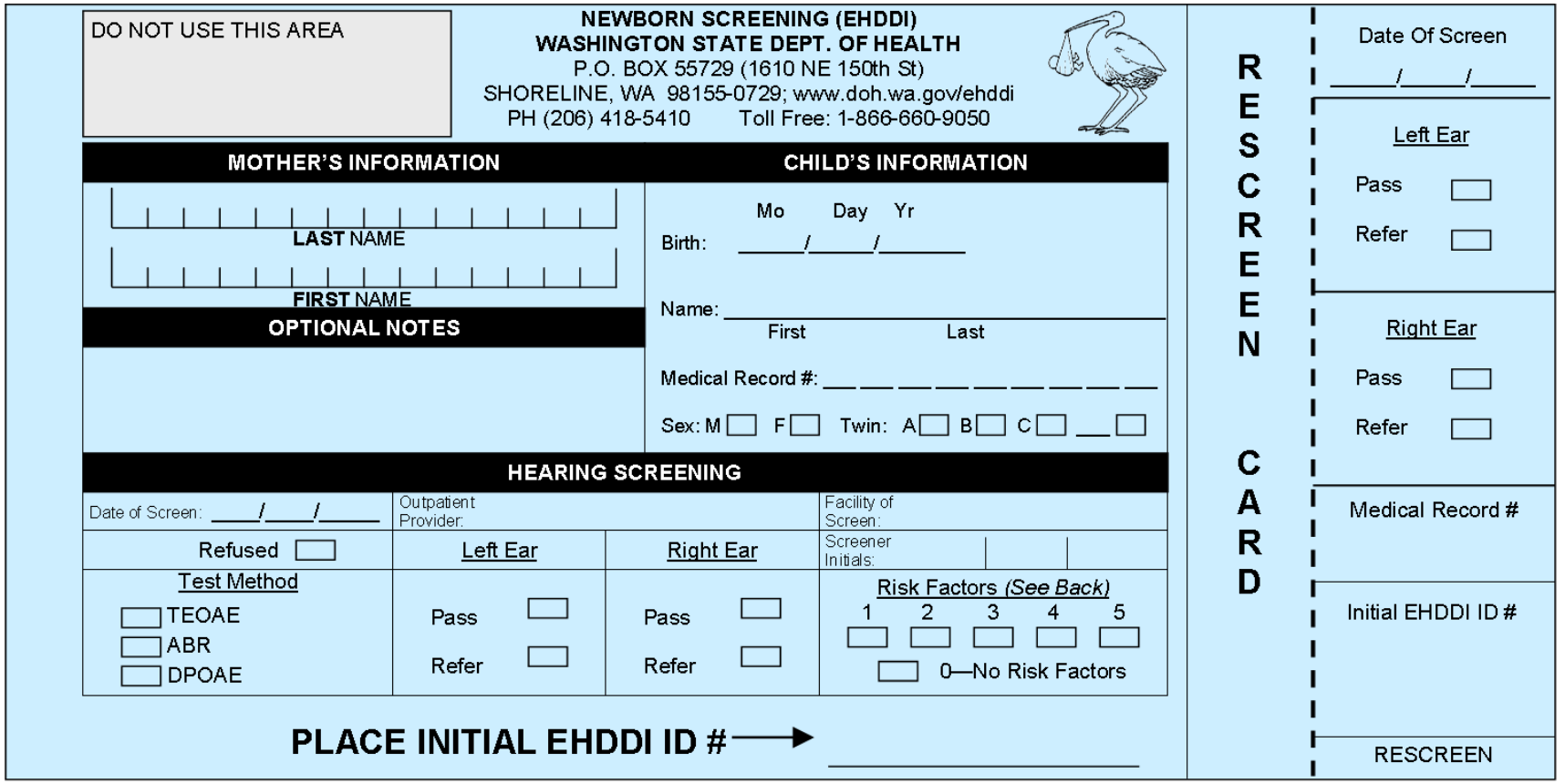


EHDDI Program Follow-up

- Monitor that EHDDI 1-3-6 goals are met by collecting and reviewing data:
    - Hearing screening results
        - Reported on hearing screen cards by hospitals, midwives, and audiologists
    - Diagnostic hearing evaluation results
        - Reported online and via fax by audiologists
    - Early intervention enrollment data
        - Obtained through an electronic data exchange with the Early Support for Infants and Toddlers (ESIT) program

How Do We Get Hearing Screen Results?





Blue "Rescreen" Card

Risk Factors for Late-Onset Hearing Loss

- Neonatal Intensive Care (NICU) stay of >five days
- Stigmata or other findings associated with a syndrome known to include hearing loss
- Family history of permanent hearing loss
- Craniofacial anomalies
- In-utero infections with **cytomegalovirus**, herpes, toxoplasmosis, rubella, or syphilis

Recommendation for baby who passes newborn hearing screening but has cCMV is to have a diagnostic hearing evaluation by three months of age and regular monitoring of hearing after that.

STATE OF WASHINGTON
DEPARTMENT OF HEALTH
Early Hearing-loss Detection, Diagnosis, and Intervention Program
1610 N.E. 150th Street · Shoreline, Washington 98155
Phone 206-418-5613 Toll Free 1-888-WAEHDDI (1-888-923-4334) Fax 206-364-0074

Action Needed: Passed Hearing Screen but has Risk Factor for Hearing Loss

9/14/2022

TO: WASHINGTON STATE PEDIATRICS

RE: LUKE SKYWALKER
DOB: May 12, 1977
Birth Facility: NEWBORN SCREENING

Mother: TEST MARCIE RIDER
EHDDI #:

Newborn Hearing Screen Results	**PASSED *BUT* AT RISK**
Risk Factor(s) for Late-onset/Progressive Loss	**IN UTERO INFECTION**
Follow-up Needed	**DIAGNOSTIC AUDIOLOGY EVALUATION**
Due Date	**3 MONTHS OF AGE FOR CYTOMEGALOVIRIUS (CMV)** **9 MONTHS OF AGE FOR OTHER IN UTERO INFECTIONS**

For a list of audiology clinics for infants, please visit **www.doh.wa.gov/infantaudiology**.

Children with cytomegalovirus infection, syndromes associated with progressive hearing loss, neurodegenerative disorders, trauma, or culture-positive postnatal infections associated with sensorineural hearing loss may need earlier and more frequent evaluations. For more information about risk factors for late-onset or progressive hearing loss, please visit **www.doh.wa.gov/hearingriskfactors**.

PLEASE FAX THE FOLLOWING INFORMATION REGARDING YOUR ACTIONS TO (206) 364-0074.

[ ] This patient was referred to _____on _____.
(name of audiology clinic) (date)

[ ] We shared the hearing screen results and recommendations with the patient's parent or legal guardian and they understand the recommendations.

[ ] This patient does not have any of the risk factors indicated.

[ ] This patient's parent or legal guardian declined further testing.

[ ] This patient is not seen at this facility. Current provider (if known):_____

[ ] OTHER_____

If you have any questions, please contact us at (206) 418-5613.

EHDDI Program Follow-up

- Recommend follow-up through primary care providers (PCPs) when an infant needs additional testing or services.
- Work with audiologists, Family Resources Coordinators (FRCs), and PCPs to ensure audiology and early intervention referrals are placed and received.
- Provide families with resources when a child is referred for diagnostic testing and identified as deaf or hard of hearing.

Washington State Department of Health is committed to providing customers with forms and publications in appropriate alternate formats. Requests can be made by calling 800-525-0127 or by email at civil.rights@doh.wa.gov. TTY users dial 711.

Process to Evaluate Conditions for Inclusion in the Required Newborn Screening Panel

September 21, 2022

Three Guiding Principles

Driven by Evidence

Decision to add a screening test should be driven by evidence. For example, test reliability and available treatment have been scientifically evaluated, and those treatments can improve health outcomes for affected children.

Accessibility

All children who screen positive should have reasonable access to diagnostic and treatment services.

Benefits Outweigh Harms

Benefits of screening for the disease/condition should outweigh harm to families, children and society.

Five Criteria

Available Screening Technology

Sensitive, specific and timely tests are available that can be adapted to mass screening.

Diagnostic Testing and Treatment Available

Accurate diagnostic tests, medical expertise, and effective treatment are available for evaluation and care of all infants identified with the condition.

Prevention Potential and Medical Rationale

The newborn identification of the condition allows early diagnosis and intervention. Important considerations:

- There is sufficient time between birth and onset of irreversible harm to allow for diagnosis and intervention.
- The benefits of detecting and treating early onset forms of the condition (within one year of life) balance the impact of detecting late onset forms of the condition.
- Newborn screening is not appropriate for conditions that only present in adulthood.

Public Health Rationale

Nature of the condition justifies population-based screening rather than risk-based screening or other approaches.

Cost-benefit / Cost-effectiveness

The outcomes outweigh the costs of screening. All outcomes, both positive and negative, need to be considered in the analysis. Important considerations to be included in economic analyses include:

- The prevalence of the condition among newborns.
- The positive and negative predictive values of the screening and diagnostic tests.
- Variability of clinical presentation by those who have the condition.
- The impact of ambiguous results. For example, the emotional and economic impact on the family and medical system.
- Adverse effects or unintended consequences of screening.

QUESTIONS?

Congenital Cytomegalovirus Infection (cCMV): Natural History, Diagnostic Testing & Available Treatments

Joseph A. Bocchini, Jr., MD, FAAP
Director of Children's Health Services
Willis-Knighton Health System
Professor and Vice Chairman
Department of Pediatrics
Tulane University

Tulane University
SCHOOL OF MEDICINE
Department of Pediatrics

Washington State Board of Health
NBS Technical Advisory Committee Meeting
September 21, 2022

WILLIS-KNIGHTON HEALTH SYSTEM

Disclosures

- Advisory Panel – Pfizer, Avalere
- Advisory Council – Moderna, Valneva
- Site PI, multicenter clinical trials – Regeneron, Pfizer, GSK
- Site Sub-I, multicenter clinical trials – Novavax

Congenital and Perinatal Infections

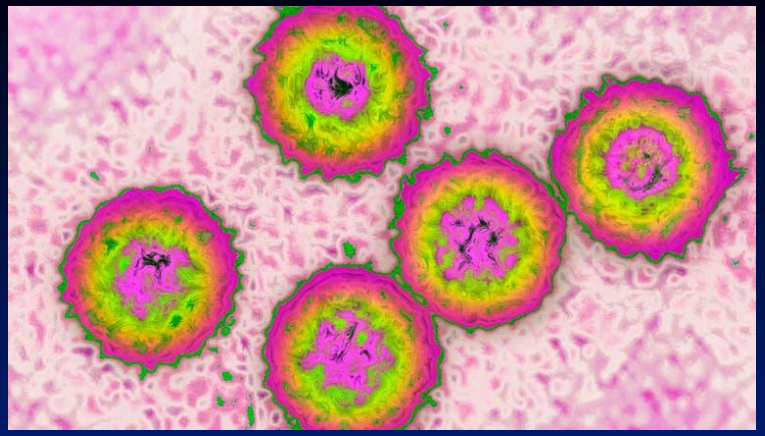
T	*Toxoplasma gondii*
O	Other: varicella, parvovirus, Zika
R	Rubella
C	Cytomegalovirus
H	Herpes simplex, hepatitis B, hepatitis C, HIV
S	Syphilis

Congenital CMV

- Most common congenital infection
  - 0.5%-0.7% of live births in US
    - 1 in 150-200 live-births
    - 20,000-31,500 newborns annually
  - Asymptomatic ~ 90%
  - Symptomatic ~ 10%

- A leading cause of sensorineural hearing loss (SNHL) and neurodevelopmental delay

Cytomegalovirus



- Herpesvirus family
  - Capacity to infect multiple types of cells
  - Life-long persistent infection
    - Latency
    - Periods of active replication
      - Intermittent shedding from infected cells
        - Urine, saliva, cervicovaginal secretions, semen, breast milk, tears, blood products, transplanted organs
        - CMV can survive on hands and contaminated surfaces

CMV: Transmission

- Horizontal
  - Children in childcare and childcare workers – saliva
  - Adolescents and young adults – young children and sexual
  - Transfusion and Transplantation – infected blood product or organ
- Vertical
  - Congenital – transplacental
  - Perinatal – during birth, breast milk

Young Children are an Important Source of CMV for Young Adults and Pregnant Women

- NHANES
  - Prevalence of CMV IgG antibody
    - 2011-12
    - 2017-18
  - Higher seroprevalence: ethnic/racial minority groups, exposure to breast milk and/or other children
- Shedding is highest in 1-2 y/o
  - Day care centers

Clinical Infectious Diseases

BRIEF REPORT

Changes in Cytomegalovirus Seroprevalence Among U.S. Children Aged 1–5 Years: The National Health and Nutrition Examination Surveys

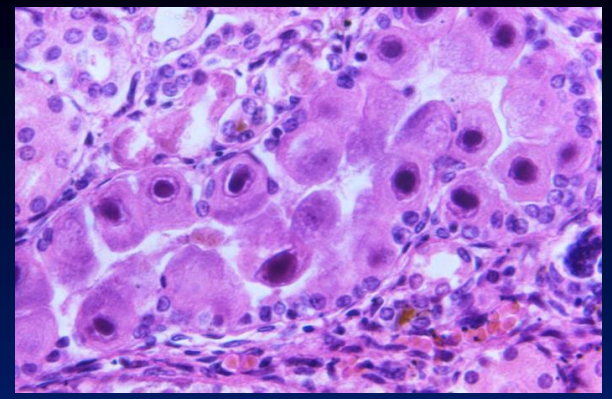
Molly R. Petersen,[1,a] Eshan U. Patel,[1,2,a] Alison G. Abraham,[2,3] Thomas C. Quinn,[4,5] and Aaron A.R. Tobian[1]

[1]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, [3]Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [4]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, and [5]Laboratory of Immunoregulation, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, Baltimore, Maryland, USA

Characteristic	2011–2012[a] Prevalence, % (95% CI)	2017–2018[a] Prevalence, % (95% CI)
Overall	20.7 (14.0, 29.0)	28.2 (23.1, 34.0)
Age, y		
1	12.3 (6.4, 20.6)	23.3 (16.4, 31.5)
2–3	20.0 (11.7, 30.7)	24.5 (16.2, 34.4)
4–5	24.2 (16.6, 33.2)	33.9 (24.0, 44.9)

Clin Inf Dis 2021;72(9):e408–11

Cytomegalovirus



- Over 50% of US population infected by age 40 yrs
- 1-4% of women will become infected with CMV during a pregnancy
- 50-75% of cCMV occurs in infants born to mothers infected before they became pregnant
  - cCMV prevalence increases with increasing maternal seroprevalence

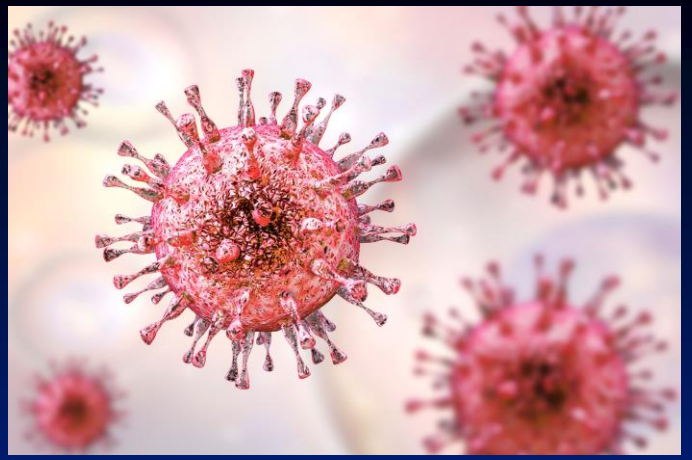
In utero CMV Transmission from Mother to Fetus

- **Primary infection**
  - **30% transmission rate**
  - **Approximately equal rate regardless of trimester infection occurs**
  - **More severe outcomes with infection in 1st trimester**

In utero CMV Transmission from Mother to Fetus

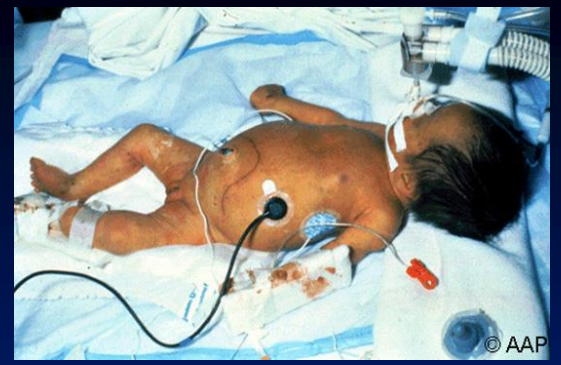
- Non-primary infection
  - Reactivation
    - Lower transmission rate, but increasing percentage of cases based on CMV prevalence
    - Infant less likely to be symptomatic
  - Reinfection
    - Immunity not complete
    - New serotype
    - Risk of cCMV may be as high as primary infection

Cytomegalovirus

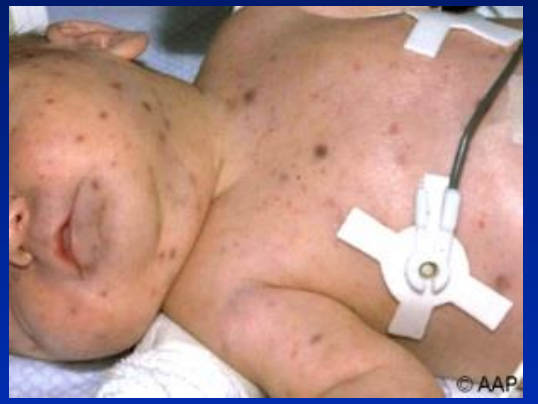


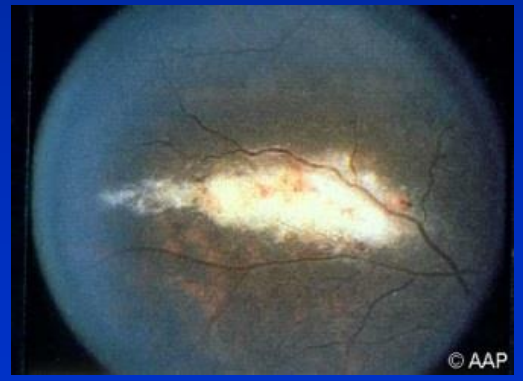
- Healthy persons – minimal manifestations
  - Pregnant women, > 90% of primary infections are asymptomatic
- Serious disease
  - Congenital infection
  - Immunosuppressed persons
    - Solid organ or bone marrow transplants, AIDS

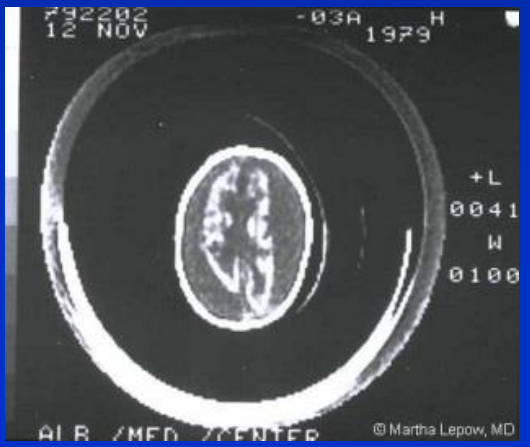
Symptomatic congenital CMV: Manifestations



- Intrauterine growth restriction (IUGR)
- Thrombocytopenia, purpura
- Hepatitis, pneumonitis
- Jaundice
- Hepatosplenomegaly
- Microcephaly
- Intracerebral calcifications
- Retinitis
- Mortality: ~ 4%







ORIGINAL ARTICLES

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Racial and Ethnic Differences in the Prevalence of Congenital Cytomegalovirus Infection

Karen B. Fowler, DrPH[1,2], Shannon A. Ross, MD[1], Masako Shimamura, MD[1], Amina Ahmed, MD[4], April L. Palmer, MD[5], Marian G. Michaels, MD[6], David I. Bernstein, MD[7], Pablo J. Sánchez, MD[8], Kristina N. Feja, MD[9], Audra Stewart, DO[8], and Suresh Boppana, MD[1,3]

- 2007-2012
- 100,322 infants from 7 medical centers
- Prevalence (per 1000 live births)
  - Overall 4.5
  - Black 9.5
  - Multiracial 7.8
  - Hispanic 3.0
  - Non-Hispanic white 2.7
  - Asian 1
- Symptomatic (9.6%) and SNHL (7.8%) same across groups

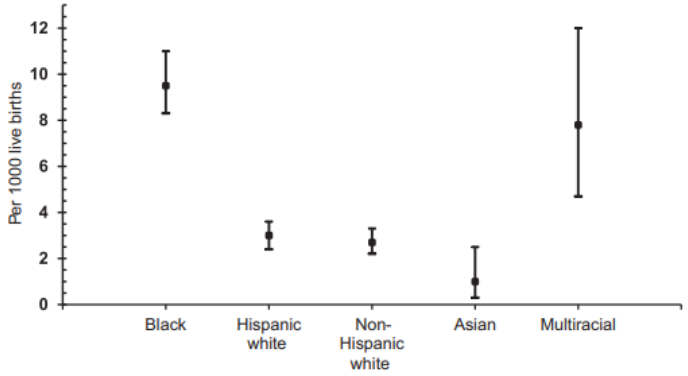


Figure 1. Prevalence per 1000 live births of congenital CMV infection and 95% CIs by race and ethnicity.

Table III. Unadjusted and aPORs for cCMV infection by race and ethnicity

	POR (95% CI)	aPOR (95% CI)*
Infant race and ethnicity		
Black, non-Hispanic	3.5 (2.8-4.5)	1.9 (1.4-2.5)
Multiracial	2.9 (1.8-4.8)	1.9 (1.1-3.0)
White, Hispanic	1.1 (0.8-1.5)	0.7 (0.5-1.0)
Asian	0.4 (0.1-1.0)	0.6 (0.2-1.2)
White, non-Hispanic	1.0	1.0

aPOR, Adjusted prevalence OR.
*Model included race and ethnicity, insurance status, and maternal age.

J Pediatr 2018;200:196-201

Congenital CMV: Outcomes

- **Symptomatic infection**
  - **40-60% develop permanent sequelae**
    - **Sensorineural hearing loss**
    - **Vestibular dysfunction**
    - **Cognitive impairment**
    - **Developmental delays**
    - **Retinitis**
- **Asymptomatic infection**
    - **Sensorineural hearing loss**
    - **Vestibular dysfunction**

SNHL with cCMV

- Most common sequelae
- Loss is variable
  - Mild unilateral to profound bilateral
  - Fluctuate
  - Delayed-onset
- Pathogenesis: may be a combination of viral-mediated damage and host inflammatory response

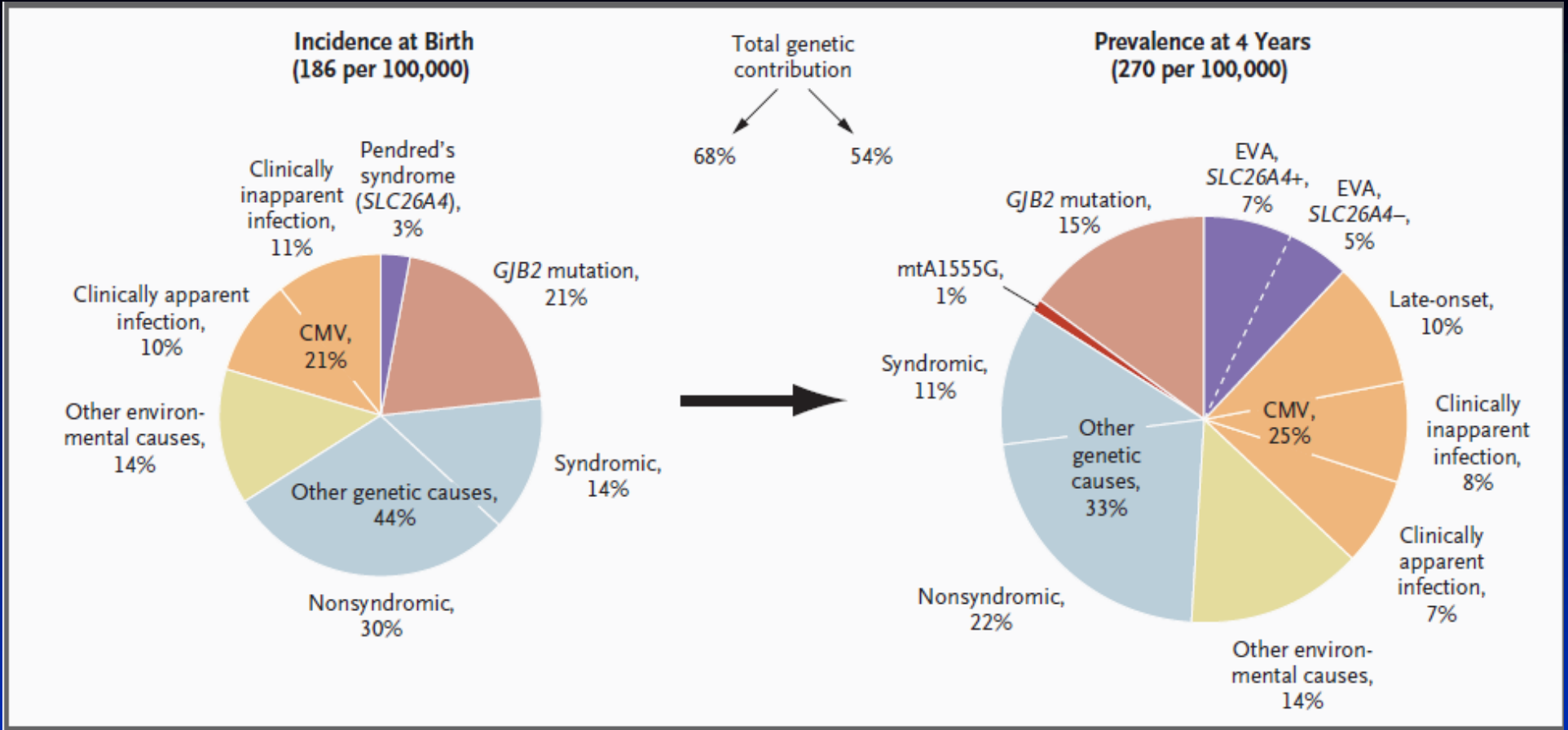


Figure 1. Estimates of Causes of Deafness at Birth and at Four Years in the United States.

The incidence of deafness at birth in the United States, and its prevalence at four years of age, were obtained by adjusting estimates from the United Kingdom[11,12] (where, in contrast with the United States, follow-up is nearly complete) to include unilateral hearing loss. The overall proportion of genetic cases at four years of age was estimated by sentinel phenotype analysis.[13] Estimates for specific causes were obtained from previously published data (as documented in the Supplementary Appendix, available with the full text of this article at www.nejm.org). No studies were available in which universal newborn testing was performed for more than one specific cause of deafness in the same population sample. CMV denotes cytomegalovirus, mtA1555G the mitochondrial A1555G mutation, and EVA enlargement of the vestibular aqueduct.

N Engl J Med 2006;354:2151-64

Natural History of Hearing Loss in cCMV

Hearing Loss	Symptomatic	Asymptomatic
Total	33-40%	7-10%
Characteristics of Loss		
Bilateral	67-71%	43-48%
Delayed onset	18-27%	9-38%
Median age (and range of delayed onset)	33 mos (6-197 mos)	44 mos (24-182 mos)
Progressive	18-54%	20-54%
Fluctuating	21-22%	24-48%
Severe-profound loss	75%	78%

Summary from 4 studies. *Antiviral Res* 2021;191:1-5

Cumulative Percentage of Sensorineural Hearing Loss by Age

Age	Symptomatic	Asymptomatic
Birth – 1 month	43.5%	25.5%
3 months	55.3%	31.4%
6 months	67.2%	43.1%
2 years	82.4%	47.1%
3 years	88.2%	58.8%
4 years	89.4%	72.5%
6 years	95.3%	86.6%
7 – 15 years	100%	100%

J Am Acad Audiol 2000;11(5):283-90

Vestibular, Gaze, and Balance Disorders in Asymptomatic Congenital Cytomegalovirus Infection

Swetha Pinninti, MD,[a] Jennifer Christy, PT, PhD,[b] Anwar Almutairi, PT, PhD,[b] Graham Cochrane, BA,[b] Karen B. Fowler, PhD,[a,c] Suresh Boppana, MD[a,d]

- **Comprehensive vestibular, gaze, and balance assessments**
- **40 children with asymptomatic cCMV**
  - **17.5% with SNHL (2 each with mild, moderate-severe and profound) vs 33 Controls**
- **RESULTS: Vestibular disorders in 45% of cohort**
  - **46% had difficulties maintaining gaze during head movement**
  - **1/3 – 1/2 with difficulties maintaining balance**

Pediatrics 2021;147(2):e20193945

Cognitive Impairment and Cerebral Palsy in Symptomatic cCMV

Outcome	Percentage
IQ < 70	40%
Motor deficits	20%
Seizures	19%

J Pediatr 2014;164:855-859 *Pediatr Infect Dis J* 2016;35:924-926 *Antiviral Res* 2021;191:1-5

Effect on Brain Development Based on Trimester of Infection

- 1st trimester
  - Neural stem cells which differentiate into neurons and glia are infected
  - Interruption of organogenesis, abnormal neuronal migration

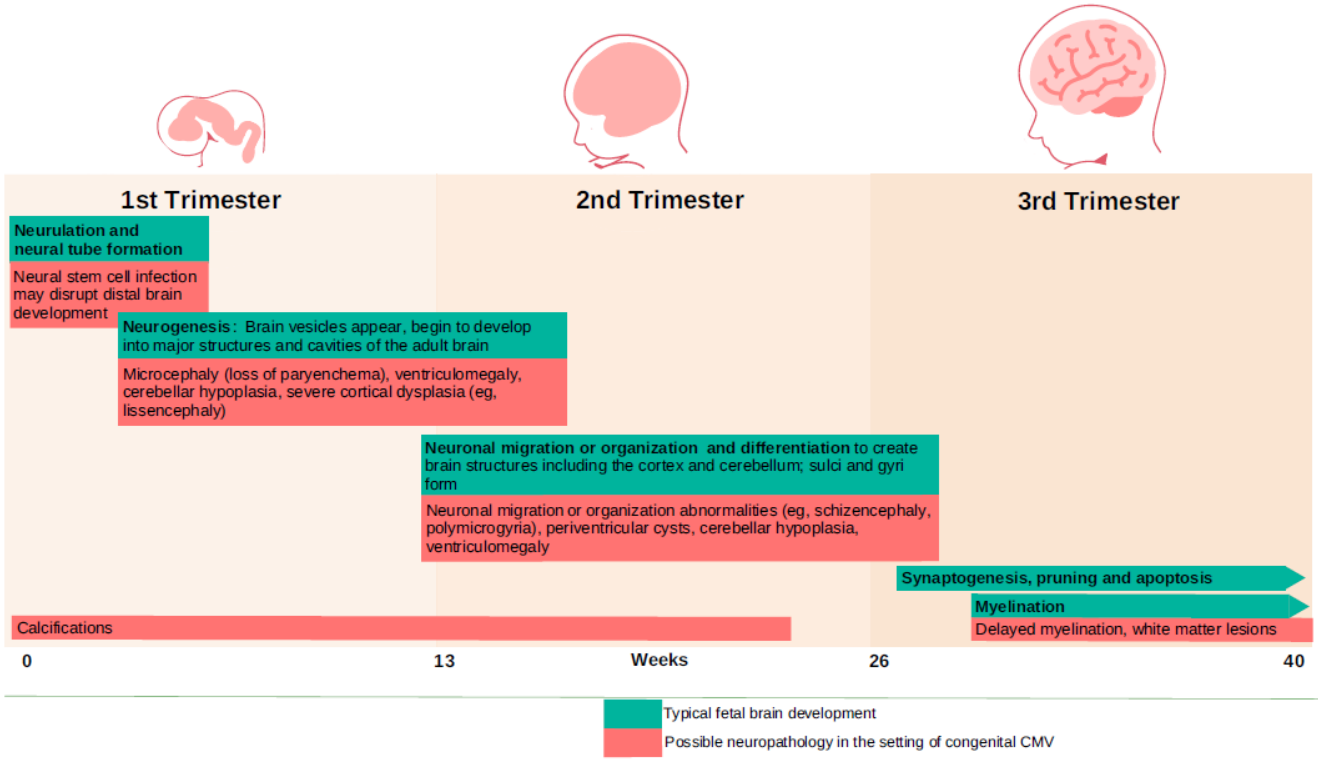


FIGURE 2
Typical fetal brain development and resultant congenital cytomegalovirus-associated neuropathology by timing of maternal infection and vertical transmission. Processes of fetal neurodevelopment distal to timing of fetal infection may be affected by CMV-associated placental injury, inflammatory response, and fetal central nervous system infection.[91,113,114]

Pediatrics 2022;150(2):e2021055896

Intelligence and Academic Achievement With Asymptomatic Congenital Cytomegalovirus Infection

Adriana S. Lopez, MHS,[a] Tatiana M. Lanzieri, MD, MPH,[a] Angelika H. Claussen, PhD,[b] Sherry S. Vinson, MD,[c,d] Marie R. Turcich, MA,[c,d] Isabella R. Iovino, PhD,[c,d] Robert G. Voigt, MD,[c,d] A. Chantal Caviness, MD, MPH,[c] Jerry A. Miller, MS, PhD,[c,e] W. Daniel Williamson, MD,[c] Craig M. Hales, MD, MPH,[a] Stephanie R. Bialek, MD, MPH,[a] Gail Demmler-Harrison, MD,[c,d] on behalf of the Congenital Cytomegalovirus Longitudinal Study Group

- Longitudinal study of infants identified by newborn screening vs controls through childhood and adolescence (92) vs unmatched controls (42) born within 6 days of infant
- 20 patients (11 by age 2 yrs, 9 moderate to profound) and 3 controls (9-15 yrs) developed SNHL

- Results:
  - No differences in IQ, vocabulary or academic achievement scores in subjects with normal hearing at age 2 yrs
  - Subjects with SNHL
    - full-scale intelligence score 7.0 points lower
    - Receptive vocabulary scores 13.1 points lower

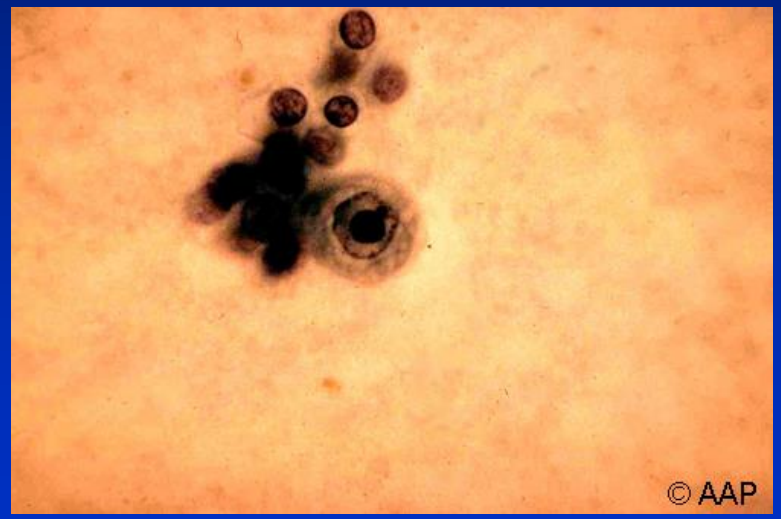
Congenital Cytomegalovirus Longitudinal Study Group. *Pediatrics* 2017;140(4):e20171517

Maternal-infant transmission of CMV

- Transplacental (Congenital)
- Intrapartum (Perinatal) – incubation period: 3-4 weeks
  - Cervical secretions
    - CMV positive: 5% - 24%, transmission rate: 26% - 56%
- Postpartum (Postnatal) – incubation period: 3-4 weeks
  - Human milk
    - CMV positive: 13% - 32%, transmission rate: 29% - 59%
- No sequalae of perinatal or postnatal infection

Diagnosis of Congenital CMV

- Virologic detection within 3 weeks of birth is necessary to differentiate cCMV from perinatal or postnatal infection transmission
- CMV DNA PCR has replaced culture
  - Urine or saliva – sensitivity 97-100%
    - Saliva – wait 1 hour after breast feeding
      - False positive rate 0.03-0.14%[1]
    - Saliva positive; confirm with urine
  - Respiratory tract, blood, CSF, amniotic fluid
- Serologic diagnosis
  - IgG – no value, maternal transfer
  - IgM – false positives common



AAP 2021 Red Book, pg 297

[1] *J Infect Dis* 2018;217:1612-1615

cCMV Treatment

- Randomized, placebo-controlled trial
  - 6 wks vs 6 mos; 96 participants
- End points
  - Primary: change in better ear at 6 months
  - Secondary: total ear hearing and developmental outcomes at 12, 24 mos
- Outcome:
  - No improvement in short term (P=0.24 at 6 mos)
  - Modest improvement in hearing and developmental outcomes in longer term

ORIGINAL ARTICLE

Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease

D.W. Kimberlin, P.M. Jester, P.J. Sánchez, A. Ahmed, R. Arav-Boger, M.G. Michaels, N. Ashouri, J.A. Englund, B. Estrada, R.F. Jacobs, J.R. Romero, S.K. Sood, M.S. Whitworth, M.J. Abzug, M.T. Caserta, S. Fowler, J. Lujan-Zilbermann, G.A. Storch, R.L. DeBiasi, J.-Y. Han, A. Palmer, L.B. Weiner, J.A. Bocchini, P.H. Dennehy, A. Finn, P.D. Griffiths, S. Luck, K. Gutierrez, N. Halasa, J. Homans, A.L. Shane, M. Sharland, K. Simonsen, J.A. Vanchiere, C.R. Woods, D.L. Sabo, I. Aban, H. Kuo, S.H. James, M.N. Prichard, J. Griffin, D. Giles, E.P. Acosta, and R.J. Whitley, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group

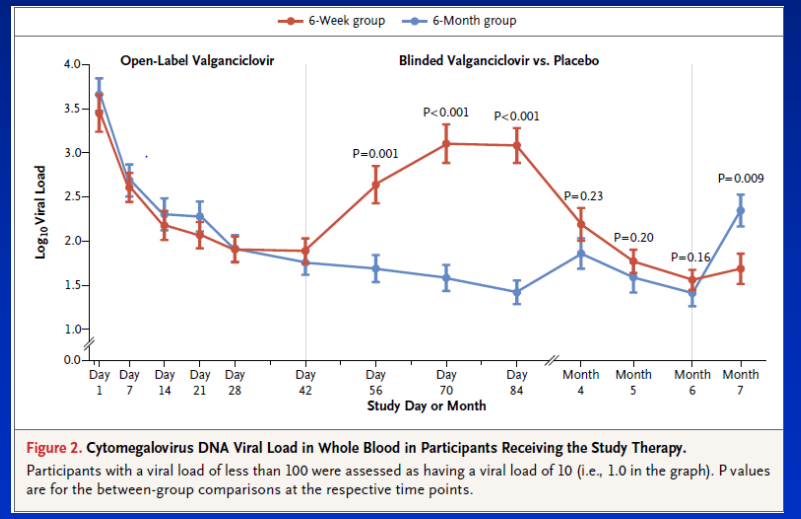
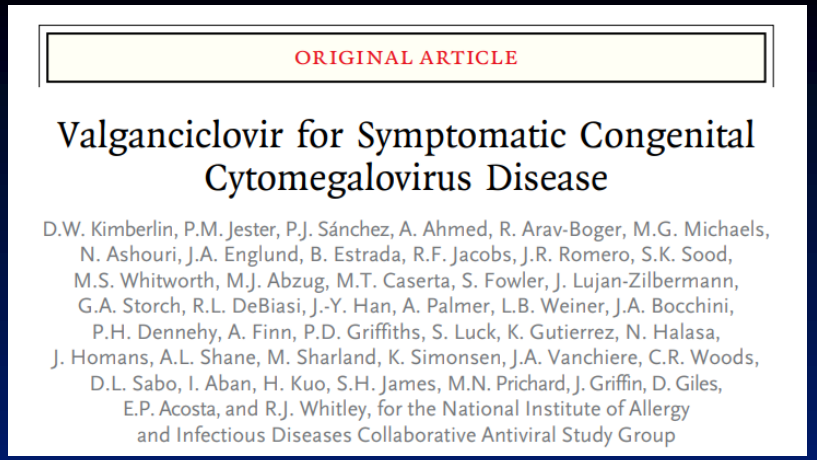


Figure 2. Cytomegalovirus DNA Viral Load in Whole Blood in Participants Receiving the Study Therapy.
Participants with a viral load of less than 100 were assessed as having a viral load of 10 (i.e., 1.0 in the graph). P values are for the between-group comparisons at the respective time points.

N Engl J Med 2015;372:933-43

cCMV Treatment



ORIGINAL ARTICLE

Valganciclovir for Symptomatic Congenital Cytomegalovirus Disease

D.W. Kimberlin, P.M. Jester, P.J. Sánchez, A. Ahmed, R. Arav-Boger, M.G. Michaels, N. Ashouri, J.A. Englund, B. Estrada, R.F. Jacobs, J.R. Romero, S.K. Sood, M.S. Whitworth, M.J. Abzug, M.T. Caserta, S. Fowler, J. Lujan-Zilbermann, G.A. Storch, R.L. DeBiasi, J.-Y. Han, A. Palmer, L.B. Weiner, J.A. Bocchini, P.H. Dennehy, A. Finn, P.D. Griffiths, S. Luck, K. Gutierrez, N. Halasa, J. Homans, A.L. Shane, M. Sharland, K. Simonsen, J.A. Vanchiere, C.R. Woods, D.L. Sabo, I. Aban, H. Kuo, S.H. James, M.N. Prichard, J. Griffin, D. Giles, E.P. Acosta, and R.J. Whitley, for the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group

- Total-ear hearing improved or remained normal
  - 12 mos (73% vs 57%. P=0.001) [OR = 3.04, 95% CI 1.26 to 7.35]
  - 24 mos (77% vs 64%, P=0.04) [OR = 2.61, 95% CI 1.05 to 6.31]
- Bayley III Components at 24 mos
  - Cognitive composite (P=0.02)
  - Language composite (P=0.004)
  - Receptive-communication (P=0.003)
  - Expressive-communication (P=0.02)
  - Gross motor (P=0.02)

N Engl J Med 2015;372:933-43

Standardizing manifestations to improve analysis of treatment outcomes

- **Mildly symptomatic**
  - Presence of 1-2 isolated manifestations, often transient
- **Moderately to severely symptomatic**
  - Presence of multiple attributable manifestations or central nervous system manifestations or both
- **Asymptomatic**
  - Normal or isolated SNHL in newborn period

Informal International Consensus Recommendations Group. *Lancet Infect Dis* 2017;17(6):e177-e188

Current Recommendations for Antiviral Therapy of Infants with cCMV

- Moderate to severe symptomatic disease
  - Valganciclovir (16mg/kg/dose, PO, BID for 6 months)
    - Begin treatment <1 month of age
    - Side-effects: neutropenia (~20%), elevated LFT's
  - Can use ganciclovir IV if PO not indicated
- Mild disease or isolated SNHL should not receive antiviral treatment

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TABLE 1 On-Going and Recently Completed Studies of Congenital Cytomegalovirus Related Therapeutics, Prevention, and Vaccines

Clinical Trial Number, Principal Investigator, Institution or Sponsor	Phase	Intervention	Primary Objective	Population
Antiviral medication for infants with cCMV				
NCT03301415 National Institute of Allergy and Infectious Diseases[115]	Phase 2	Valganciclovir, 16 mg/kg per dose provided orally twice daily for 4 mo	To evaluate valganciclovir as a treatment to prevent development of SNHL in infants with asymptomatic cCMV infection	229 newborns with asymptomatic cCMV without baseline SNHL
NCT03107871 Albert Park, University of Utah, National Institute of Deafness and Other Communication Disorders, Genentech, Inc.[116]	Phase 2	Valganciclovir, 16 mg/kg per dose or placebo provided orally twice daily for 6 mo	To determine if valganciclovir treatment reduces the mean slope of total hearing thresholds over the 20 mo after randomization compared with placebo in cCMV-infected asymptomatic infants with isolated hearing loss	52 infants with asymptomatic cCMV and isolated SNHL
NCT02005822 Ann C.T.M. Vossen, Leiden University Medical Center, Netherlands[117]	Phase 3	Valganciclovir, 16 mg/kg per dose provided orally twice daily for 6 wk	To investigate whether early treatment with oral valganciclovir of infants with both congenital cytomegalovirus infection and sensorineural hearing loss can prevent progression of hearing loss	37 infants with cCMV and SNHL

Maternal immunoglobulin to prevent vertical transmission				
NCT05170269 Biotest AG	Phase 3	Cytotect CP Biotest (BT097), 200 U/kg IV weekly every 2 wk until at least GW 17	To demonstrate efficacy and safety of Cytotect CP Biotest in preventing maternal-fetal transmission of CMV	80 pregnant women with primary CMV infection
Maternal behavioral intervention to prevent CMV infection				
NCT04615715 Karen Fowler, University of Alabama at Birmingham[49]	NA	Prenatal clinic-based CMV risk-reduction behavioral intervention versus control	To evaluate whether a brief prenatal clinic-based CMV risk-reduction behavioral intervention will prevent maternal CMV infections during pregnancy in women	840 pregnant women
Antiviral medication for congenitally infected fetuses				
NCT04732260 Yves Ville, Assistance Publique - Hôpitaux de Paris, France[118]	NA	1 tablet of Letermovir (240 mg or 480 mg /d) for 3 d	To measure the Letermovir transplacental transfer in the second trimester and its accumulation in the amniotic fluid and the placenta in the second trimester	10 pregnant women undergoing termination of pregnancy for fetal abnormality

CMV vaccine trials				
NCT03486834 Merk Sharp and Dohme Corp.[119]	Phase 2	Vaccine V160 vs placebo	To evaluate the safety, tolerability, and efficacy of the CMV vaccine (V160) and whether administration of a 3-dose regimen reduce the incidence of primary CMV infection compared with placebo	2200 healthy seronegative women aged 16 to 35 y with direct exposure to young children
NCT05089630 GlaxoSmithKline[120]	Phases 1 and 2	Recombinant protein subunit vaccine	To assess the safety, reactogenicity, and immunogenicity of the candidate CMV recombinant protein subunit, regardless of baseline CMV sero-status	320 healthy adults 18 to 50 y of age
NCT05085366 ModernaTX, Inc.[121]	Phase 3	mRNA-1647 vaccine versus placebo	To evaluate the efficacy of mRNA 1647 vaccine in CMV-seronegative female participants and to evaluate the safety and reactogenicity of mRNA-1647 vaccine in all participants	6900 healthy seronegative participants aged ≥20 y old with direct exposure to at least 1 child ≤ 5 y old

Use of Valacyclovir During Pregnancy

- 100 women with preconceptionally or 1st trimester primary CMV infection
- Oral valaciclovir vs placebo, amniocentesis at 21-22 weeks.
- cCMV: Valaciclovir – 11% Placebo – 30% (p=0.027)

Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial

Keren Shahar-Nissan*, Joseph Pardo*, Orit Peled, Irit Krause, Efraim Bilavsky, Arnon Wiznitzer, Eran Hadar†, Jacob Amir†

Lancet 2020;396(10253):779-785

- Symptomatic fetuses, treated in utero from diagnosis (median 25.9 wks' gestation) until delivery or termination, severe CNS disease not included
- 43 treated, 34 asymptomatic at birth (82%, vs literature – 43%), all asymptomatic at 12 months

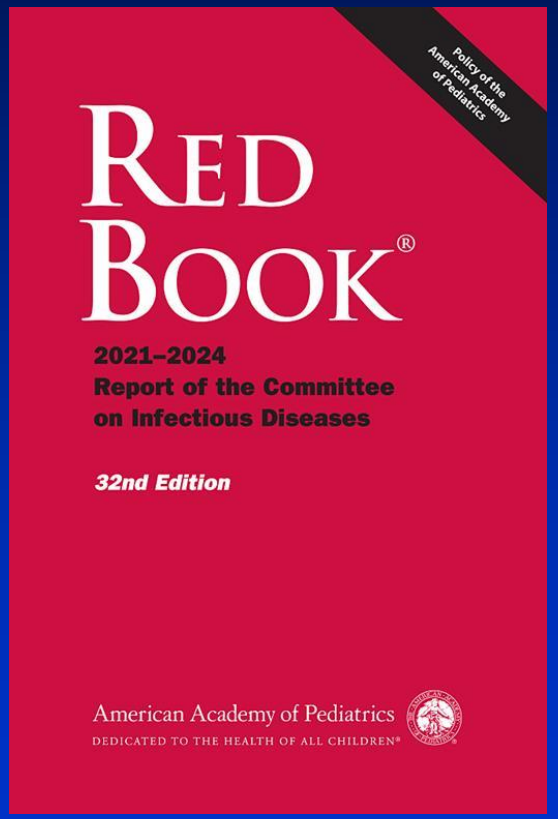
In utero treatment of congenital cytomegalovirus infection with valacyclovir in a multicenter, open-label, phase II study

Marianne Leruez-Ville, MD, PhD; Idir Ghout, MSc; Laurence Bussières, PhD; Julien Stirnemann, MD, PhD; Jean-François Magny, MD; Sophie Couderc, MD; Laurent J. Salomon, MD, PhD; Tiffany Guilleminot, BA; Philippe Aegerter, MD, PhD; Guillaume Benoist, MD, PhD; Norbert Winer, MD; Olivier Picone, MD, PhD; François Jacquemard, MD; Yves Ville, MD, FRCOG

Am J Obstet Gynecol 2016;215(4):462.e461-462.e410

American Academy of Pediatrics Committee on Infectious Disease Recommendations for Infants with cCMV

- **Asymptomatic or Symptomatic Disease**
  - Hearing testing at 4, 6, 9, 12, 15, 18, 24, 36 mos
  - Standard hearing assessments at 4, 5, 6, 8, 10 yrs



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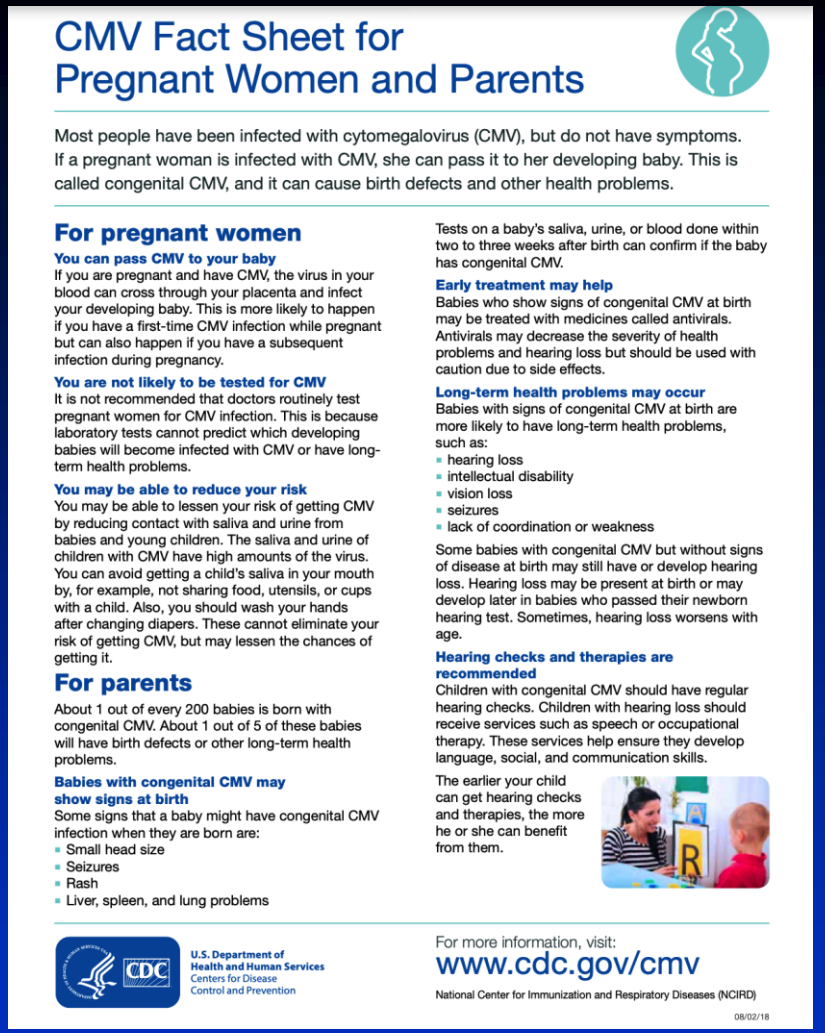
Prevention

- Increasing awareness
- Education
  - Hygiene prevention measures

https://www.nationalcmv.org



CMV Fact Sheet for Pregnant Women and Parents

Most people have been infected with cytomegalovirus (CMV), but do not have symptoms. If a pregnant woman is infected with CMV, she can pass it to her developing baby. This is called congenital CMV, and it can cause birth defects and other health problems.

For pregnant women

You can pass CMV to your baby
If you are pregnant and have CMV, the virus in your blood can cross through your placenta and infect your developing baby. This is more likely to happen if you have a first-time CMV infection while pregnant but can also happen if you have a subsequent infection during pregnancy.

You are not likely to be tested for CMV
It is not recommended that doctors routinely test pregnant women for CMV infection. This is because laboratory tests cannot predict which developing babies will become infected with CMV or have long-term health problems.

You may be able to reduce your risk
You may be able to lessen your risk of getting CMV by reducing contact with saliva and urine from babies and young children. The saliva and urine of children with CMV have high amounts of the virus. You can avoid getting a child's saliva in your mouth by, for example, not sharing food, utensils, or cups with a child. Also, you should wash your hands after changing diapers. These cannot eliminate your risk of getting CMV, but may lessen the chances of getting it.

For parents

About 1 out of every 200 babies is born with congenital CMV. About 1 out of 5 of these babies will have birth defects or other long-term health problems.

Babies with congenital CMV may show signs at birth
Some signs that a baby might have congenital CMV infection when they are born are:
- Small head size
- Seizures
- Rash
- Liver, spleen, and lung problems

Tests on a baby's saliva, urine, or blood done within two to three weeks after birth can confirm if the baby has congenital CMV.

Early treatment may help
Babies who show signs of congenital CMV at birth may be treated with medicines called antivirals. Antivirals may decrease the severity of health problems and hearing loss but should be used with caution due to side effects.

Long-term health problems may occur
Babies with signs of congenital CMV at birth are more likely to have long-term health problems, such as:
- hearing loss
- intellectual disability
- vision loss
- seizures
- lack of coordination or weakness

Some babies with congenital CMV but without signs of disease at birth may still have or develop hearing loss. Hearing loss may be present at birth or may develop later in babies who passed their newborn hearing test. Sometimes, hearing loss worsens with age.

Hearing checks and therapies are recommended
Children with congenital CMV should have regular hearing checks. Children with hearing loss should receive services such as speech or occupational therapy. These services help ensure they develop language, social, and communication skills.

The earlier your child can get hearing checks and therapies, the more he or she can benefit from them.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

For more information, visit:
www.cdc.gov/cmv

National Center for Immunization and Respiratory Diseases (NCIRD)

08/02/18

https://www.cdc.gov/cmv/fact-sheets/parents-pregnant-women.html

UNIVERSAL NBS for cCMV

Washington State Department of Health

cCMV Universal Screening

- Test all babies for cCMV (~84,000 babies/year)
  - Urine
    - Best sample type – highest sensitivity
    - Cumbersome to collect
    - No system for collecting urine for all babies
  - Saliva
    - Good sensitivity
    - Higher false positive rate than urine
    - No system for collecting saliva for all babies

cCMV Universal Screening

- cCMV DNA can be detected in dried blood specimens
- Viral load in blood is 100x lower than in urine or saliva
  - Current DBS assays require three times the amount of blood as other NBS tests
    - Would likely require an additional blood spot for testing (new total = 6 blood spots)

cCMV Universal Screening

- Dried blood spot screening test performance

- Sensitivity: 75.0%
  - False(-) rate: 25% (no benefit from NBS)

- Specificity: 99.88%
  - False(+) rate: 0.12%

Blood spot test - cCMV

Ontario – combined method - 2 lab developed tests

- Real-time qPCR method for cCMV
- MassArray for 2 genes associated with hearing loss

Minnesota – for research use only

- Real-time qPCR method

Blood spot test - cCMV

Minnesota method

- $15/baby for the kits

- Cost does not include
  - Instrumentation
  - Salaries/Benefits for NBS staff
    - Laboratory testing
    - Follow-up
    - Long-term follow-up

Universal cCMV Screening

Newborn screen collected within 48h of birth

Dried blood specimen delivered to PHL within 72h of collection

CMV PCR performed at 2-5 days of age

cCMV screen–

NBS results report sent to specimen submitter; no further action unless the baby develops symptoms of cCMV infection

cCMV screen+

Follow-up reports abnormal screen to PCP and refers for diagnostic testing

cCMV+

cCMV–

Report to PCP; no further action

Confirmed with diagnostic testing (often urine)

Treatment and additional testing/referrals if indicated

Diagnostic hearing test by 3 months of age

Deaf/Hard of Hearing infant - known cause (cCMV)

Early intervention by six months of age

Hearing infant

Regular monitoring for changes in hearing

Hearing child (no more testing after 6y old)

Late-onset hearing loss from cCMV: diagnosed (6m – 6y)

Intervention as soon as hearing loss is detected

Surveillance for late-onset hearing loss

months of age	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60	66	72
ABR	X																	
OAEs	X	X	X	X	X	X	X	X	X	X	X	X	X					
Tympanometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VRA		X	X	X	X	X	X											
Condition play audiometry								X	X	X	X	X	X					
Select picture								X	X	X	X	X	X					
Standard audiometry														X	X	X	X	X
Pediatric speech testing														X	X	X	X	X

Based on Utah's EHDI hearing assessment schedule

Surveillance for late-onset hearing loss

months of age	3	6	9	12	15	18	21	24	27	30	33	36	42	48	[illegible]	[illegible]0	66	72
ABR	X																	
OAEs	X	X	X	X	X	X	X	X	X	X	[illegible]		X					
Tympanometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VRA		X	X	X	X	X	X											
Condition play audiometry								X	X	X	X	X	X					
Select picture								X	X	X	X	X	X					
Standard audiometry														X	X	X	X	X
Pediatric speech testing														X	X	X	X	X

Whose responsibility is this?

Based on Utah's EHDI hearing assessment schedule

Universal cCMV Screening

Newborn screen collected within 48h of birth

Dried blood specimen delivered to PHL within 72h of collection

CMV PCR performed at 2-5 days of age

cCMV screen–

NBS results report sent to specimen submitter; no further action unless the baby develops symptoms of cCMV infection

cCMV screen+

Follow-up reports abnormal screen to PCP and refers for diagnostic testing

Confirmed with second sample (often urine)

cCMV+

cCMV–

Report to PCP; no further action

Treatment and additional testing/referrals if indicated

Diagnostic hearing test by 3 months of age

Typical Blood Spot Follow-up End

Deaf/Hard of Hearing infant - known cause (cCMV)

Typical EHDDI Follow-up End

Early intervention by six months of age

Hearing infant

N=247/year

Regular monitoring for changes in hearing

Hearing child (no more testing after 6y old)

N=216/year

Late-onset hearing loss from cCMV: diagnosed (6m – 6y)

N=31/year

Intervention as soon as hearing loss is detected

NBS for cCMV elsewhere

- Targeted screening: UT, IA, VA, NY, CT, IL

- Utah
  - legislation 2013 established a public education program for CMV
  - Work group meets monthly
  - cCMV Clinic at the UofU/Primary Children's Hospital

NBS for cCMV elsewhere

- Minnesota
  - Vivian act (2107, 2021) – convened advisory committee to review CMV
  - If passed, increase NBS fee by $43/baby
  - Conditions readiness review
    - Evaluation of public health laboratory and medical system for introducing cCMV screening

Summary

- Dried blood spot test is available
  - Requires extra blood (three punches)
  - Low sensitivity (25% of cases missed)
  - Adequate specificity (0.12% false(+) rate)
  - Testing kit available (moderately expensive)

- There are infrastructure needs to perform long-term follow-up for an additional ~250 babies needing surveillance for hearing loss

~Thank you~

Together we protect the lives of
Washington's youngest citizens.

Washington State Department of Health

Washington State Department of Health

EARLY HEARING DETECTION, DIAGNOSIS, AND INTERVENTION PROGRAM

The EHDDI Program

Marcie Rider

Program Manager

Marcie.Rider@doh.wa.gov

Phone: 206-418-5666

EHDDI

SCREENING METHODS AND TARGETED CONGENITAL CYTOMEGALOVIRUS (CCMV) SCREENING

Newborn Hearing Screening Methods

Otoacoustic Emissions (OAE)

Automated Auditory Brainstem Response (ABR)

Newborn Hearing Screening

- Point-of-Care testing
- Immediate result provided “pass” or “refer”
- Non-invasive
- Baby asleep
- Physiologic test
- Automated test
- Quick ~2-10 minutes
- Effectively identifies which babies need further testing

Newborn Hearing Screening

Initial screen

- Before hospital discharge (2 attempts)
- With midwife or audiologist before one month of age if not completed in a hospital

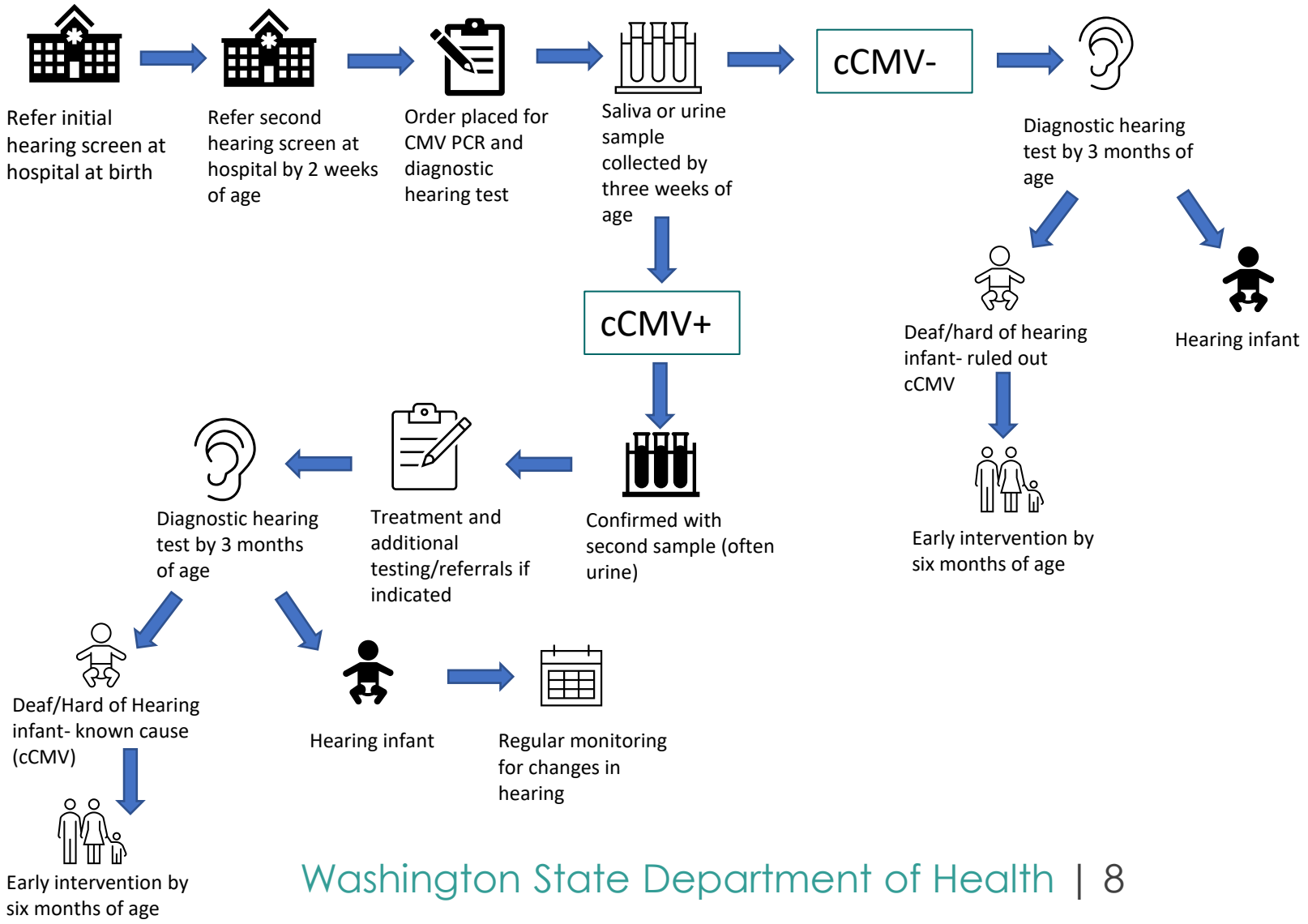
Repeat screen

- As outpatient at hospital or audiology clinic before one month of age

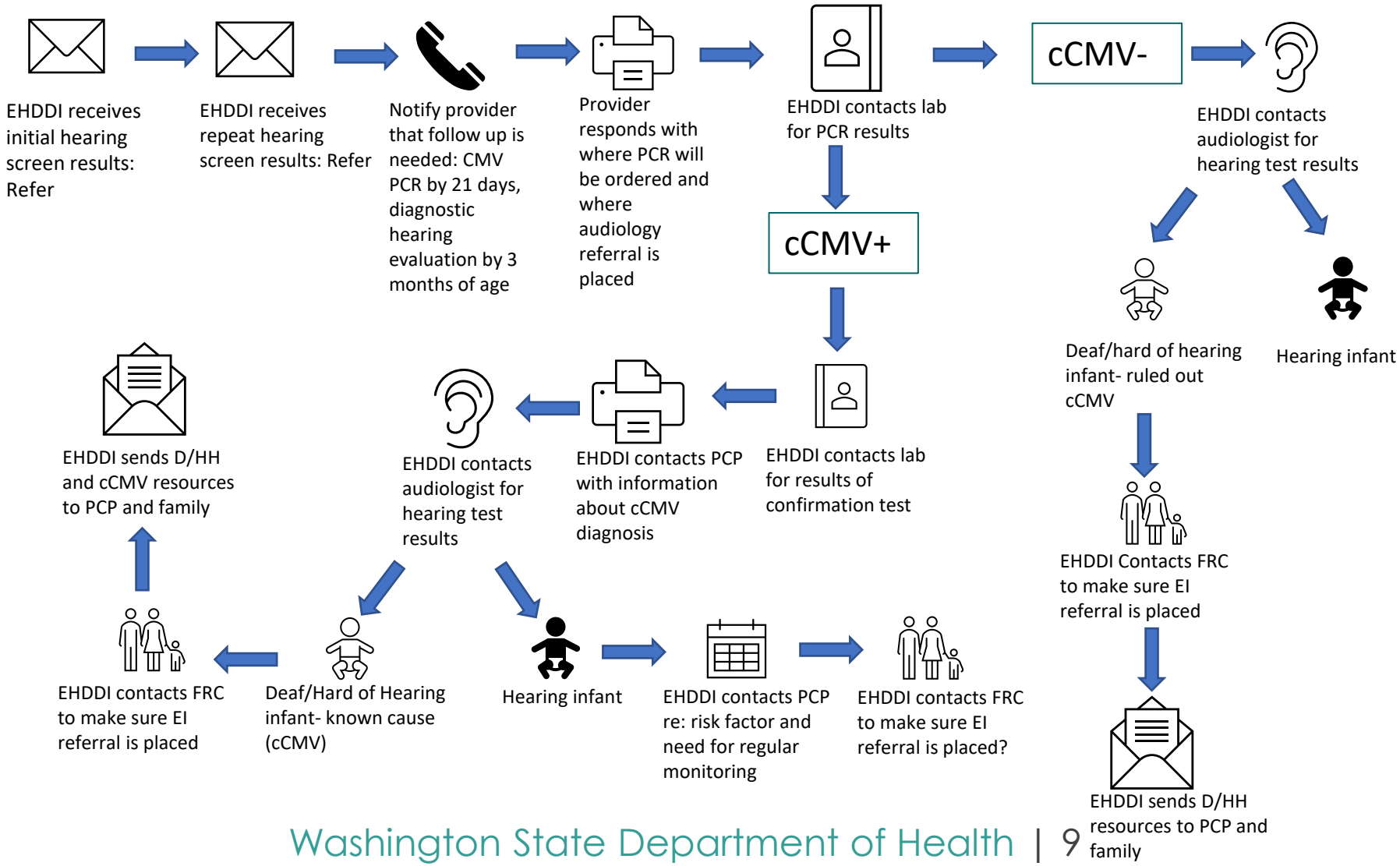
Targeted cCMV Screening

- Urine or saliva is collected from an infant after they do not pass their second newborn hearing screening
- Polymerase chain reaction (PCR) test
- Helps determine whether cCMV is the cause of a child's hearing loss
- Must test for CMV within 21 days of life to determine if CMV infection is congenital

Targeted cCMV Screening



Targeted cCMV Screening- EHDDI Program



EHDDI's Role

Education and outreach regarding new protocol

Follow-up work to ensure:

- Hearing screening and reporting happen within 21 days of life
- PCR was done after child did not pass hearing screen
- PCR results are received and shared with primary care provider and audiologist
- Infants who test positive receive appropriate follow up care, early intervention and information about cCMV

Targeted cCMV Screening Reliability

Polymerase chain reaction (PCR) of saliva or urine

- High sensitivity (>97%) and specificity (99%)
- Positive result should be confirmed with second sample (often urine)

Targeted screening lacks sensitivity

- Unable to identify infants with cCMV whose hearing loss develops later or have other impacts
- Approximately 10-15% of children with cCMV will have hearing loss
- Newborn hearing screening identified 57% of all CMV-related hearing loss that occurred in the neonatal period (Fowler et al. 2017)

Six states mandate targeted screening

- UT, IA, VA, NY, CT, IL

Newborn Hearing Screening Considerations

There is no mandate for hearing screening in Washington

Currently 27% of second hearing screenings occur after 21 days of life

- Average age of second screen = 22 days
- Median age of second screen = 15 days

Special considerations need to be made for infants with extended stays in the Neonatal Intensive Care Units (NICU)

Logistics for placing the order for the PCR test at the time of referral on second hearing screening

Challenges with timely reporting of hearing screening results

Washington State Department of Health is committed to providing customers with forms and publications in appropriate alternate formats. Requests can be made by calling 800-525-0127 or by email at civil.rights@doh.wa.gov. TTY users dial 711.

Washington State Department of Health

ECONOMIC ANALYSIS FOR ADDING NEWBORN SCREENING FOR CONGENITAL CYTOMEGALOVIRUS

Caitlin Maloney, MPHc
John Thompson PhD, MPH, MPA
Newborn Screening Program

Washington State NBS Criteria

1. Available Screening Technology: Sensitive, specific and timely tests are available that can be adapted to mass screening.

2. Diagnostic Testing and Treatment Available: Accurate diagnostic tests, medical expertise, and effective treatment are available for evaluation and care of all infants identified with the condition.

3. Prevention Potential and Medical Rationale: The newborn identification of the condition allows early diagnosis and intervention. Important considerations:

- There is sufficient time between birth and onset of irreversible harm to allow for diagnosis and intervention.
- The benefits of detecting and treating early onset forms of the condition (within one year of life) balance the impact of detecting late onset forms of the condition.
- Newborn screening is not appropriate for conditions that only present in adulthood.

4. Public Health Rationale: Nature of the condition justifies population-based screening rather than risk-based screening or other approaches.

5. Cost-benefit/Cost-effectiveness: The outcomes outweigh the costs of screening. All outcomes, both positive and negative, need to be considered in the analysis. Important considerations to be included in economic analyses include:

- The prevalence of the condition among newborns.
- The positive and negative predictive values of the screening and diagnostic tests.
- Variability of clinical presentation by those who have the condition.
- The impact of ambiguous results. For example the emotional and economic impact on the family and medical system.
- Adverse effects or unintended consequences of screening.

Strategy

Decision Tree

- Status quo (no screening) vs. universal (dried blood spot) vs. hearing targeted (failed hearing screen)

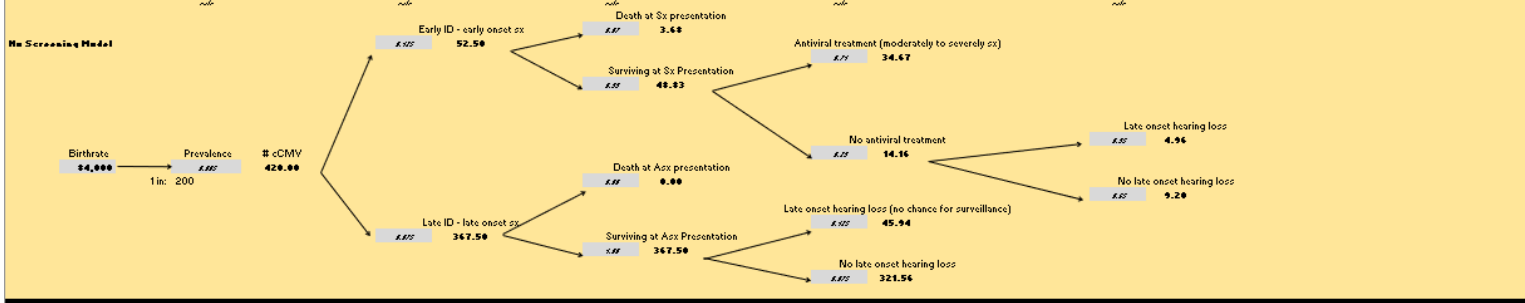
Research

- Primary literature and expert opinion
- NBS programs with state-mandated congenital CMV (cCMV) education and/or screening

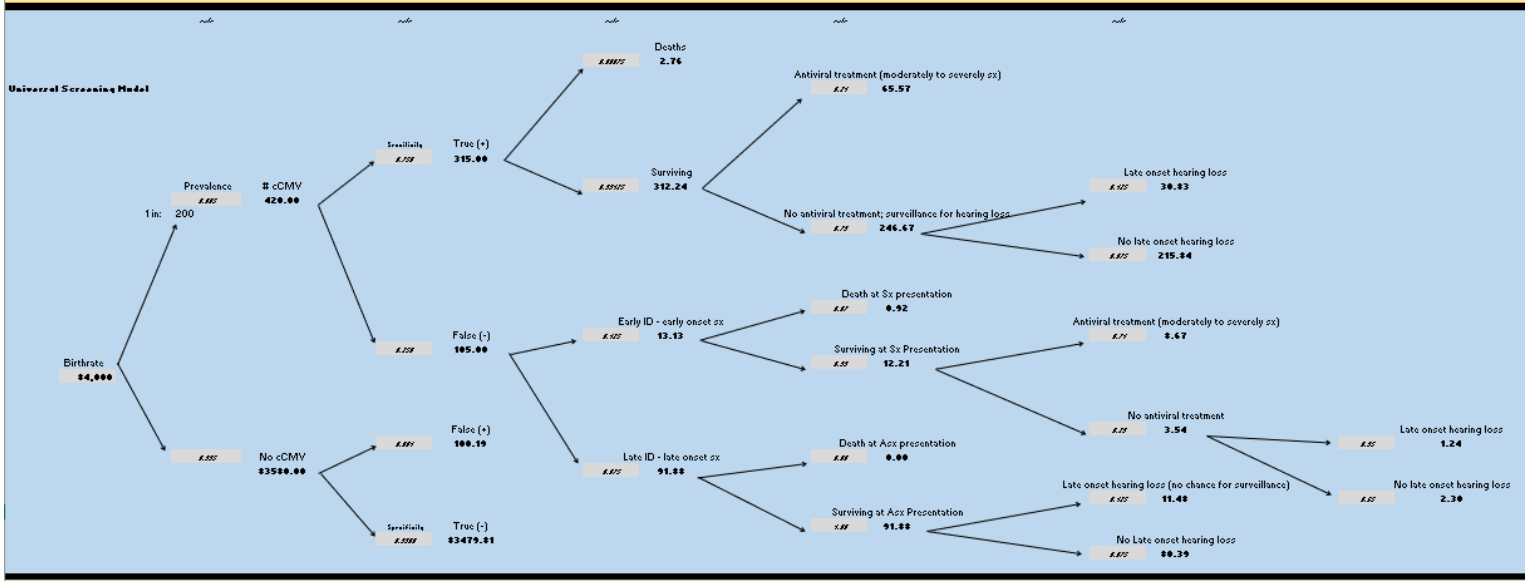
Sensitivity analysis

- High and low estimates for parameters

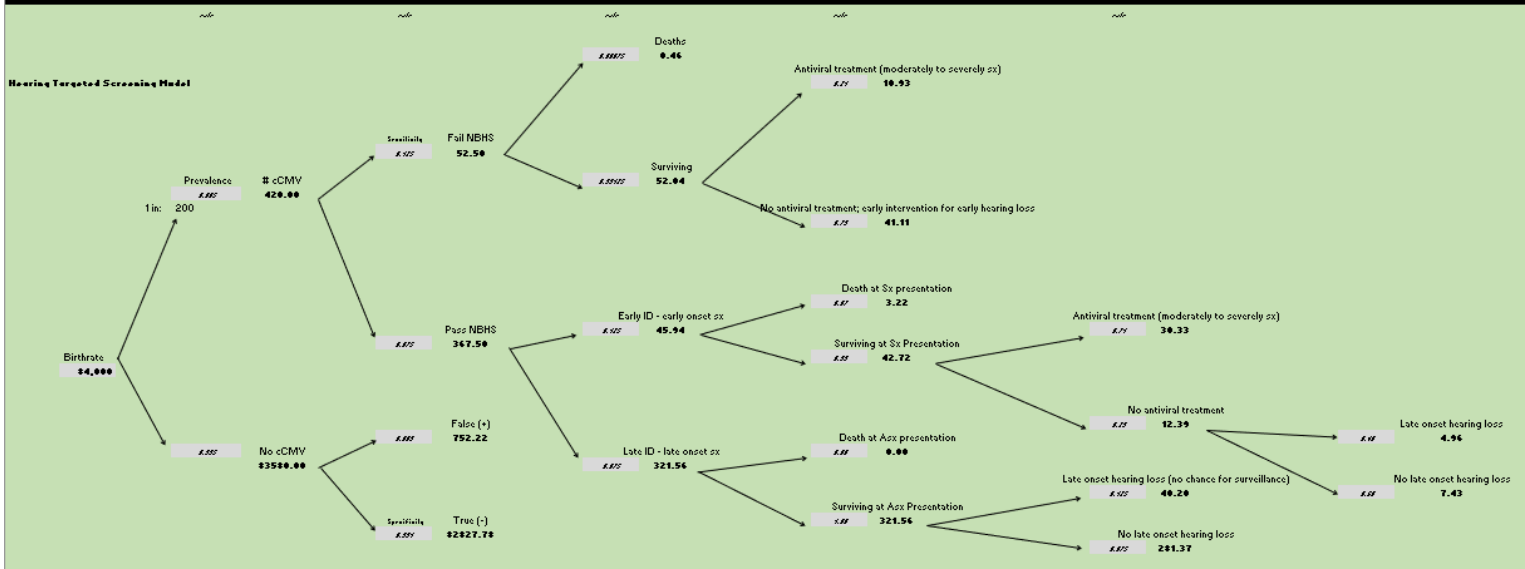
No Screening



Universal Screening



Hearing Targeted Screening



Decision Tree

cCMV does not fit traditional newborn screening (NBS) rationale

- No quantifiable difference in morbidity and mortality at this time
- Antiviral treatment may provide short-term relief, but will not reverse or prevent symptoms

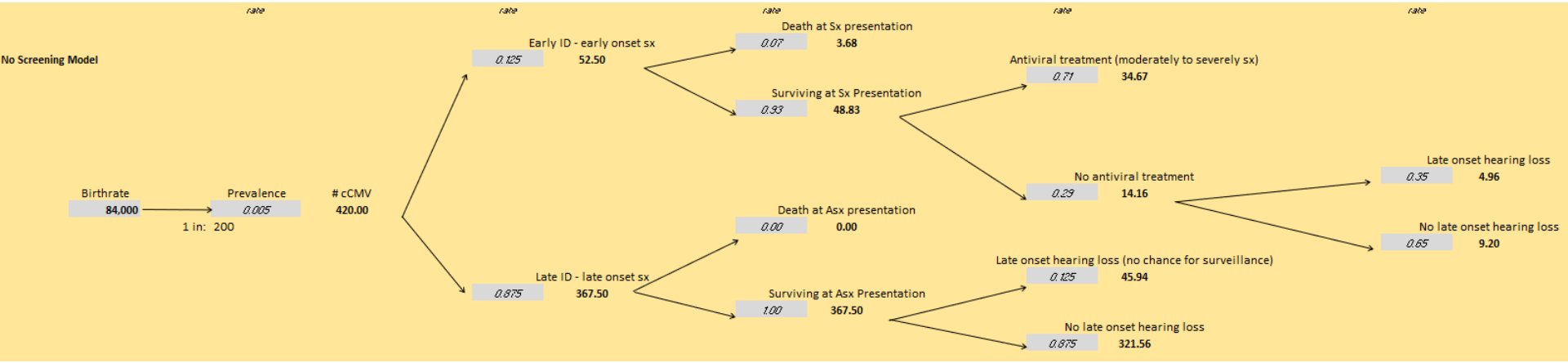
Decision Tree

cCMV does not fit traditional newborn screening (NBS) rationale

- No quantifiable difference in morbidity and mortality at this time
- Antiviral treatment may provide short-term relief, but will not reverse or prevent symptoms

Focus: early identification for infants with asymptomatic cCMV infections for surveillance and early intervention through EHDDI

No Screening Model



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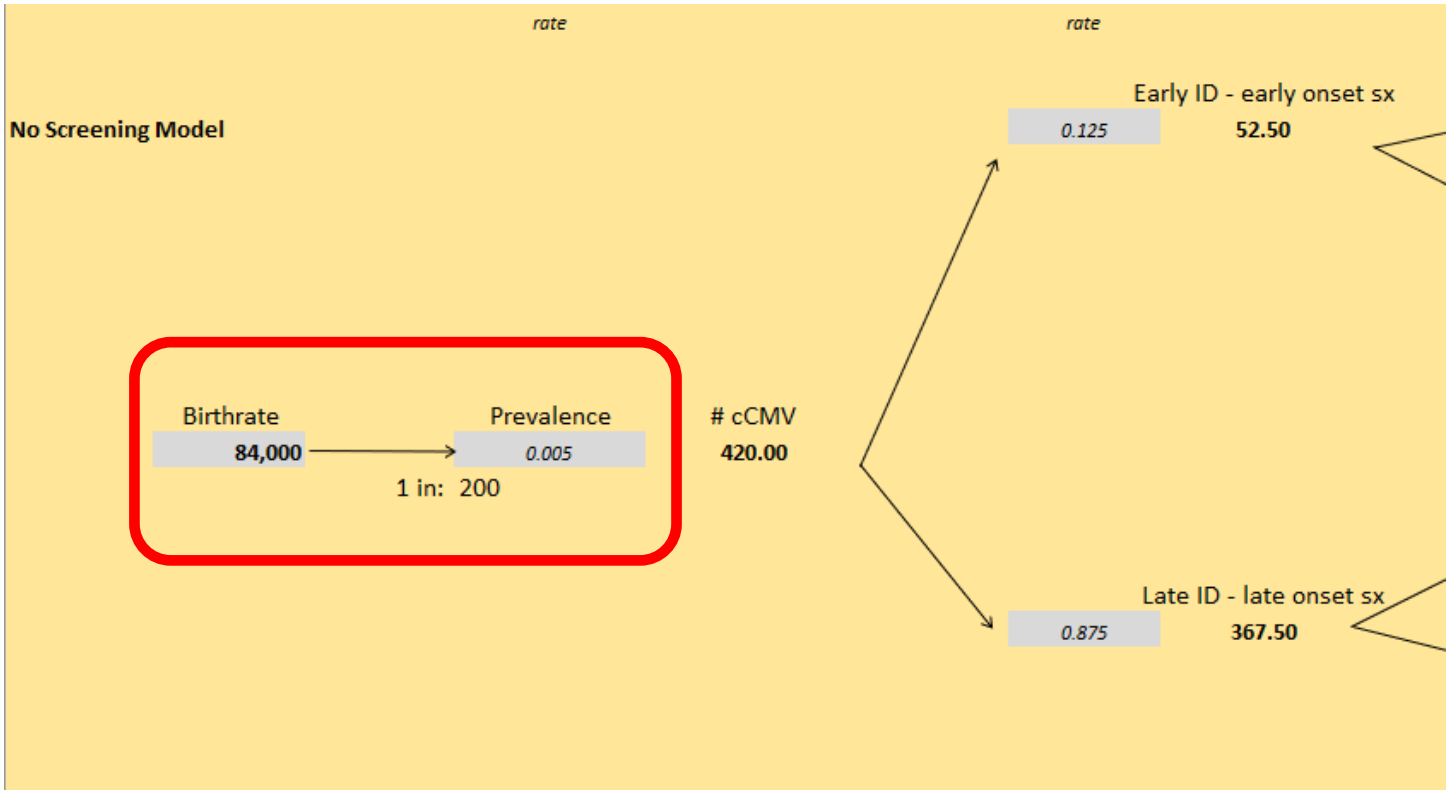

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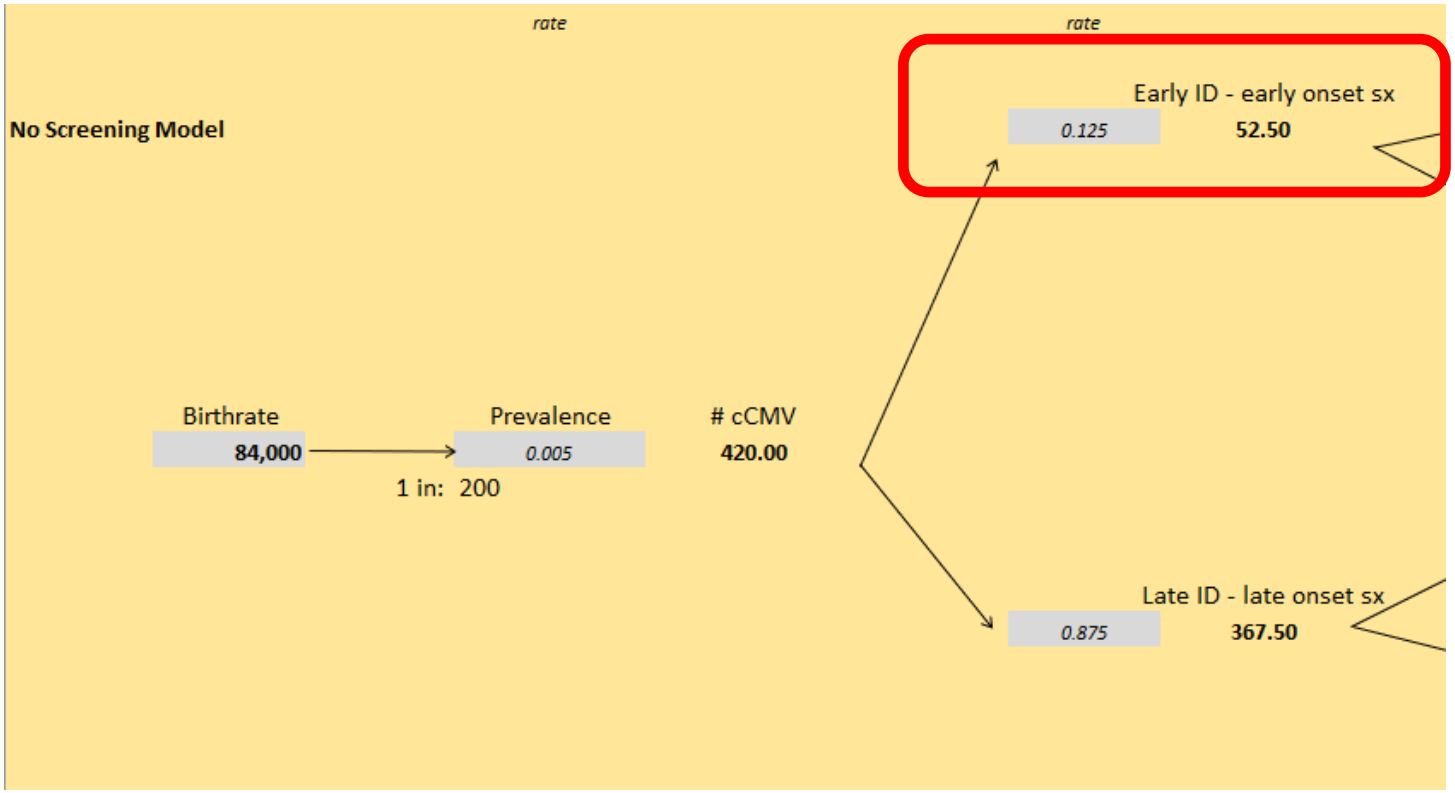

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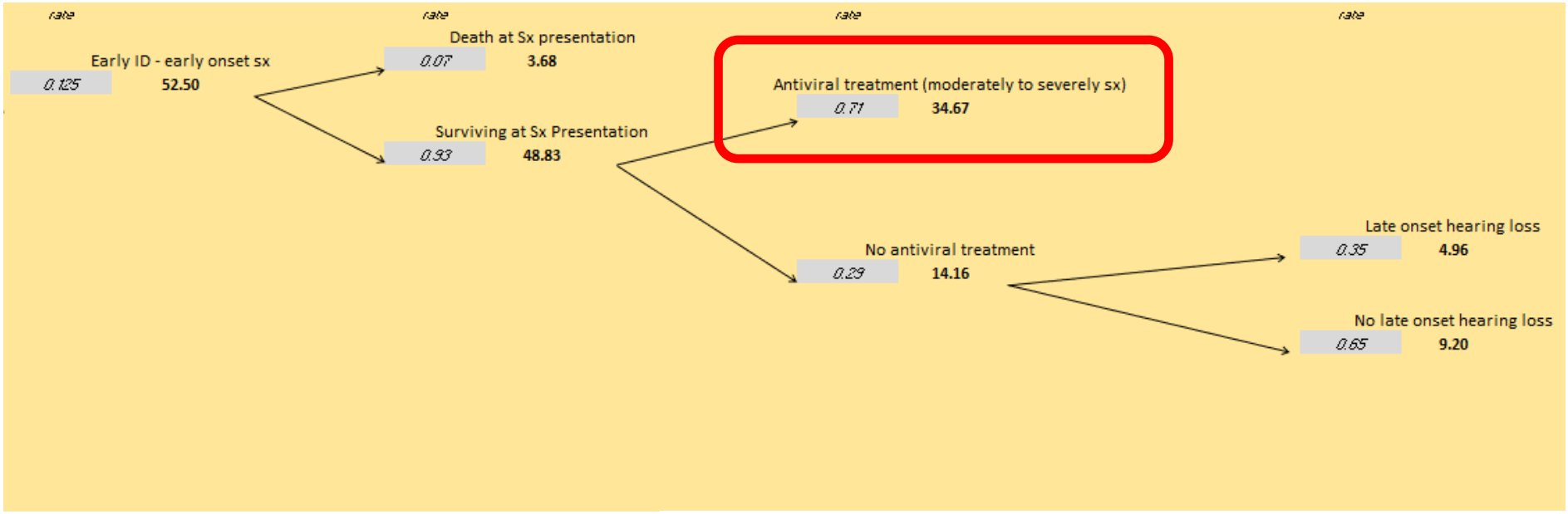

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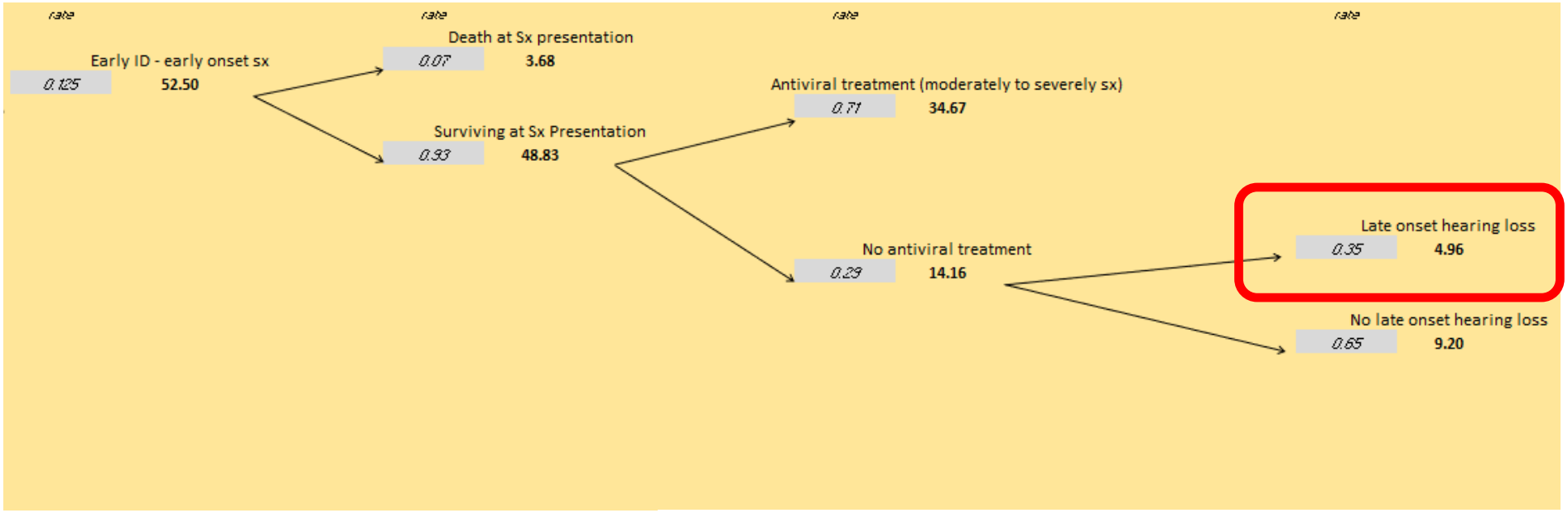

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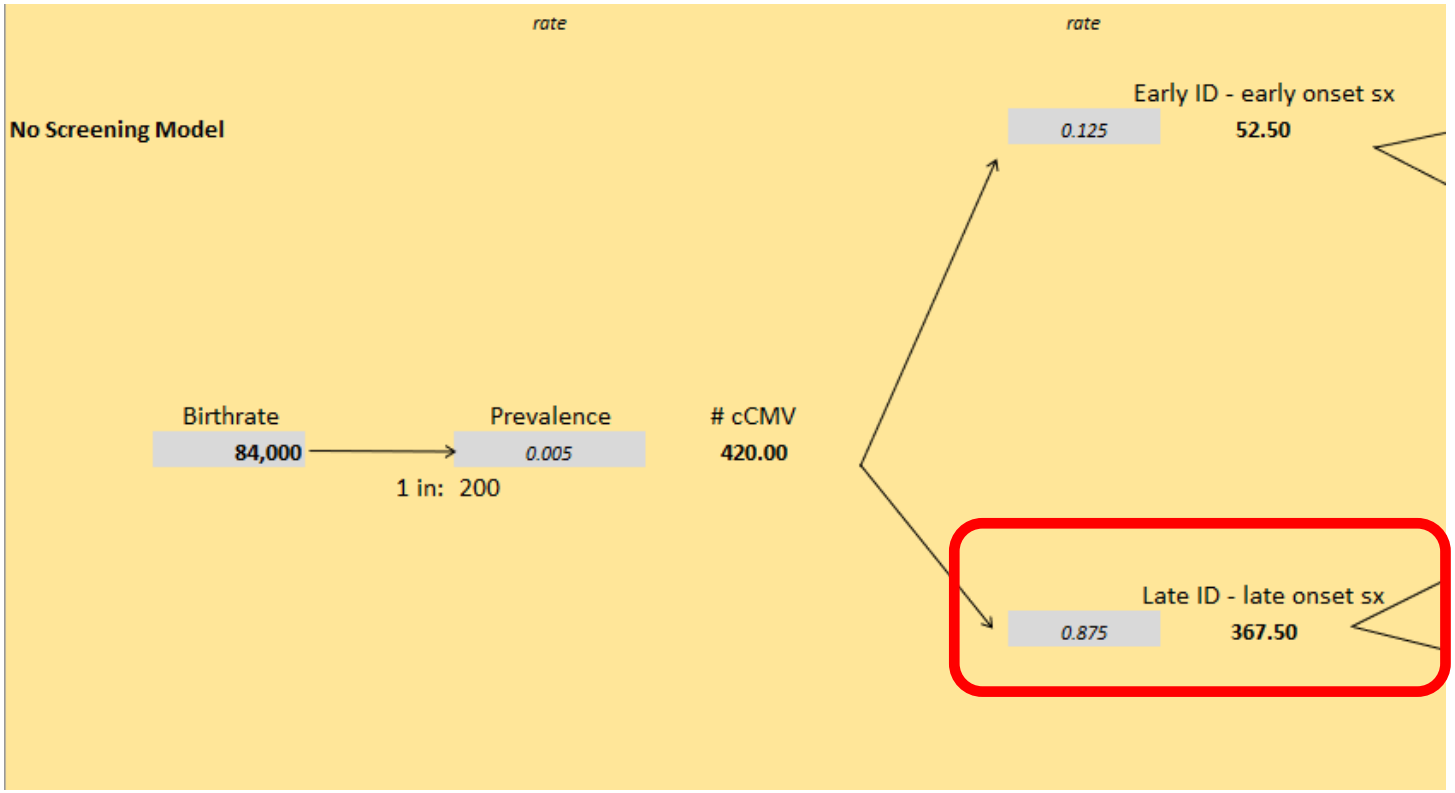

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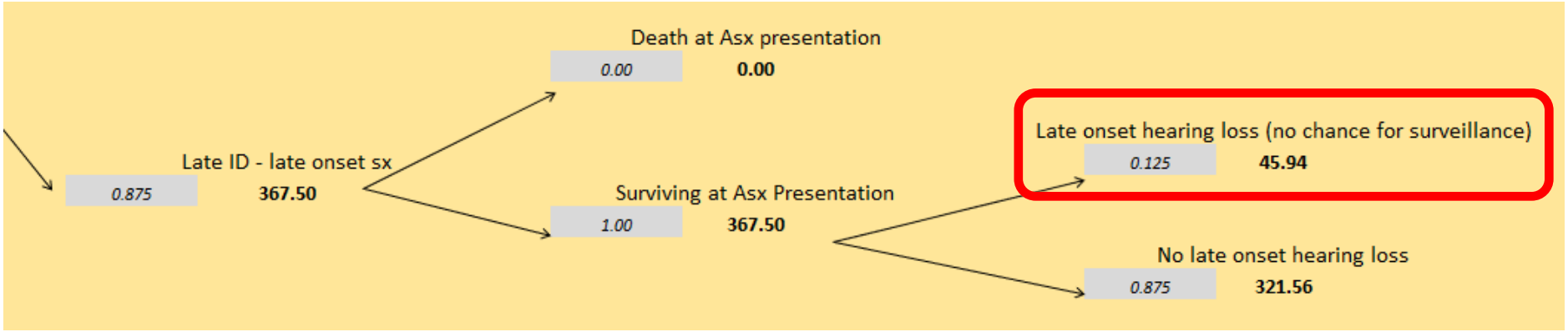
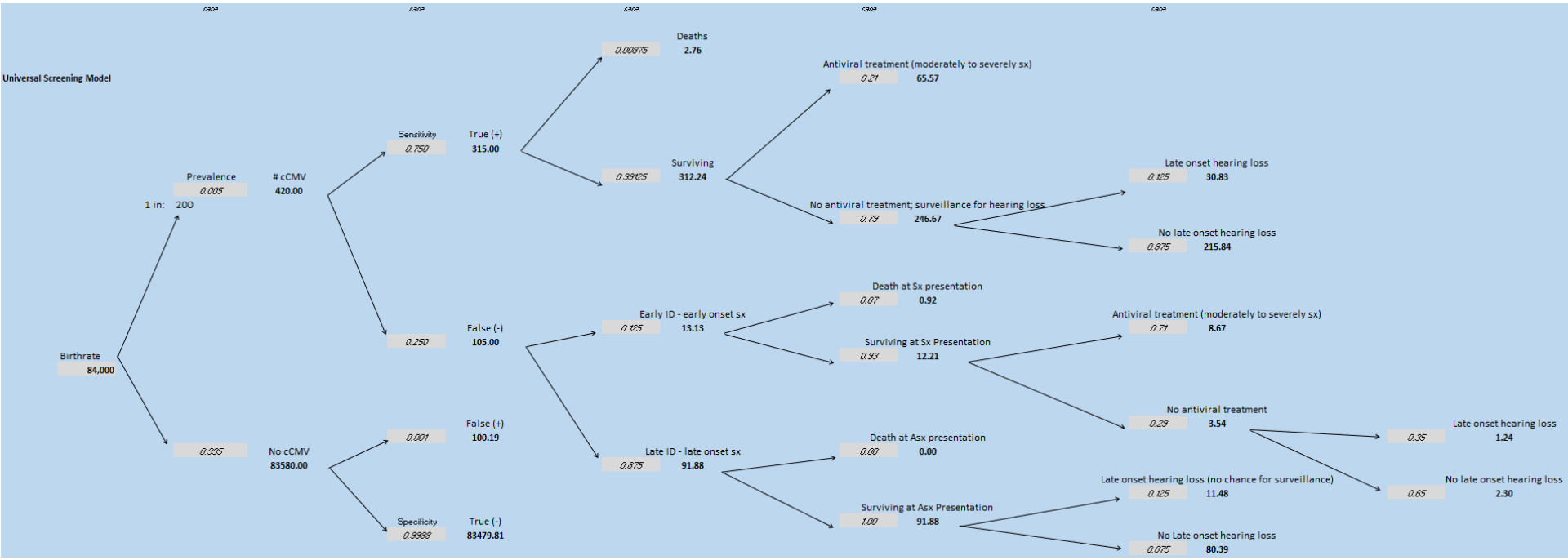
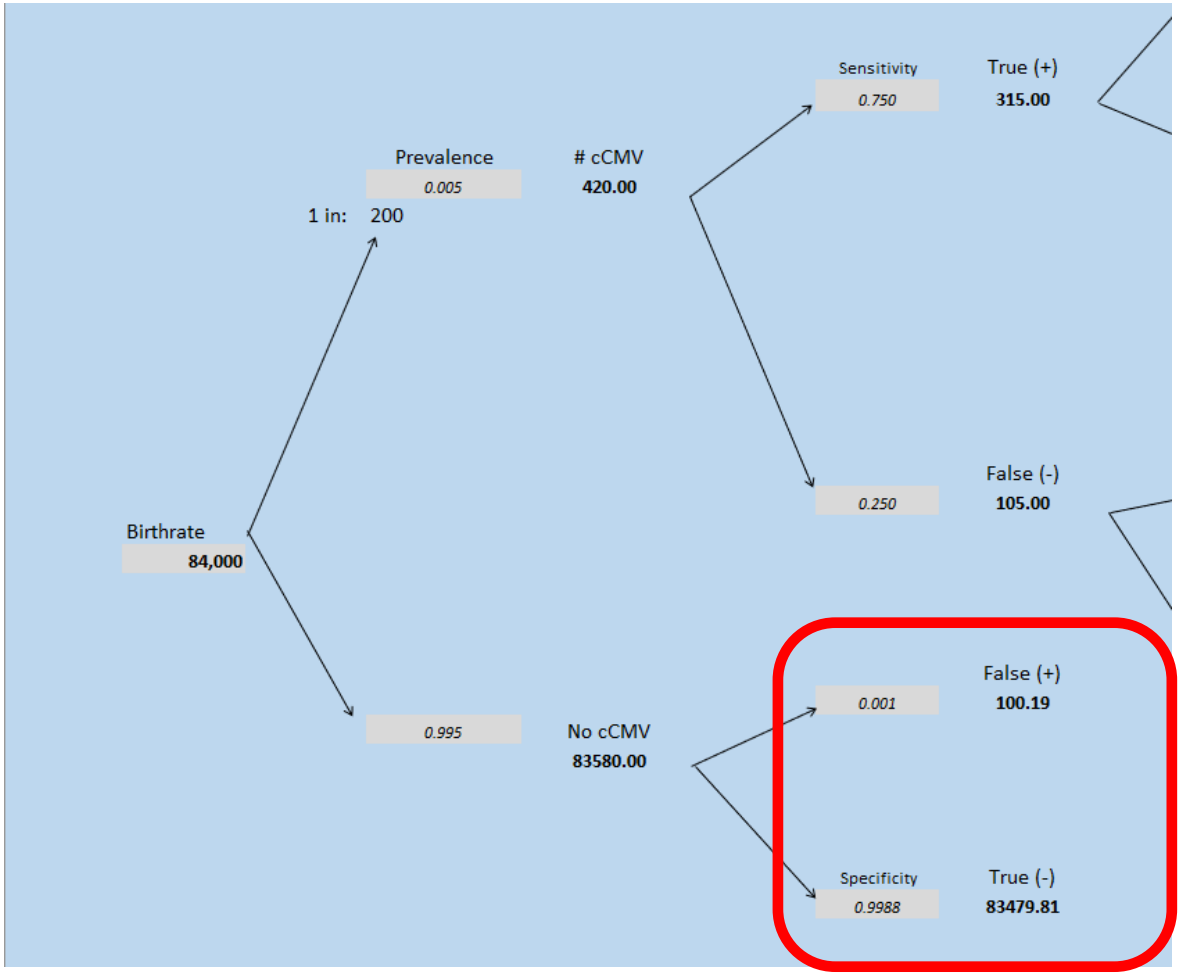


Universal Screening Model



Universal Screening Model



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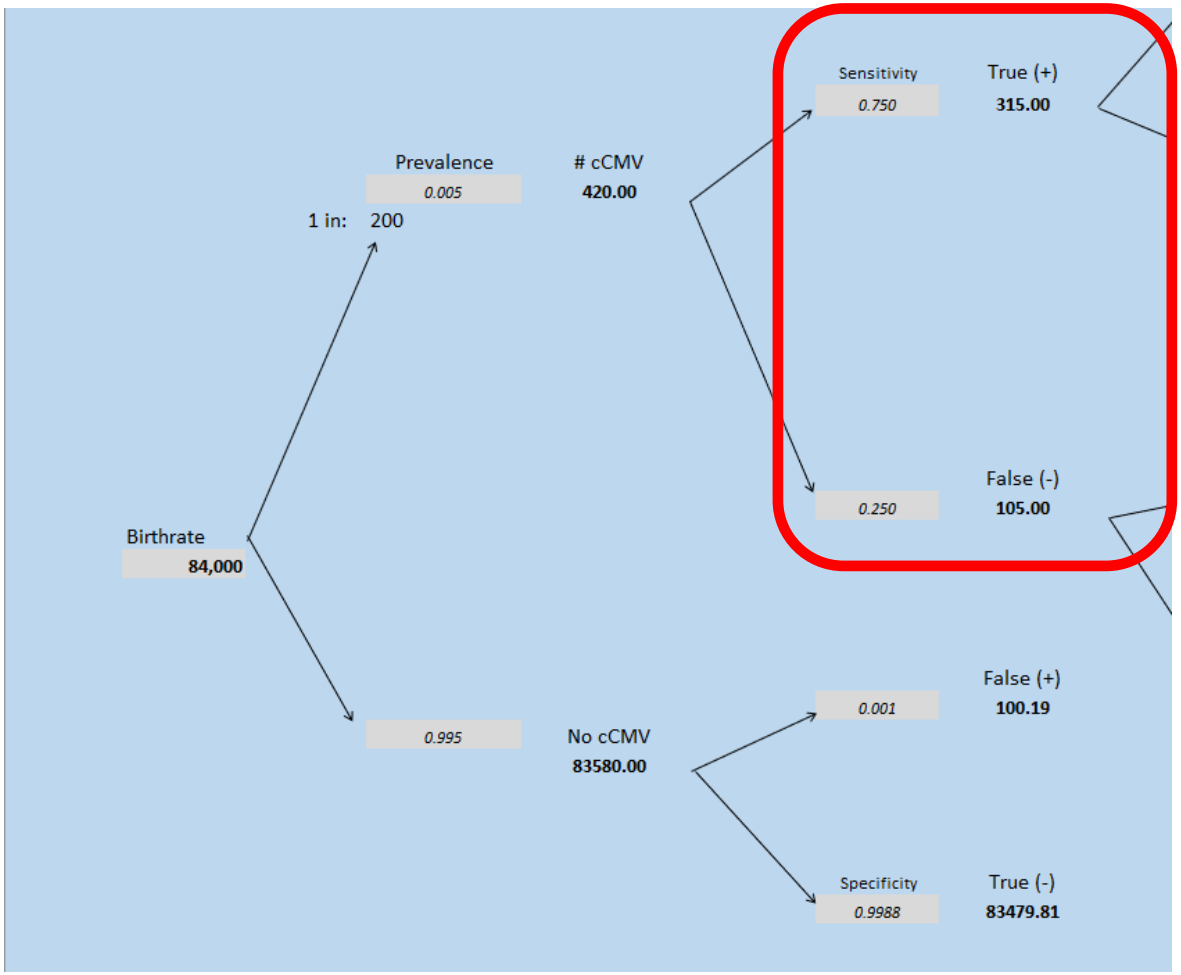

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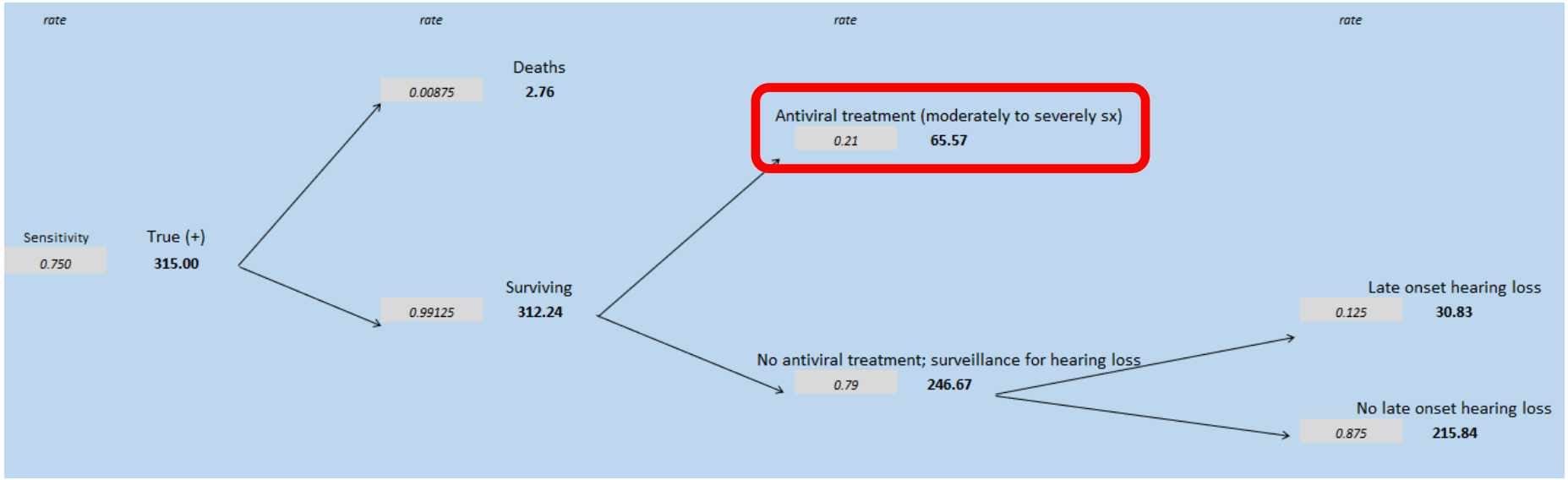

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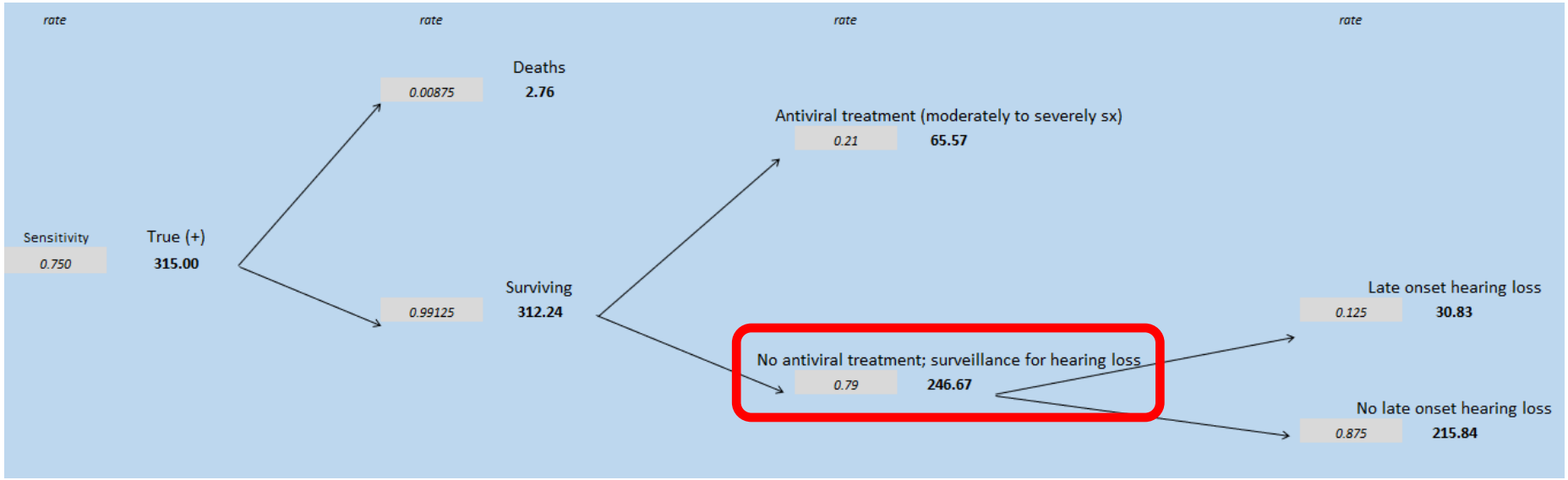

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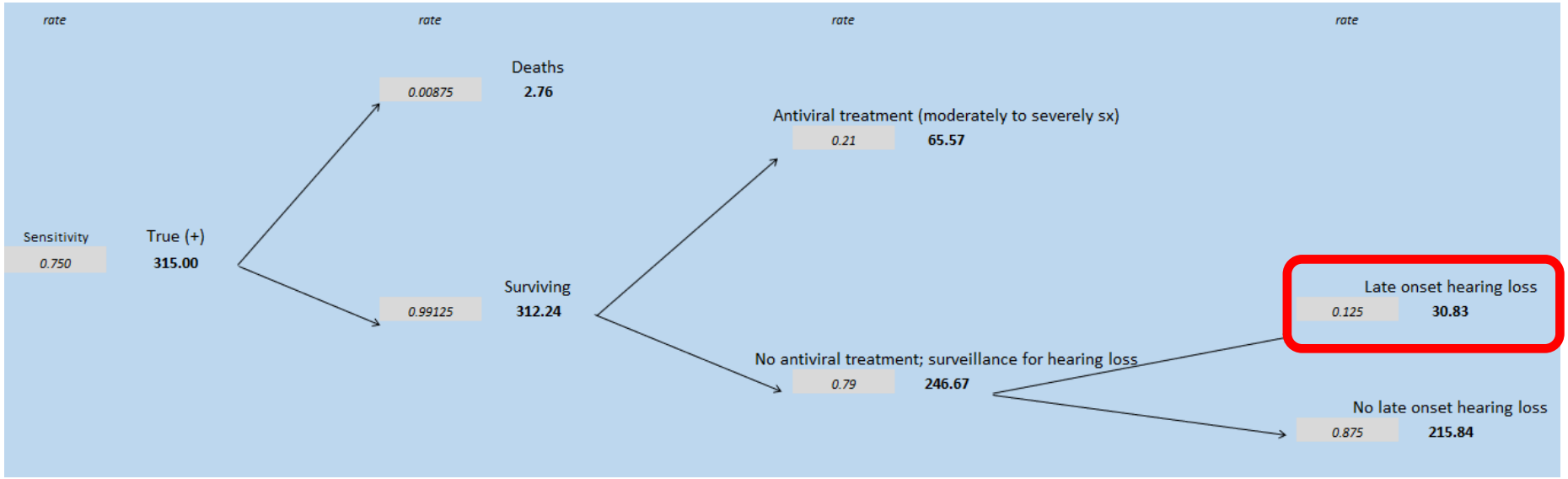

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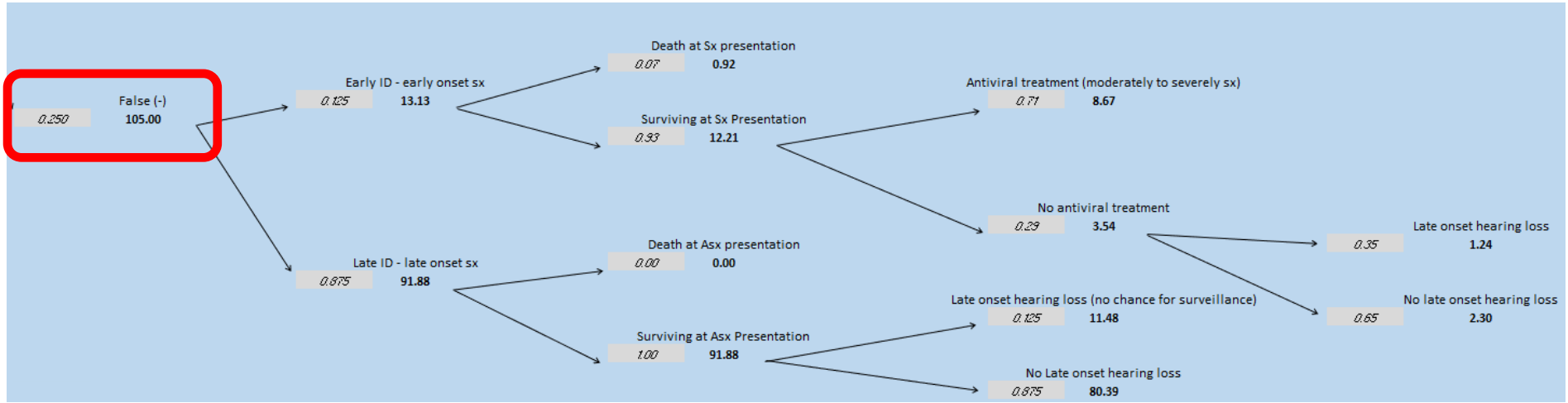
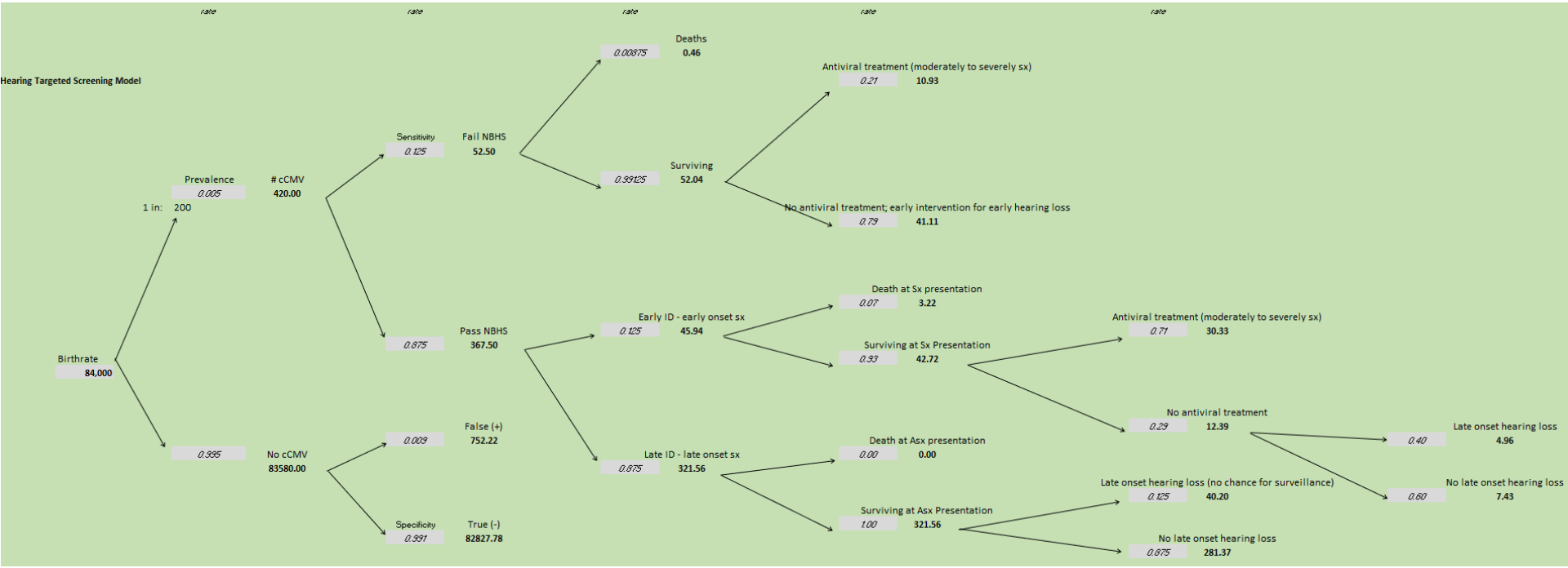


Hearing Targeted Screening Model



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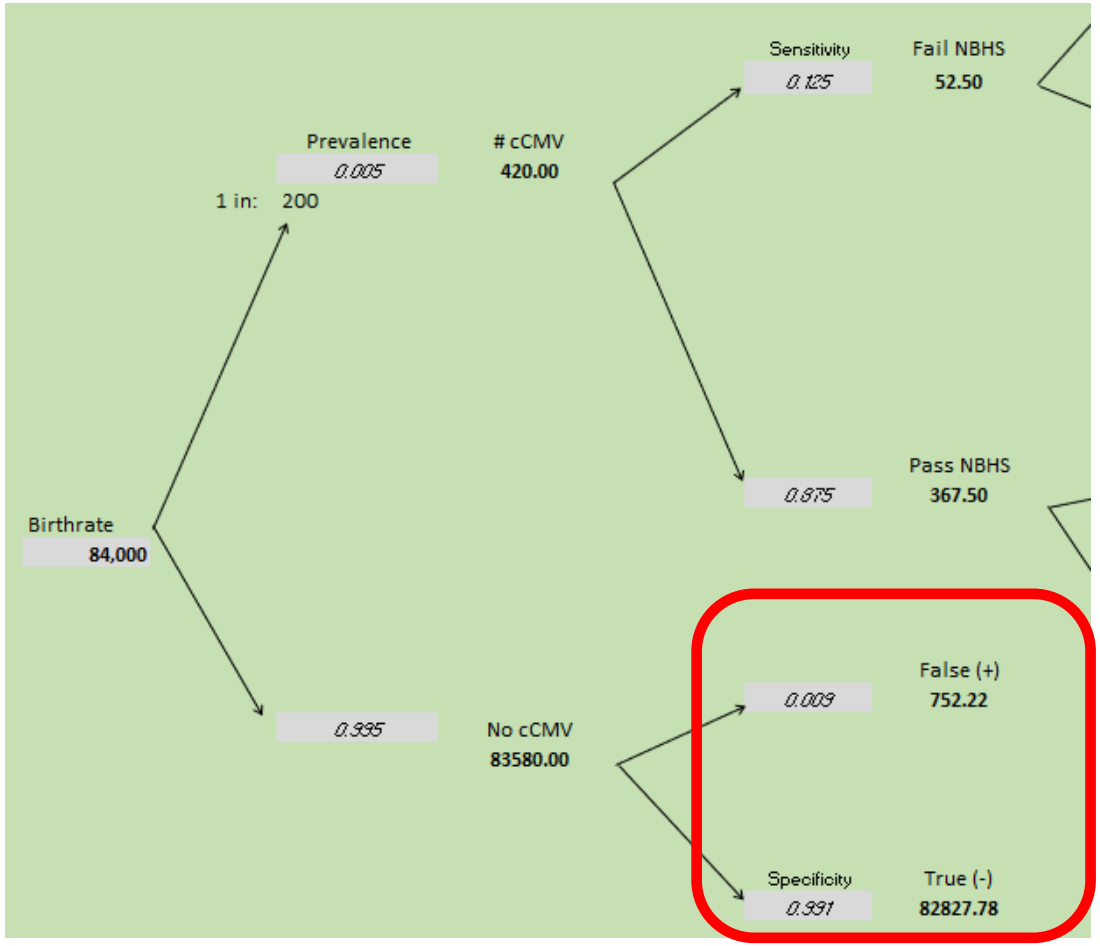

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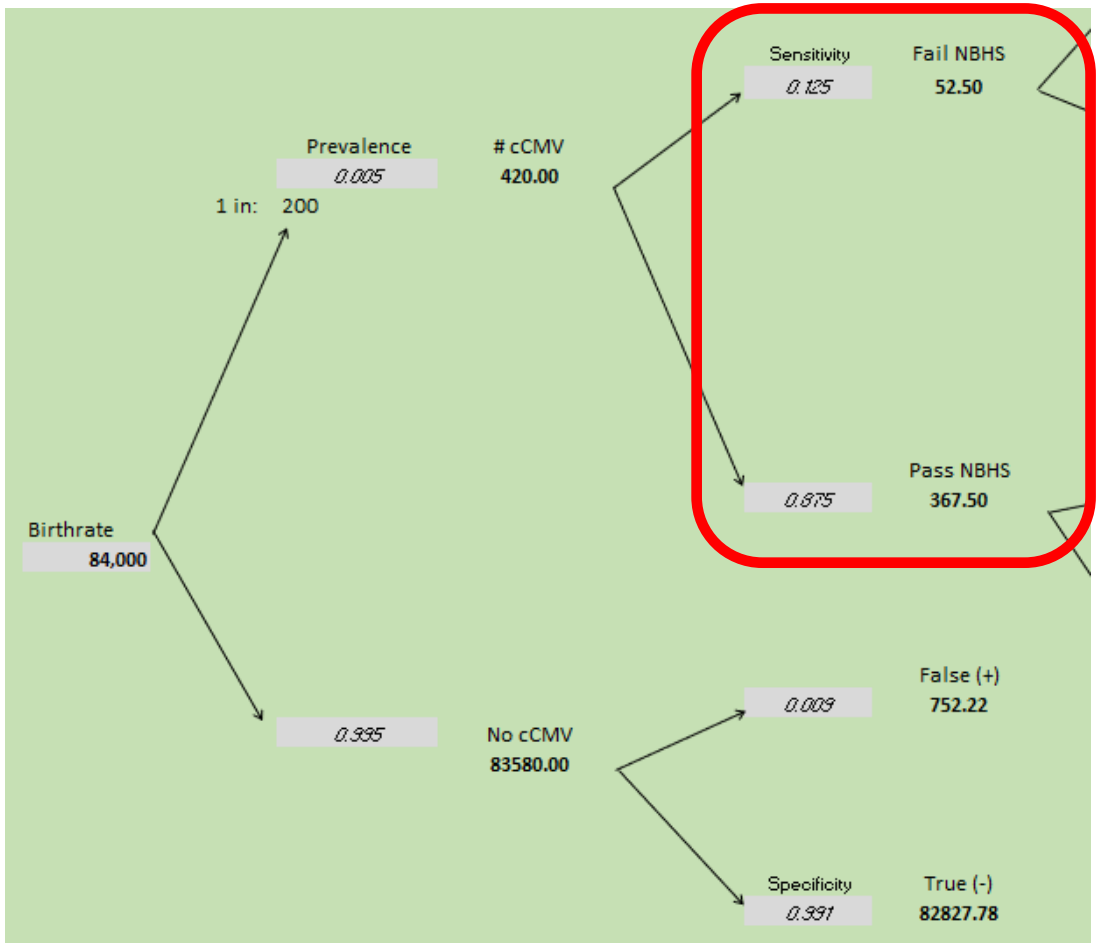

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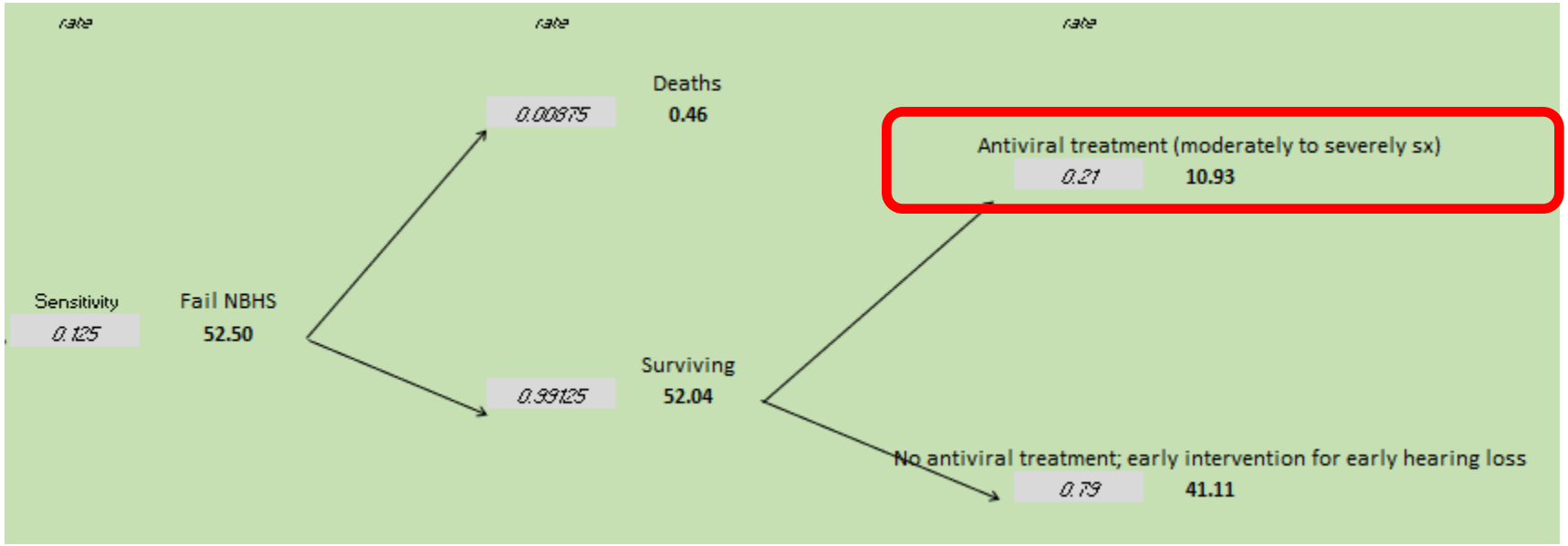

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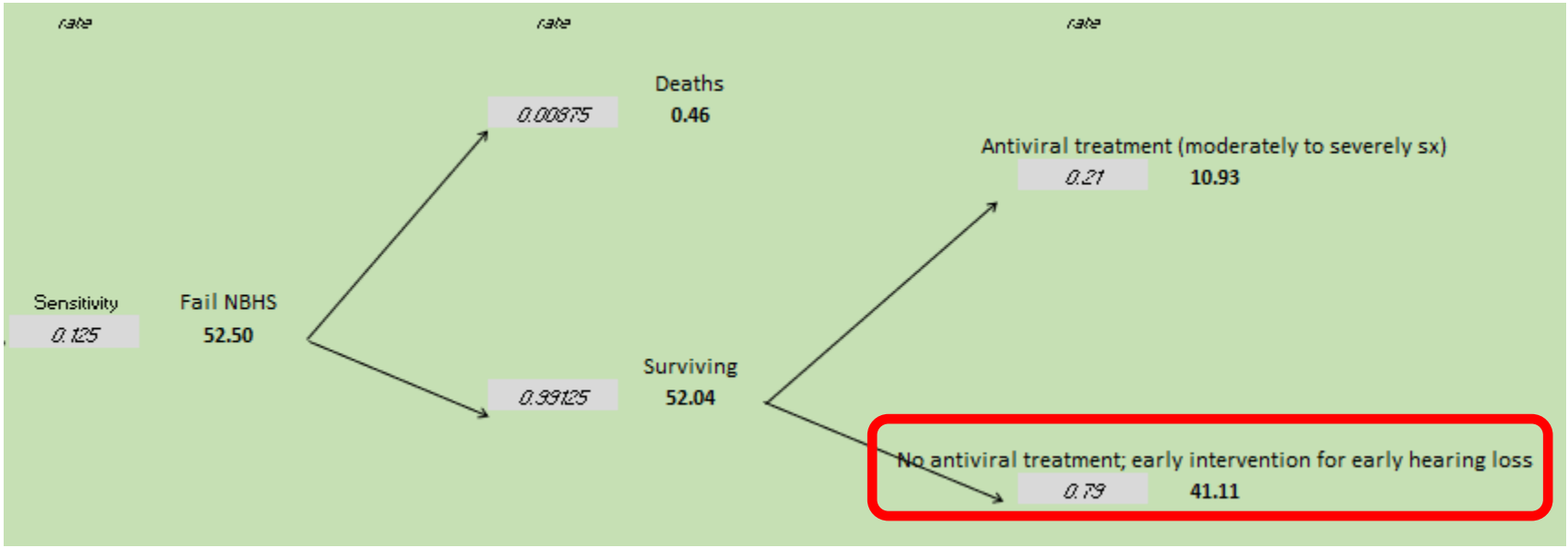

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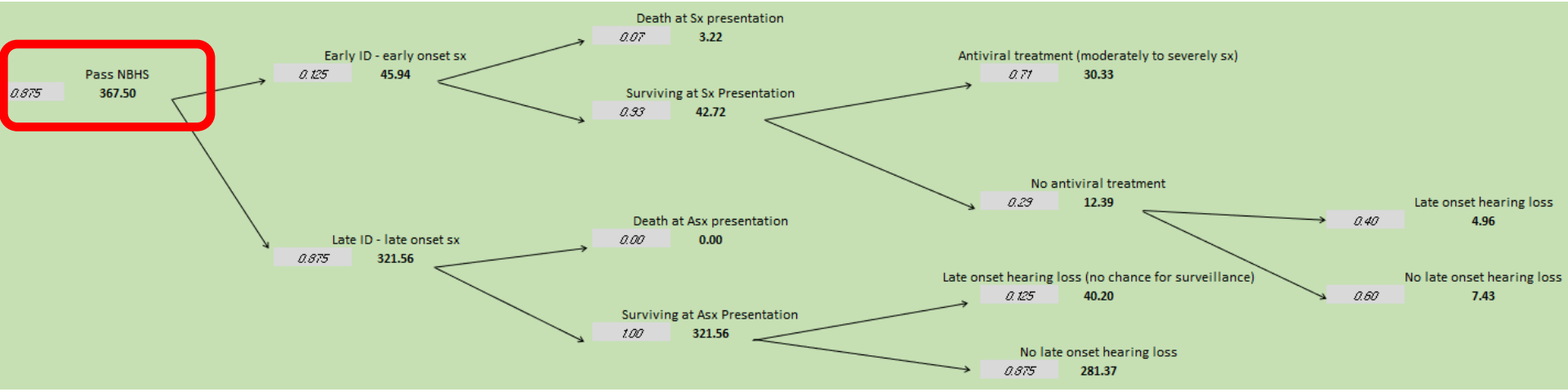


No Screening vs. Universal Screening

No screening	Deaths # of babies with dx testing # of babies treated with antivirals Surviving with LOHL and early intervention Surviving with no HL but 6 years of surveillance
Universal screening	Deaths # of babies with dx testing # of babies treated with antivirals Surviving with LOHL and early intervention Surviving with no HL but 6 years of surveillance

No Screening vs. Universal Screening

No screening	Deaths	3.68
	# of babies with dx testing	52.50
	# of babies treated with antivirals	34.67
	Surviving with LOHL and early intervention	4.96
	Surviving with no HL but 6 years of surveillance	9.20
Universal screening	Deaths	3.68
	# of babies with dx testing	415.19
	# of babies treated with antivirals	74.24
	Surviving with LOHL and early intervention	32.07
	Surviving with no HL but 6 years of surveillance	215.84

No Screening vs. Universal Screening

No screening	Deaths	3.68
	# of babies with dx testing	52.50
	# of babies treated with antivirals	34.67
	Surviving with LOHL and early intervention	4.96
	Surviving with no HL but 6 years of surveillance	9.20
Universal screening	Deaths	3.68
	# of babies with dx testing	415.19
	# of babies treated with antivirals	74.24
	Surviving with LOHL and early intervention	32.07
	Surviving with no HL but 6 years of surveillance	215.84
SHIFT		
	Deaths averted	0.00
	Additional babies with dx testing	362.69
	Additional babies treated with antivirals	39.57
	Additional babies surviving with LOHL and early intervention	27.12
	Surviving with no HL but 6 years of surveillance	206.63

Benefits vs. Costs: Universal Screening

BENEFITS		
	Value per life saved	$11,600,000
	Value per baby with early identification for hearing loss	$44,200
COSTS		
	Cost per baby NBS	$31.10
	Cost per baby diagnostic testing (CMV DNA test)	$487.50
	Cost per baby antiviral treatment	$5,868.61
	Cost per baby surveillance for hearing loss	$1,826.19

Benefits vs. Costs: Universal Screening

BENEFITS				Totals
	Value per life saved	$	11,600,000.00	
	Total value of lives saved			**$0.00**
	Value per baby with early identification for HL	$	44,200.00	
	Total value of LOHL intervention			**$ 1,198,583.21**
	Total benefits			**$1,198,583.21**
COSTS				**Totals**
	Cost per baby NBS	$	31.10	
	Total cost NBS			**$ 2,612,121.22**
	Cost per baby dx testing (CMV DNA test)	$	487.50	
	Total cost dx testing			**$ 176,812.25**
	Cost per baby antiviral treatment	$	5,868.61	
	Total cost antiviral treatment			**$ 232,231.90**
	Cost per baby surveillance for HL	$	1,826.19	
	Total cost surveillance for HL			**$ 426,876.02**
	Total costs			**$ 3,448,041.39**

Benefits vs. Costs: Universal Screening

BENEFITS				Totals
	Value per life saved	$	11,600,000.00	
	Total value of lives saved			**$0.00**
	Value per baby with early identification for HL	$	44,200.00	
	Total value of LOHL intervention			**$ 1,198,583.21**
	Total benefits			**$1,198,583.21**
COSTS				**Totals**
	Cost per baby NBS	$	31.10	
	Total cost NBS			**$ 2,612,121.22**
	Cost per baby dx testing (CMV DNA test)	$	487.50	
	Total cost dx testing			**$ 176,812.25**
	Cost per baby antiviral treatment	$	5,868.61	
	Total cost antiviral treatment			**$ 232,231.90**
	Cost per baby surveillance for HL	$	1,826.19	
	Total cost surveillance for HL			**$ 426,876.02**
	Total costs			**$ 3,448,041.39**

Benefit/Cost ratio = 0.35

Net benefit = -$2,249,458.18

No Screening vs. Targeted Screening

No screening	Deaths # of babies with dx testing # of babies treated with antivirals Surviving with LOHL and early intervention Surviving with no HL but 6 years of surveillance
Targeted screening	Deaths # of babies with dx testing # of babies treated with antivirals Surviving with LOHL and early intervention

No Screening vs. Targeted Screening

No screening	Deaths	3.68
	# of babies with dx testing	52.50
	# of babies treated with antivirals	34.67
	Surviving with LOHL and early intervention	4.96
	Surviving with no HL but 6 years of surveillance	9.20
Targeted screening	Deaths	3.68
	# of babies with dx testing	804.72
	# of babies treated with antivirals	41.26
	Surviving with LOHL and early intervention	4.96

No Screening vs. Targeted Screening

No screening	Deaths	3.68
	# of babies with dx testing	52.50
	# of babies treated with antivirals	34.67
	Surviving with LOHL and early intervention	4.96
	Surviving with no HL but 6 years of surveillance	9.20
Targeted screening	Deaths	3.68
	# of babies with dx testing	804.72
	# of babies treated with antivirals	41.26
	Surviving with LOHL and early intervention	4.96
SHIFT		
	Deaths averted	0.00
	Additional babies with dx testing	752.22
	Additional babies treated with antivirals	6.60
	Additional babies surviving with LOHL and early intervention	0.00

Benefits vs. Costs: Targeted Screening

BENEFITS		
	Value per life saved	$11,600,000
	Value per baby with early identification for HL	$44,200
COSTS		
	Cost per baby NBS	$4.03
	Cost per baby dx testing (CMV DNA test)	$487.50
	Cost per baby antiviral treatment	$5,868.61
	Cost per baby surveillance for HL	$1,826.19

Benefits vs. Costs: Targeted Screening

BENEFITS			Totals
	Value per life saved	$ 11,600,000.00	
	Total value of lives saved		$0.00
	Value per baby with early identification for HL	$ 44,200.00	
	Total value of LOHL intervention		$0.00
	Total benefits		$0.00

COSTS			Totals
	Cost per baby NBS	$ 4.03	
	Total cost NBS		$ 338,707.97
	Cost per baby dx testing (CMV DNA test)	$ 487.50	
	Total cost dx testing		$ 366,707.25
	Cost per baby antiviral treatment	$ 5,868.61	
	Total cost antiviral treatment		$ 38,705.32
	Cost per baby surveillance for HL	$ 1,826.19	
	Total cost surveillance for HL		$0.00
	Total costs		$ 744,120.53

Benefits vs. Costs: Targeted Screening

BENEFITS			Totals
	Value per life saved	$ 11,600,000.00	
	Total value of lives saved		$0.00
	Value per baby with early identification for HL	$ 44,200.00	
	Total value of LOHL intervention		$0.00
	Total benefits		$0.00

COSTS			Totals
	Cost per baby NBS	$ 4.03	
	Total cost NBS		$ 338,707.97
	Cost per baby dx testing (CMV DNA test)	$ 487.50	
	Total cost dx testing		$ 366,707.25
	Cost per baby antiviral treatment	$ 5,868.61	
	Total cost antiviral treatment		$ 38,705.32
	Cost per baby surveillance for HL	$ 1,826.19	
	Total cost surveillance for HL		$0.00
	Total costs		$ 744,120.53

Benefit/Cost ratio = 0.00 **Net benefit = -$744,120.53**

Parameters

Parameter	Base
birthrate	84,000
birth prevalence	1:200
sensitivity	75.00%
specificity	99.88%
cost of universal NBS	$31.10
cost of diagnostic test	$487.50
cost antiviral treatment	$5,868.61
cost surveillance for hearing loss	$1,826.19
% surviving with antiviral treatment	21.00%
% asymptomatic with late onset hearing loss	12.50%
value per baby with early intervention for late onset hearing loss	$44,200.00

Parameters

Parameter	Base
birthrate	84,000
birth prevalence	1:200
sensitivity	75.00%
specificity	99.88%
cost of universal NBS	$31.10
cost of diagnostic test	$487.50
cost antiviral treatment	$5,868.61
cost surveillance for hearing loss	$1,826.19
% surviving with antiviral treatment	21.00%
% asymptomatic with late onset hearing loss	12.50%
value per baby with early intervention for late onset hearing loss	$44,200.00

Intangible Benefits and Costs

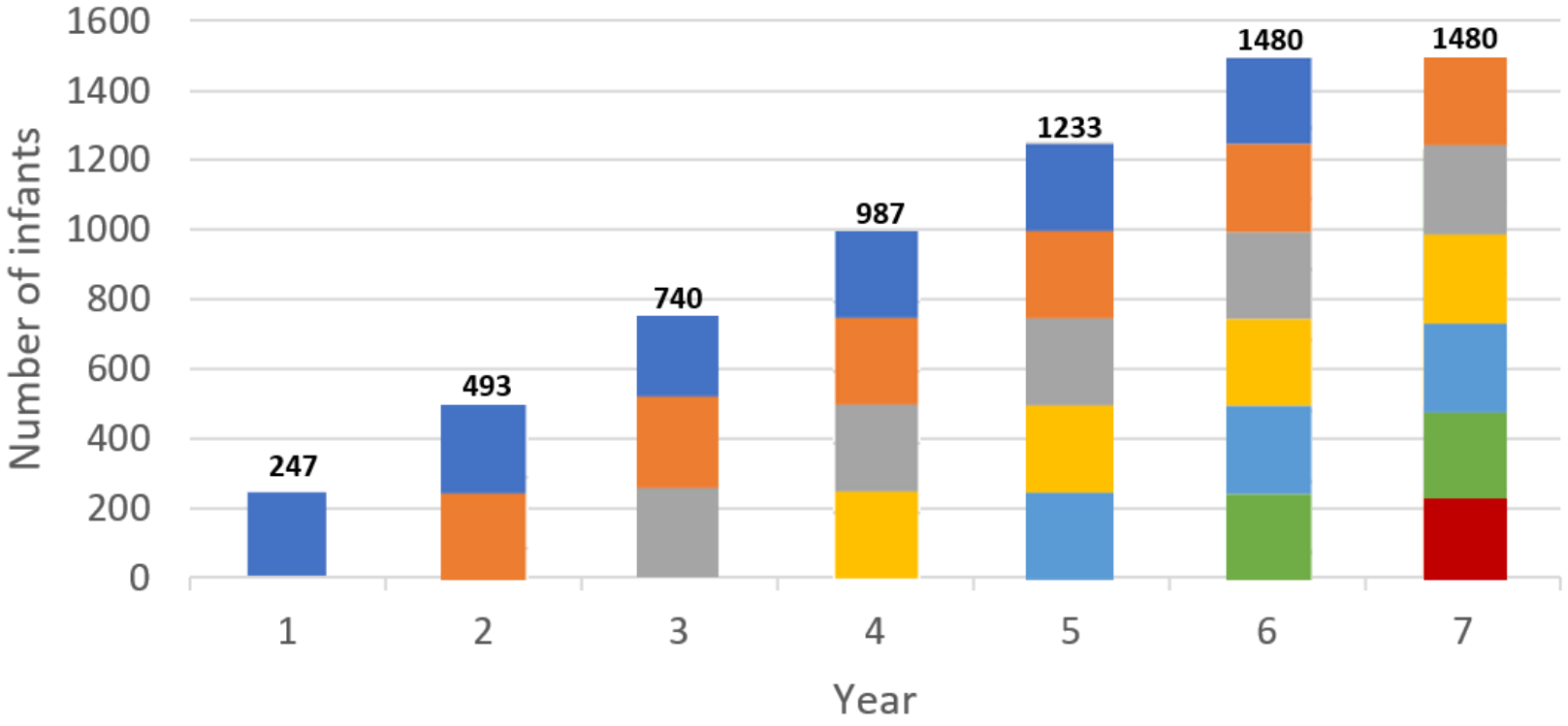
Emotional impact on individuals and families

Surveillance for Hearing Loss

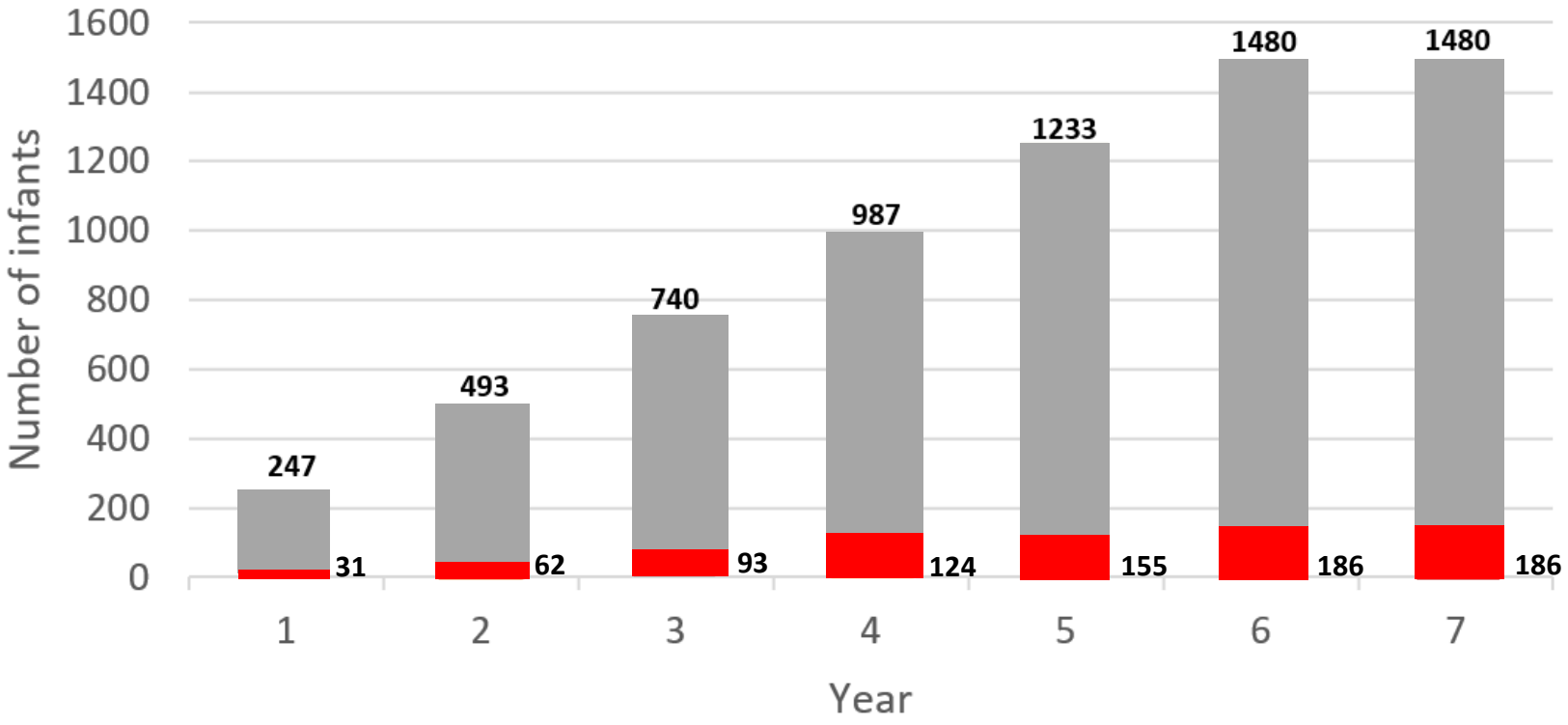
months of age	3	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60	66	72
ABR	X																	
OAEs	X	X	X	X	X	X	X	X	X	X	X	X	X					
Tympanometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VRA		X	X	X	X	X	X											
Condition play audiometry								X	X	X	X	X	X					
Select picture								X	X	X	X	X	X					
Standard audiometry														X	X	X	X	X
Pediatric speech testing														X	X	X	X	X

Based on Utah's EHDI hearing assessment schedule

Surveilling cCMV Positive Infants for Hearing Loss



cCMV Positive Infants Who Develop Late Onset Hearing Loss



Intangible Benefits and Costs

Emotional impact on individuals and families

- 31 infants benefit from surveillance and early identification
- 216 infants will go through surveillance and not receive benefits from early identification

Intangible Benefits and Costs

Emotional impact on individuals and families

- 31 infants benefit from surveillance and early identification
- 216 infants will go through surveillance and not receive benefits from early identification

Wages lost for parents and families

Intangible Benefits and Costs

Emotional impact on individuals and families

- 31 infants benefit from surveillance and early identification
- 216 infants will go through surveillance and not receive benefits from early identification

Wages lost for parents and families

CMV infections prevented from prenatal education and outreach

Acknowledgements

Advocates

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- Gail Demmler-Harrison
- Mallory Baker
- Marcie Rider
- Karin Neidt

Newborn Screening

- Ontario: Lauren Gallagher, Jessica Dunn
- Idaho: KD Carlson, Claudia Coatney
- Utah: Stephanie Mcvicar
- Minnesota: Jill Simonetti

Questions?

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Sensitivity Analysis

			B/C ratio		
	B/C ratio swing low		0.35		B/C ratio swing high
		low	base	high	
birthrate	0.35	73,000	84,000	95,000	0.35
birth prevalence - 1 in:	0.29	250	200	71	0.69
sensitivity	0.34	73.20%	75.00%	85.70%	0.38
specificity	0.34	99.76%	99.88%	100.00%	0.35
cost of universal NBS	0.56	$15.55	$31.10	$46.65	0.25
cost of dx test	0.36	$243.75	$487.50	$4,875.00	0.24
cost antiviral tx	0.36	$2,934.31	$5,868.61	$58,686.10	0.22
cost surveillance for HL	0.37	$792.89	$1,826.19	$2,516.07	0.33
% surviving with antiviral tx	0.42	10.50%	21.00%	42.00%	0.23
% asx with LOHL	0.15	6.25%	12.50%	25.00%	0.74
value per baby with EI for LOHL	0.17	$22,100.00	$44,200.00	$88,400.00	0.70