Howard E Williams Oration

A career in neonatal research – really?

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Howard E Williams Oration

A career in neonatal research in parallel with changing outcomes of babies born extremely tiny or immature

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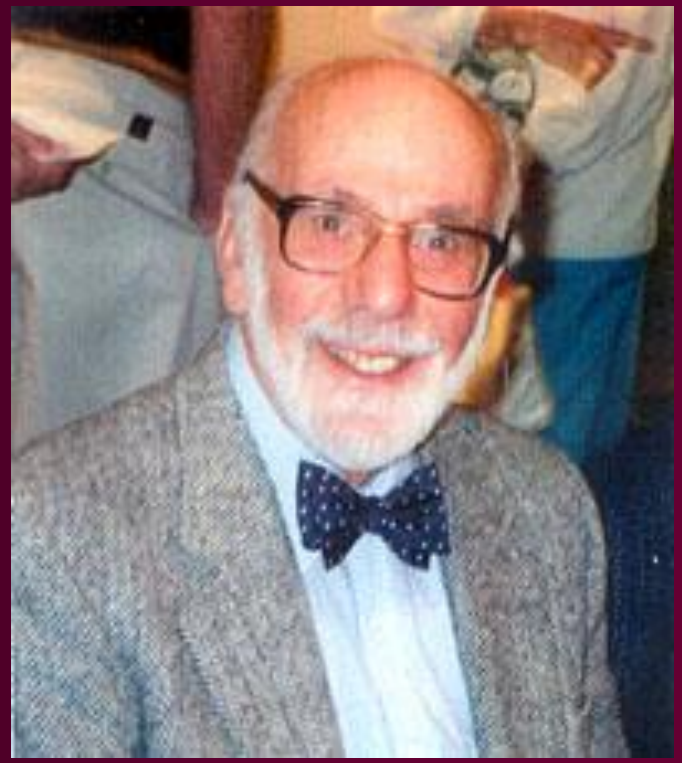
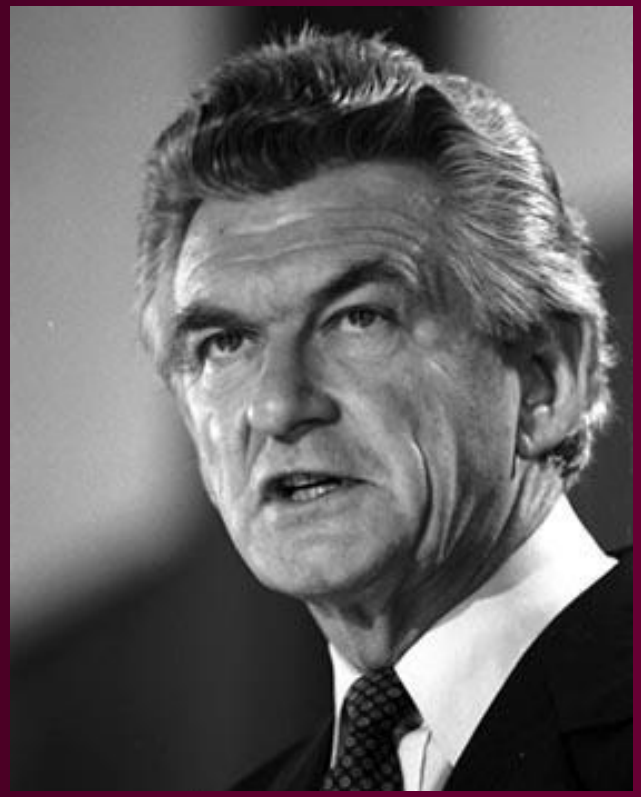
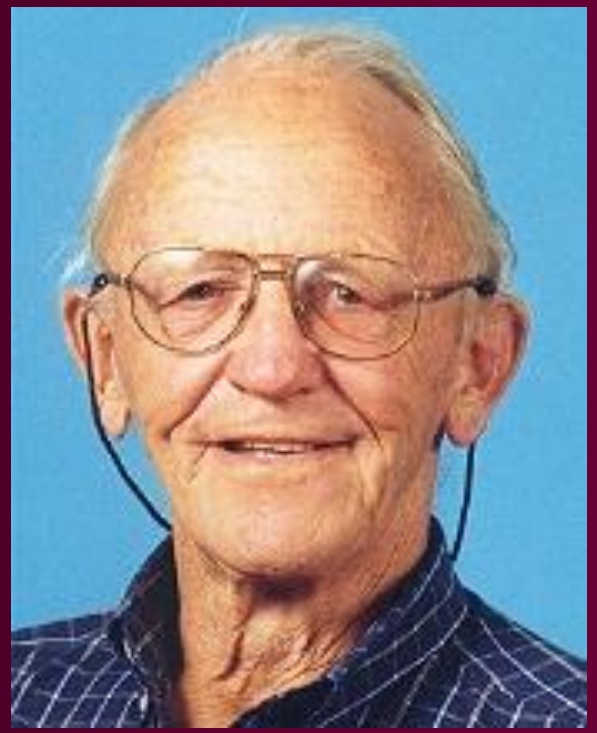
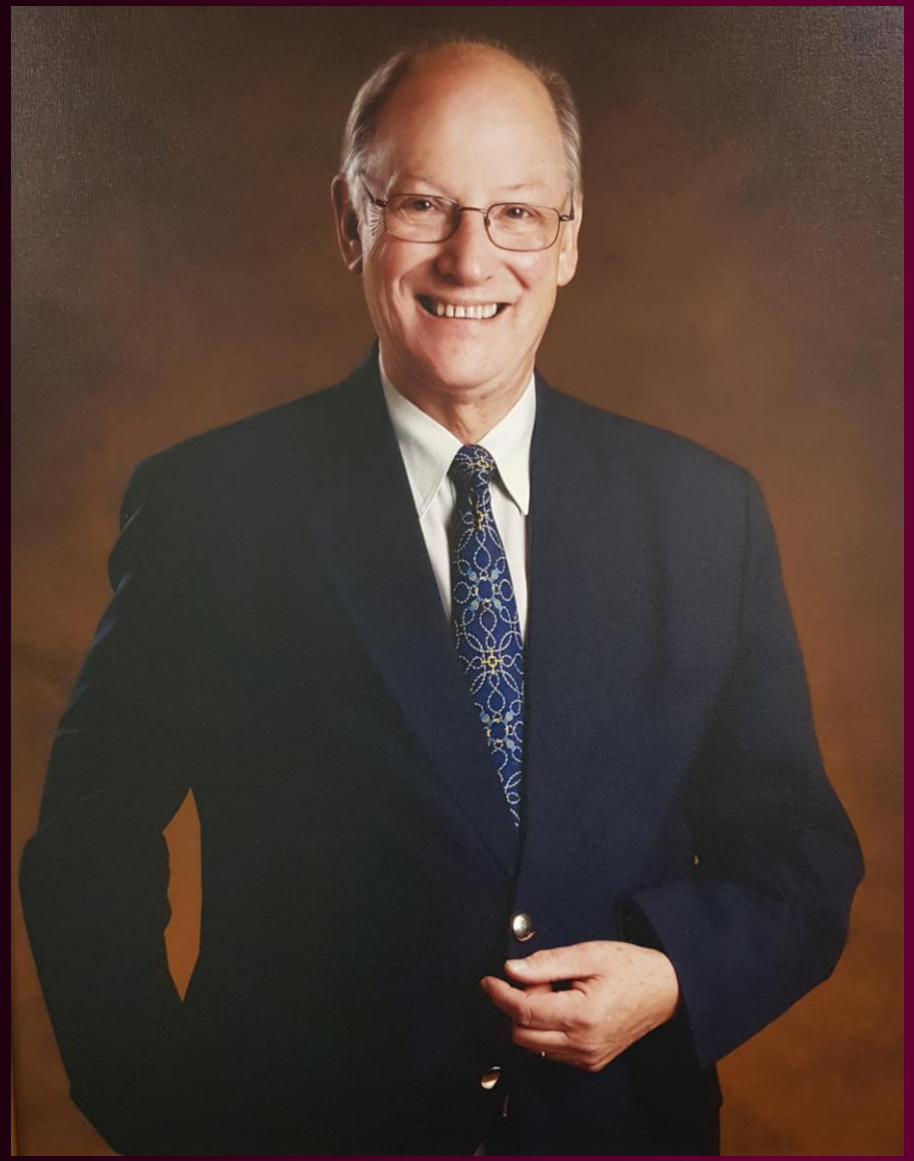
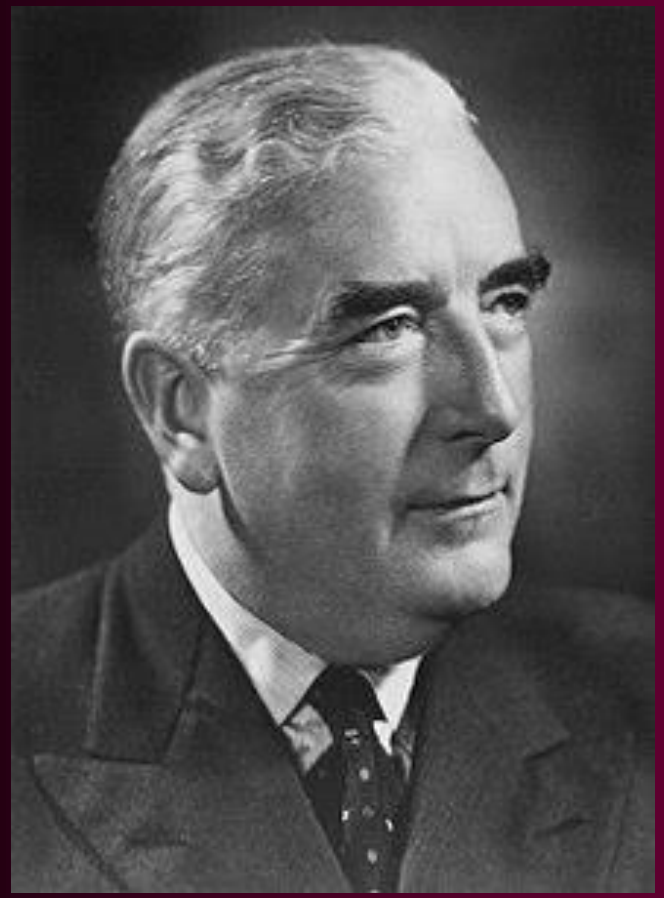









miscarriage



1940s-1950s

- Care for very preterm infants

"Spartan" approach

"Pink" – Little help for breathing problems

"Warm" – Temperature control "poor" – "poikilotherms"

"Sweet" – Babies not fed for several days

1940s-1950s

- Few survivors <1500 g or < 32 weeks
- Long-term outcomes for survivors poor – Cecil M Drillien, Edinburgh – outcomes for babies weighing less than 3 pounds (1361 g)

1940s-1950s

- Commonest cause of death of preterm infants - respiratory distress caused by hyaline membrane disease (HMD) (surfactant deficiency)

Treatments

Oxygen

Assisted Ventilation

Surfactant

Treatments

Oxygen

Assisted Ventilation

Surfactant


PREMATURE INFANT HUMIDICRIB, 1949
Designed and built at the Women's Hospital by Dr Refshauge and the hospital engineering, Mr J Murphy, this cot was a major improvement in the care of premature infants.
The humidicrib was designed to be portable, to transport premature babies from one hospital to another while ensuring a certain temperature and flow of oxygen. It was the forerunner of the Newborn Emergency Transport Service (NETS) of the Women's Hospital today.
Before the development of the incubator, the survival chances for premature babies were slim, mainly due to babies becoming too cold after birth. The need for a special incubator was recognised as early as 1876 by The Women's Hospital when Honorary Medica. Staff asked the Committee of Management, "that a special incubator for the reception of premature infants be purchased".
THIS COT SAVES LIVES
WOMAN'S DAY ARTICLE ABOUT THE HUMIDICRIB (7 NOVEMBER 1949)
TRANSPORT INCUBATOR, R.W.H., 1947


TRANSPORT INCUBATOR, R.W.H., 1947

Oxygen

- Oxygen therapy in nurseries in 1930s
- 1940s – more oxygen introduced into nurseries through specially-designed incubators – 60%-70% oxygen
- –“routine” inspired oxygen >50% for >28 days for infants <1500 g birthweight
- “Boston disease” – retrolental fibroplasia (RLF)
- retinopathy of prematurity (ROP)

Why give oxygen?

- oxygen reduced periodic breathing

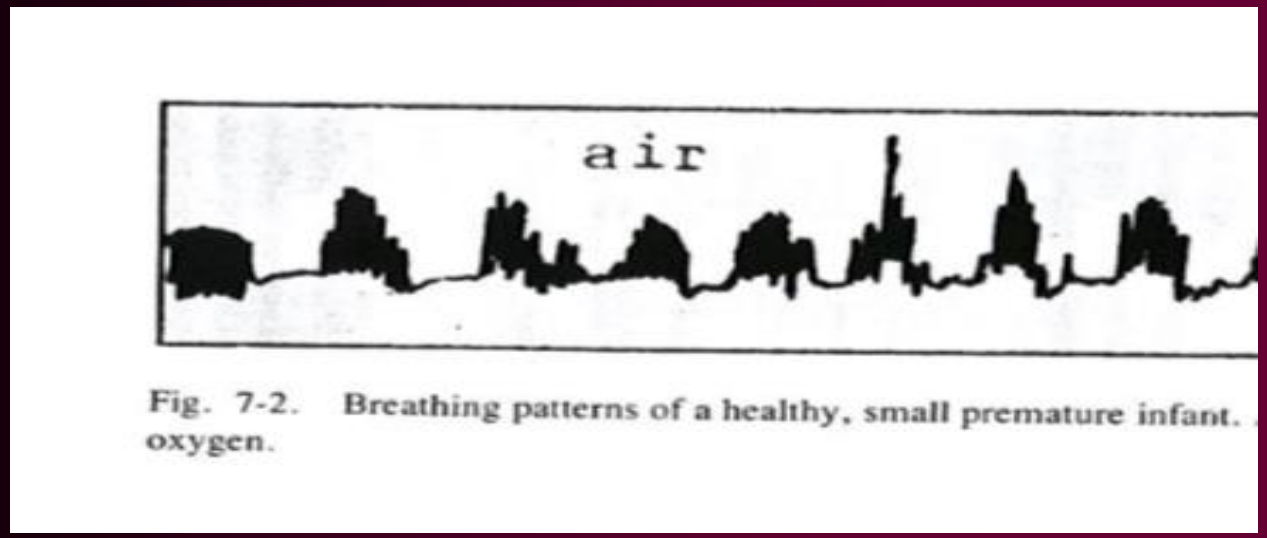


Fig. 7-2. Breathing patterns of a healthy, small premature infant.
oxygen.

Why give oxygen?

- oxygen reduced periodic breathing

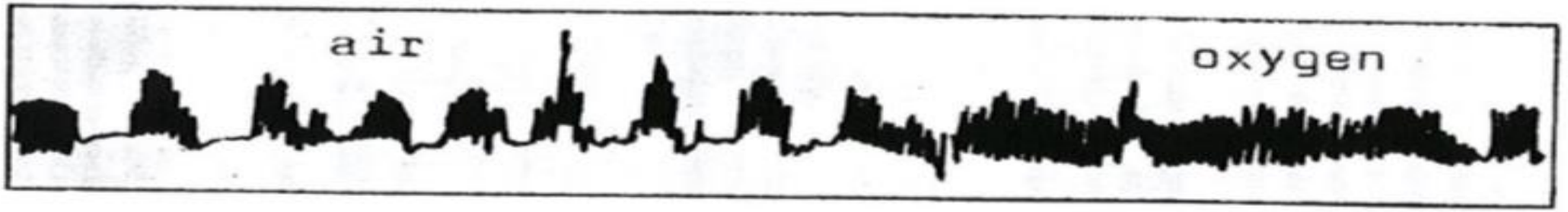


Fig. 7-2. Breathing patterns of a healthy, small premature infant. A "periodic" pattern in room air, "regular" in 70-percent oxygen.

Oxygen

- 1948 – NHS in Britain
- sudden appearance of RLF
- 1951 – Mary Crosse (Birmingham) speculated on oxygen as possible cause – comparing UK and USA

Oxygen

Dame Kate Campbell

Oxygen

- Campbell K. Intensive oxygen therapy as a possible cause of retrolental fibroplasia: a clinical approach.
Med J Aust 1951;2:48-50.

"I heard from colleagues returning from overseas, the suggestion that oxygen might be responsible for causing retrolental fibroplasia."

Oxygen

- Campbell K.
- 3 hospitals 1948-1950

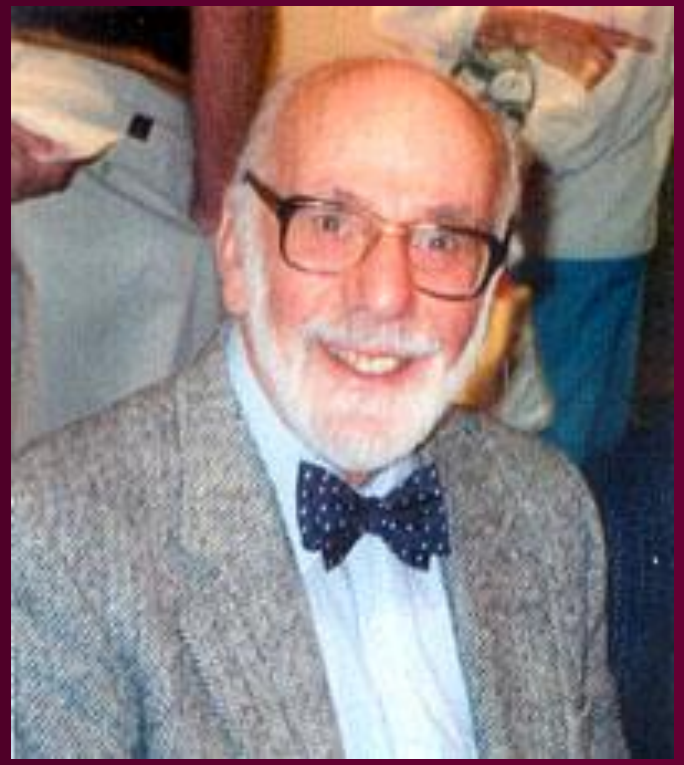
  One hospital – could afford oxygen therapy – piped into ward and given via oxygen cot 40%-60%

  RLF 19%

  Two hospitals – restricted oxygen

  RLF 7%

Oxygen



Bill Silverman
(WA Silverman)
Retrolental Fibroplasia
– a Modern Parable

Oxygen

- Subsequent “RCT” of “routine” vs “curtailed” oxygen (O_2 only if needed, <50%) in USA
- <=1500 g, survived 48 hours
- Competing risks of blindness vs death or brain injury
- First 3 months from July 1, 1953 – random allocation to “routine” vs. “curtailed” in 1:2 ratio.
- If not a difference in mortality – next 9 months all “curtailed”

Oxygen

	n infants
Singletons	
Routine	47
Curtailed	425
Multiples	
Routine	6
Curtailed	108

Oxygen

	n infants	scarring RLF
Singletons		
Routine	47	17%
Curtailed	425	5%
Multiples		
Routine	6	67%
Curtailed	108	14%

End of the epidemic of scarring RLF

Oxygen

Era of oxygen restriction

- Mortality increase from hyaline membrane disease
- in RCT infants >48 hours old!
- 16 deaths for each case of blindness prevented
- Cerebral palsy increase, especially spastic diplegia
- The Cooperative Trial in the USA was going to follow-up the babies, but it never happened!
- Trial largely run predominantly by ophthalmologists!

Oxygen

Switch from inspired oxygen to

- 1960s - arterial pO_2
- 1970s - added transcutaneous pO_2
- 1980s-1990s - added oxygen saturation (sat O_2)
- arterial pO_2 and transcutaneous pO_2 now less common

Oxygen

Bill Silverman - 2004

“ To put it bluntly, there has never been a shred of convincing evidence to guide limits for the rational use of supplemental oxygen in the care of extremely premature infants.”

Pediatrics 2004; 113:394-396

Oxygen

2005 – NHMRC in Australia funding for “BOOST2”

- RCT of different levels of sat O_2

85-89% vs 91-95%

4 other similar trials around the world – New Zealand, Canada, USA, UK

Oxygen

NEOPROM Collaboration – prospective IPD meta-analysis

5 RCTs oxygen targeting in infants <28 weeks

4965 infants worldwide (Askie et al. JAMA 2018)

	85-89%	91-95%	RR (95% CI)	P-value
ROP requiring treatment	11%	15%	0.74 (0.63, 0.86)	<0.001
Blindness	1.3%	1.2%	1.12 (0.60, 2.08)	0.73
Mortality	20%	17%	1.17 (1.03, 1.31)	0.01
Death or major disability	53.5%	51.6%	1.03 (0.98, 1.09)	0.21

at 18-24 months

Oxygen

Most units have gone back to targeting 90-95%

Oxygen

In 2019, do we really know:

How and when to give oxygen?

How and when to monitor oxygen therapy?

The correct saturation range to target?

How to treat ROP?

– Bevacizumab intraocular injection

Bevacizumab RCT

N Engl J Med 2011; 364:603-15 – BEAT-ROP Trial

Infants <1500 g or <30 weeks with Stage 3+ ROP

Primary outcome – recurrence of ROP requiring treatment

Bevacizumab	– 4% (6/140 eyes)	5/75 died
Laser therapy	– 22% (32/146 eyes)	2/75 died

OR 0.17 (95% CI 0.05, 0.53) P=0.002

Long-term neurodevelopmental follow-up on 16 children!!!

Run by ophthalmologists!

History in danger of repeating itself

Bevacizumab

Observational Study Canada Pediatrics 2016; 137:10.1542/peds.2015-3218

Worse outcome in infants treated with Bevacizumab

Treatments

Oxygen

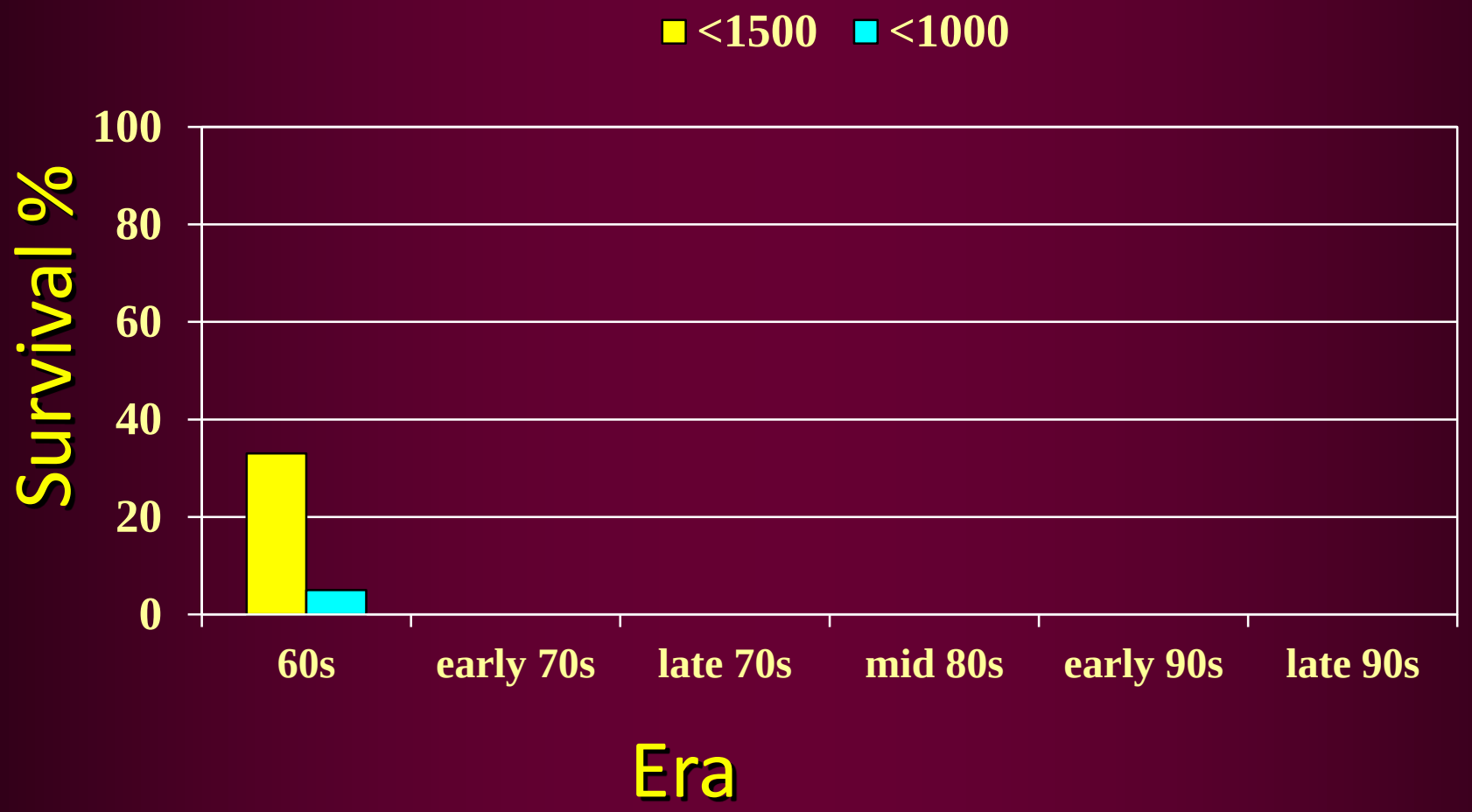
Assisted Ventilation

Surfactant

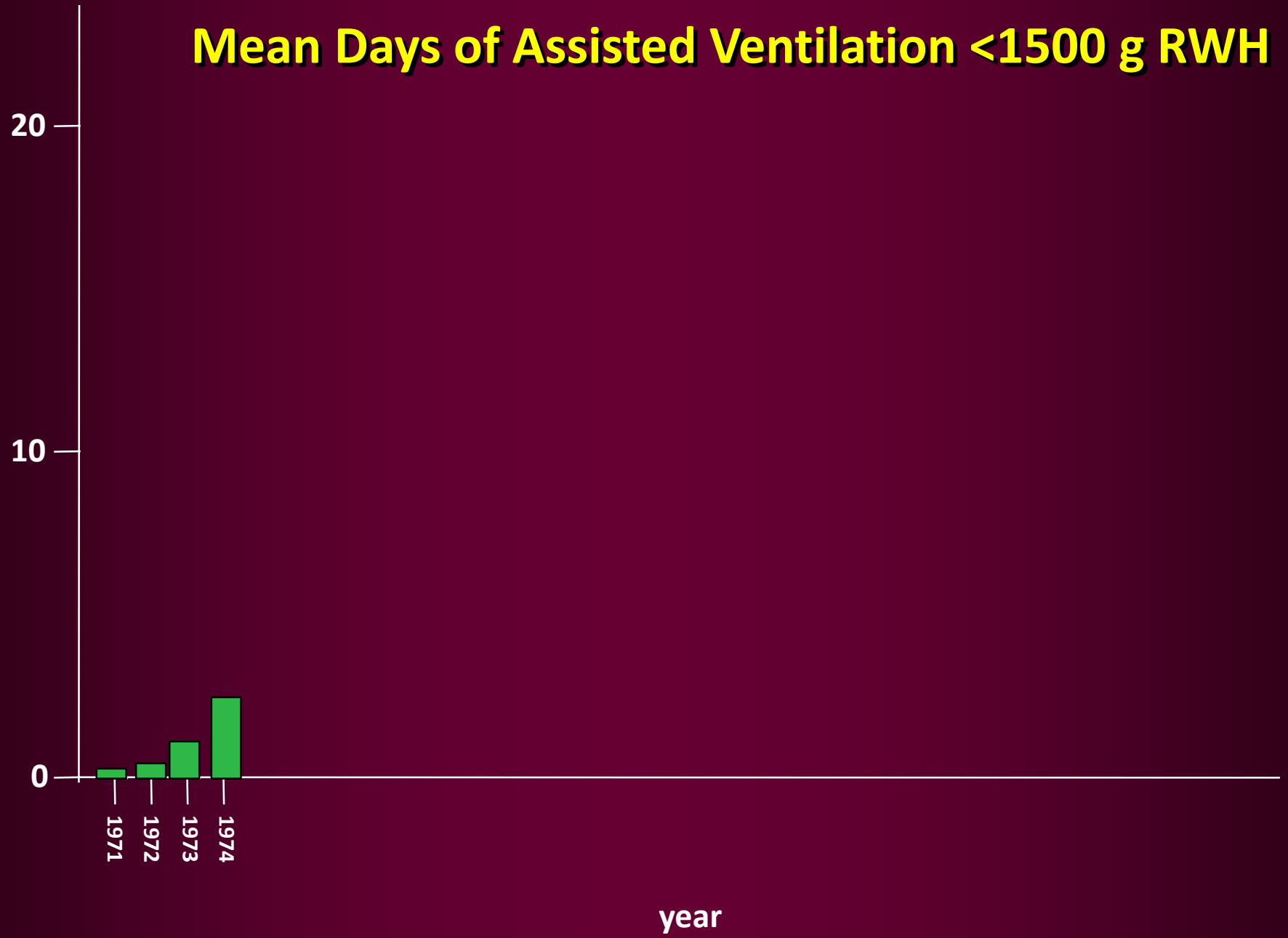
Assisted Ventilation

1960s
adult ventilators
used as last resort in dying babies
survival rates very low
“work of the devil”
1970s
infant ventilators
used earlier in the course of the disease
survival rates rose

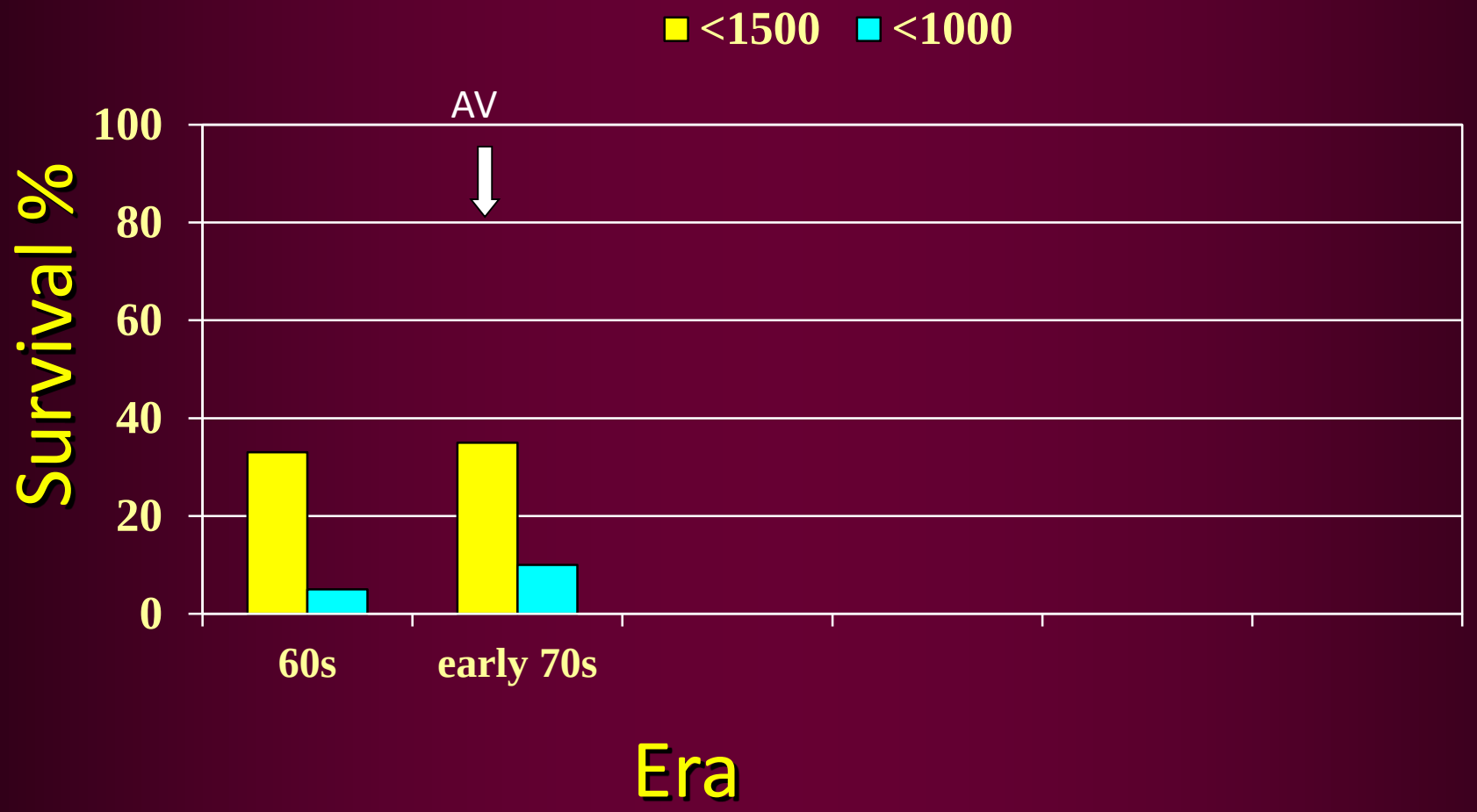
Survival Rates <1500 g RWH



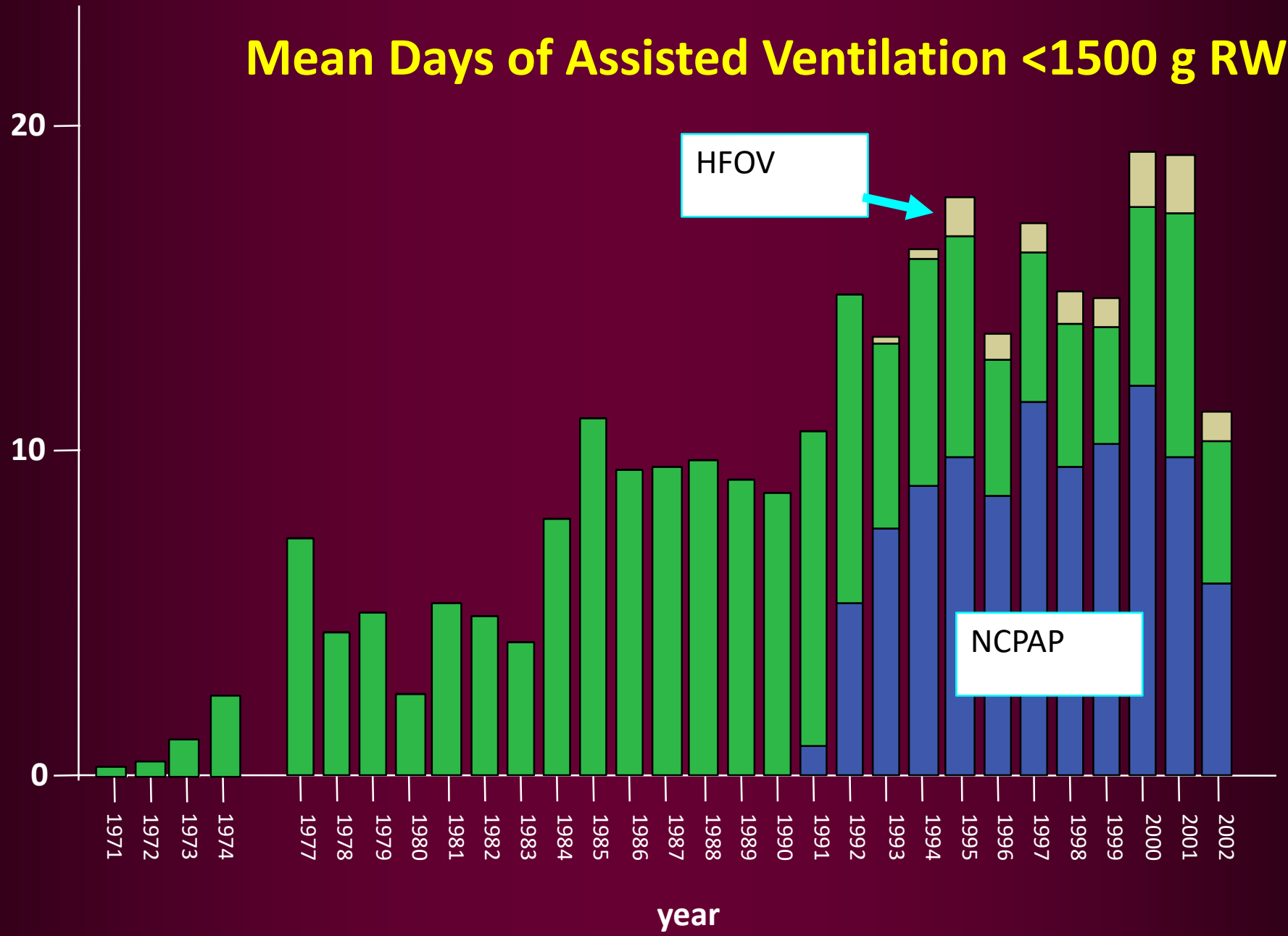
Mean Days of Assisted Ventilation <1500 g RWH



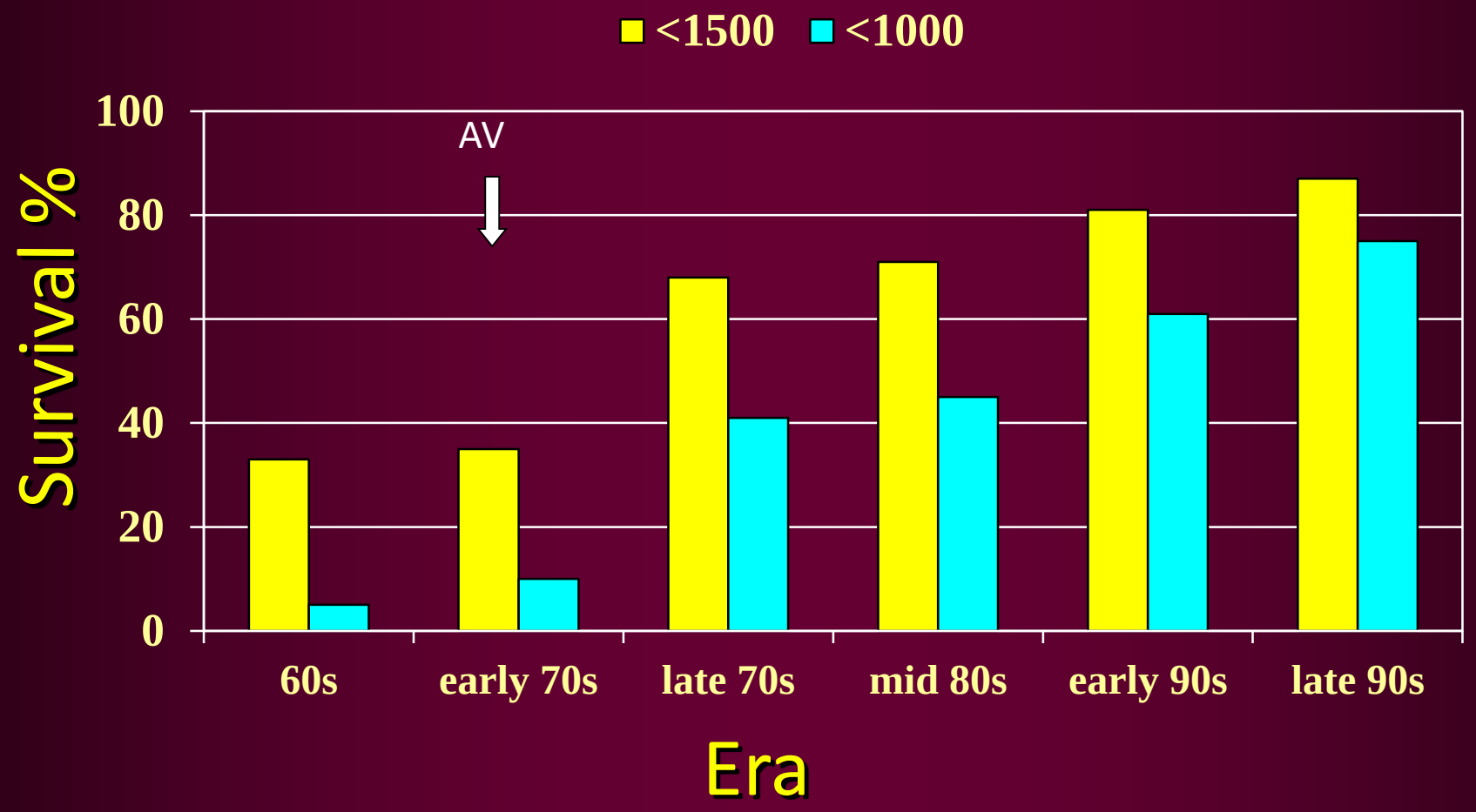
Survival Rates <1500 g RWH



Mean Days of Assisted Ventilation <1500 g RWH



Survival Rates <1500 g RWH



Treatments

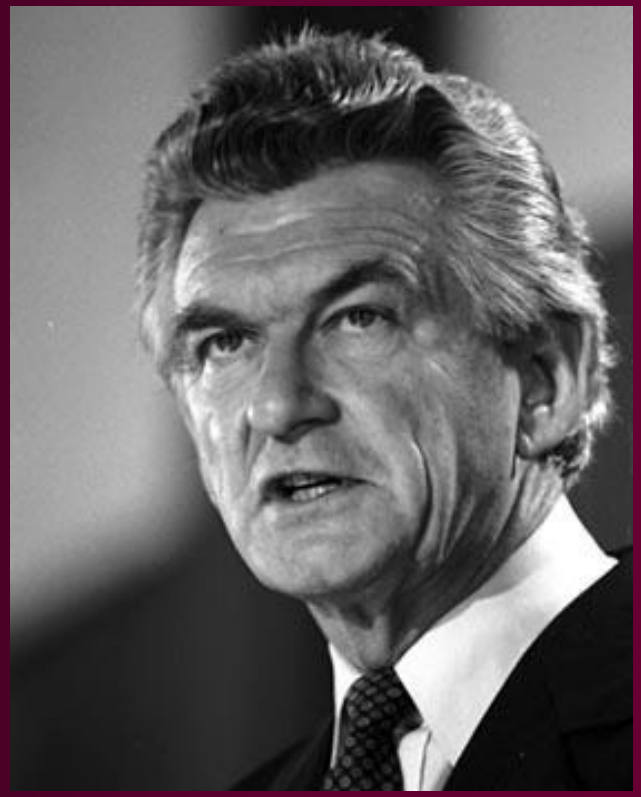
Oxygen

Assisted Ventilation

Surfactant

Why is surfactant important?

A lack of surfactant has affected everyone in this room!



What do these two men have in common?

August 1963!

Bob Hawke

- Robert J Hawke Jr.
- 33 weeks' gestation
- Born 1st August 1963
- Died after 4 days from respiratory distress
- Almost certainly hyaline membrane disease (HMD – surfactant deficiency)

JFK

- Patrick Bouvier Kennedy
- 34 weeks' gestation
- Born 7th August 1963
- Died after 39 hours from respiratory distress
- Almost certainly HMD (surfactant deficiency)
- Tried hyperbaric oxygen
- Assisted ventilation considered but not offered

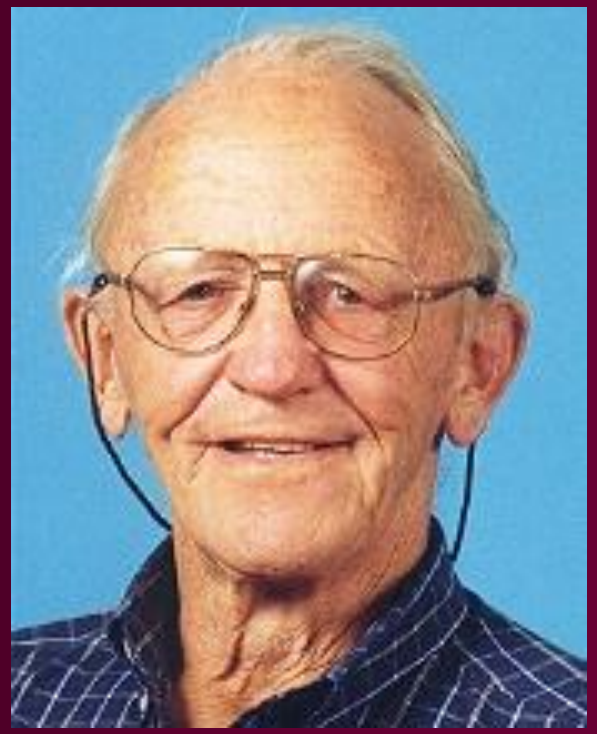
Babies 33 or 34 weeks

- Almost impossible to die from hyaline membrane disease (surfactant deficiency) today!

Just over 3 months later
November 22, 1963 – Dallas, TX

Death of JFK
World history changed forever by lack of surfactant!

Graham “Mont” Liggins



“Mont” Liggins

Antenatal corticosteroid therapy in the 1960s to induce preterm labour in sheep

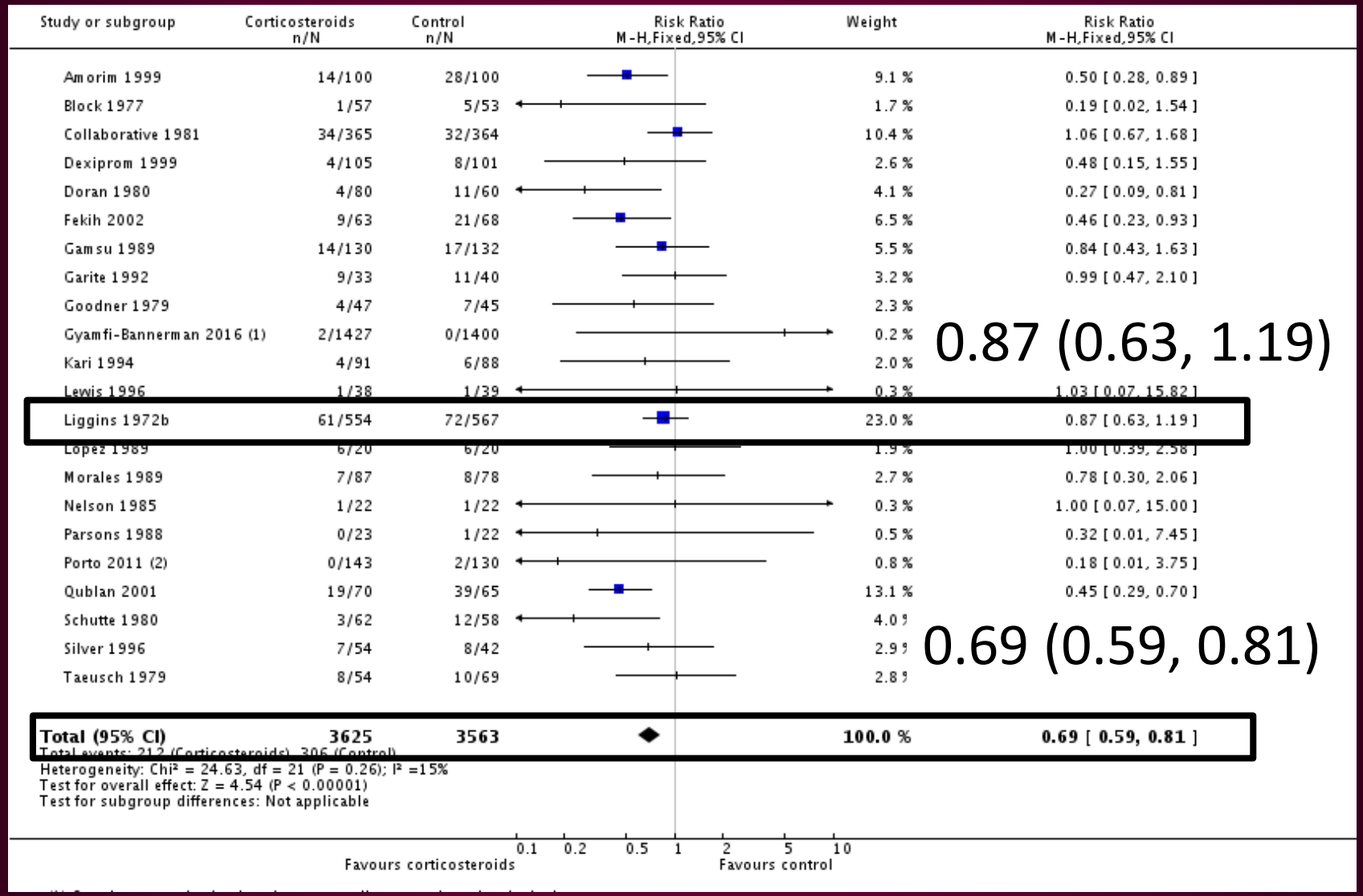
Preterm lambs after antenatal corticosteroids had stable lungs

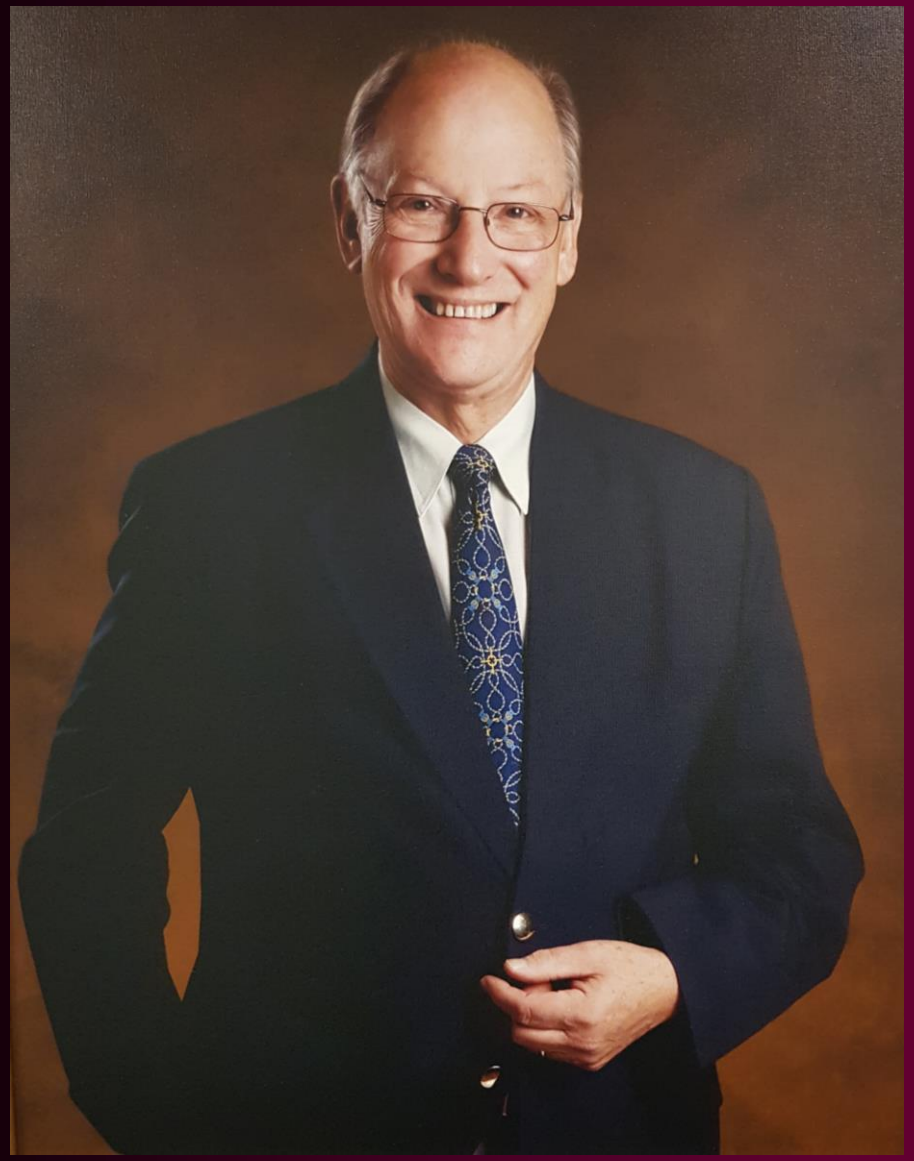
What about humans?

RCT (Howie and Liggins, Pediatrics 1972)

Roberts et al – CDSR 2017

Neonatal death





Roger Pepperell

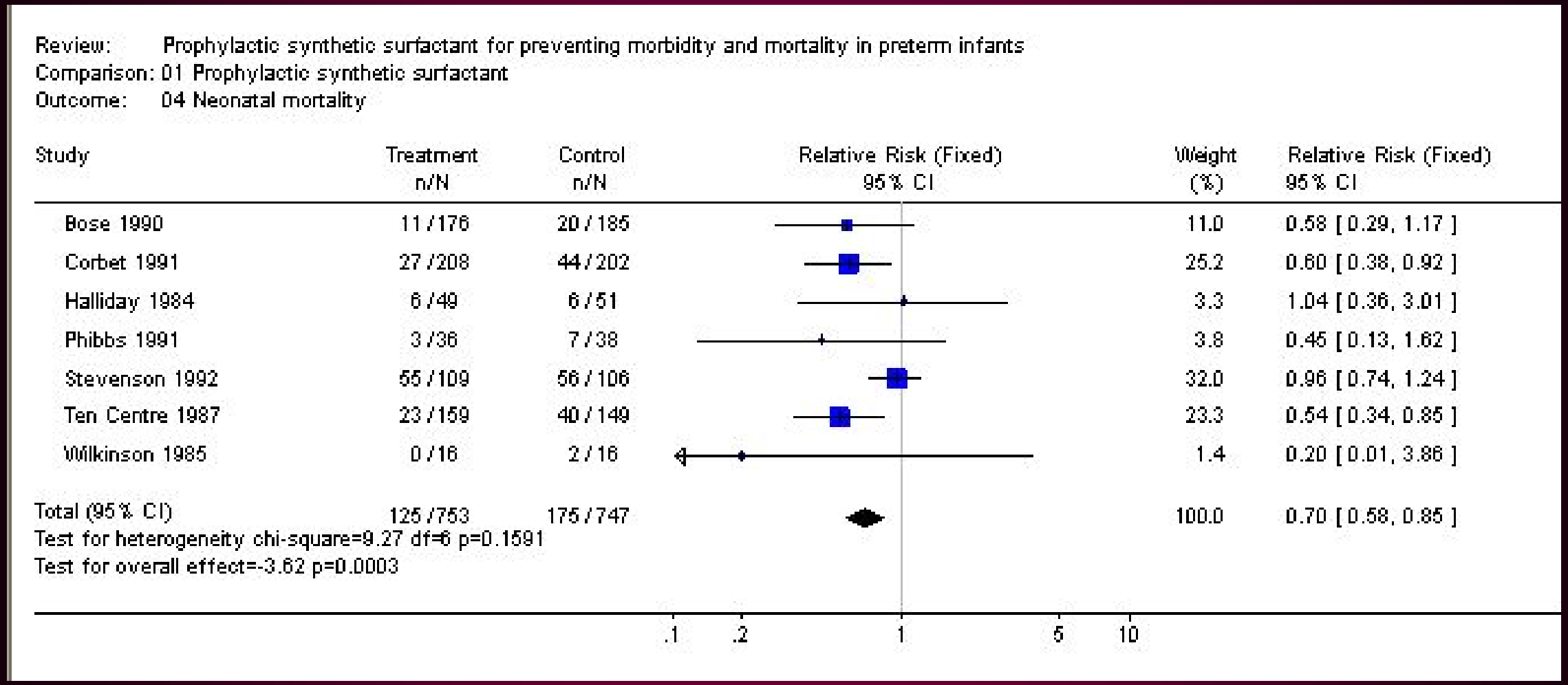
Professor O&G RWH

Clinical trial of antenatal corticosteroids

Neonatal data

“spreadsheet”

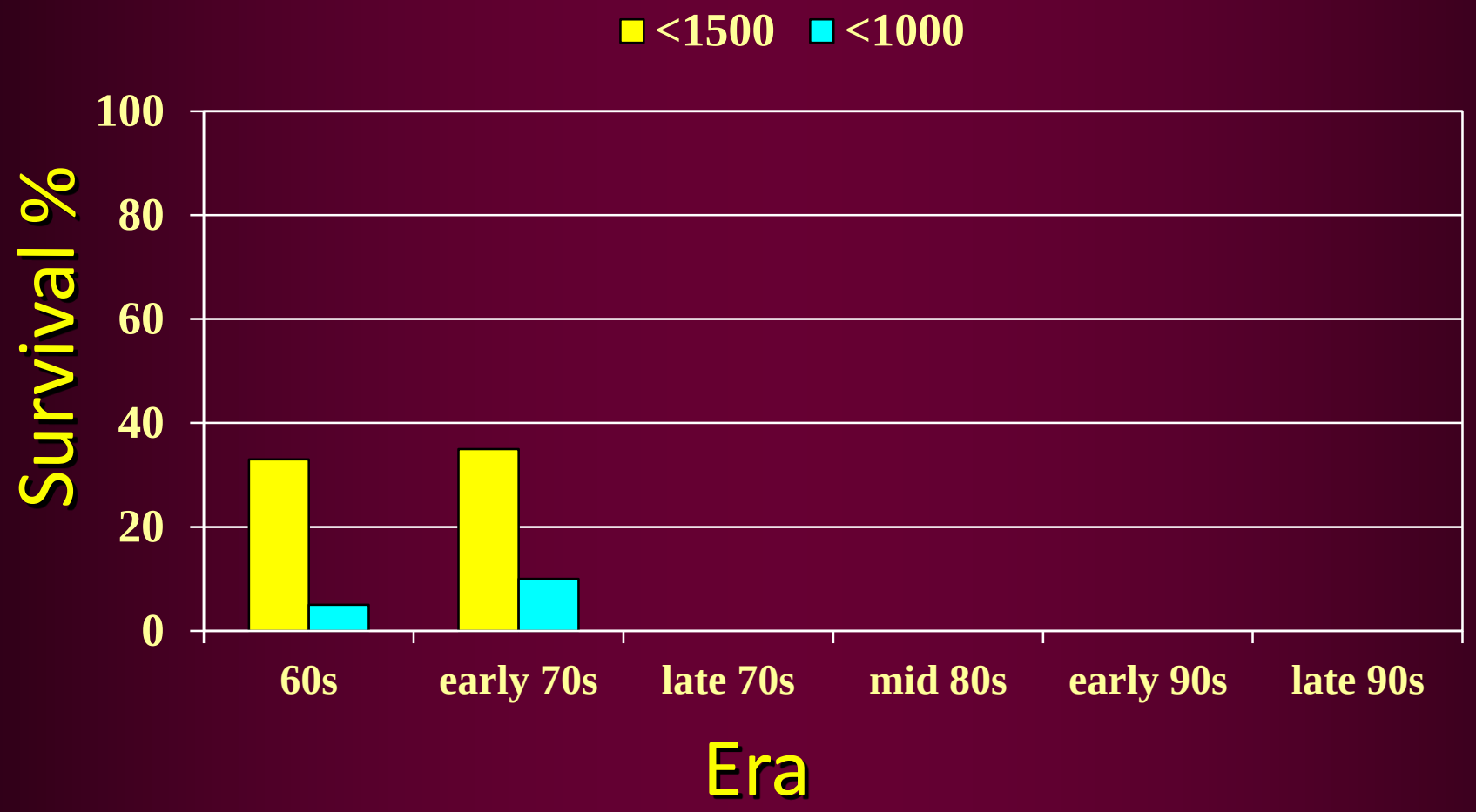
Exogenous surfactant



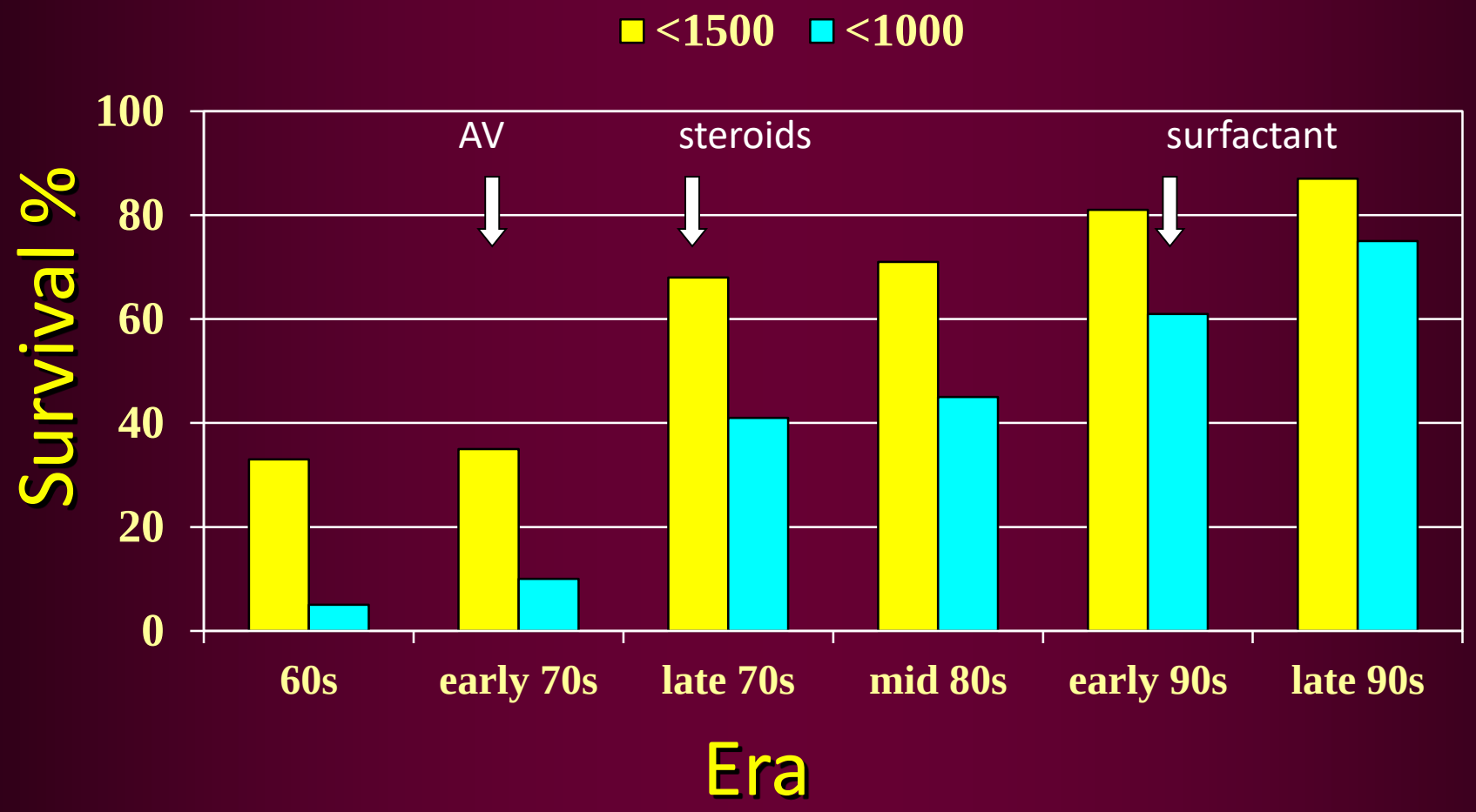
Exogenous surfactant

From March 1991 in Australia

Survival Rates <1500 g RWH



Survival Rates <1500 g RWH



What has happened since the early 1990s?

Between 1991-92 and 2005 in Victoria

More and better surfactant

Outcomes should get better?

No!!!

Increased consumption of resources – assisted ventilation and oxygen

Increased oxygen dependency at 36 weeks

Worse respiratory airflow at 8 years

Doyle et al NEJM 2017; 377:329-337

What has happened since the early 1990s?

Since 2005

More non-invasive ventilation

Nasal CPAP/Nasal HiFlo

Are the babies any better off?

What about other long-term outcomes?

WH (Bill) Kitchen

5th Howard Williams Medalist

WH (Bill) Kitchen

- First trial of “intensive care” in Australia
- 1966-1970 Royal Women’s Hospital
- Ability to measure pO_2, infuse glucose and HCO_3^-
- 1000-1500 g birthweight
- increased survival
- increased “handicap” in survivors

One – hospital – limited viewpoint

State of Victoria – Victorian Infant Collaborative Study (VICS) Group

Victoria – 8 years of age

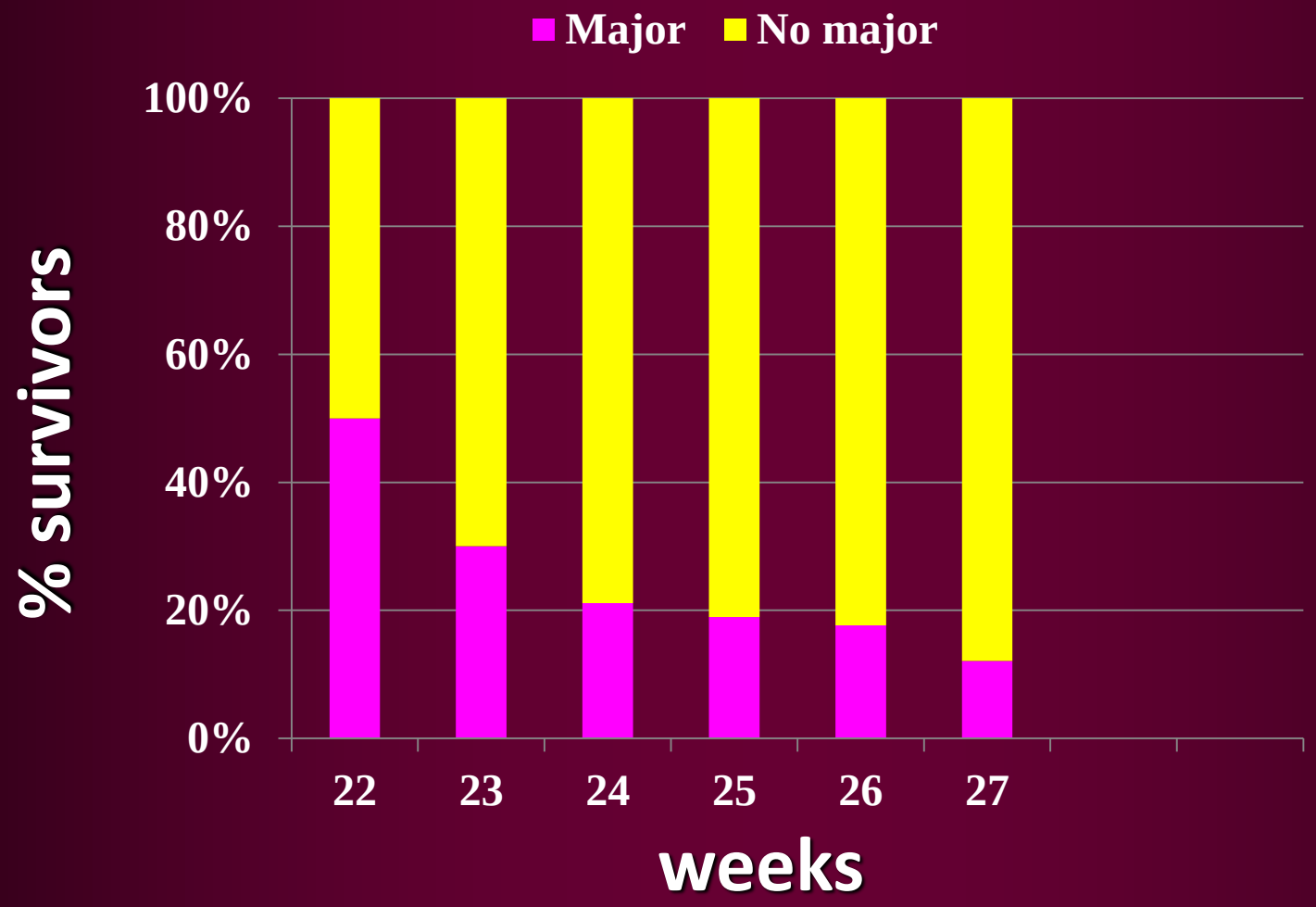
3 VICS cohorts: 1991-92, 1997, 2005
Major disability rates

Major problems with thinking, hearing, seeing, walking or talking at 8 years of age

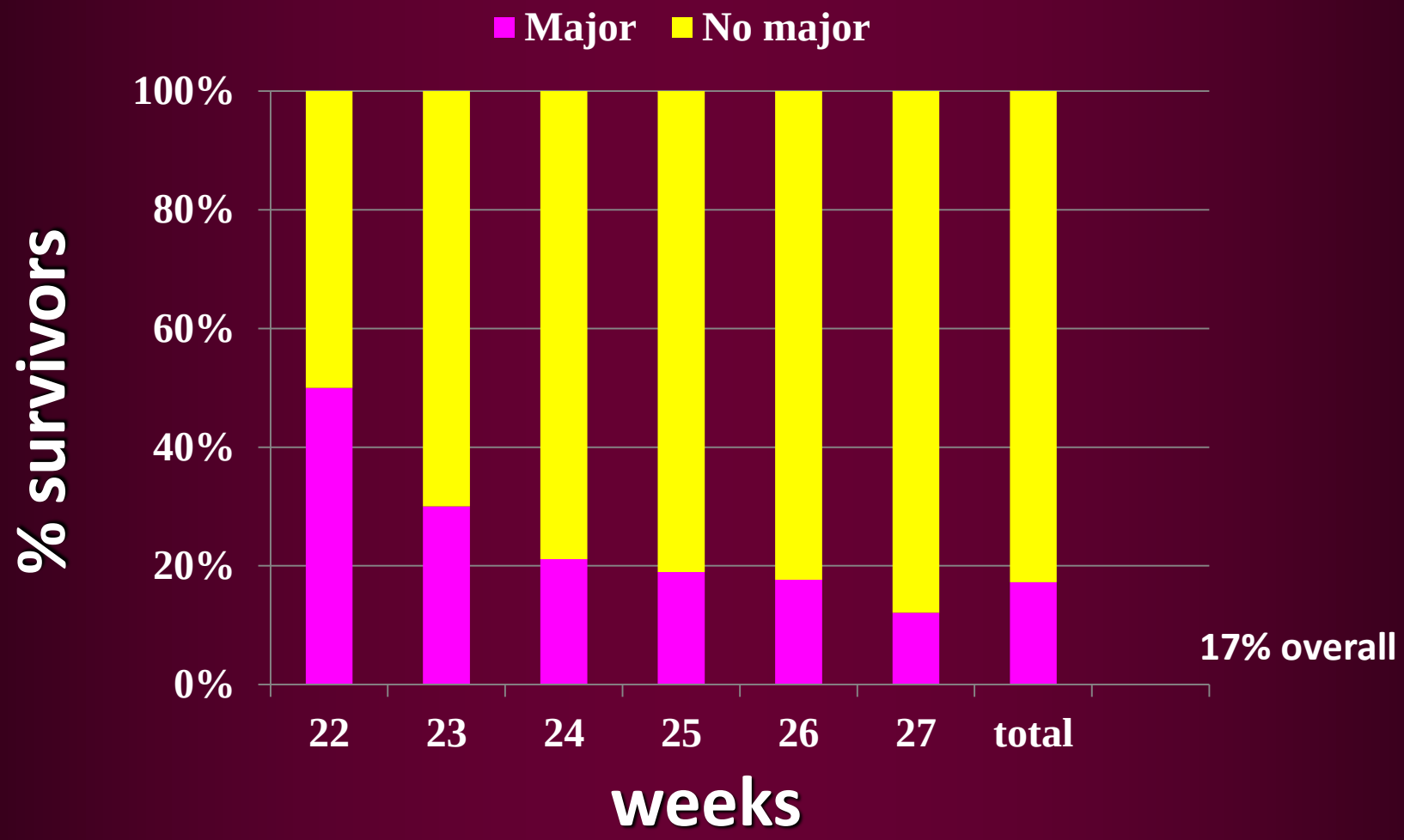
Major neurosensory disability
    Severe or moderate CP (GMFCS 2-5), blindness, deafness, IQ <-2 SD

Follow-up rate 92% overall

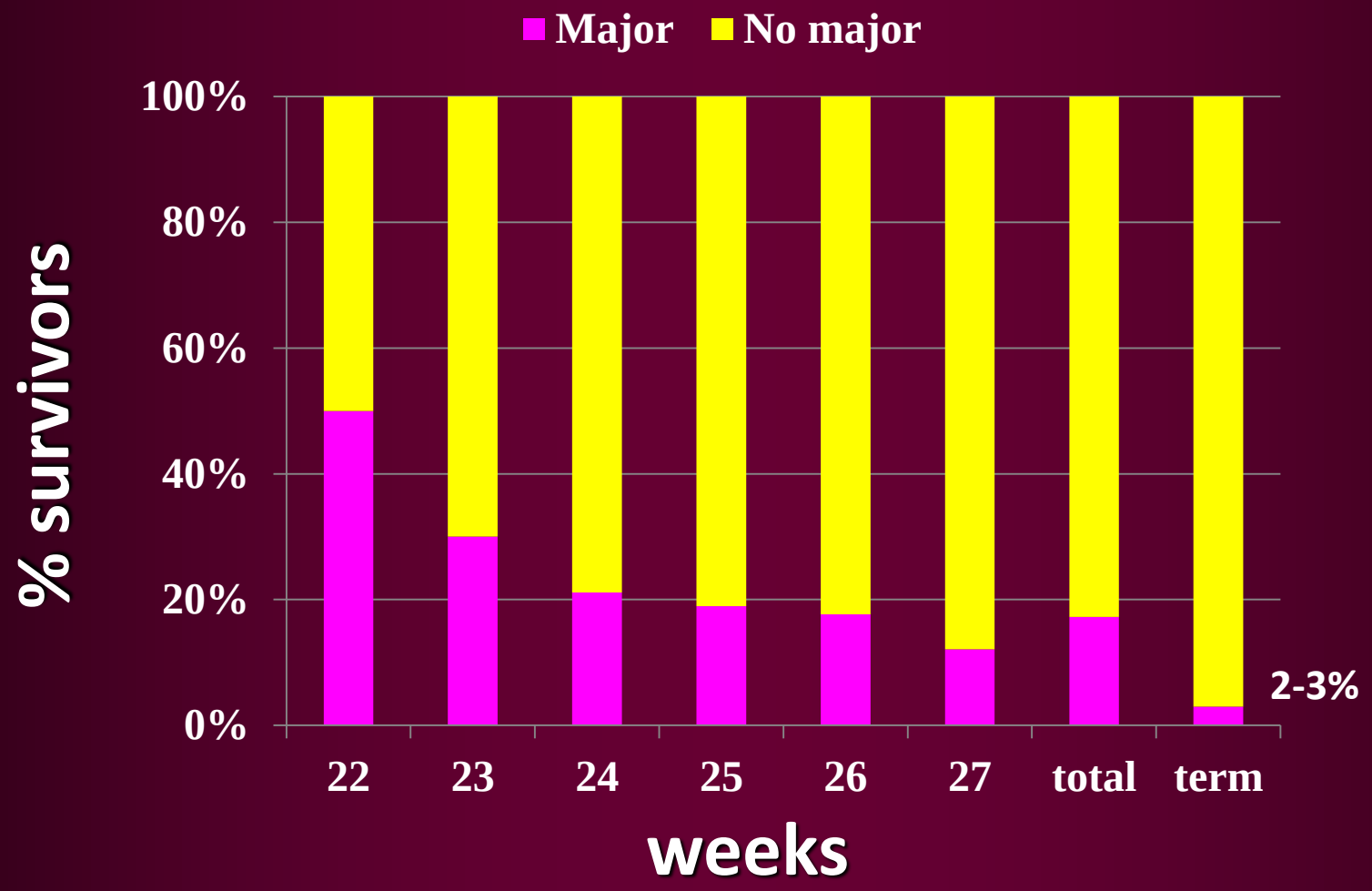
Major Disability



Major Disability



Major Disability



Why bother treating <28 weeks?

Will we flood our resources for disabled children?

State of Victoria

200 EP livebirths per year

75% survive = 150 per year

17% major disability = 26 per year

72000 term livebirths 2017

99.7% survive = 71784

2% major disability = 1437 per year

Why bother treating <28 weeks?

Will we flood our resources for disabled children?

State of Victoria

200 EP livebirths per year

75% survive = 150 per year

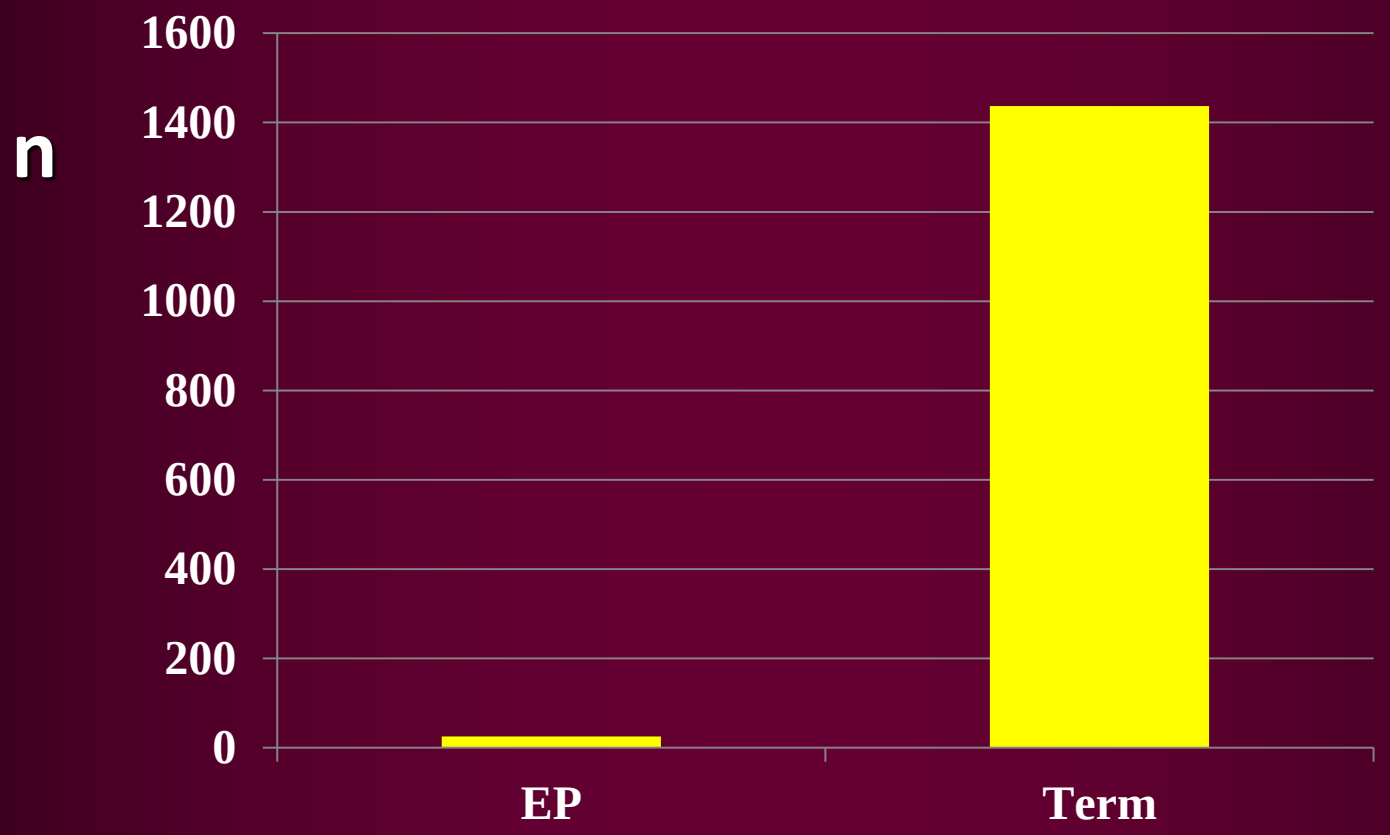
17% major disability = 26 per year

72000 term livebirths 2017

99.7% survive = 71784

2% major disability = 1437 per year

Number per year with major disability



What about other outcomes over time?

- Consumption of resources for assisted ventilation and oxygen are increasing
- Lung function — Doyle et al NEJM 2017; 377:329-337
- Academic progress — Cheong et al Pediatrics 2017; 139: e20164086
- Motor function — Spittle et al Pediatrics 2018:10.1542/peds.2017-3410
- Executive function — Burnett et al Pediatrics 2018 :141:e20171958

All getting worse!

Howard E Williams Oration

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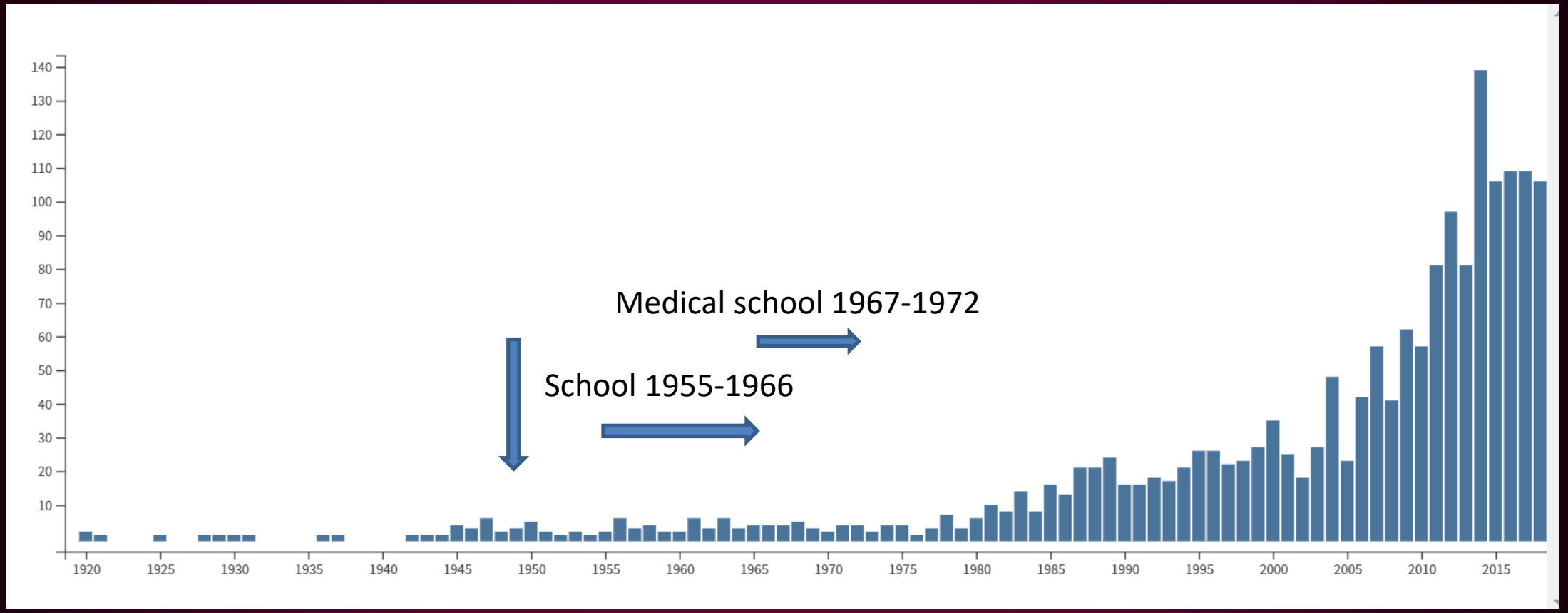
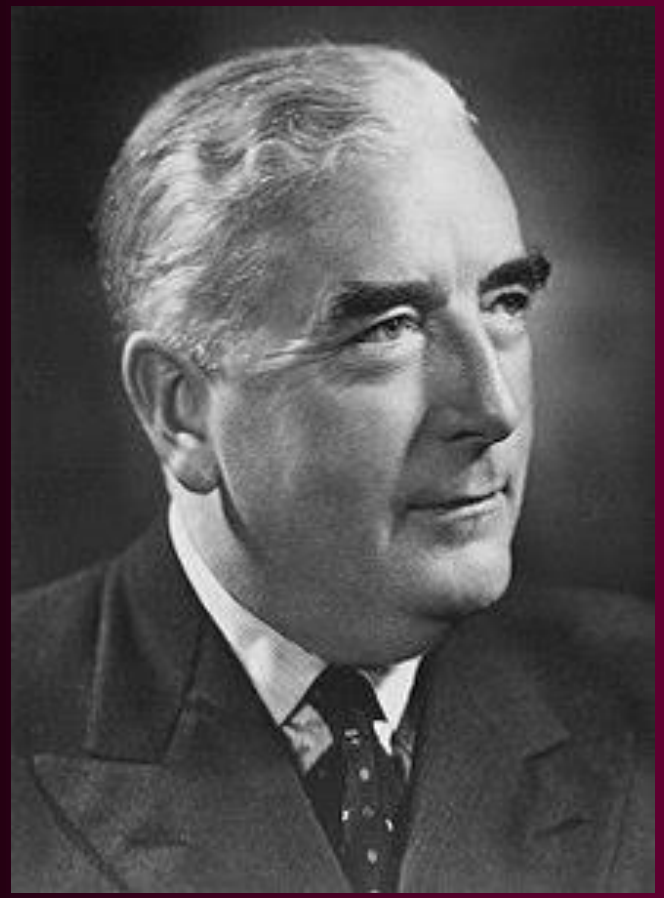
Publications per year – Doyle L*



1920

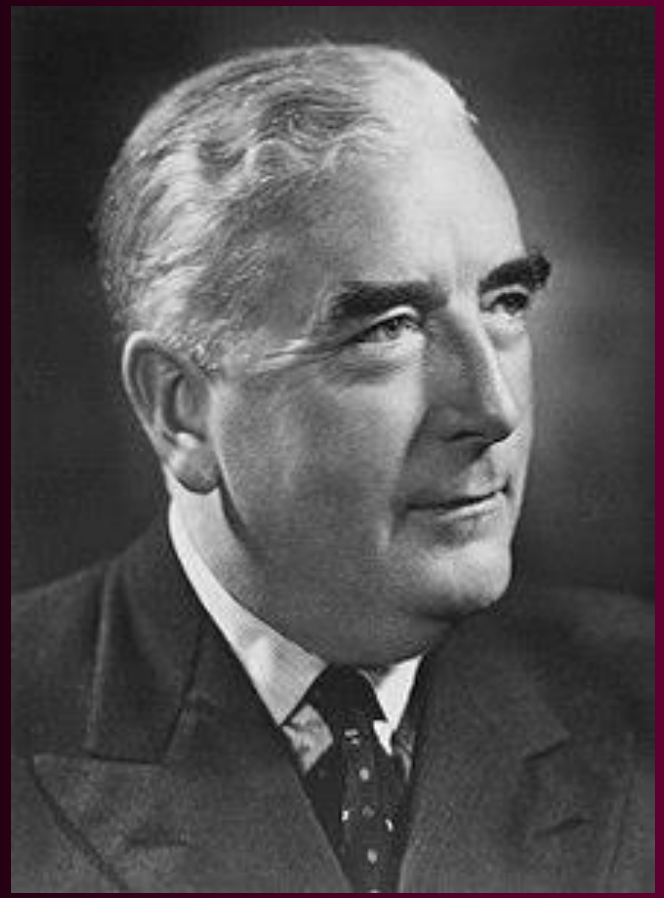


RG Menzies

Prime Minister of Australia

1939-1941

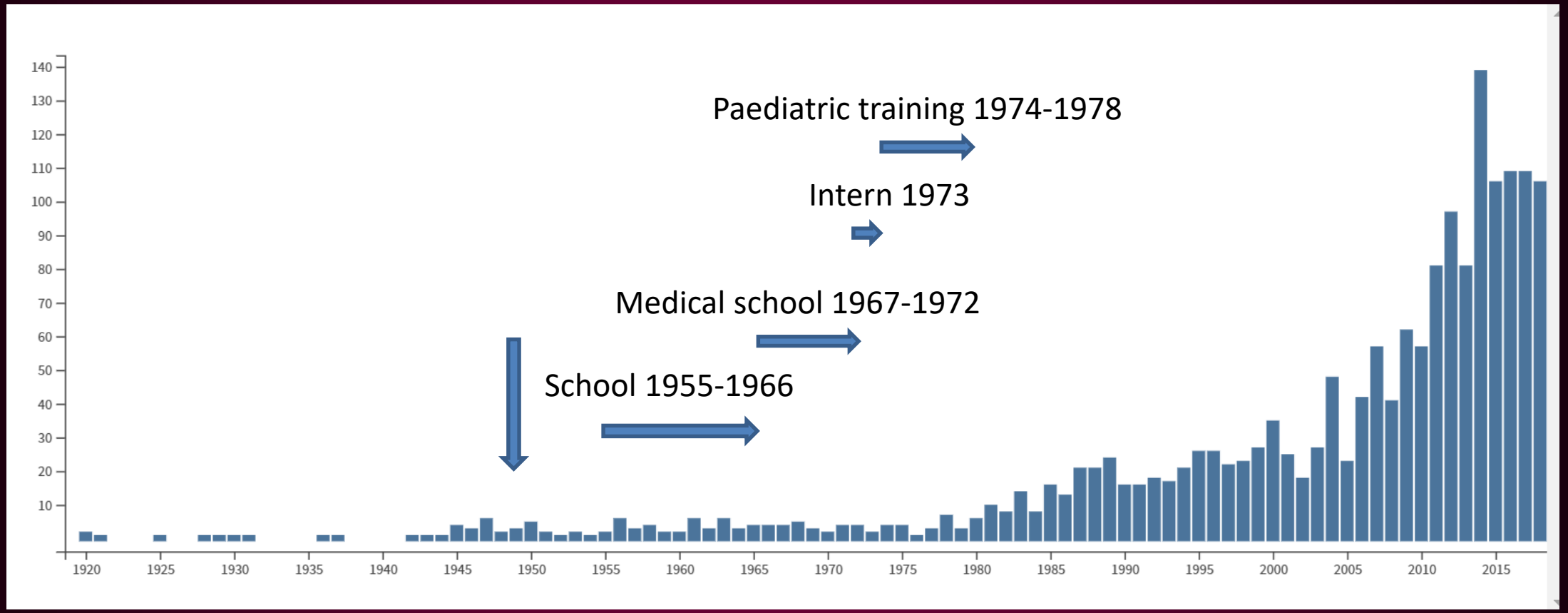
1949-1966



Commonwealth Scholarships

- High School
- University
- Why Medicine?
  - 6 years!

Publications per year – Doyle L*



1920

LWD – medical training

Internship 1973

Paediatric training 1974-1978

Royal Children's Hospital (RCH), Melbourne

Royal Women's Hospital (RWH), Melbourne

LWD – Neonatal training

1974

RCH JRMO

no neonates

LWD – Neonatal training

RCH registrar 1975

- Haematology rotation
- Covering neonatal unit on weekends
- First weekend coincided with Annual Meeting ACP!

LWD – Neonatal training

RCH/RWH registrar 1975 – 4 month rotation

one of two RCH registrars; 1 “fellow” (O&G registrar)

responsible for 40% of public babies (not ventilated)

100 babies in the nursery

normal babies in hospital 7-8 days; 9-10 days if caesarean

nursed in communal nursery

rotavirus epidemic

Importance of RWH rotavirus

1. Rotavirus discovered in faeces of neonates from RWH
2. Original strain used in a current rotavirus vaccine

LWD – Neonatal training

RWH ventilation 1975

Three Loosco (“Amsterdam”) ventilators

max rate 60, maximum I:E ratio 1:1

One Baby Bird – invariably lethal

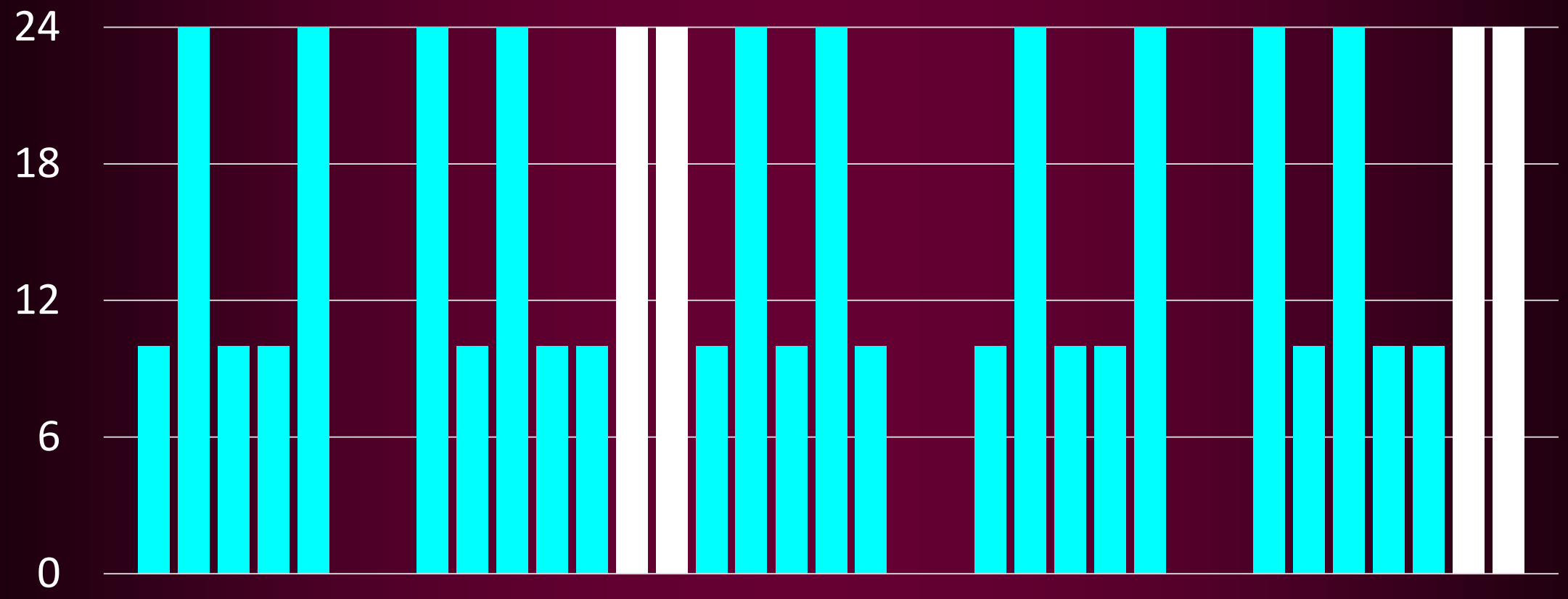
“Square” pressure waveform; I:E 2:1; rate 30-35

High rate of air leak

– air into “strange” places, including neck, scrotum, pericardium and

circulation (air embolism) – air angiogram!

Daily hours worked over a 5-week cycle



2/5 nights and weekends (weekly: 78 hrs x 3; 126 hrs x 2)

LWD – Neonatal training

1976

Passed Part 1 FRACP

Level-2 rotation 6 months

NETS Victoria Oct 1976

LWD – Neonatal training

RCH neonatal unit 1977 – 4 months

no ventilators!

LWD – Neonatal training

Advised not to do neonatology!

RWH “fellow” 1978 – “senior lecturer”

2 RCH registrars; 2 RWH registrars

Director of NICU (Laurie Murton)

Bourns BP 200 (time cycled, pressure limited)

24 hours x 1; NICU Fridays + NETS 24 hours; 1 weekend in 5

(weekly: 64+ hrs x 4; 112 hrs x 1)

1000th NETS trip

1st international NETS trip – to Nauru

Graeme Barnes

Gastroenterologist RCH

19th Howard Williams Medalist

Study in gnotobiotic lambs – oral gammaglobulin prevents rotavirus diarrhoea.

RCT in humans (Barnes et al Lancet 1982)

LWD – Anecdotes

Uncertainty of gestational age

- a case of “bad wind”
- paediatric assessment of GA - Dubowitz
- delivery room dilemma at 26 weeks??

Obstetric solution

- “laying on of the hands”
- early antenatal ultrasound
  - “God-like powers of creation”

LWD

Fellowship McMaster University 1979-1982

Bourns LS 104

Volume limited ventilator

Wind up the volume to maximum then regulate pressure with a blow off valve

“Slave” labour for Canadians

MSc Clinical Epidemiology and Biostatistics

John C Sinclair (Jack)

"Father" of Australian neonatology

Problem-based, self-directed learning

LWD

Research at McMaster 1979-1982

Insensible water loss

Potter Baby Scale

PET Scanning of baby brains

LWD

Return to Melbourne 1983

a. Senior Lecturer O&G, University of Melbourne

b. Consultant paediatrician, RWH, Melbourne

- Director of NICU (Laurie Murton)
- Bourns BP 200 (time cycled, pressure limited)
- More house staff
- Infant Star

LWD

- Death of Laurie Murton 1993

  More clinical work for LWD
- Appointment of Colin Morley 1998
- Patient-triggered, assist control, volume guarantee
- Dräger ventilator – too many “knobs”
- Full time research/teaching from 2006

LWD

2006 - End of my clinical career

What about my research career?

LWD

1982-83

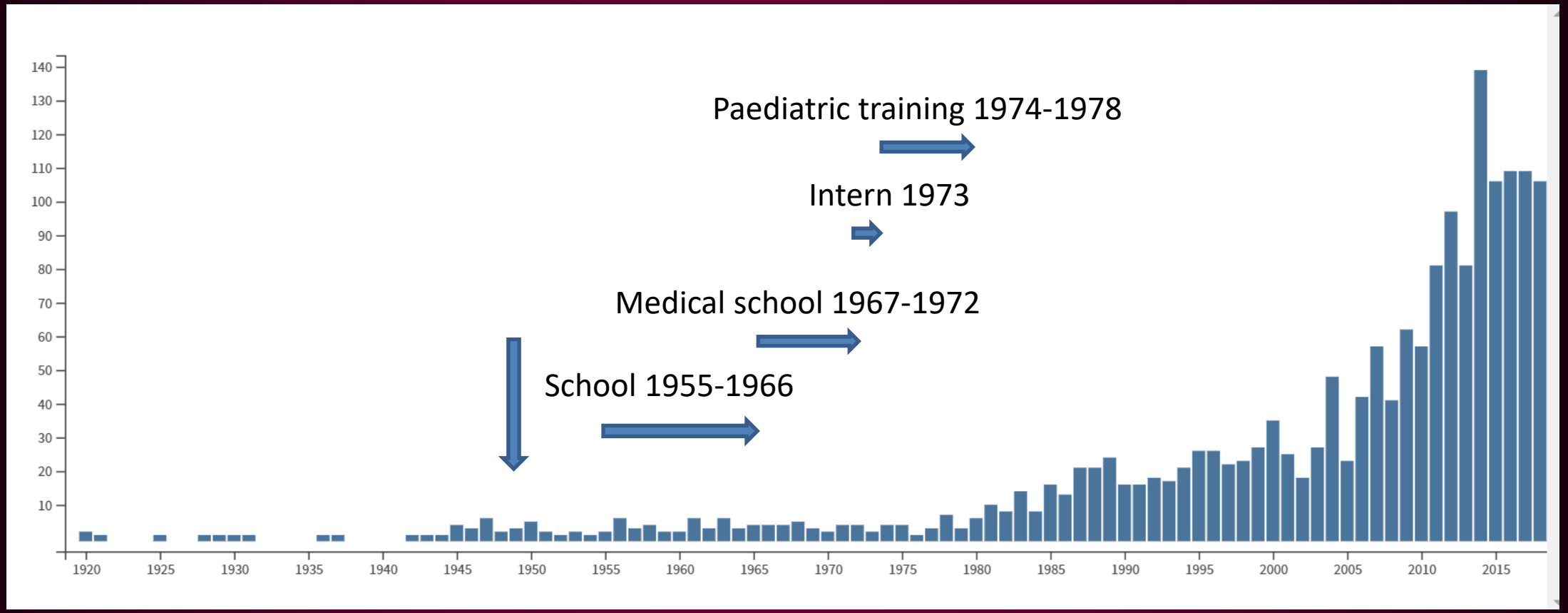
- Designed 2 large RCTS
  1. Fluid restriction to prevent BPD

     - Fluid restriction the norm!
  2. Oral gammaglobulin to prevent NEC

     - withdrawn at NHMRC interview

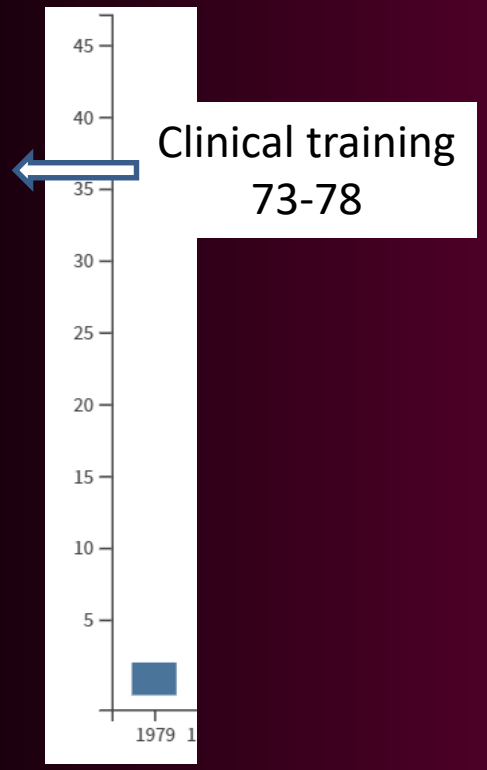
     Research struggling!

Publications per year – Doyle L*



1920

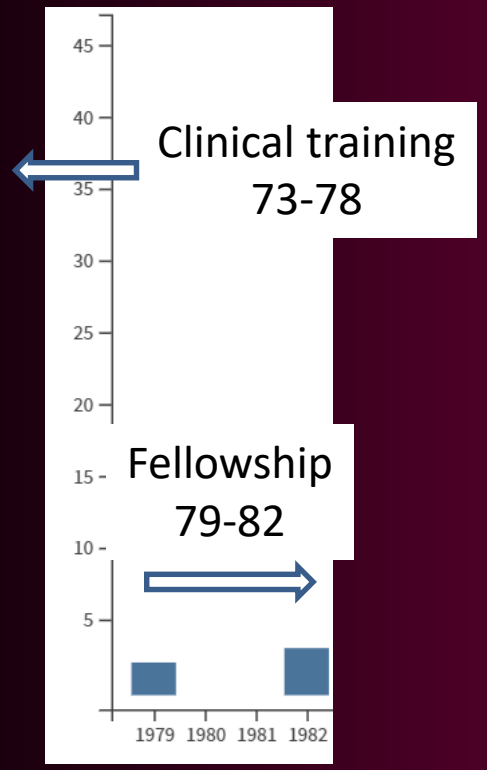
Publications per year



Clinical training
73-78

Relative to opportunity!

Publications per year



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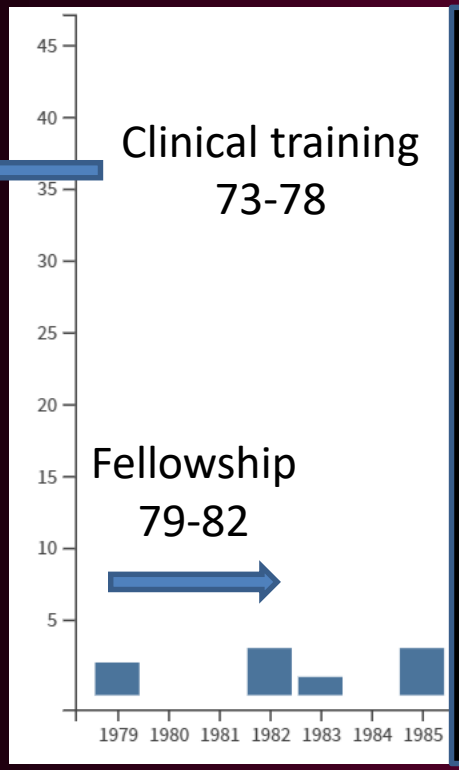
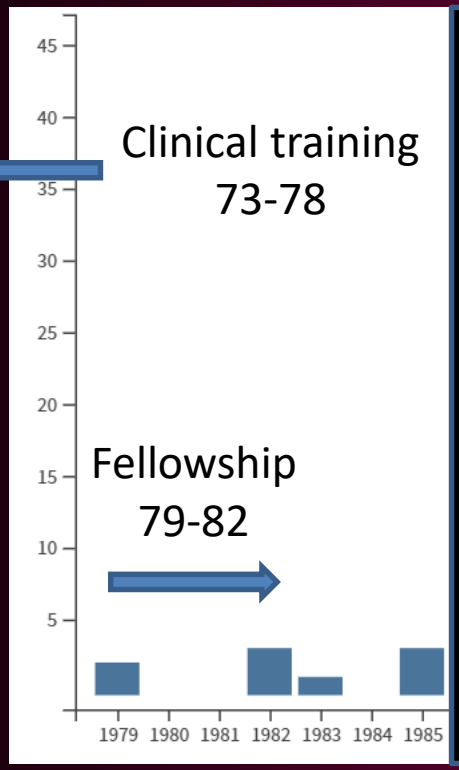


WH (Bill) Kitchen

“crumbs” of data

Publications per year



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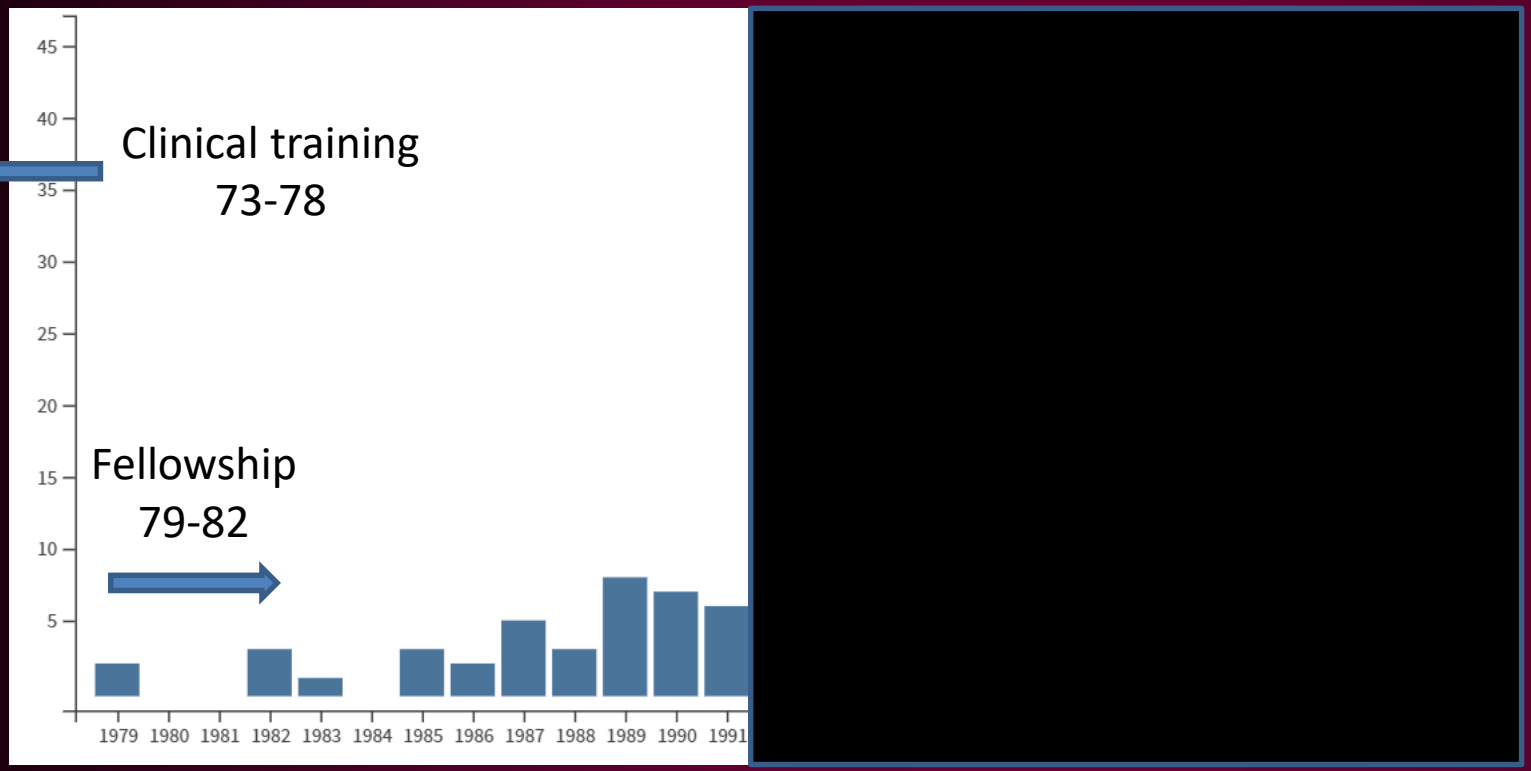

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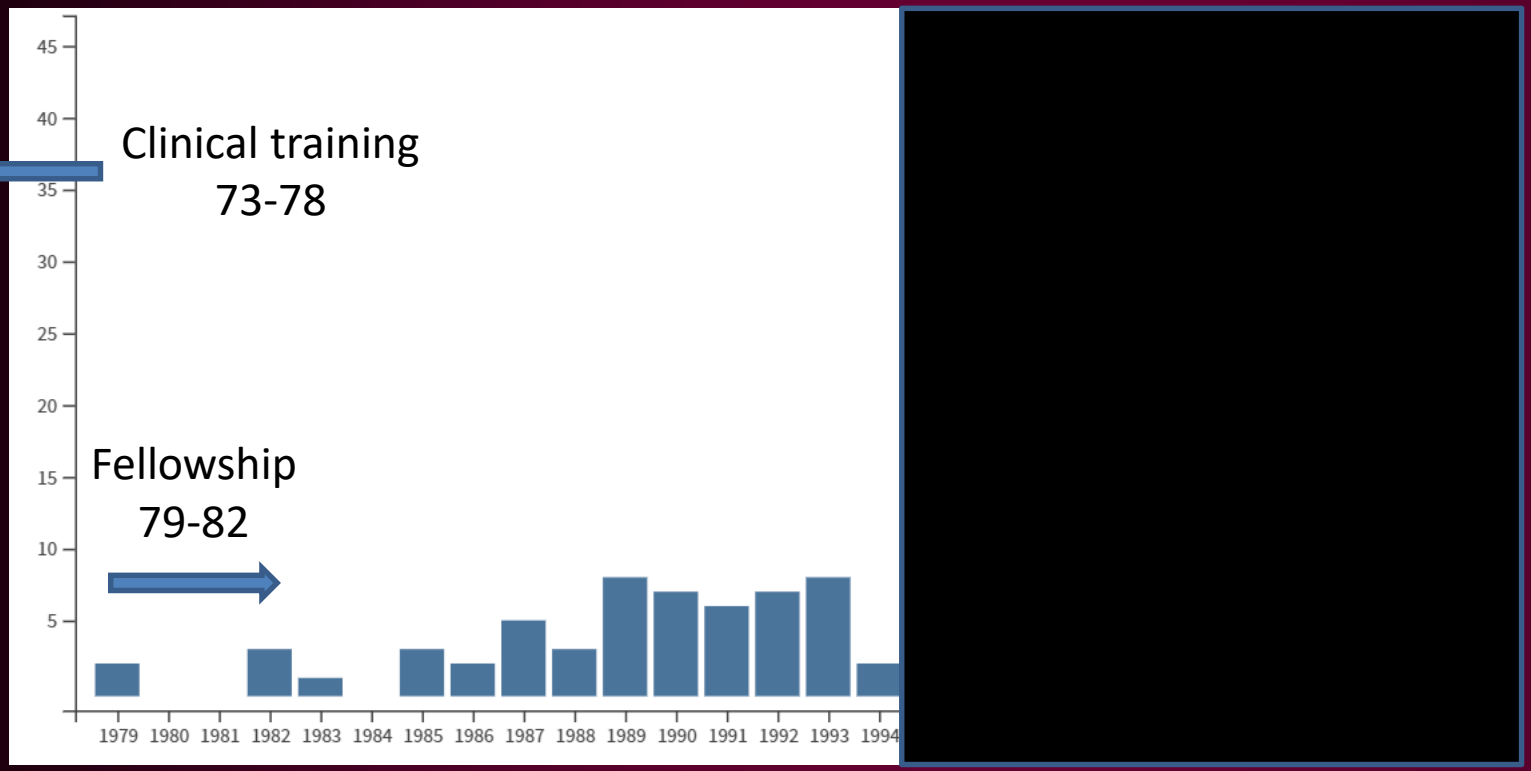
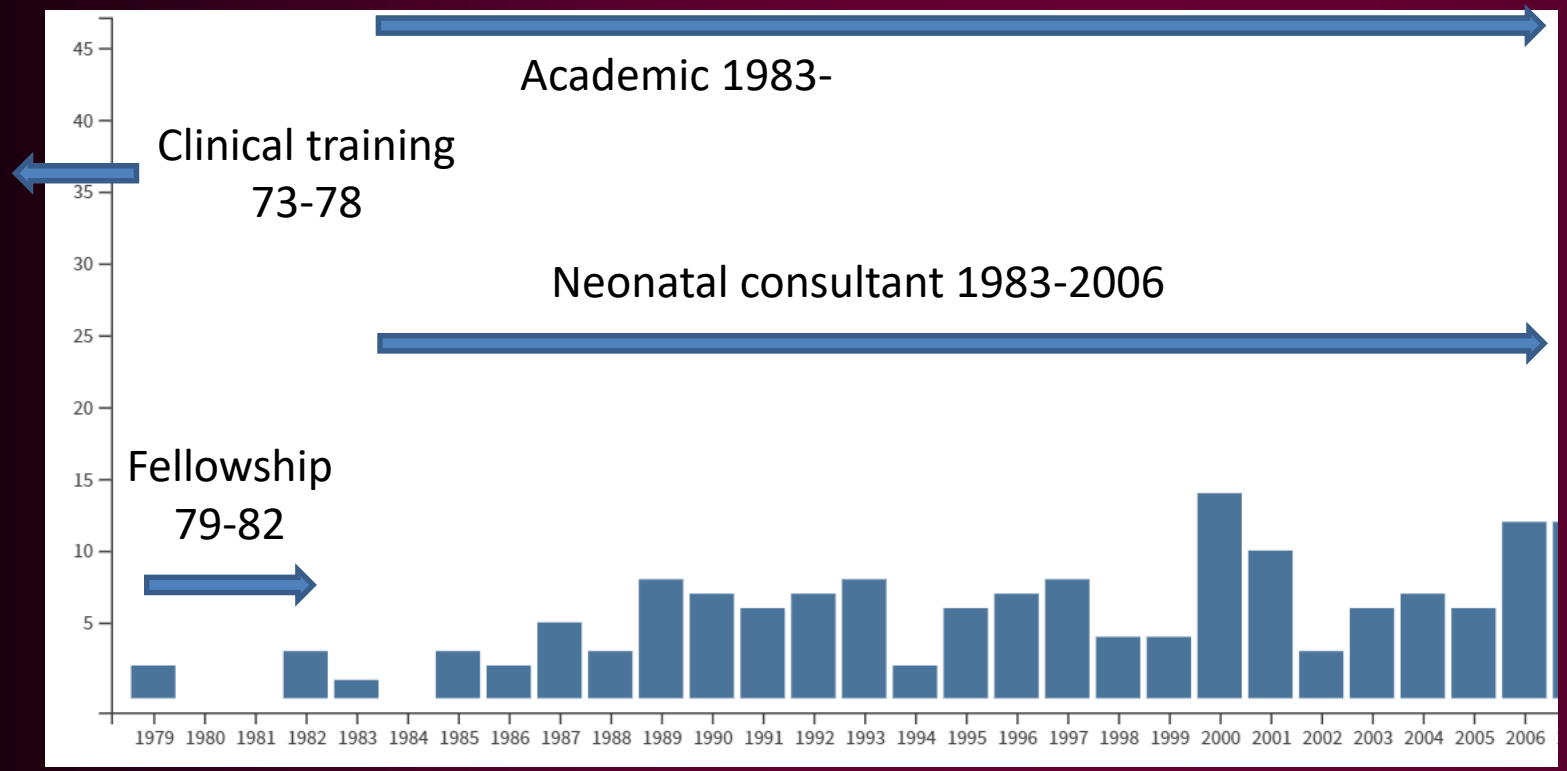
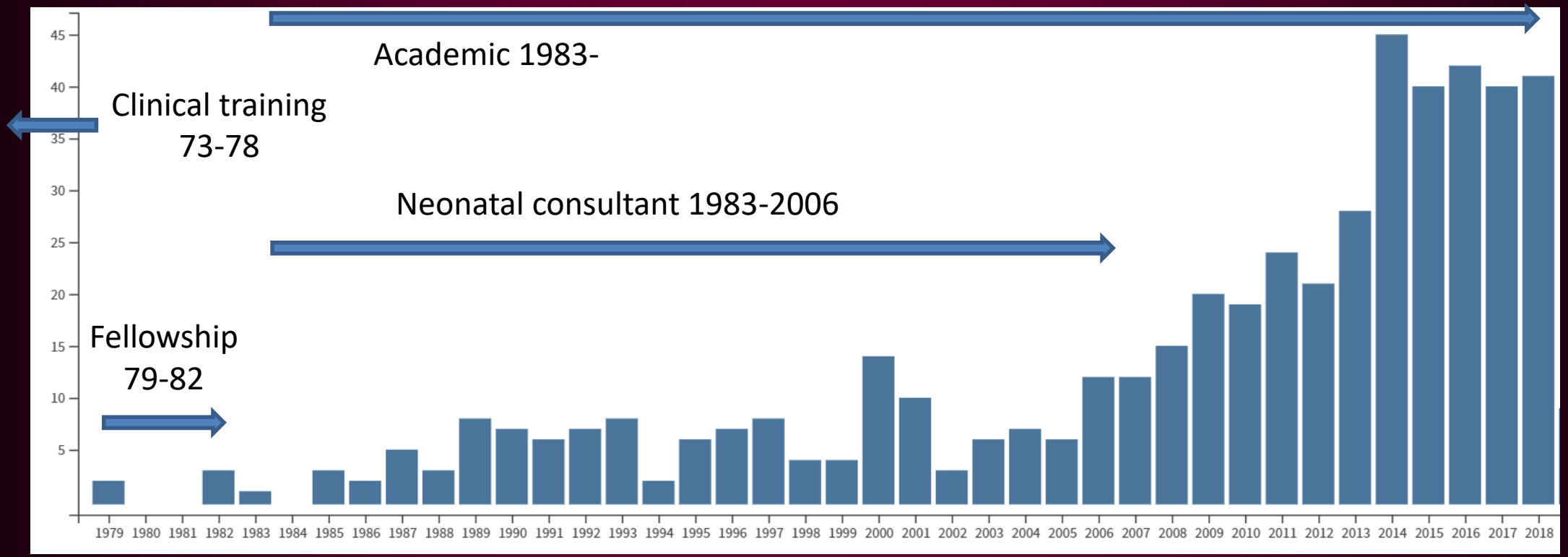


Caroline Crowther
Obstetrician

Publications per year



Publications per year



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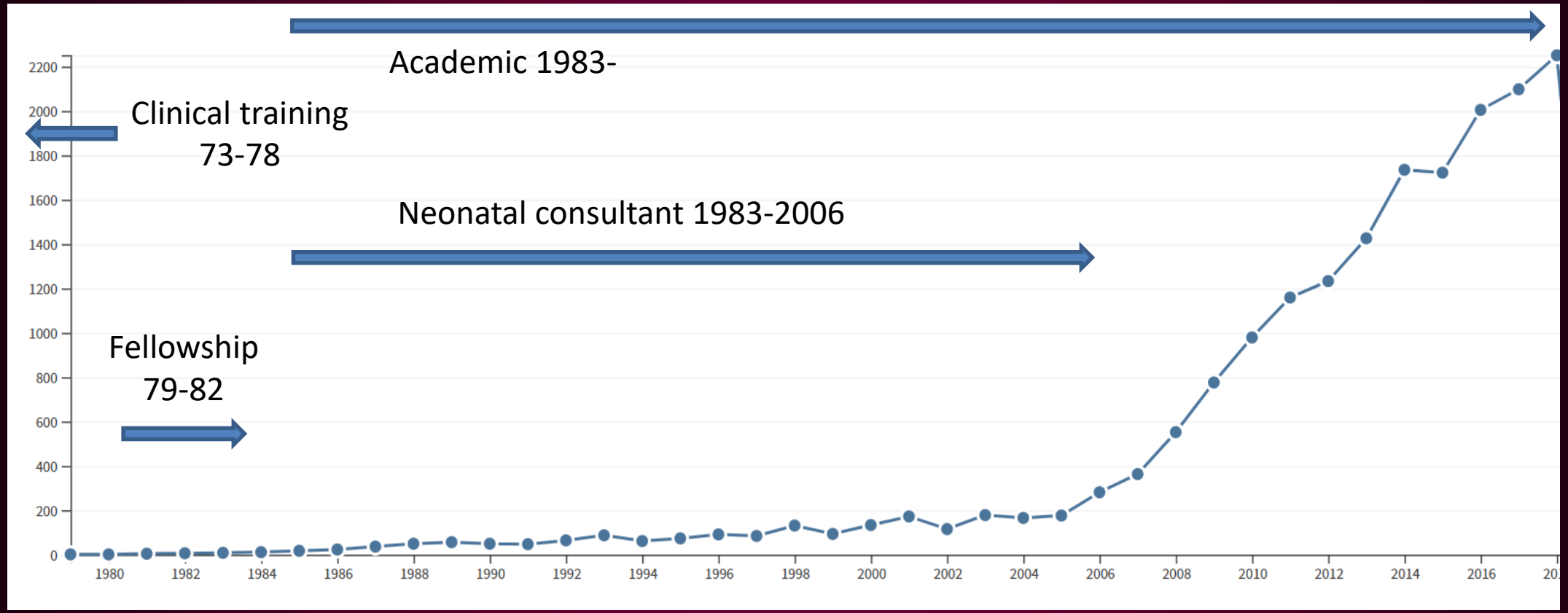

Challenges for the next generation (1)

Remember history!

a. Oxygen a mess!
    i. Treatment of ROP???
b. What are we doing to the lungs of tiny babies?
c. Need to improve long-term outcomes

Finding time for research

a. Need support from administration
b. Learn to say “no”

Challenges for the next generation (2)

How to do research?

Asking answerable questions

PICOT structure

Need persistence, patience

Need plenty of “friends”

They do all the work!

Research you do will help someone one day!

Howard E Williams Oration

A career in neonatal research – really?

Lex W Doyle

Royal Women's Hospital

University of Melbourne

Murdoch Children's Research Institute

Melbourne, Australia

Victorian Infant Collaborative Study (VICS) Group

Jeanie Cheong, Peter Anderson, Merilyn Bear, Alice Burnett, Rose Boland, Elizabeth Carse, Margaret P Charlton, Mary-Ann Davey, Noni Davis, Lex Doyle, Julianne Duff, Marie Hayes, Leah Hickey, Elaine Kelly, Marion McDonald, Emma McInnes, Gillian Opie, Gehan Roberts, Alicia Spittle, Michael Stewart, Anne-Marie Turner, Andrew Watkins, Amanda Williamson.

Royal Women's Hospital, Mercy Hospital for Women, Monash Children's Hospital, Royal Children's Hospital, Newborn Emergency Transport Service, Victorian Perinatal Data Collection Unit, Murdoch Childrens Research Institute, and University of Melbourne, Melbourne, Australia

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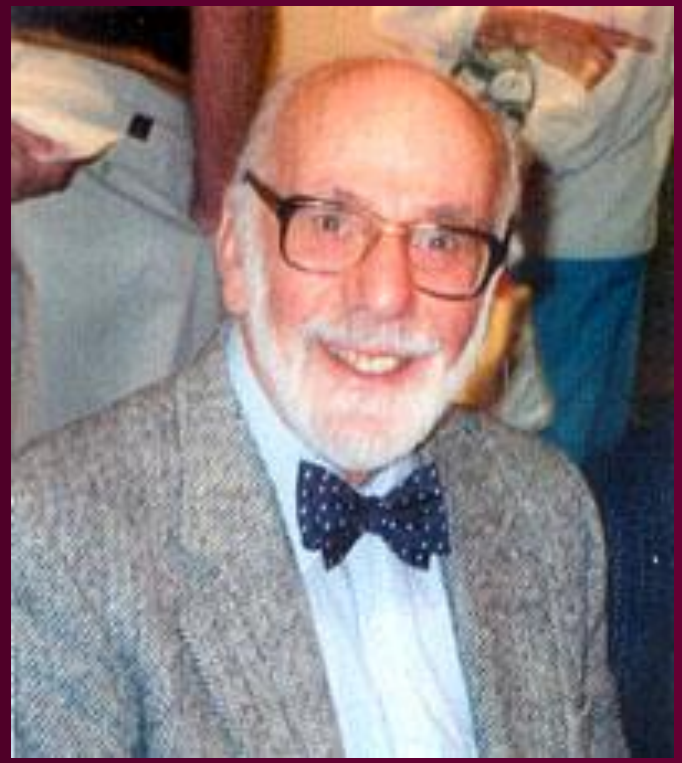
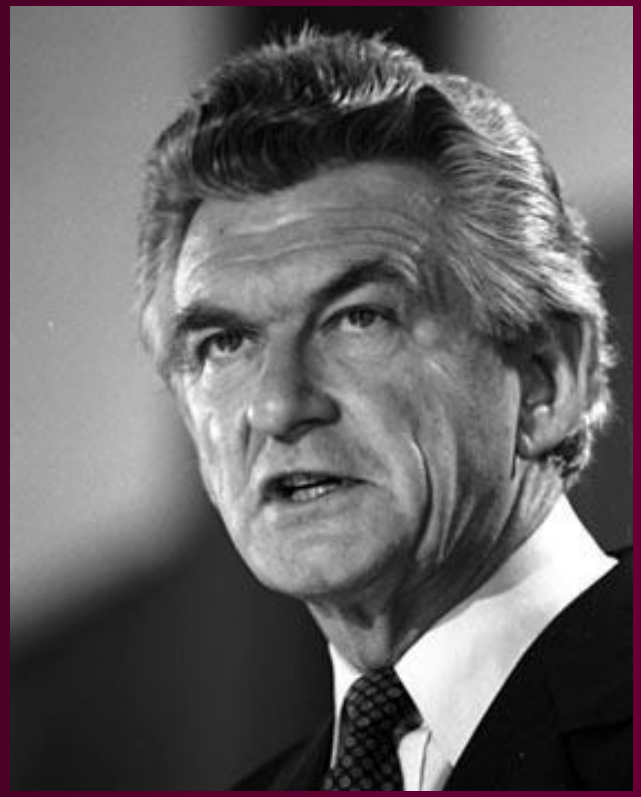
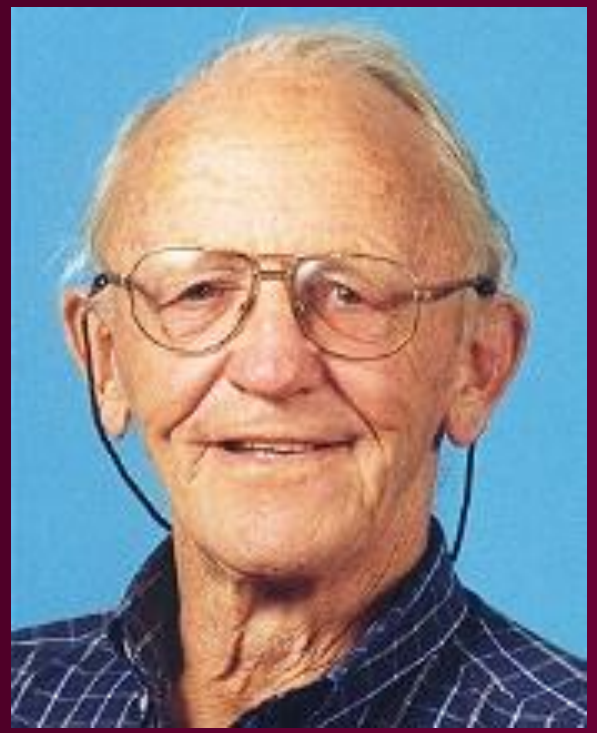
Rosemarie Boland
Joseph Yang
Richard Beare
Chris Adamson

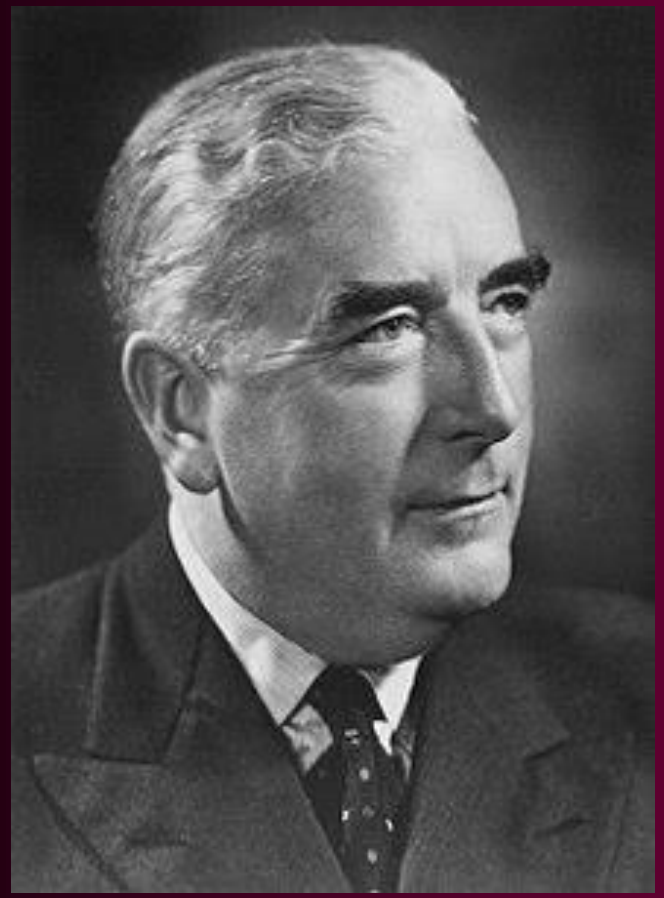
Collaborating Centres: Murdoch Children's Research Institute, Monash University, The Royal Women's Hospital, The University of Melbourne, Harvard Medical School, Washington University (St Louis), Children's MRI Centre (Royal Children's Hospital)

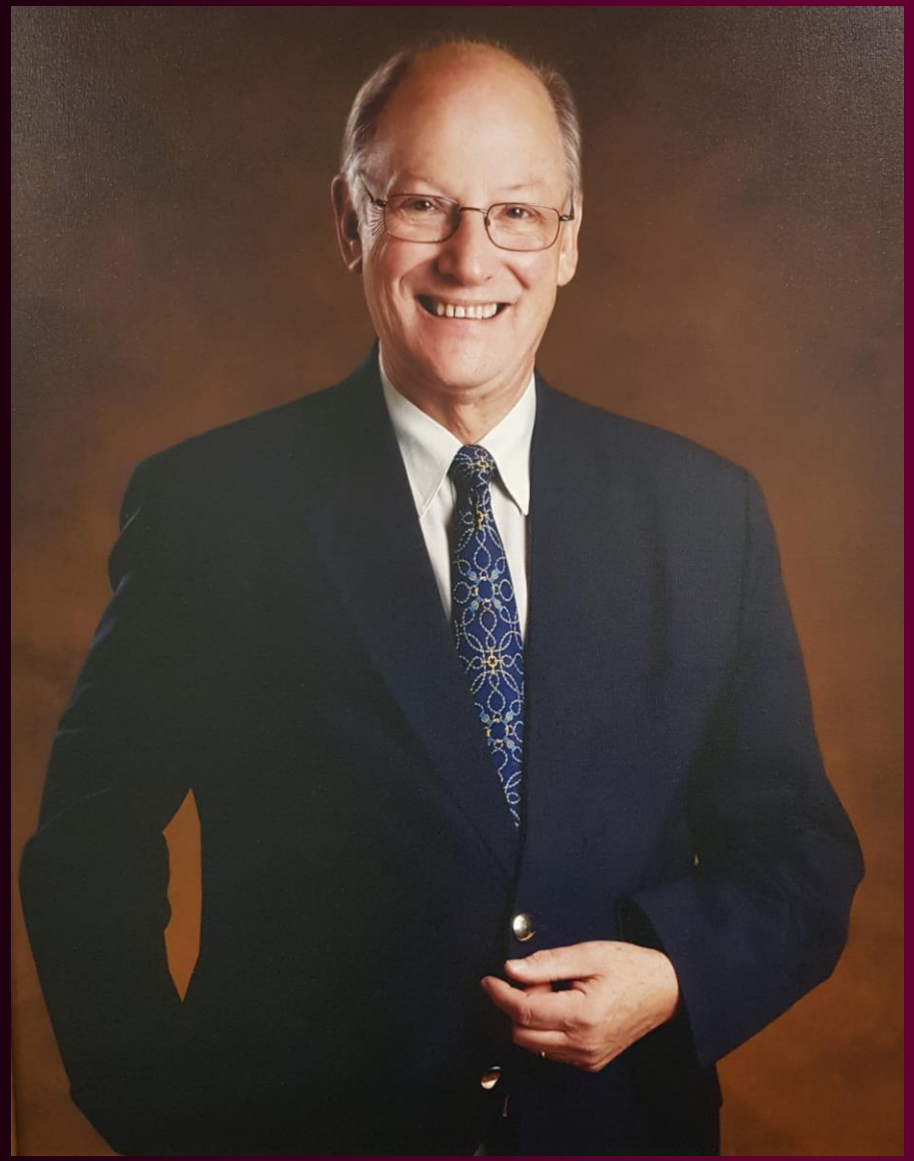
Funding support: NHMRC, National Institutes of Health, Jack Brockhoff Foundation, Murdoch Childrens Research Institute, Howard Florey Institute, Royal Women's Hospital Foundation, Thyne Reid Foundation, Myer Foundation, CP Foundation, CCRE Newborn Medicine





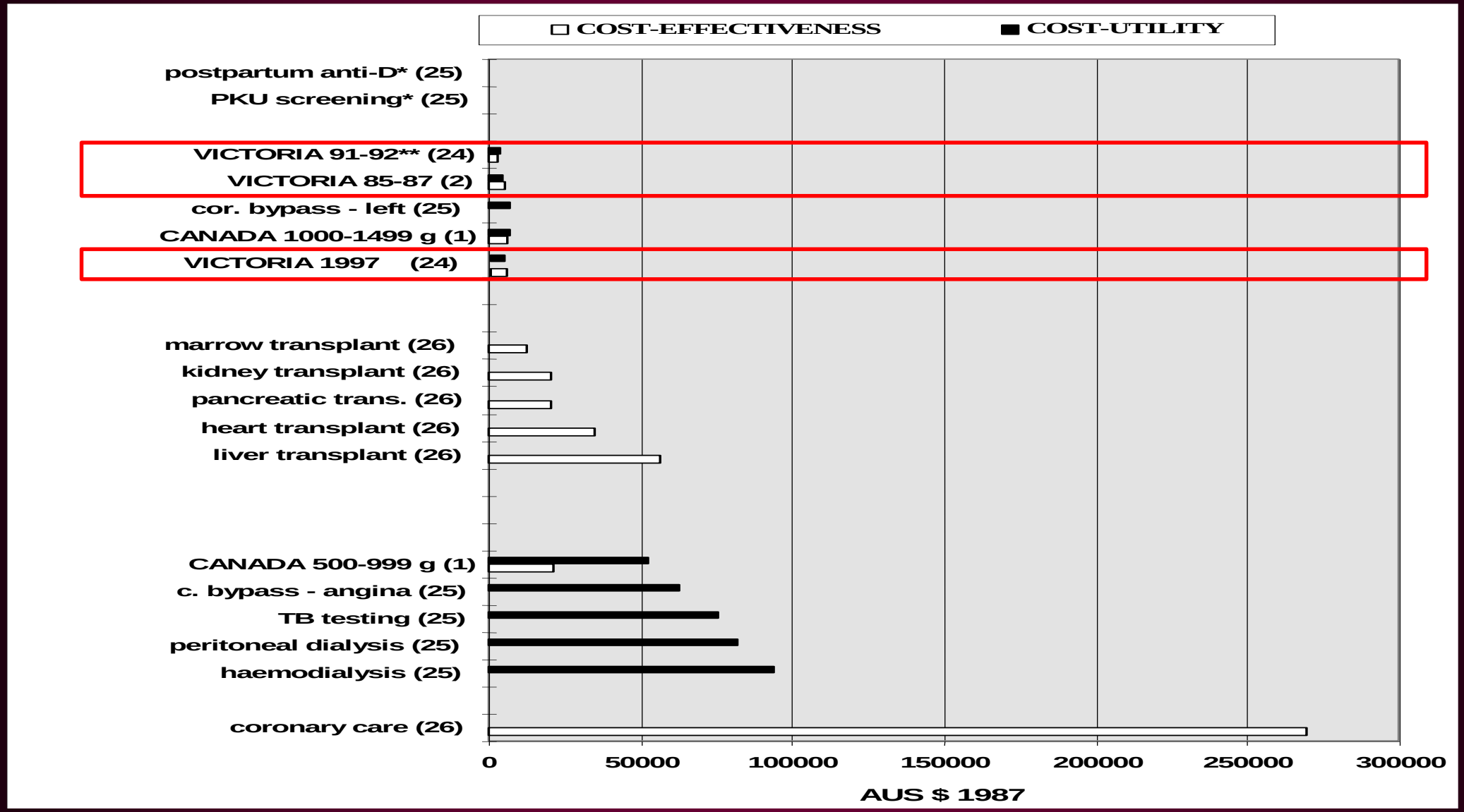




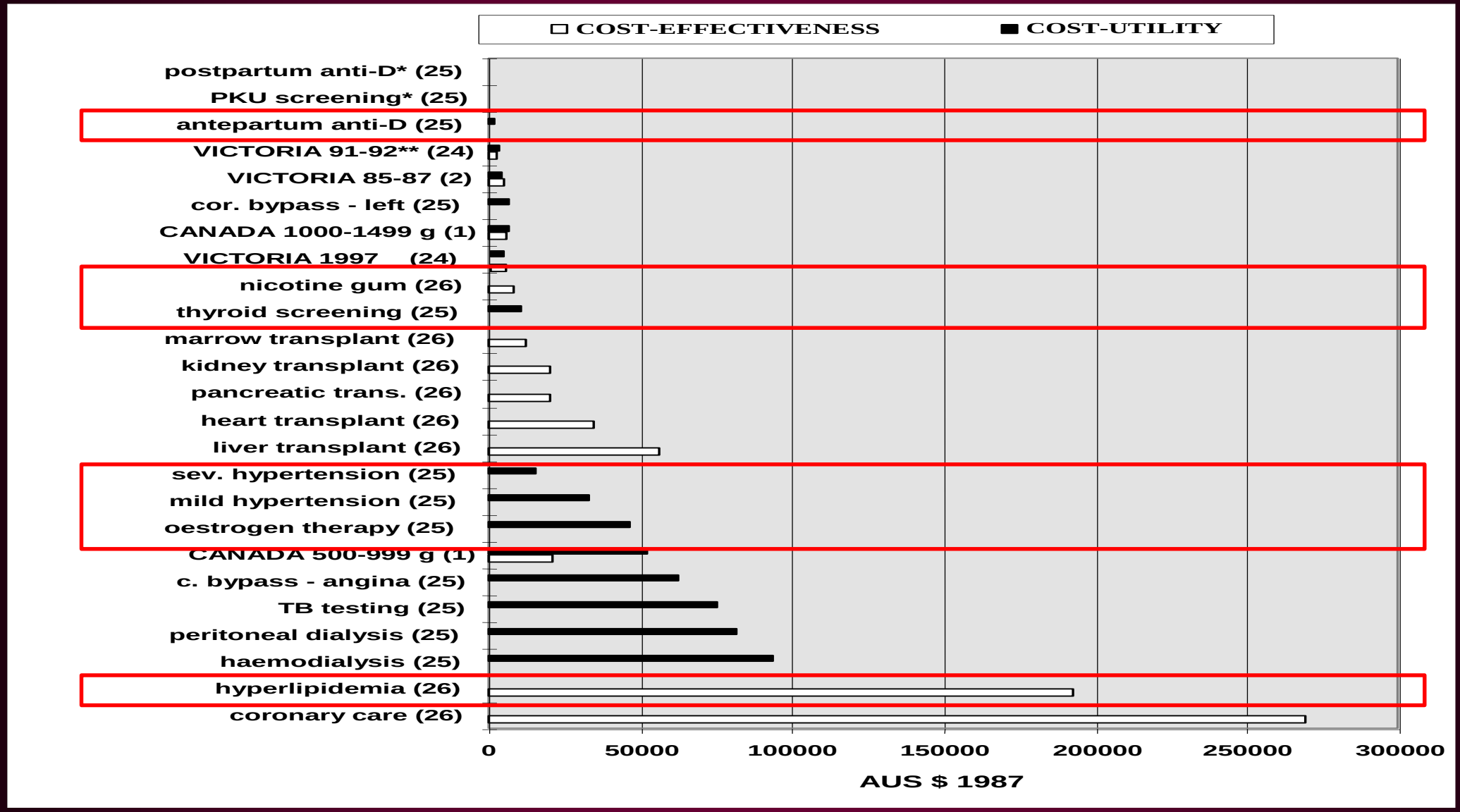



miscarriage

What about the cost?



What about the cost?



Where to for LWD?

unclear

a. The team is in excellent hands
b. The work must go on
c. Synergy grant