Diagnosis and management of congenital / perinatal viral infections

Cheryl Jones

Disc. Paediatrics & Child Health

Immunology & Infectious Diseases

University of Sydney & CHW

9845-0521

cherylj@chw.edu.au

Overview

- Incidence of viral congenital/perinatal infections
- Congenital CMV infection
- Neonatal HSV infection
- Congenital Varicella
- Congenital Rubella

Incidence of viral congenital & perinatal infection

Infectious agent	/10^5 live births	NSW/yr	% symp. at birth
CMV	200-3000	425-850	5-10%
Enterovirus	50-360	?	20%
Hepatitis C	%	5?	0%
HSV	3-20	3-5	? 100
Rubella	1.4	0.85	33%
HIV	1-2*	1	10%
VZV	0.8	1	10%
Hepatitis B	? <0.1	?	≤5%
Parvovirus	sporadic	?	

Congenital CMV infection…

Maternal diagnosis

Fetal risk

Outcome in newborn

Management

Maternal indications for CMV testing

- Routine antenatal testing?
- History suggestive of CMV illness
- Exposure to known CMV infected individual or blood product
- Immunocompromised
- Abnormalities on routine antenatal ultrasound

Presence and type of Maternal infection?

- Serology
  - IgM 75%, IgG seroconversion (2-4 wks aprt)
  - IgG avidity
- Direct virus detection
  - culture
  - PCR

Sensitivity

disease: DFA = 70 – 80% PCR = 50 – 90%

infection: DFA = 80-90%,PCR = 95 – 100%

Specificity:

DFA = 95 – 100%,

Virus isolation = 5 – 100%

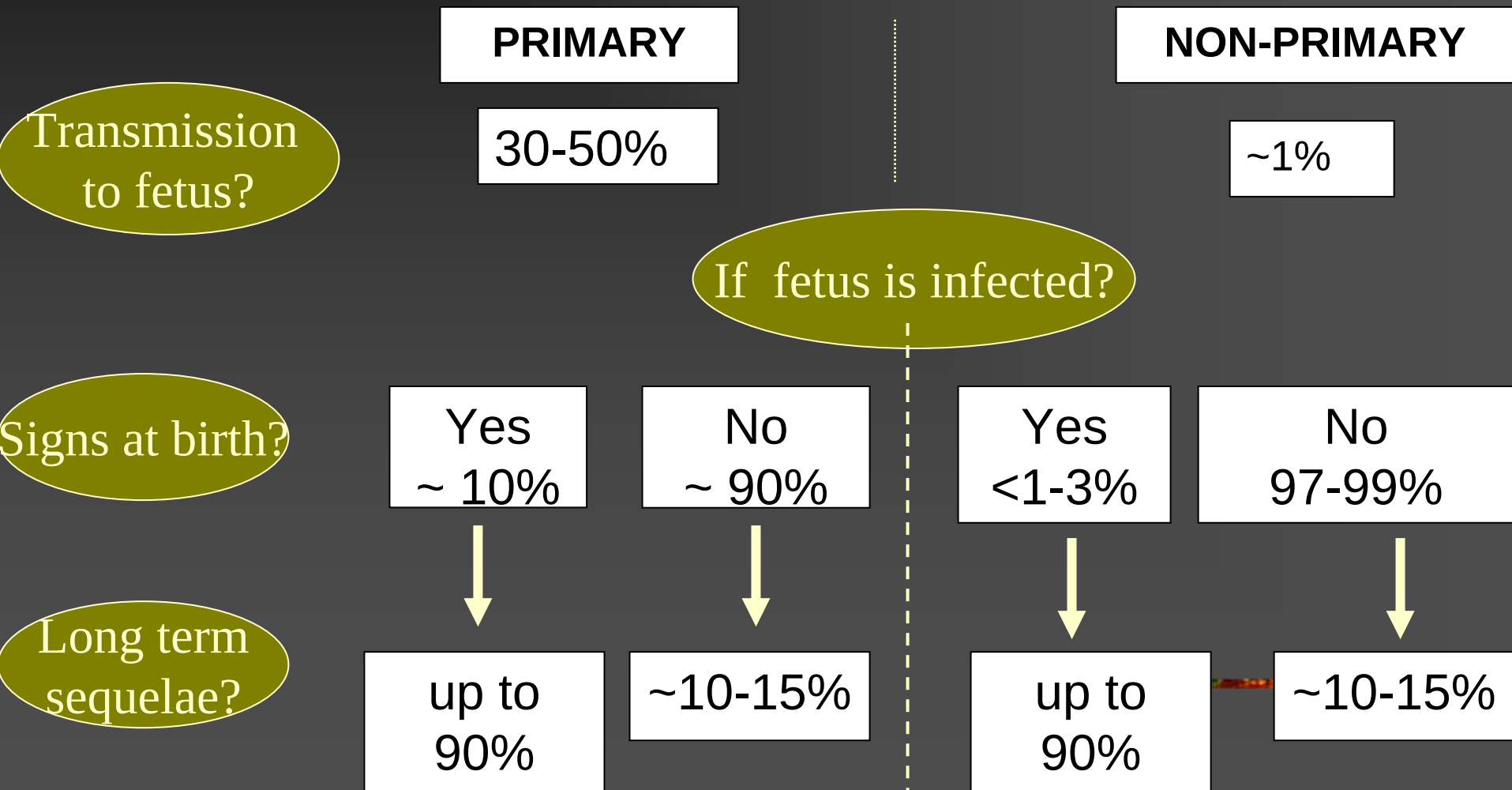
PCR = 40 – 50%

Rawlinson, 1999

Intrauterine transmission of CMV to fetus?

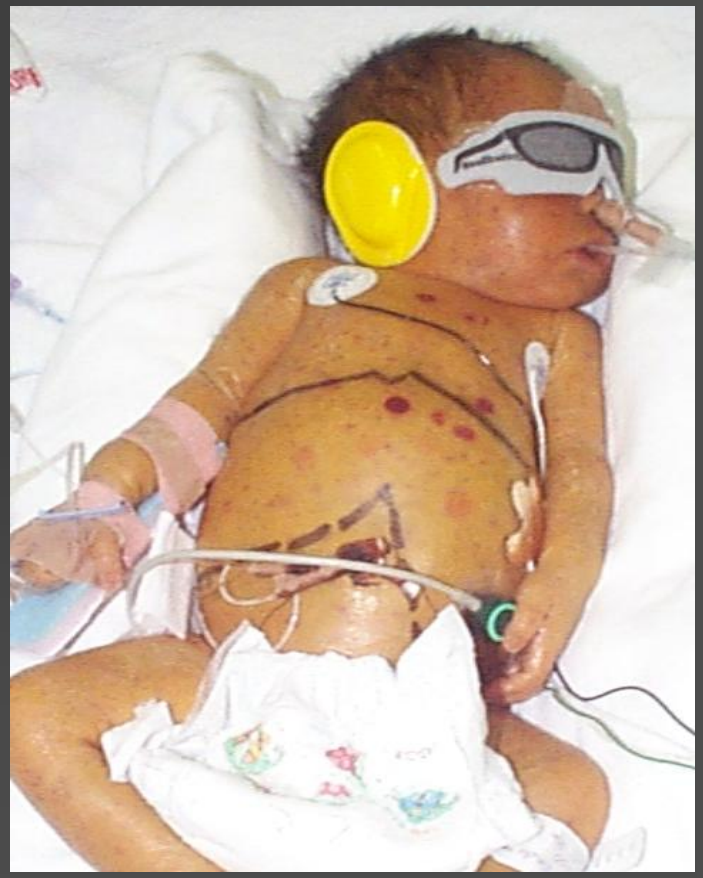
- Fetal imaging
  - Fetal ultrasound
  - Fetal MRI
- Amniocentesis
  - viral culture
  - CMV PCR:
    - +ve = 1:10 risk
    - qualitative PCR >10^5 risk= 1:2 to 2:3 risk
- Fetal blood sampling

Fetal risk after congenital CMV infection?



Congenital CMV infection: What do parents want to know?

- How will my child be affected?
- Epidemiology
  - How did I get it?
  - Can I pass it on?
- Treatment and Prevention
  - What can we do to treat it?
  - Is there a vaccine?



SEQUELAE AFTER SYMPTOMATIC DISEASE AS NEWBORN Boppana et al, Pediatrics 1997

- Sensorineural hearing loss ~59%
- Severe Motor Deficit ~49%
- Mental retardation (IQ <70) ~47%
- Chorioretinitis ~12%
- Seizures ~11%
- Other: dental defects, inguinal herniae (males)

Early predictors of poor CNS outcome? Boppana et al, Pediatr 1997 Noyola et al, J Pediatr 2001

- **poor cognitive outcome**
  - Microcephaly (adjusted) most specific predictor,
  - Abnormal head CT most sensitive predictor
- **long term motor disability**
  - Abnormal head CT strong, sensitive predictor
  - chorioretinitis insensitive, but specific predictor
- **Not predictive**
  - SN hearing loss, jaundice,↓ platelets, increased LFTs, hepatosplenomegaly, growth retardation

Sequelae after ASYMPTOMATIC INFECTION AS NEWBORN

- Sensorineural hearing loss 10-15%
- ? Chorioretinitis

Long term outcome?

- If no CNS abnormality by one year, unlikely to be at increased risk for subsequent neurodevel/CNS impairment

Prospective mother/infant studies

- Sweden
  - Ivarsson et al, Pediatr 1997; Scand Infect Dis J 1999)
- USA
  - Fowler et al, NEJM 1992; Temple et al, J Dev Behav Ped 2000)

Will I or my child pass it onto pregnant friends?

- Ubiquitous
- Predominantly asymptomatic infection
- Virus shed in urine, saliva, genital secretions, +/-blood
- Low infectivity- pregnant woman: strict attention to hand washing

Could my next child have symptoms too?

YES

But the risk is very low

- Ahlfors et al, Scand Infect Dis J 1999
- Bopanna et al, Pediatrics 1999

Epidemiology: Congenital CMV

- Can a CMV seropositive women be REINFECTED with a new CMV strain?
- If so, does this result in transmission, +/- disease in her offspring?
- Crucial to understand components required for effective vaccine against congenital CMV disease

Results Boppana et al, NEJM 2001

New AB b/n pregnancies?	Infected infants N=16	Mothers of Uninfected infants N=30
YES	**10 (62)**	**4 (13)***
NO	6 (38)	26 (87)

3 symptomatic

Indications for treatment Congenital CMV infection

- Current only recommended for life or sight-threatening disease
  - IV ganciclovir: dose? duration?
  - 5mg/kg/dose IV q12h
- Treatment of symptomatic infant to reduce long term CNS sequelae?
  - Kimberlin et al, Pediatrics 2003

HSV

- in pregnancy
- neonatal HSV disease

Vertical transmission of HSV

Most genital HSV infections are asymptomatic

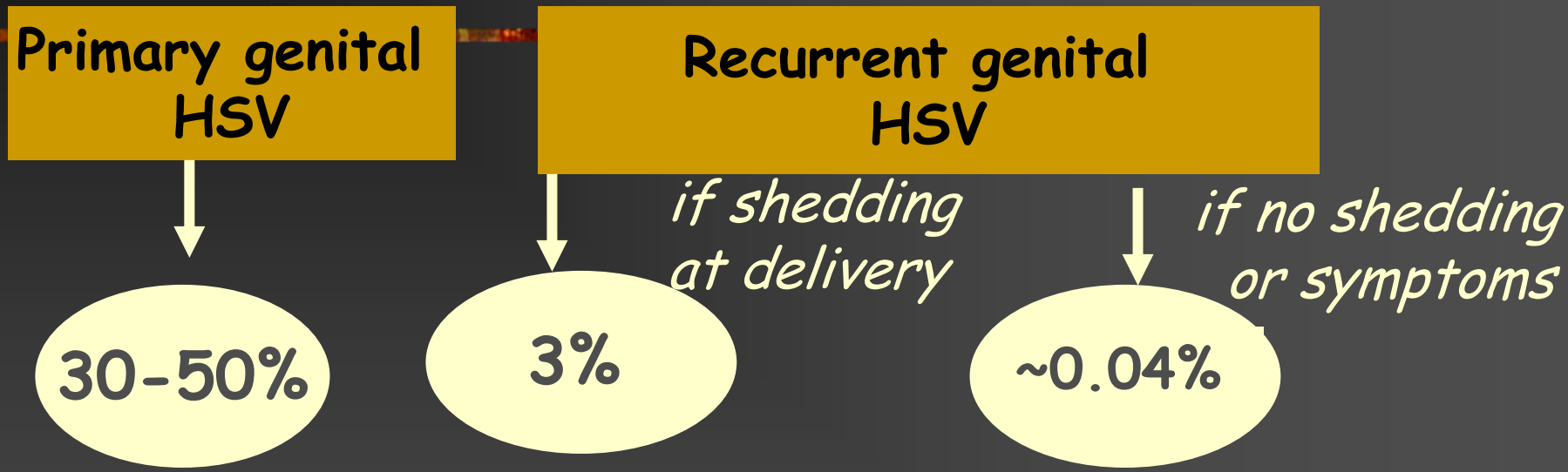
(Primary or Recurrent)

PERINATAL
85%

70%

No knowledge of genital HSV disease

Maternal HSV
Risk of transmission



Brown et al, 1991

Risk of transmission greatest if HSV seroconversion has not occurred prior to onset of labour

Brown et al, 1997

Neonatal HSV infection…

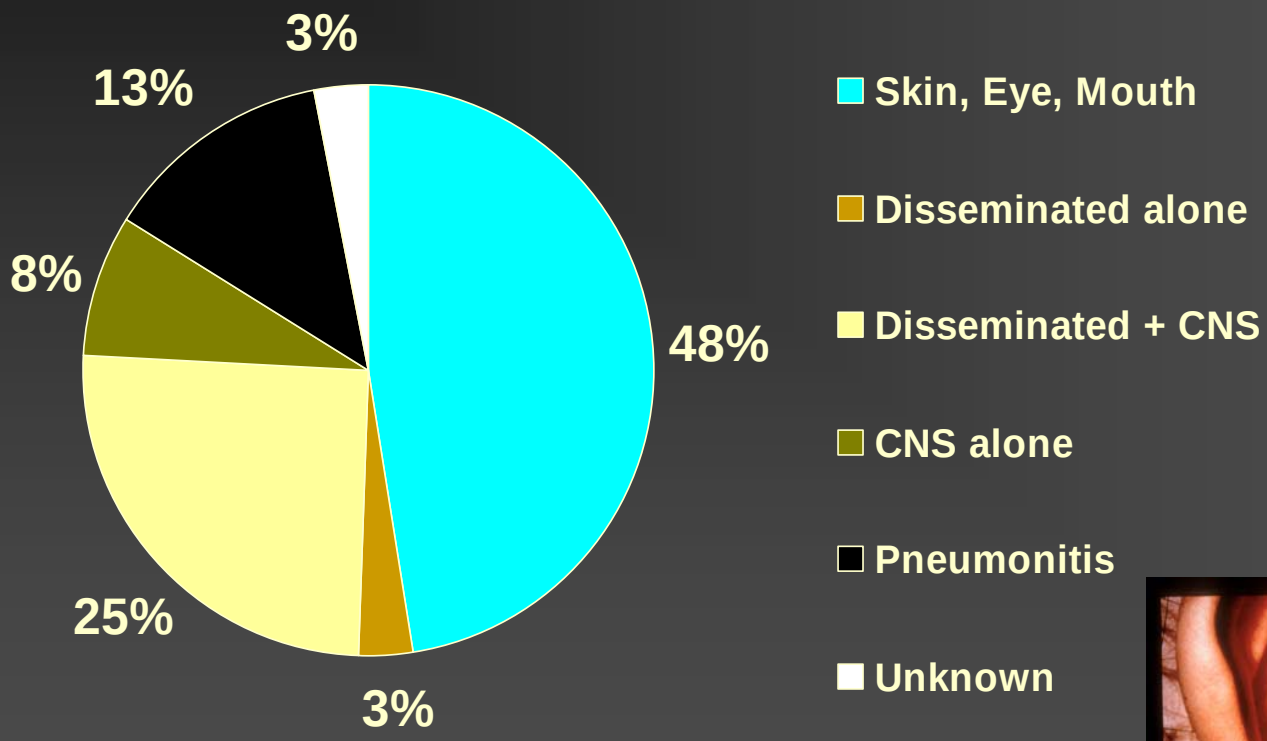
Neonatal HSV infection APSU study 1997-2002

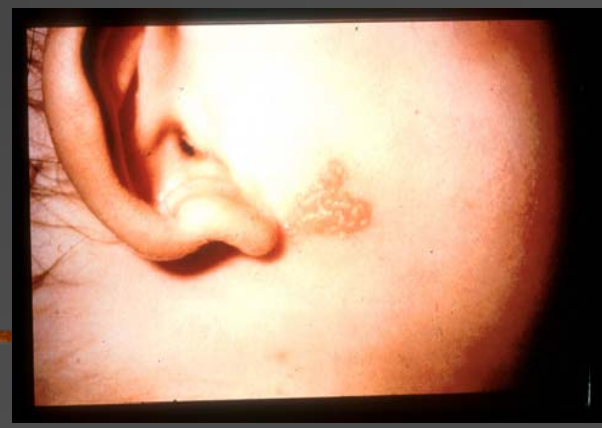
CA Jones, D Isaacs, P McIntyre, A. Cunningham, S. Garland

AIMS OF SURVEILLANCE

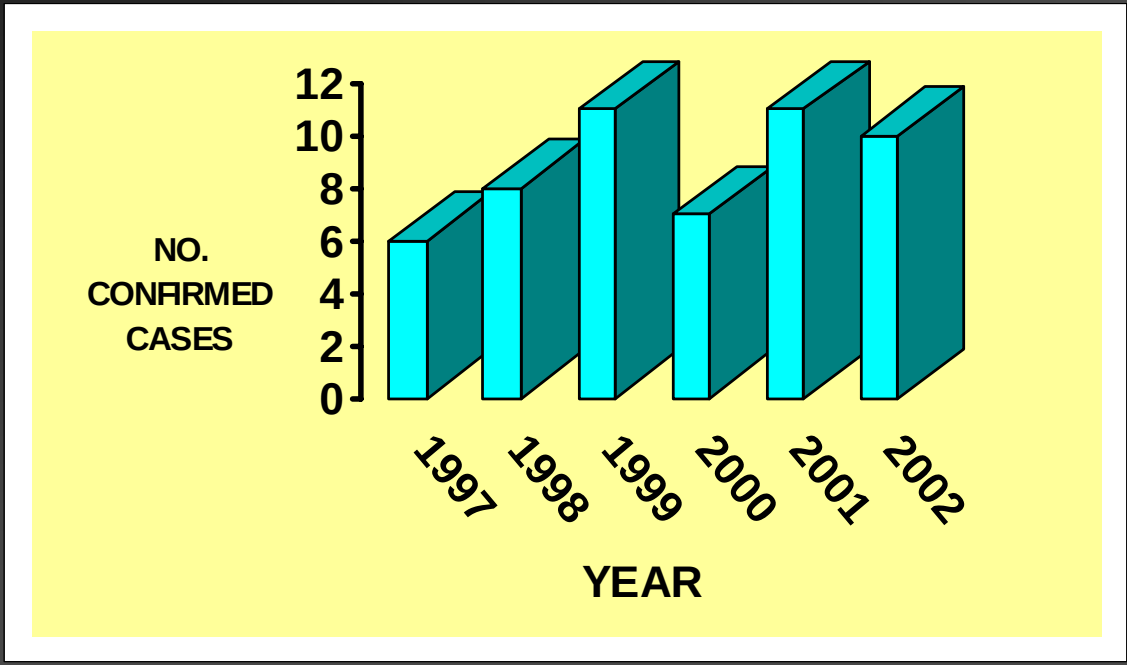
- reported incidence in Australia?
- mode of acquisition?
- clinical presentation, investigation, management, acute outcome?
- *outcome at one year follow up?*

Neonatal HSV in Australia
Mode of presentation ‘97-’02





Incidence of neonatal HSV infection Australia? APSU DATA '97-'02



- 53 CONFIRMED CASES '97-'02
- > 95% response rate
- Reported incidence: 3.9/100,000 LIVE BIRTHS

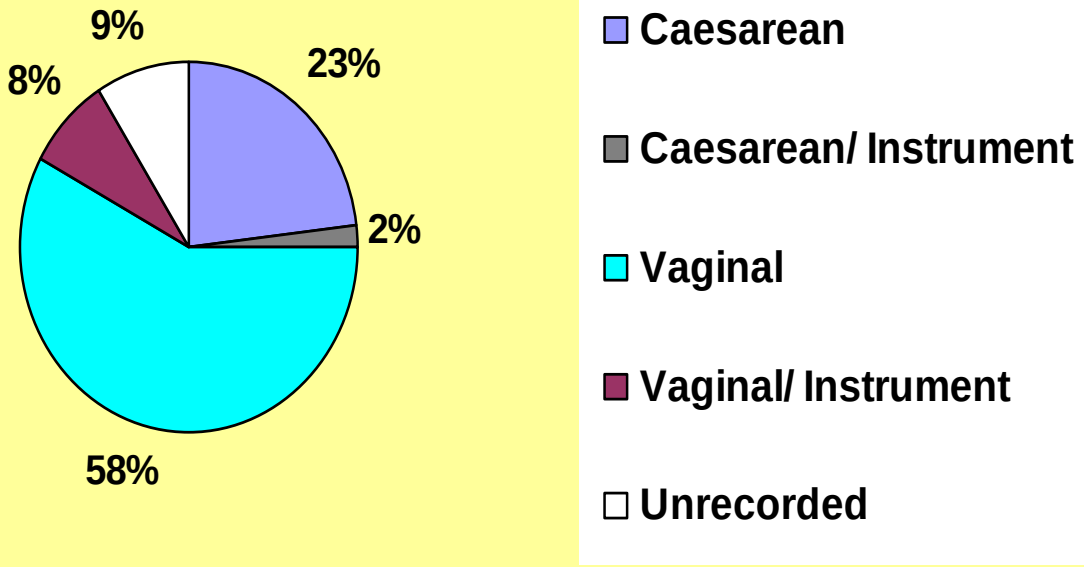
Source of perinatal infection?

- Mo Hx Known Genital HSV disease?
  - Y= 6/53
  - N= 40/53
  - Unrec= 7/53
  - Father Known genital HSV 4/41
- Orolabial HSV
  - Mo Y= 4/53
  - Fa Y= 5/53
  - Other = 2/53 (also mother)
- Hospital acquired
  - No evidence 51/53
  - Possible 2/53

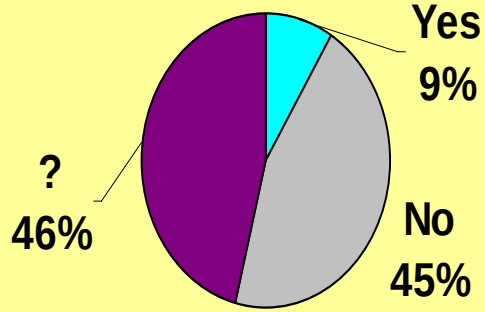
Possible postnatal

10/53

Mode of Delivery?



Scalp Electrodes?



C. Section + Intact membranes?

C. Section 14/48:

Intact 3/14

Unrecorded 5/14

ROM > 6 Hrs 6/14

Survival ?

- 24.5% acute mortality
- Gestation of infants that died?

  < 37 weeks 11/13*

  <30 weeks 5/13*

- Category of disease

*1 *Death of preterm infant at 56 days ? due to other cause*

SEM	*1/13
Disseminated	5/13
I/uterine death	1/13
Pneumonitis	4/13
CNS alone	0/13

Delay in initiation of Rx?

	TOTAL?	DIED?
Unrecorded	10/53	1/10
Antenatal dx	1/43	1/1
No delay	18/43	2/18
< 2 days	9/43	4/9
3-7 days	4/43	1/4
8+ days	9/43	6/14

Diagnosed at PM ? 7/53

USA:
no advances in reducing interval between onset of symptoms and initiation Rx

Kimberlin et al, 2001

Mx neonatal HSV

- 3 scenarios
  - Suspicious clinical signs
  - Infant born to women with active genital herpes at delivery
  - Infant born to women with Hx recurrent genital HSV disease

Neonatal HSV- clinical signs

vesicles/bulli, seizures, unexplained sepsis (Bld cx neg, no response to Abx), resp distress in Term baby d3+, DIC, hepatitis, thrombocytopenia

irrespective of maternal Hx:

Ix & commence empiric IV aciclovir immediately

Neonatal HSV- Ixns

- skin lesion, nose, throat, conjunctiva swab: Cx/ PCR
- skin lesion: indirect IF (rapid)
- CSF exam

  wcc, pr, gluc, HSV PCR, cx, viral cx
- CNS imgaing
- Blood: FBC, LFTs, coags,
- serology: little role to play

Neonatal HSV- delivered through HSV birth canal

- Mother Primary or Recurrent HSV?
- Known Maternal primary infn or unknown
  - investigate & commence immediate treatment- 14 days if no CNS signs/PCR neg, 21 days if +Ve
- Recurrent disease? surface swabs at 24 hours?, if +Ve or clinical signs- full Ix and Rx (unless severe disease)

Neonatal HSV
Hx recurrent genital HSV

- Risk to infant negligible
- Educate parents about signs of HSV disease
- surface swabs on infant at 24 hrs if high parental concern?

Current aciclovir recommendations: neonatal HSV disease

- Aciclovir 20mg/kg/dose given 8th hourly
  - Duration:

    21 days if encephalitis/ disseminated infection or LP not performed

    14 days for disease localised to skin, eye or mouth

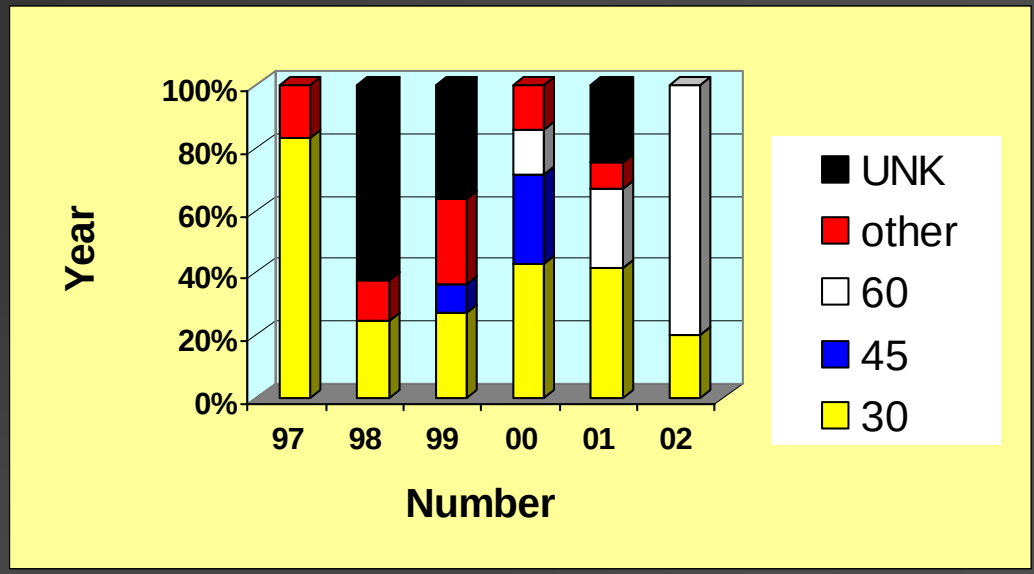
- Open label- safety, and estimate efficacy: historic low dose controls.

  Kimberlin et al, Pediatrics, 2001

Neonatal HSV in Australia IV Aciclovir Dose '97-'02

41/53 received antiviral therapy:

- 30 mg/kg/day 46%
- 45 mg/kg/day 7%
- 60 mg/kg/day 32%
- Other 10%



Neonatal HSV infection Management of recurrences

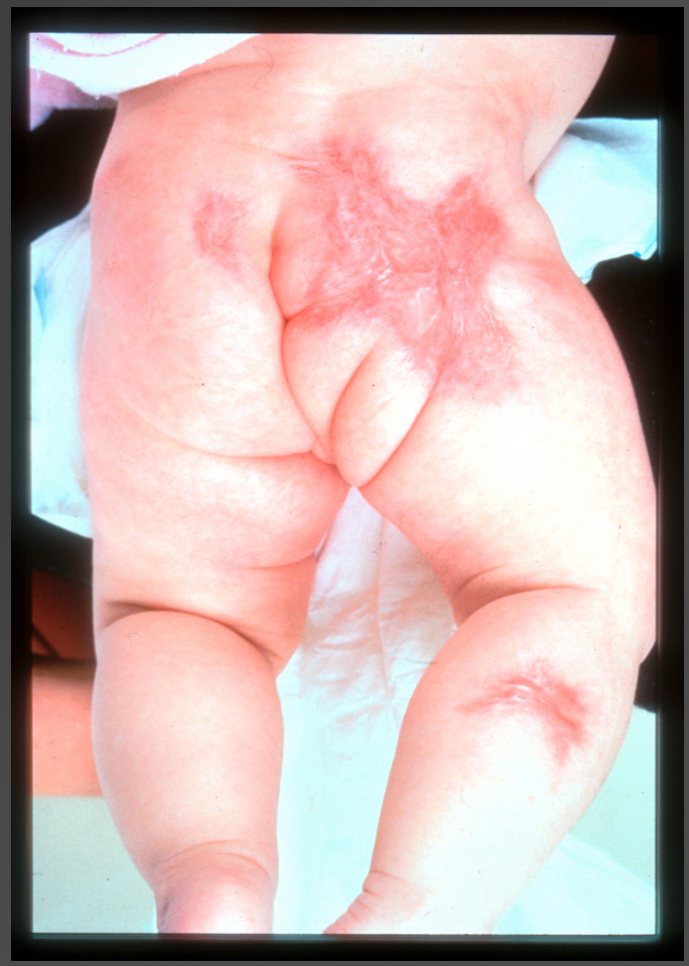
CONTROVERSIAL

- Role of suppressive therapy
  - Not established yet
  - Ph 2 trial: Oral aciclovir 300mg/m^2/dose 3 times/day- prevented HSV recurrence after CNS disease, effect on CNS outcome unknown, neutropenia in 46%- Trial ongoing
- Investigations:
  - Include LP to exclude CNS recurrence
  - IV aciclovir therapy for 14 days if –ve, 21 days if +ve?
  - Until when? 6 months

Congenital & Perinatal Varicella……

Congenital Varicella infection: sequelae

- Skin scars ~80%
- Eye abnormalities 60%
- Limb abnormalities ~70%
- Prematurity, LBW 50%
- Cortical atrophy, mental retardation 46%
- Poor sphincter control 32%
- Early death 29%
- “herpes zoster” as infant
- Diagnosis: clinical



Risk of fetal sequlae post maternal VZV infection

- Overall risk ~2%
- Timing of maternal infection

< 12 wks gest'n	12-20 wks gest'n	>20 wks gestation
0.4%	**2%**	Isolated cases Latest ~28 wks

- Maternal investigations?
  - Regular fetal ultrasound
  - VZV fetal serology is unhelpful
  - Consider amniocentesis -veVZV PCR may be reassuring

APSU Congenital VZV Study ‘95-97

Forrest, Burgess J P Ch H,1999

- 7 cases of congenital VZV in 3 years
  (1 in 107,000 pregnancies)
  UK 1-2/100,000 pregnancies

Managemant of infant post perinatal maternal chicken pox ?

Mx infants of mothers with perinatal chickenpox

Time of maternal infection

> 7 days b'fo

No ZIG to infant (unless ≤28 weeks or ≤1000g and still active lesions)

No isolation of infant from mum

Breast feeding OK

If infant gets chickenpox
no Rx needed unless ≤28 weeks or ≤1000g
IVacyclovir

Mx infants of mothers with perinatal chickenpox

Time of maternal infection → ≤ 7 days b'fo to 48 hr after

- Give ZIG immediately
  - < 24 hours
  - up to 72 hours
- Discharge term infants ASAP, plans to review if unwell, or gets c'pox
- Don't isolate infant from mum
- Breast feeding OK
- If gets c'pox?
  - Admit/ Rx if rash

Mx infants of mothers with perinatal chickenpox

Time of maternal infection → > 48 hr- 28 days after

- Give ZIG immediately
  - < 24 hours
  - up to 72 hours
- Discharge term infants ASAP, plans to review if unwell, or gets c'pox
- Don't isolate infant from mum
- Breast feeding OK
- If gets c'pox?
  - Review
  - Admit/ Rx if preterm, or severe/ resp symptoms in term

Mx neonates exposed to VZV:
NICU/ p’natal wards /home...

Mx neonates exposed to VZV: NICU/ p'natal wards /home

- Was exposure significant?

  same open ward pt
  5 min face to face
  ≥ 1 hour contact uncov'd lesions/ zoster, or staff/pt gets VZV ≥ 24 hrs later

- Gestation? < 28 wks/<1000g
  - Yes: Give ZIG, If VZV, Rx IV aciclovir

Mx VZV exposed term neonate

- No?, check maternal serol. urgently
- If mat serol. negative, or unavailable

- Administer ZIG to infant
- If on ward, isolate 7-28 days (7-21 days if no ZIG)
- No isolation from sibling required

- Medical review if infant develops chickenpox
- Admit to hospital for intravenous acyclovir
  if unwell (tachypnoeic, poor feeding)
  isolate until lesions crusted

APSU Neonatal varicella 1995-1997

Forrest J, Burgess M. J P Ch Health, 1999

44 cases of NNV in 3 years (1 in 17,000 pregnancies)

No. of cases	**44**
Sex	**19M : 22F (3 ?)**
Day of rash in infant	**13 (1-26)**
Severity: ZIG	
severe	**2 : -**
moderate	**10 : 4**
mild	**30 : 20**
not stated	**2 : -**

Congenital VZV Conclusions

- All infants with neonatal varicella recovered
- 2 severe cases (maternal infection intrapartum & day 14 pp) — neither given ZIG

Because of consistent incidence of congenital VZV

- vaccinate non-immune women before pregnancy

Congenital rubella in Australia

1996-2003 Burgess M & Forrest J

2004- Jones CA,

Rubella vaccination in Australia

1971 Adolescent girls (10-16 years)

1989 Infants (MMR) (12 months)

1994 Adolescent girls & boys (10-16 years)

1998 MMR to all primary schoolchildren

1999 Infants & school entry (12/12 & 4-5 years)

Forrest & Burgess

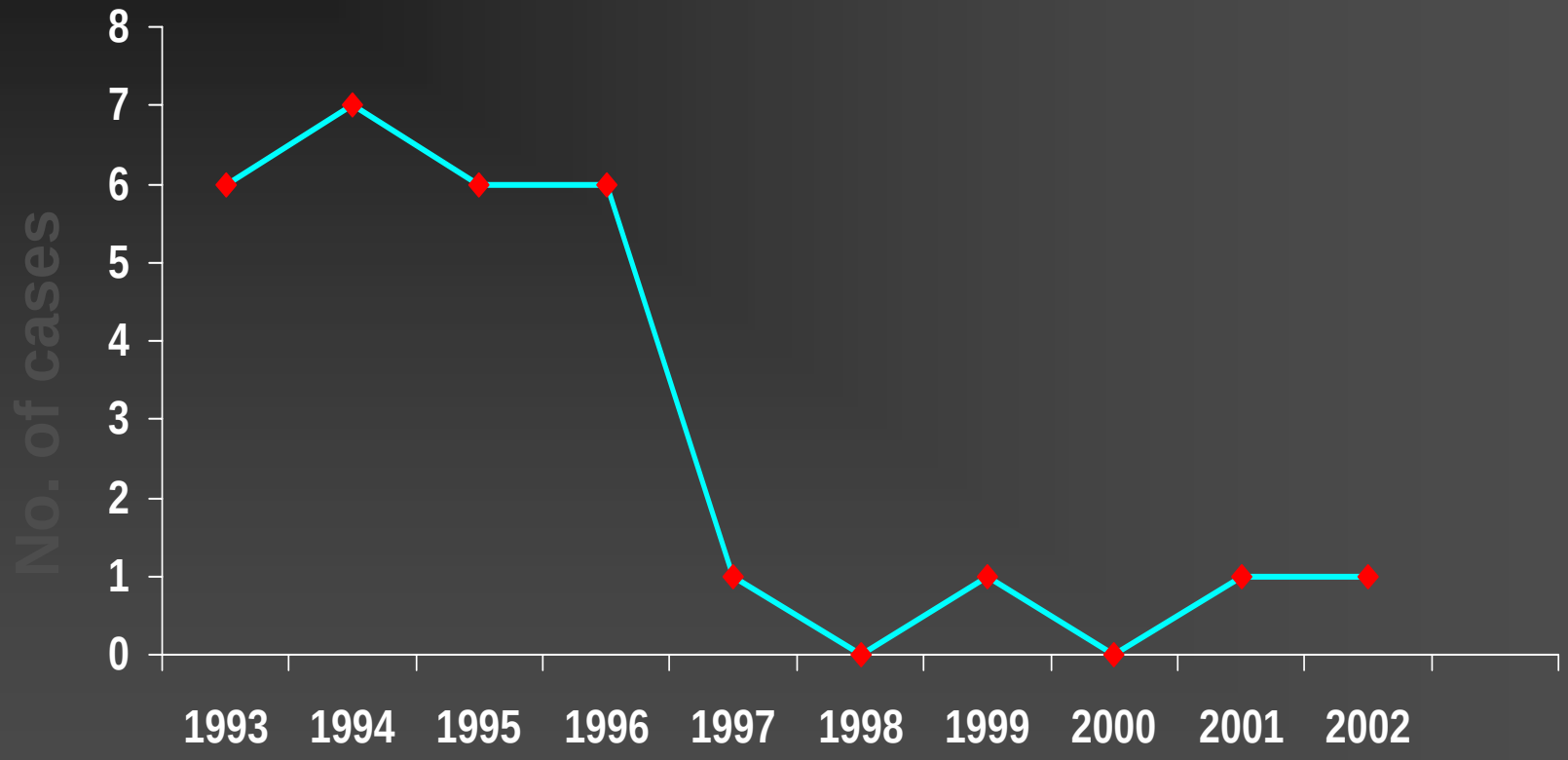
Congenital rubella syndrome

A live or stillborn infant with clinically compatible defects, and one of the following

- isolation of virus from infant
- rubella-specific IgM +ve
- persistence of rubella-specific IgG
- laboratory-confirmed maternal rubella in pregnancy

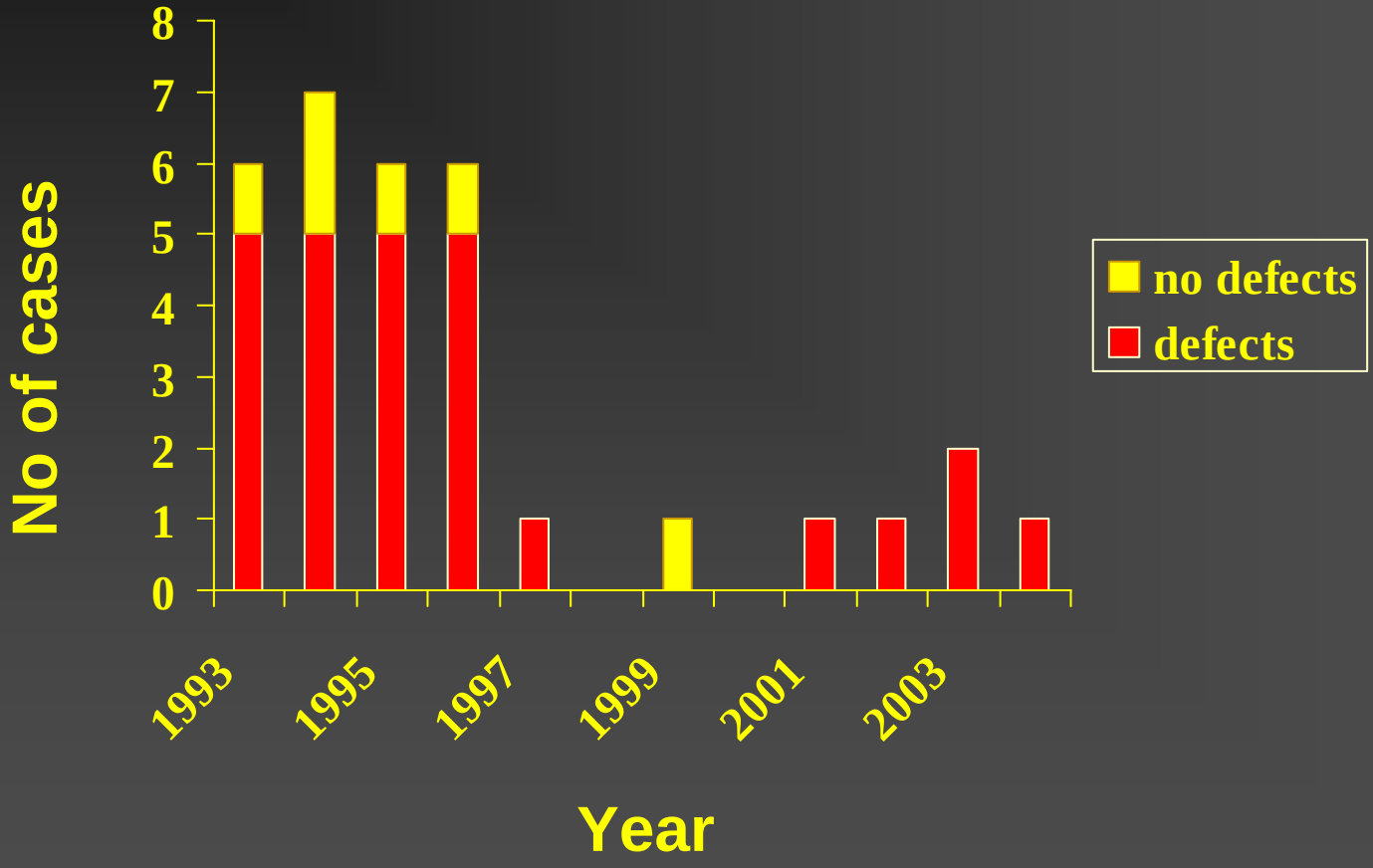
Forrest & Burgess

Congenital rubella born in Australia



Forrest & Burgess

Congenital rubella born in Australia



Forrest & Burgess

Congenital rubella in Australia

Why is it still with us?

- missed opportunities to immunise
- failure to confirm infection in pregnancy
- imported cases - infection in countries without immunisation programs

Forrest & Burgess

Acknowledgements

- Contributors to the APSU
- APSU staff and sponsors
  - NCDC
  - Commonwealth Department of Health & Aged Care
  - Financial Markets Foundation

HSV study

D. Isaacs, A. Cunningham, S. Garland, P. McIntyre

VZV & Congenital Rubella

M. Burgess, J. Forrest, S. Mego, C. Cooper, J. Wojtulewicz, S. Arbuckle