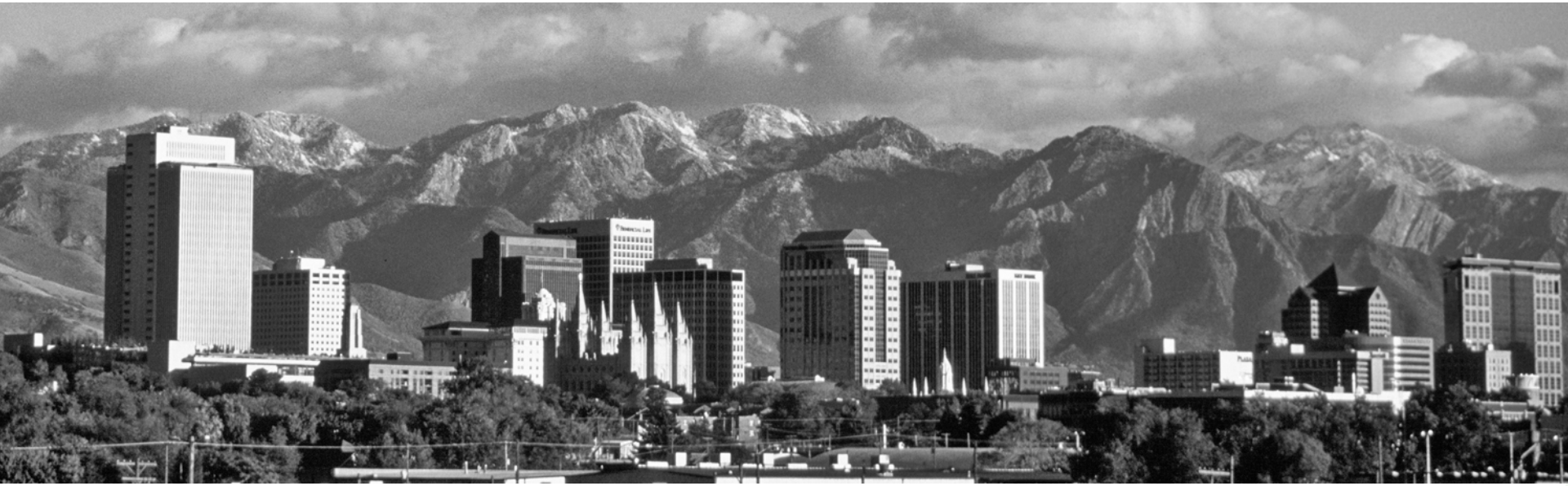
CMV Conference 2014

Salt Lake City Utah

September 26-27

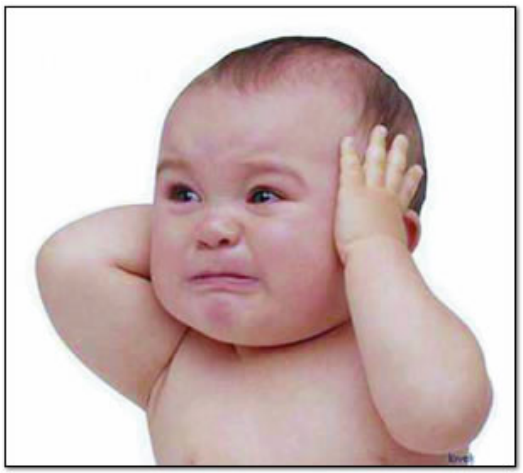


CYTOMEGALOVIRUS
PUBLIC HEALTH & POLICY
CONFERENCE

Plenary V: Is Newborn Screening for Congenital Cytomegalovirus Good Public Health Policy?

Prof Bill Rawlinson
w.rawlinson@unsw.edu.au

Utah September 2014



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INSTRUCTIONS

Considering the Wilson and Jungner 1968 criteria for when screening should be done, summarize recommendations whether newborn screening for congenital CMV should be done for all newborns.

If yes, how should it be done?

If no, why not?

In either case, what additional research/ information is needed to facilitate effective screening?

FURTHER INSTRUCTIONS

KEEP TO 7 MINUTES

Or else

OUTLINE

1. Neonatal screening congenital CMV?
   - Why do it?
   - Ways to screen neonates
2. Benefits and problems
3. A way forward
   - Directed vs universal
   - Additional research

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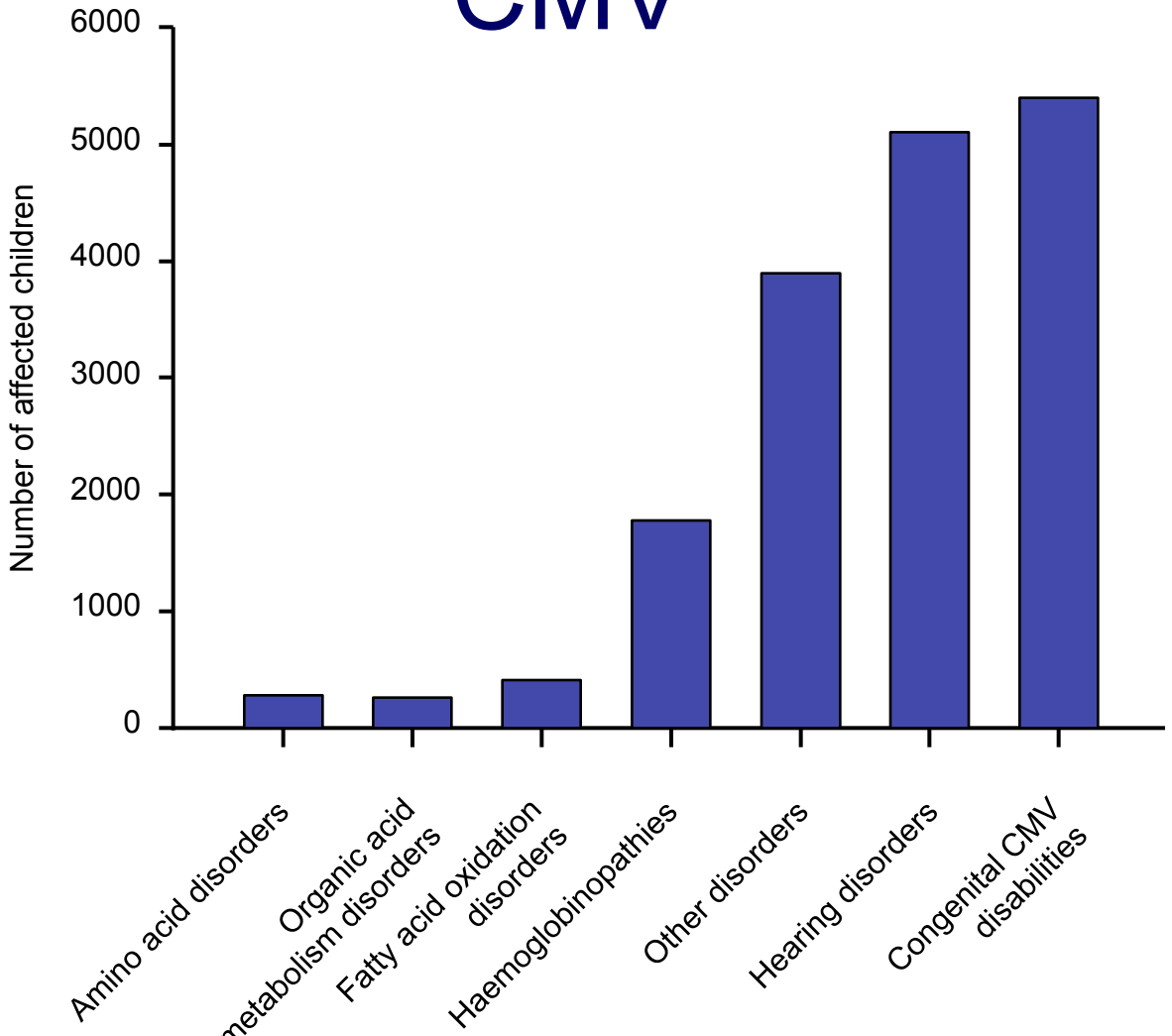
Annual incidence of conditions screened compared with congenital CMV



Cannon, 2014

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SCREENING

- Procedure to identify, in an organised way, a specified disease or condition among asymptomatic individuals [Peters 1996]
- Application of a test to people who are as yet asymptomatic for the purpose of classifying them with respect to their likelihood of having a particular disease [Hennekens 1987]
- Presumptive identification of unrecognised disease or defects by means of tests, other procedures that can be applied rapidly, to identify pre disease, early disease, risk markers [WHO]

Potential testing algorithms

- Test at risk populations
  - Hearing loss on UNHS
  - Primary infections
  - Symptomatic women
  - Symptomatic infants preterm, IUGR, CP
- Screen all neonates

Potential testing algorithms

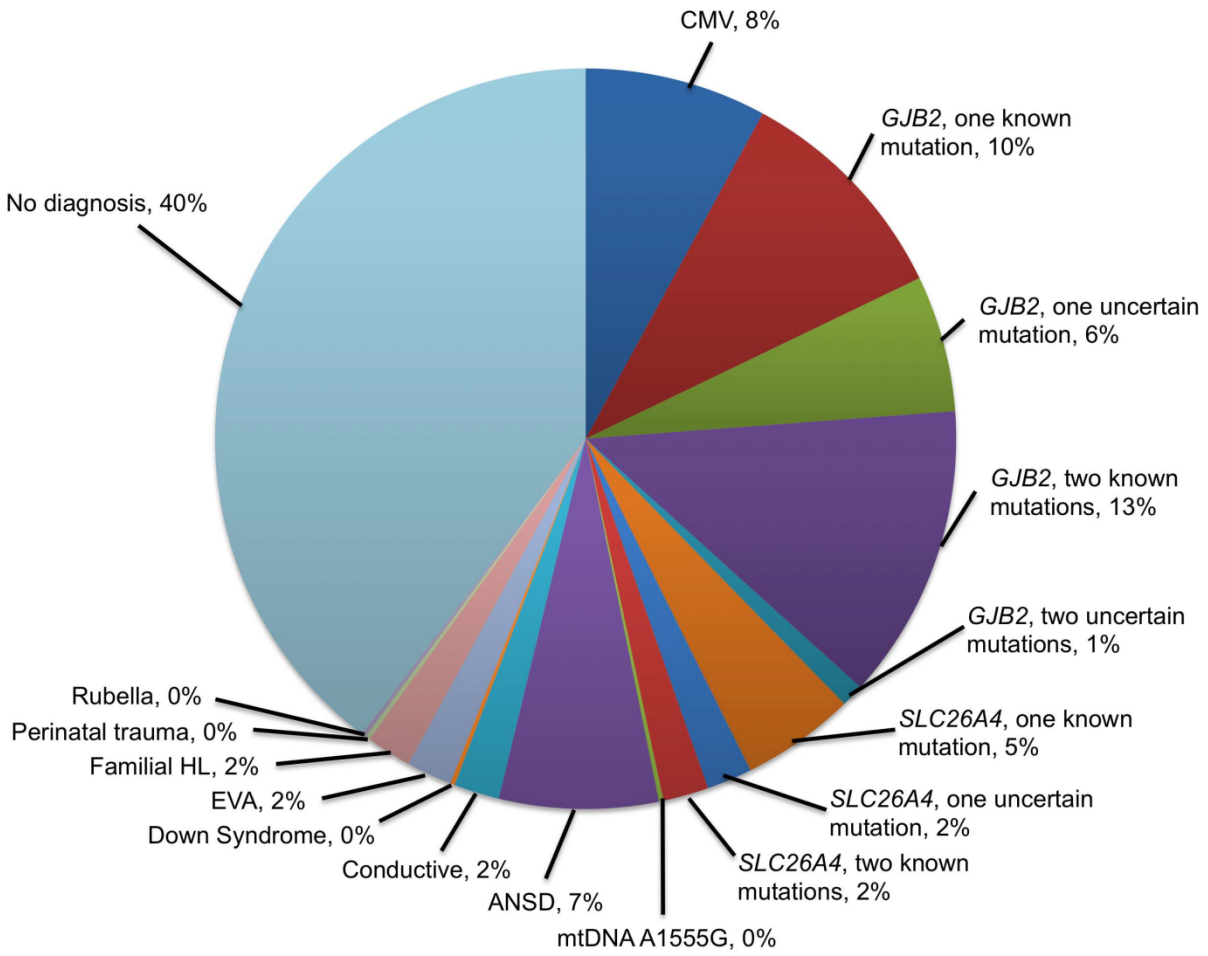
- Test at risk populations
  - Hearing loss on UNHS
  - Primary infections
  - Symptomatic women
  - Symptomatic infants preterm, IUGR, CP

- Some evidence for most groups

Potential testing algorithms

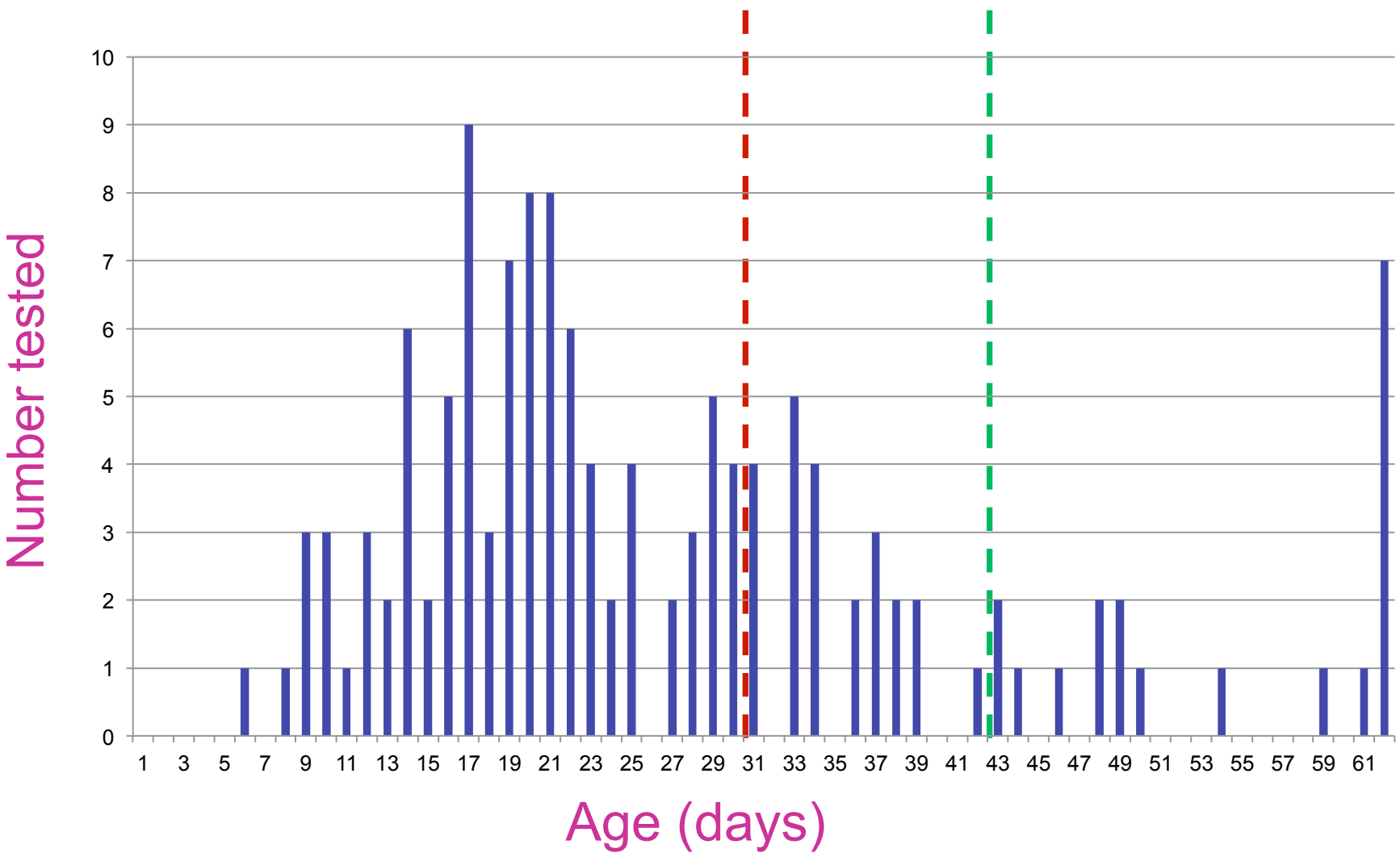
- Test at risk populations
  - Hearing loss on UNHS
  - Primary infections
  - Symptomatic women
- Issues
  - 7.2% cCMV (9/125), 8% [Dahl 2013]
  - Test <21 dys difficult
  - Sample urine + saliva

Hearing loss aetiology



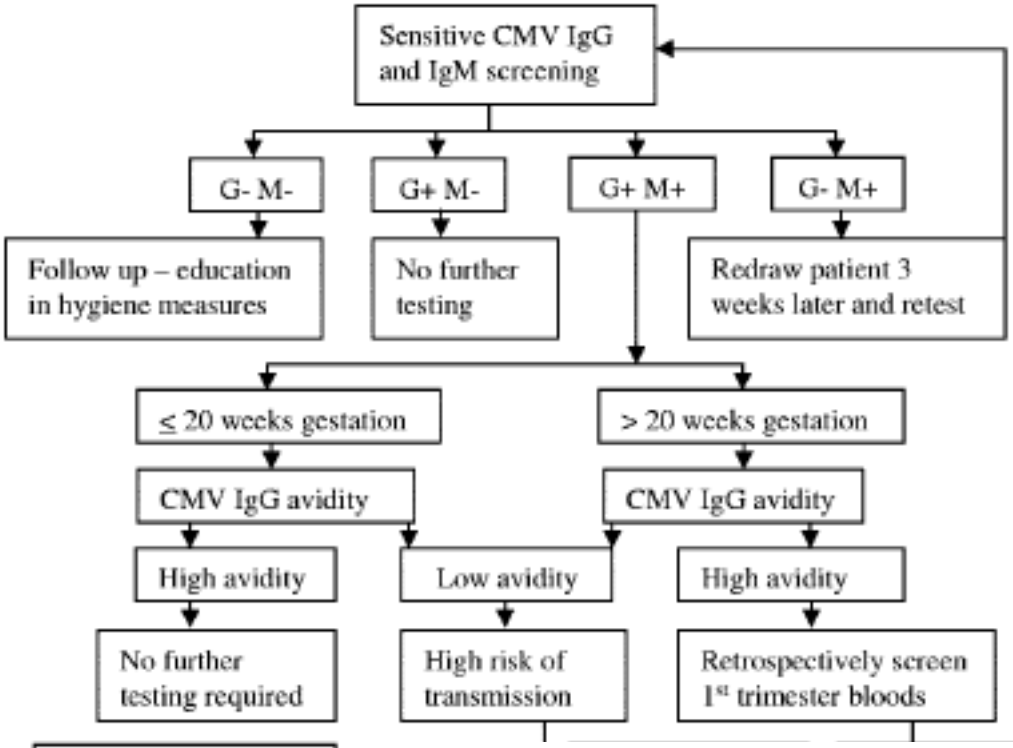
Dahl 2013

Testing abnormal UNHS

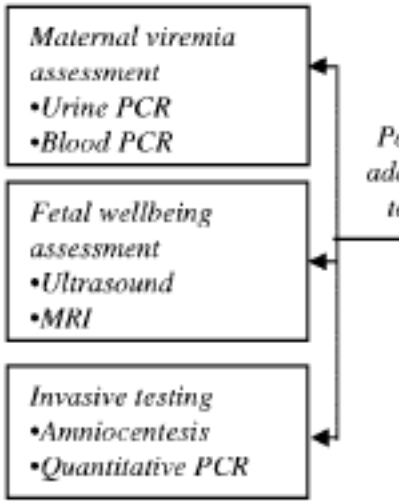


Potential testing algorithms

- Test at risk populations
  - Hearing loss on UNHS
  - Primary infections
  - Symptomatic women
- Issues
  - Identification serologically



SCREENING ALGORITHM



CMV immunoglobulin status			No. of women at:		Total no. of women examined
IgG	IgM	IgG avidity	≤20 weeks gestation	>20 weeks gestation	
−	−	ND	169	90	259
+	−	ND	202	106	308
+	+	Low	5	2	7
+	+	High	20	6	26

[a] +, positive; −, negative; ND, not done; low, <35%; high, ≥35%.

Potential testing algorithms

- Test at risk populations
  - Hearing loss on UNHS
  - Primary infections
  - Symptomatic women

- Issues
  - Low symptomatic rate
  - Non specific symptoms
  - Improves timing when combined with serology

Potential testing algorithms

- Test at risk populations
  - Hearing loss on UNHS
  - Primary infections
  - Symptomatic women
  - Symptomatic infants preterm, IUGR, CP
- Screen all neonates

Potential testing algorithms

- Use saliva ± urine
- Nucleic acid test (PCR)
- Test at birth
- Target at risk populations
- Followup NBSC

- Screen all neonates

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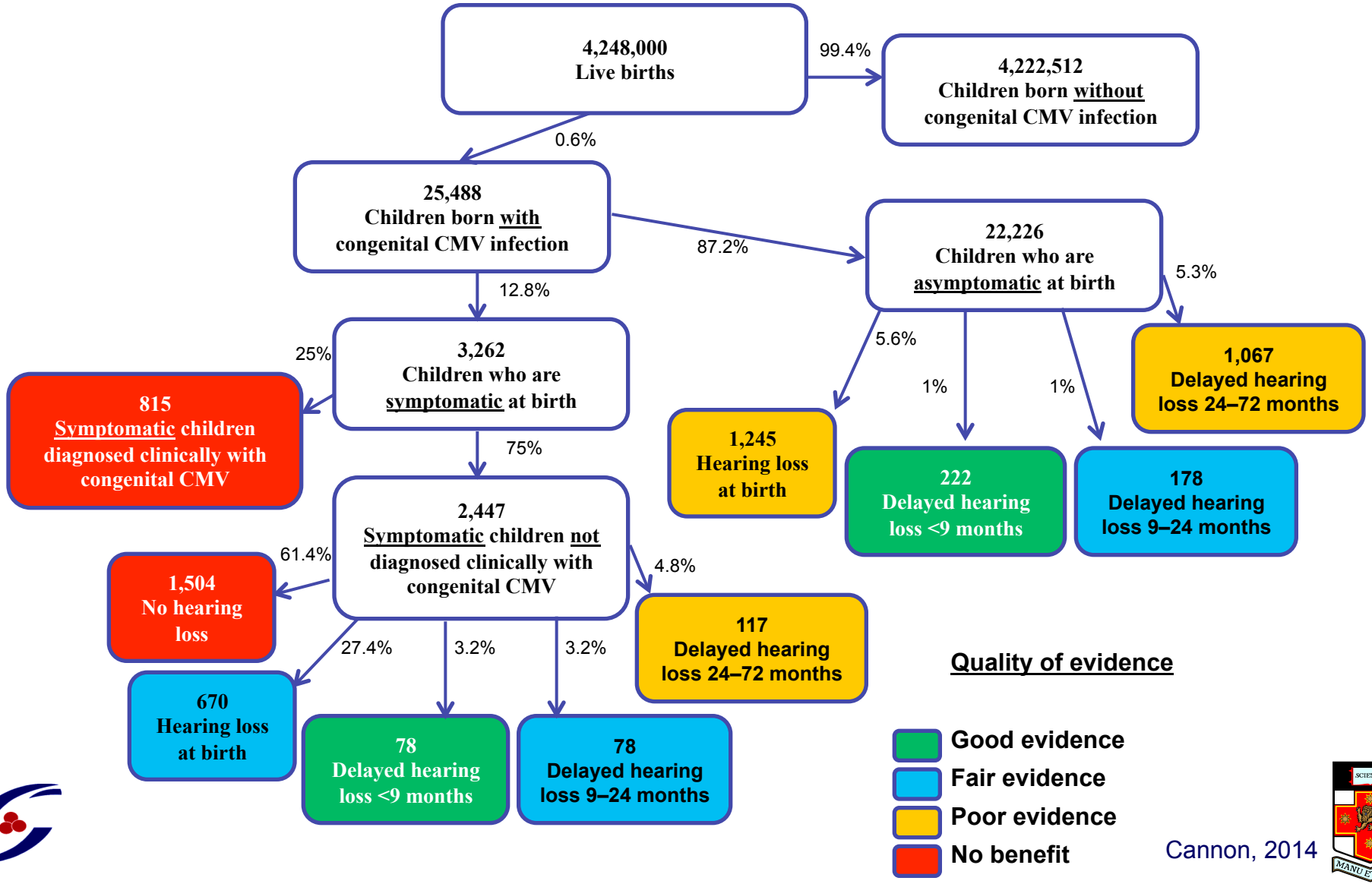
Potential benefits of screening neonates

- Improve the lives of these children and others

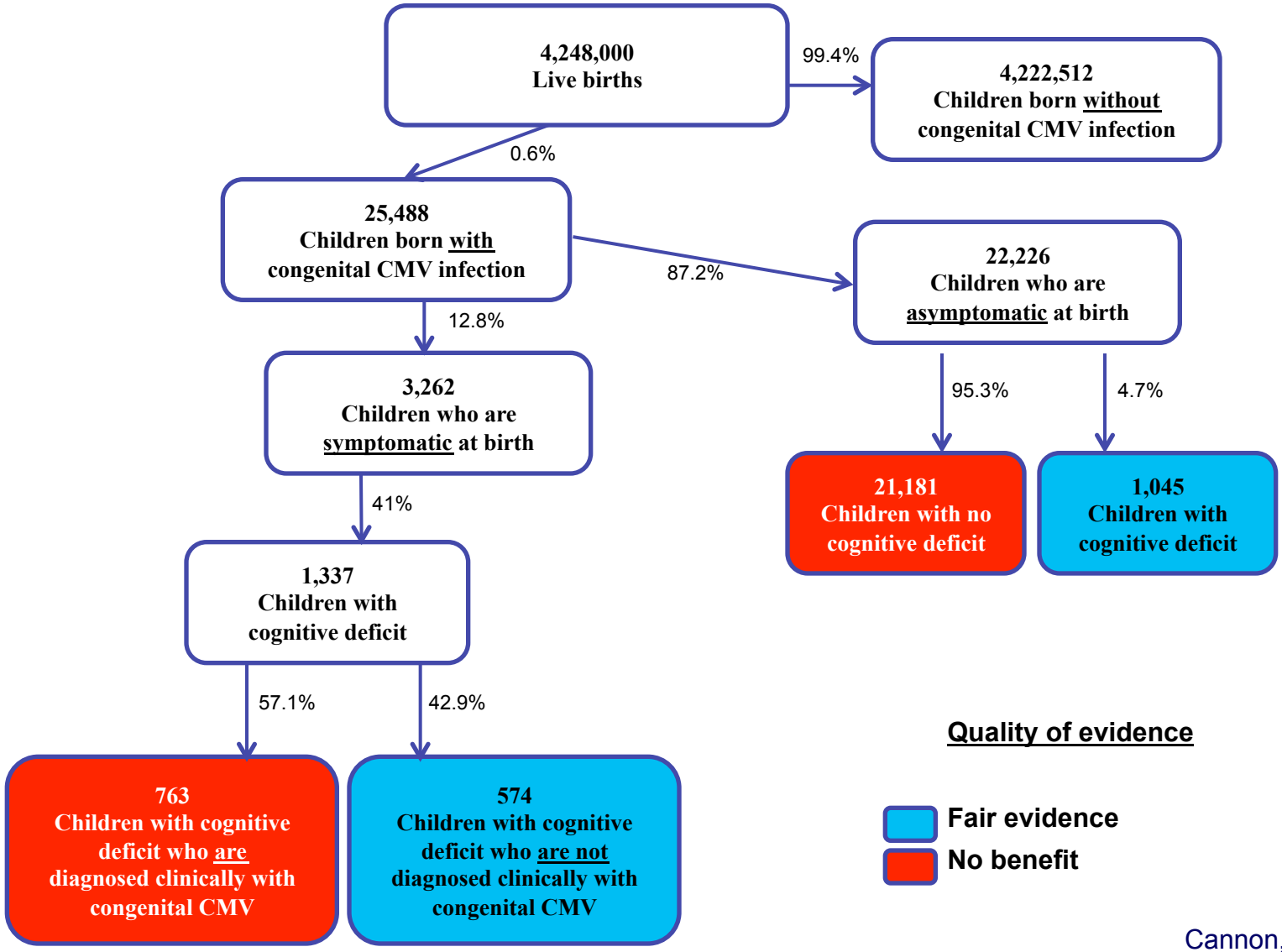
- Cost savings
  - Reduce testing, hospitalisation, therapy
- Prognostic information
  - Genetic cause very unlikely
  - Reduced stress
- Therapy directed at CMV
  - Antivirals

Screening neonates – hearing loss



Cannon, 2014

Screening neonates – cognitive deficit



Cannon, 2014

OUTLINE

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Potential problems of screening all neonates

- Costs
  - NAT assays (~$50)
  - Serology assays (~$5)
  - Additional testing CNS
- Parental stress
  - False positive diagnosis
- Unnecessary therapy
  - GCV
  - GCV adverse effects

RISK OF SCREENING

- Issues
  - Type of screen proposed
  - Resources available

- Additional stress studies (of metabolic screening)
  - Additional discussions arise and usu allay stress
  - False positives lead to stress [Fyro 1987, 1988]
  - False positives do not reduce early health care utilisation [Lipstein 2009]

RISK OF SCREENING

- Additional stress studies of CMV screening
  - Most women view cCMV information positively [Adler 2004]
  - 14 - 20% of US women heard of CMV, ranks last as known cause of birth defects [Jeon 2006, Ross 2008]
- Inappropriate action if assay imperfect
  - Assays NAT/PCR and IgG highly developed
  - False +ve and -ve
- Testing of neonatal Saliva ± Urine ± NBSC
  - Differing characteristics

ROBIN NOTICED THE PROBLEM
ALMOST IMMEDIATELY

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OUTLINE

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   - Why do it?
   - Ways to screen neonates

2. Benefits and problems

3. A way forward
   - Directed testing vs universal screening
   - Additional research

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Potential testing algorithms

- Use saliva (Boppana 2011, Ross this mtg) ± urine
- Nucleic acid test (PCR)
- Screen at birth
- Followup NBSC

- Screen all neonates
- Establish guidelines

- Test at risk populations

DRAFTING CONSENSUS RECOMMENDATIONS

And on sunscreen

Be careful whose advice you buy, but, be patient with those who supply it. Advice is a form of nostalgia, dispensing it is a way of fishing the past from the disposal, wiping it off, painting over the ugly parts and recycling it for more than it's worth.

[Mary Schmich 1997]

We now have enough information to move forward with consensus recommendations

Virology Division

Department of Microbiology - SEALS

March 2013

30 April – 2 May 2015

Katoomba, Blue Mountains

Annual intensive clinical virology update for clinicians, scientists and trainees in this discipline

Focused specifically in 2015 congenital infection, blood borne viruses, antiviral therapy

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Screening introduction requires

- ✓significant health problem
- ✓detailed knowledge of the effect of condition on child
  - ?but depends on timing and maternal factors
- ✓highly accurate & specific test available for definitive diagnosis
  - CMV NAT ± serology
- ✓the test and any actions based on results ethically acceptable
  - ?antiviral toxicity
- ?economic implications of either performing or not performing the test evaluated

Peters, 1996

Measures to control cCMV

- Postnatal
  - Screening high risk (hearing loss)
  - Treating high risk (antivirals)
  - Screening all neonates

- Antenatal
  - Education
  - Screening of some
- During pregnancy
  - Behavioural changes incl reduce high risk food sharing, hand washing
  - Avoid/reduce contact < 2 yr olds and childcare

Testing neonates

- Saliva
- Urine
- (Blood)

➢Correlation >99%

- NBSC
  - ➢Sens 30-50%
  - ➢Spec >99%

Neonatal screening - parameters

- Numbers
  - Birth prevalence 0.6%
  - Likely clinical diagnoses without screening 25% (3.8-25%)
- Illness
  - Hearing loss delayed
    - Until 9 mths 3.2 + 1 %
    - Until 3 yrs 4.8 + 4.8%
  - Neurodevelopmental delay
  - Vision impairment 6.3 + 3.1%

What is the problem?

- Congenital CMV most common infectious cause of congenital malformation in developed, increasing developing

- In Australia of ~296,000 live births pa
  - 594 babies with cerebral palsy
  - 346 babies with congenital CMV disease
  - 330 (of 781) babies with Down syndrome

Laws, 2010 AIHW

OUTLINE

1. Screening neonates for congenital CMV?
   - What do we do currently
   - Why do it?
   - Why not do it?
2. What problems arise with screening?
   - How to screen
   - Parental counselling
3. A way forward
   - Monitoring, data needed
   - Directed vs universal
   - What additional research

NEONATES IDENTIFIED WITH CONGENITAL CMV

- With symptoms (particularly CNS)
  - Intervention with speech and language therapy, sound amplification, cochlear implants
  - Antiviral therapy with ganciclovir
- Without symptoms
  - Followup for deficits esp Hearing
- There is considerable rationale for implementing neonatal screening now

  [Adler 2006]

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Questions for the panel members to discuss

- What are the advantages and disadvantages of saliva vs. blood vs. urine?
- Should screening be mandatory, selective, opt-out, opt-in?
- What are counseling/consent needs of parents, including issues about uncertain prognoses?
- How should monitoring be carried out among infected children?
- Given that there are no FDA approved treatments for cCMV, can newborn screening be justified?

OBJECTIVE

As a result of the panel discussion, the audience will understand the pros and cons of screening for cCMV using various approaches and what additional information is needed to move forward.

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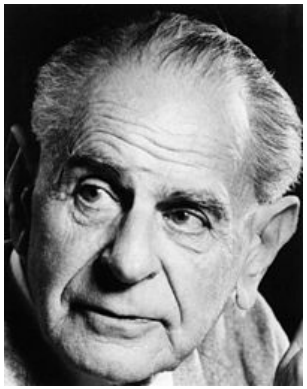
- Conjectures, falsification and refutations

- "I would be happy if I could see where I am in error" [24/12/92]



However, I am now well over 90 years old and very slow; and I have, unfortunately, several other pressing obligations. And I receive every day a lot of letters—far more than I can answer.

It may well be true that I have misunderstood Fries-Nelson: I tried hard to understand them. It is not easy, as you are bound to know.

I suppose (and hope) that you have access to Leonard Nelson Gesammelte Schriften in Neun Bänden – 9 beautiful volumes which I am fortunate to own. In volume II, p. 485 ff there are lots of things which I fail to understand; especially in Nelson's reply to Schiller. My hypothesis so far was that Nelson is ununderstandable because he is wrong: if genuine Erkenntnis is something that is always true (and only our Urteile can-and are-often mistaken-than, I suggest, Erkenntnis in Nelson's sense just does not exist. But I would be happy if I could see where I am in error with this Urteil.

I take this to be extremely important. But it is almost as important to have received a letter from a man who takes philosophy (or anything) seriously. I thought the breed had died out.

Yours sincerely

Karl Popper

Concerning Russell: have you forgotten Principles of Mathematics and Principia Mathematica?

I cannot write more – too much pressure of urgent work.

What is the problem?

- Congenital CMV is the most common infectious cause of congenital malformation in developed countries

- In Australia each year (of ~296,000 livebirths)
  - 594 babies with cerebral palsy
  - 346 babies with congenital CMV disease
  - 330 (of 781) babies with Down syndrome

[Laws 2010 AIHW]

Congenital CMV observations

- Not all congenitally infected infants develop clinical disease
- Not all pregnant women with primary CMV infection transmit virus to their baby
- CMV placental infection precedes fetal infection by 8-12 weeks, suggesting blocking of transplacental virus movement

1. Apoptosis of STB Layer

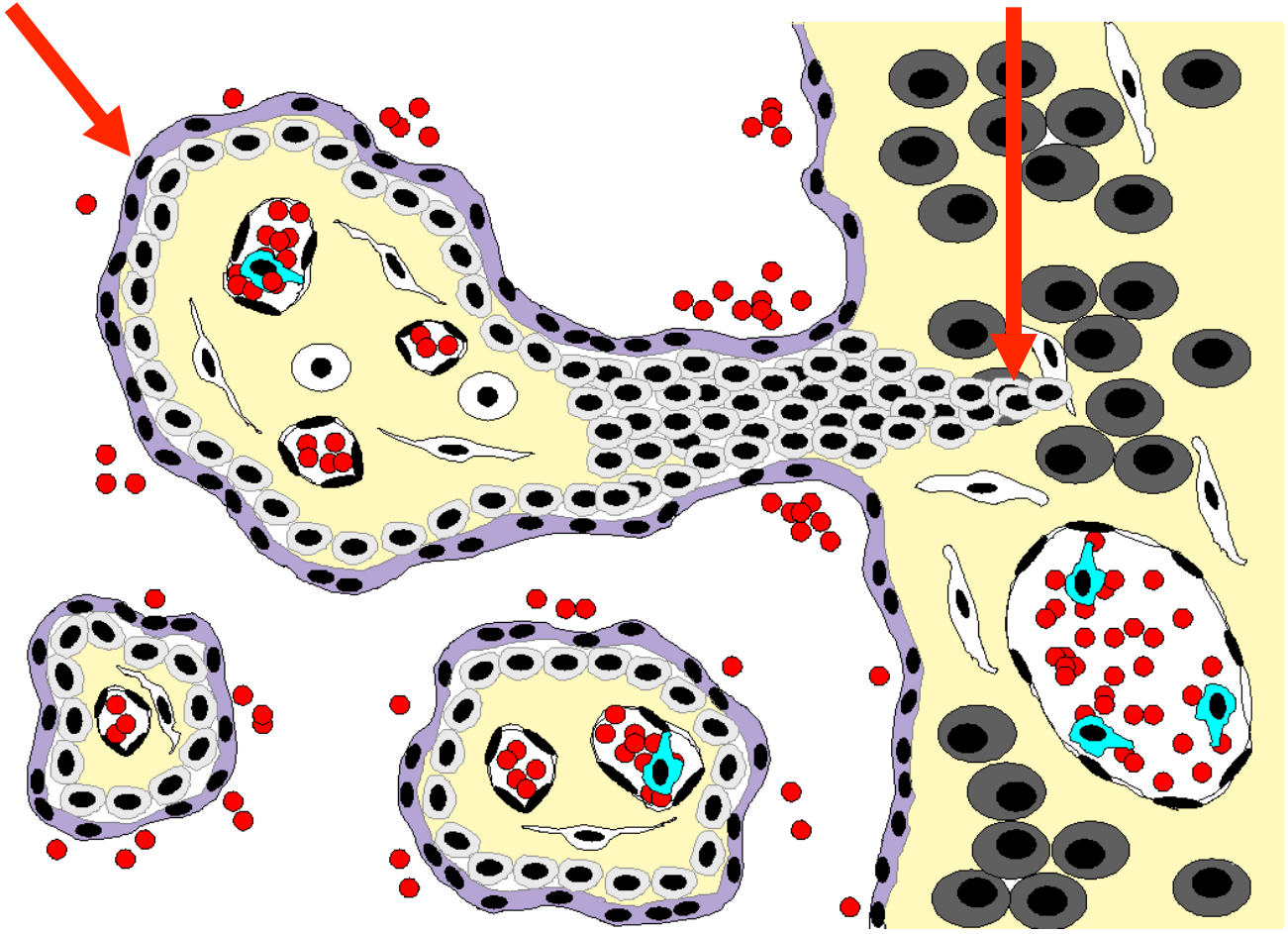
Reduced Gas & Nutrient Transfer

Increased CMV Dissemination

2. Reduced Cytotrophoblast Invasion

Shallow Placentation

Reduced Gas & Nutrient Supply to Placenta



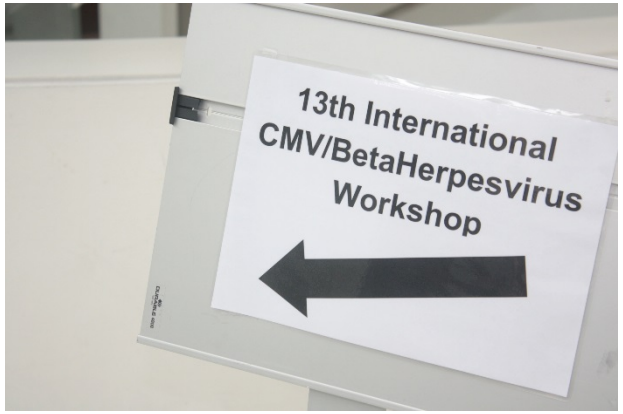
3. Downstream Effects on Other Proteins

Shallow Placentation

Affects on Placental Development/Function

4. Loss of Immune Tolerance

Rejection of Placenta



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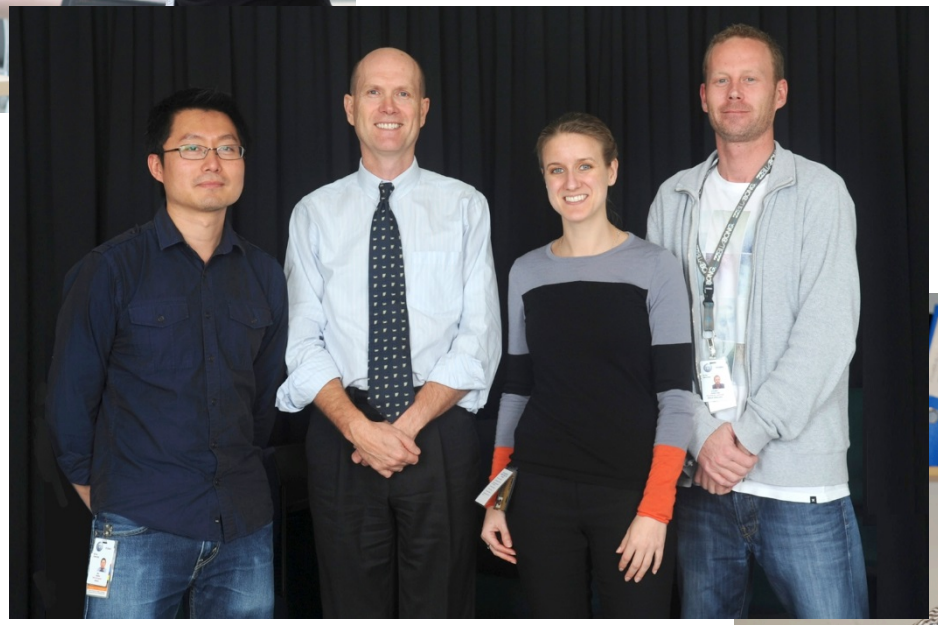

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Measures to Control CMV

- Before Pregnancy
  - Education
  - Screening
- During pregnancy
  - Handwashing
  - Avoid contact < 2 yr olds and childcare
  - Screening
- Following Birth
  - Screening high risk (hearing loss)
  - Treating high risk (antivirals)

Measures to Control CMV

- Some data exist for a number of potential options to treat and prevent CMV in pregnant women*:
  - Vaccination
  - Antivirals
  - Immunoglobulin
- Efficacy of these options can only be determined by well-designed clinical trials.

*None of these therapies are registered for the treatment or prevention of CMV in pregnant women

What is the problem?

- Congenital CMV (cCMV) is the most common infectious cause of congenital malformation in developed countries

- In Australia each year (livebirths)
  - 594 babies with cerebral palsy
  - 465 babies with congenital CMV disease
  - 330 (781 incl top) babies with trisomy 21
  - 59 (211 incl top) babies with trisomy 18
  - 18 (77 incl top) babies with trisomy 13

[Laws 2010 AIHW]

APPROACHES TO SCREENING

- Screen all pregnant women prior to pregnancy
  - ➢Proportion of pregnancies planned
  - ➢Highest risk are those unplanned, adolescent, other STI, previous problems
- Screen women in T1 with CMV IgG IgM IgG avidity
  - ➢"routine, self motivated screen" [Schlesinger 2007]
  - ➢CDC does not recommend routine maternal screening for CMV infection during pregnancy [CDC current]

APPROACHES TO SCREENING

- Screen pregnant women at risk
  - Who?
  - 89% asymptomatic
- Screen all babies
  - Healthy infants are not routinely tested for CMV infection [CDC current]
- Screen some babies
  - Hearing impairment
  - Premature
  - Screen babies with consistent syndrome
  - Misses 95% in Australia [Munro 2005; McMullan 2011]

CMV SCREENING

- Women antenatally
  - Not routine
- Women during T1
  - Adhoc
- High risk babies
  - Increasingly screened
  - Testing of infected