

.... but what do you do ?

Dr Rob Black

Associate Professor, University of Queensland.

Senior Consultant in Paediatric Otolaryngology

Mater Children's Hospital, Brisbane, Australia

UK Data

- 1930's - Tonsillectomy – a prophylactic ritual carried out for no particular reason with no particular result. Medical Research Council
- 1957 – Are T's & A's really necessary? Fry J, BMJ 1,124-129 (1957)
- 1999 - Children suffer pointless tonsil operations. BBC
<http://news.bbc.co.uk/2/hi/health/522914.stm>

UK Data

- Scottish Intercollegiate Guidelines Network - Management of Sore Throat and Indications for Tonsillectomy. SIGN publication 34, 2001
 - Disabling tonsillitis – 5 per year
- National Prospective Tonsillectomy Audit. BAOHNS & RCS 2005
 - Accepts SIGN recommendations
 - Other indications for tonsillectomy may include obstructive sleep apnoea
- NESSTAC: a pragmatic randomised controlled trial with a parallel non-randomised preference study. Health Technology Assessment 14:13. 2010
 - Clinical & cost effectiveness
- Indications for Tonsillectomy Position Paper. ENT UK 2009
 - OSA – serious effects on health and well being

OSAS in children

- adeno-tonsillar hypertrophy
- mid-face development
- tone

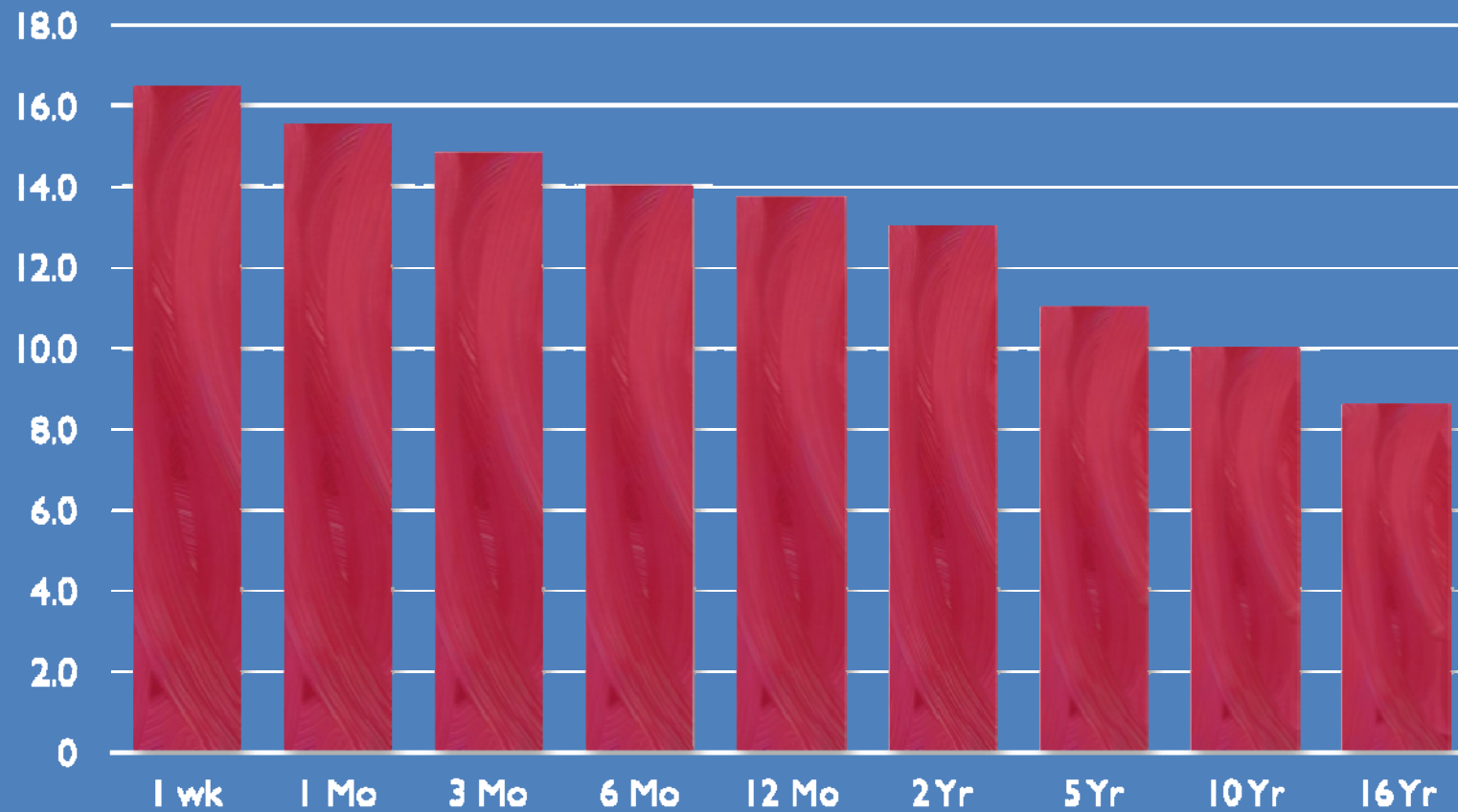
Why do people sleep?

Why is sleep disordered breathing important?

- Coping with darkness;
- Low energy requiring;
- Essential for normal wake neuronal function.

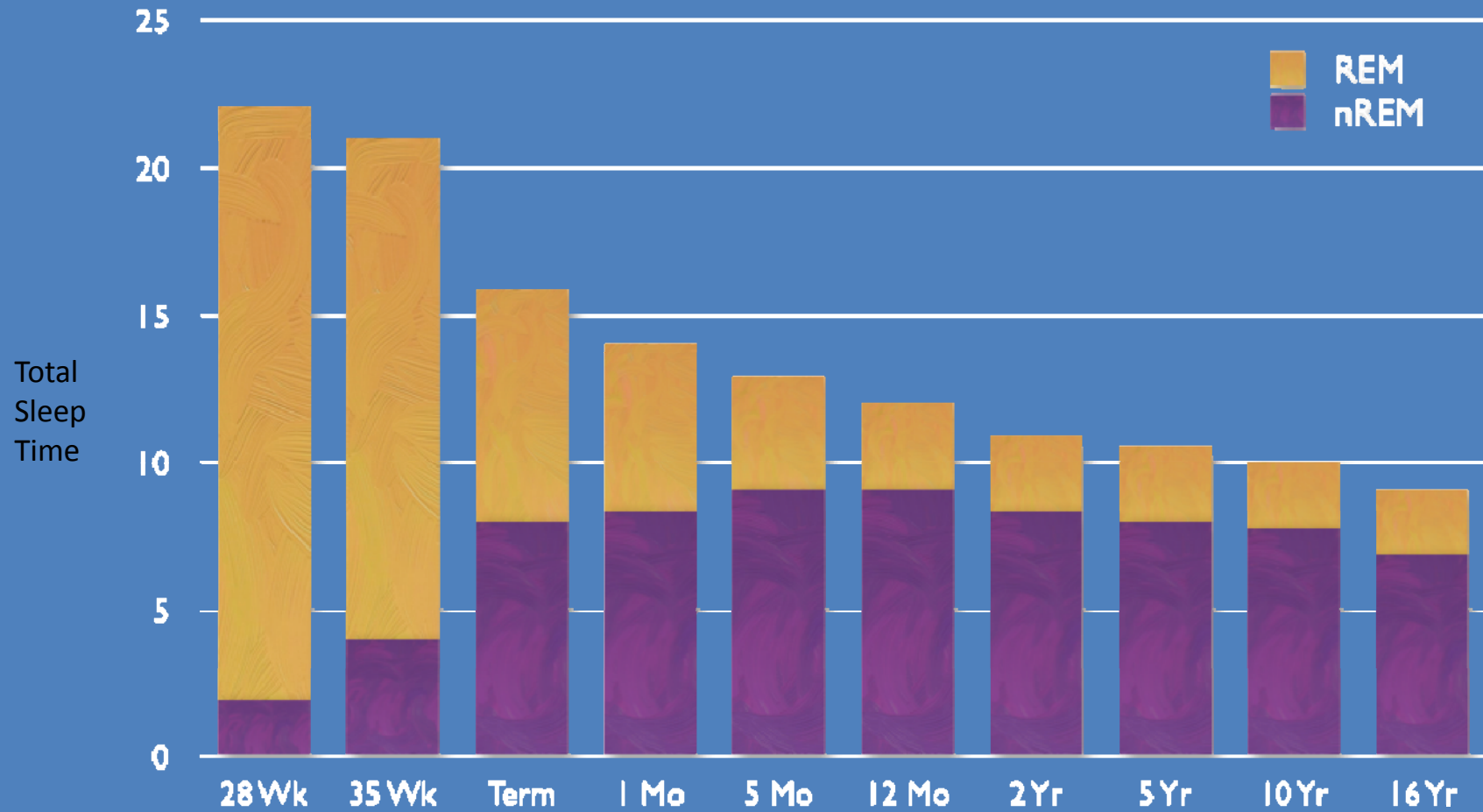
Sleep duration evolution with age

Hours



Modified from FERBER R.: Solve your child's sleep problems. New York. Simon & Shuster, 1985, p19

Ontogeny of REM and NREM Sleep



Sheldon SH, Spire J-P, Levy HB: Pediatric Sleep Medicine. Philadelphia. WB Saunders. 1992, p24

Present understanding of the role of sleep

REM sleep

Infants and children

- Neuronal network formation REM dependant
- Myelination - maximal during REM sleep
- Memory - short term to long term REM enhanced

1 obstructive event per hour

1 obstructive event per hour

- Adult – time based
- Children
 - Obstruction of 2 respiratory cycles
 - Partial with alveolar hypoventilation
 - Includes hypopnoea (3% desaturation associated with a 50% drop in air flow)

Nixon GM, Brouillette RT: Sleep 8: paediatric obstructive sleep apnoea. Thorax 60(6), 511-516, 2005

Neurocognition

- Cardio-respiratory
- Growth
- Immunological
- Hypoxia / hypercapnia
- Arousals / sleep fragmentation

Cardio-respiratory

- Increased pulmonary vascular resistance
- cor pulmonale
- Left ventricular hypertrophy & raised diastolic

Marcus CL, Green MG, Carroll JL. Blood pressure in children with obstructive sleep apnoea. Am J Respir Crit Care Med 157 (4Pt1), 1098-1103, 1998

→ alteration in cerebral blood flow velocities
(neuropsychological effects)

Hill CM et al, Cerebral blood flow velocity in children with mild sleep disordered breathing: a possible association with abnormal neuropsychological function. Pediatrics 118(4), 1100-1108, 2006

Growth

- Growth hormone SWS
- IGF-1
- protective effect on neurocognition

Gozal D et al, Plasma IGF-1 levels and cognitive dysfunction in children with obstructive sleep apnoea. Sleep Med 2008

- intelligence

Gunnell D, Miller LL, Rogers I, Holly JM. Association of insulin like growth factor 1 and insulin like growth factor – binding protein-3 with intelligence quotient among 8 to 9 year old children in the Avon Longitudinal Study of Parents and Children. Pediatrics 116(5), e681-686, 2005

Immunological

- C-reactive protein

Gozal D et al, Plasma IGF-1 levels and cognitive dysfunction in children with obstructive sleep apnoea. Sleep Med 2008

➔ neurotransmitter expression

➔ obesity

Hypoxia / Hypercapnia

- Central abnormalities of regulation
- Intermittent hypoxia

Beebe DW, Gozal D. Obstructive sleep apnoea and the pre-frontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioural deficits. *J Sleep Res* 11(1), 1-16. 2002

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➤ HIF- α

➤ Endothelial dysfunction

➤ Neuronal loss (pre-frontal cortex)

Arousals / sleep fragmentation

- **Sleep fragmentation**

Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol* 25(1), 117-129, 2005

- **Arousal**

Kohyama J, Hasegawa T. Subcortical arousal response in child patients with obstructive sleep apnoea. *Sleep Med* 3 Suppl 2, S33-36, 2002

- **Disrupted sleep without OSAS**

Heussler HS. Changes in behaviour and psychological variables in children undergoing adenotonsillectomy. Doctorate Thesis, Division of Child Health, Univ Nottingham 2008. p63

8% habitual snorers - 3% OSAS

10 point IQ difference

Garetz SL Behaviour, cognition, and quality of life after adenotonsillectomy for pediatric sleep-disordered breathing: summary of the literature. *Otolaryngol Head Neck Surg* 138(1Suppl) S19-26. 2008

Recovery of function

Duval J et al. Brain lesions and IQ: recovery versus decline depends on age of onset. *J Child Neurol* 23(6), 663-668. 2008

Everts R et al. Cognitive functioning, behaviour, and quality of life after stroke in childhood. *Child Neuropsychol* 14(4), 323-338. 2008

Does adenotonsillectomy improve neurocognition in pre-school children with mild obstructive sleep apnoea

- The Children's Hospital at Westmead (University of Sydney, NSW):
- The Mater Hospital, Brisbane (University of Queensland, QLD)
- John Hunter Children's Hospital (Newcastle University, NSW)
- Women's and Childrens Hospital (Adelaide University & University of South Australia, SA);
- Princess Margaret Hospital for Children (University of Western Australia, WA)

1. T&A improve IQ compared to no T&A over 24 months?
2. Health care costs for children with OSA change following T&A

Neurobehavioural & neurocognitive testing

Woodcock-Johnson III Test of Cognitive Abilities

Behavioural parameters

Parent Rating Scale of Behaviour Assessment System for Children II

Behaviour Rating of Executive Functioning (Brief-P)

Polysomnography

Mild OSA 1-5

Health economic data

Health Related Quality of Life (HRQoL)

Health Utilisation Index 2 (HUI2)

<http://www.sleeptrials.net/>

Professor Karen Waters

Dr Margaret Harris

- Snoring - 8% all children
- OSA - 3% children

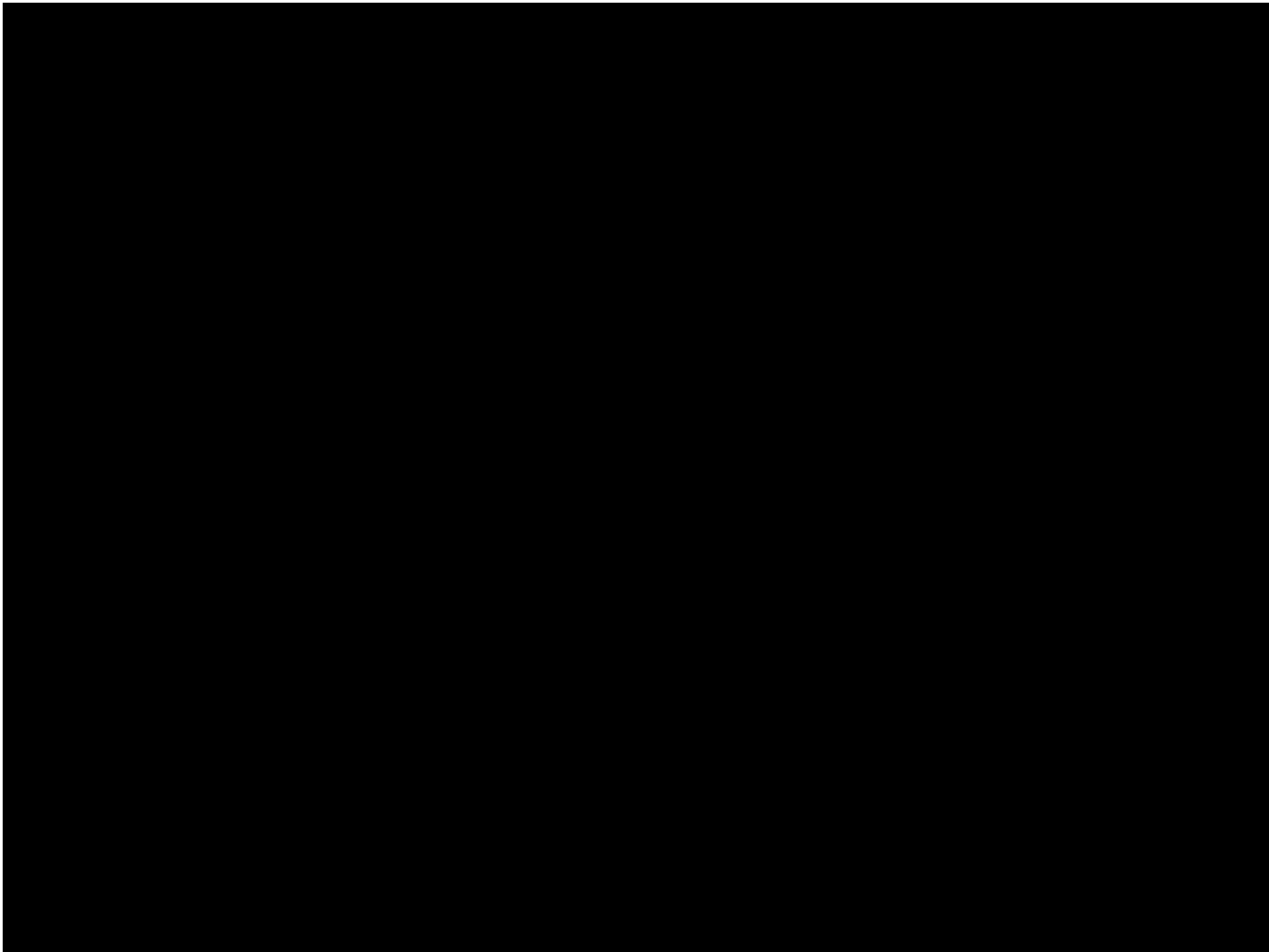
- 3% with OSA = 183,000 (England) Office of National Statistics

- T & A's performed = 28,000 = 0.46% ENT UK publication
= 7,000 = 0.12%

1 in 25 (1 in 7)

155,000 to 176,000

643,000



JoRRP

HPV 6 & 11

Incidence .24 per 100,000

Prevalence 1.11 per 100,000

Average number of procedures 7

Age as presentation 4 years

Majority are first born

Campisi P et al. The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database. Laryngoscope 120:1233-1245. June 2010

Young age at diagnosis = severe disease $P < .0001$ **

Buchinsky FJ, Donfack J, Derkay CS et al, Age of child, more than HPV type, is associated with clinical course in recurrent respiratory papillomatosis. Public Library Science 3:e2263. 2008

HPV 11

Wiatrak BJ et al, Recurrent respiratory papillomatosis: a longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population. Laryngoscope 132:392-394. 2004

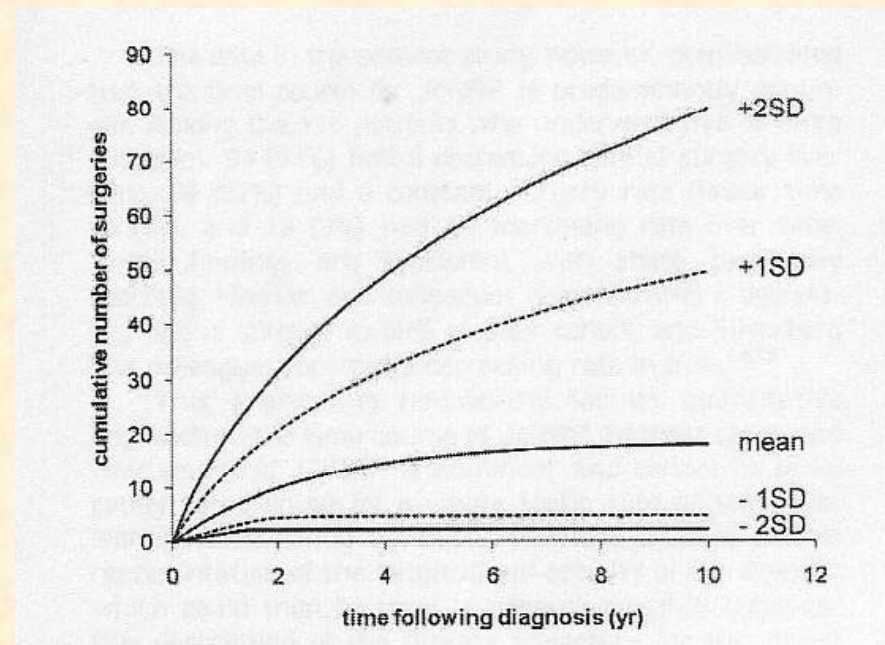
Natural History of JoRRP

Surgical procedures - non linear time course

64% had a decreasing rate of surgery

27% - constant rate

9% - increasing rate over time



Genital HPV is increasing

Health Protection Agency. Health Protection Report.

2007.<http://www.hpa.org.uk/infections>

– 83,745 new diagnoses of genital warts

Transmission ?

JoRRP

Diathermy & forceps

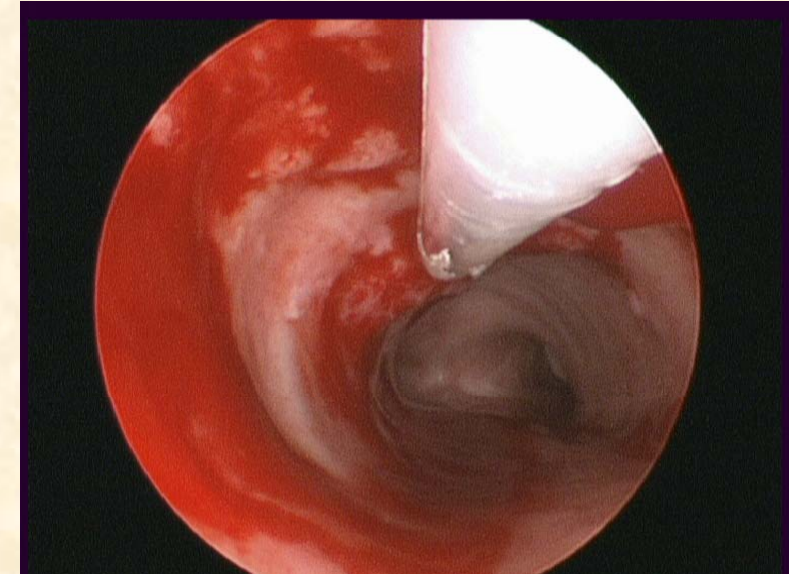
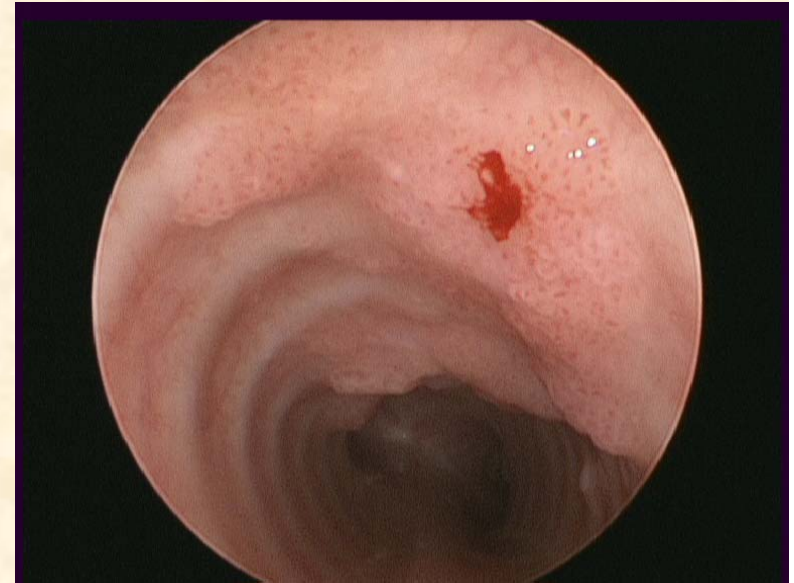
CO₂ Laser

Microdebrider

Interferon α 2a

Cidofovir (5mg/ml)

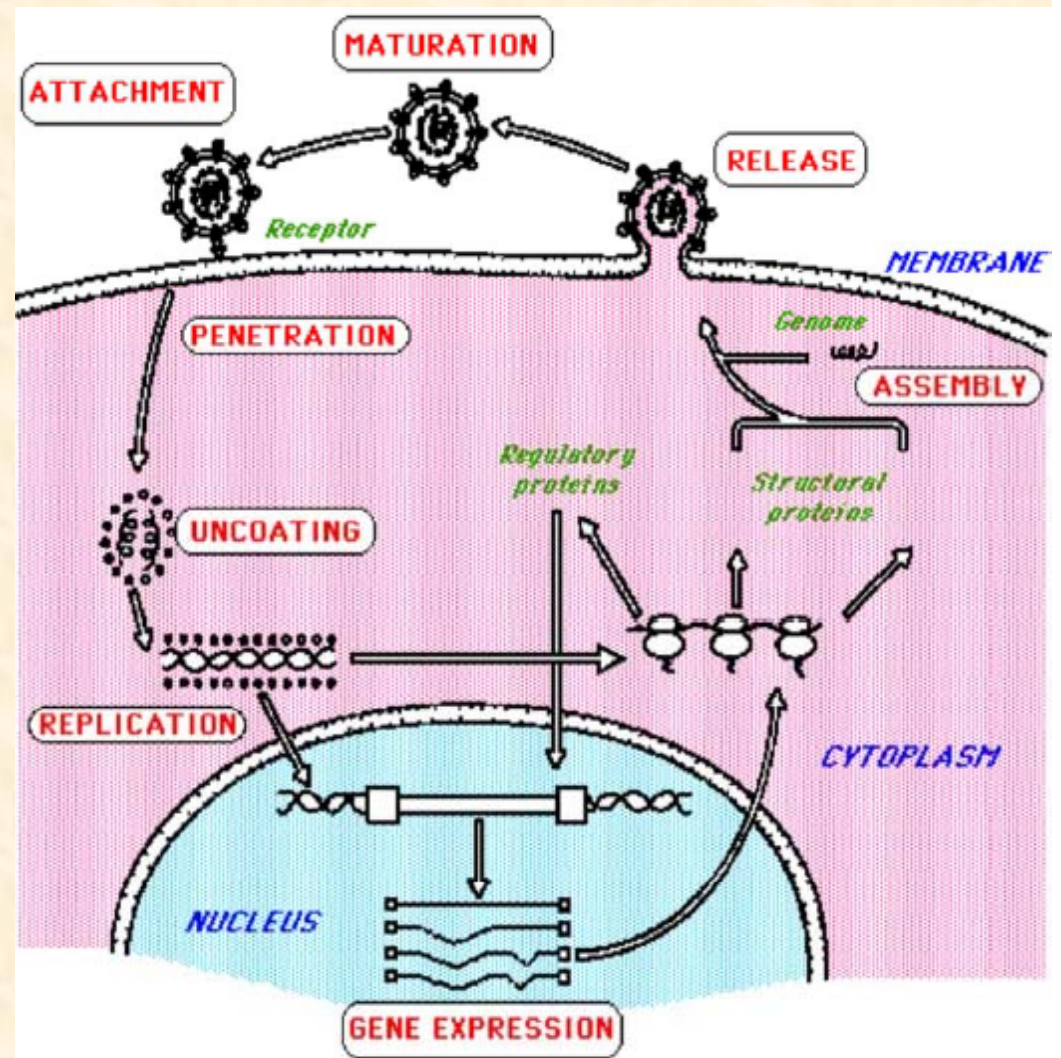
Vaccines

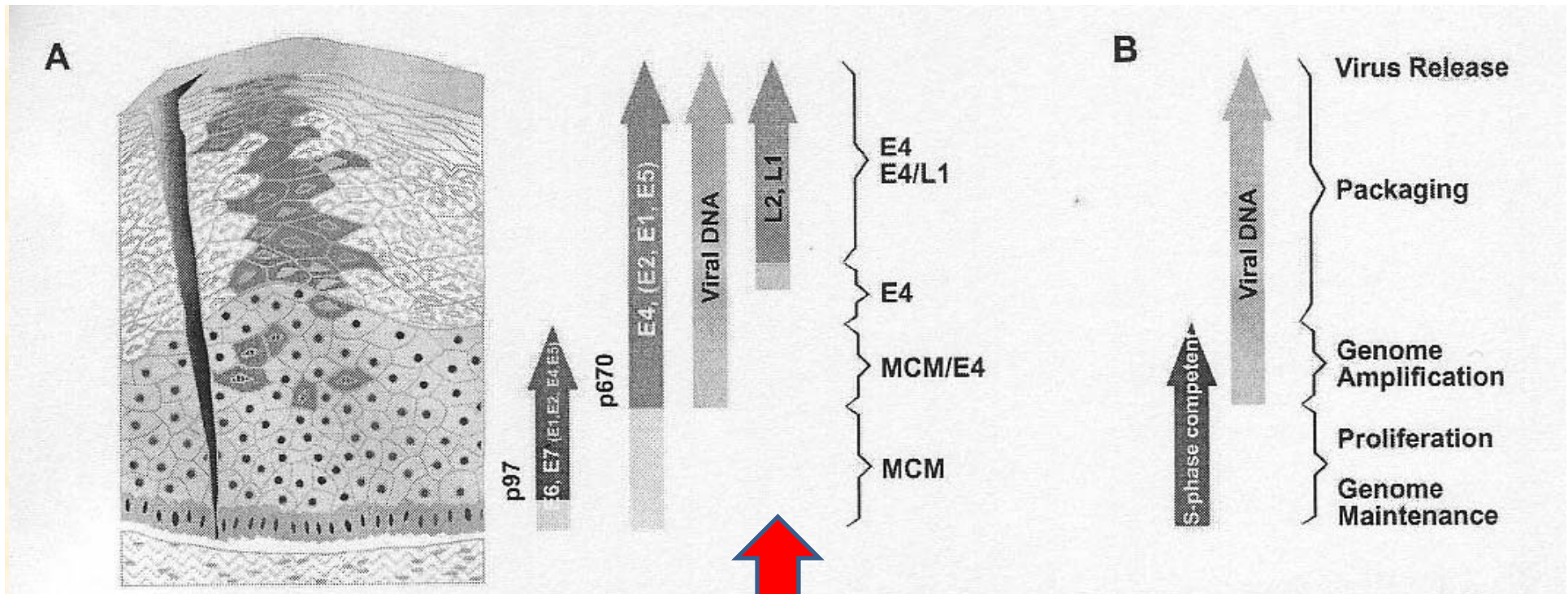


Life cycle of HPV

Phases

1. Primary infection
2. Cell proliferation
3. Viral genome ampl.
4. Assembly & release





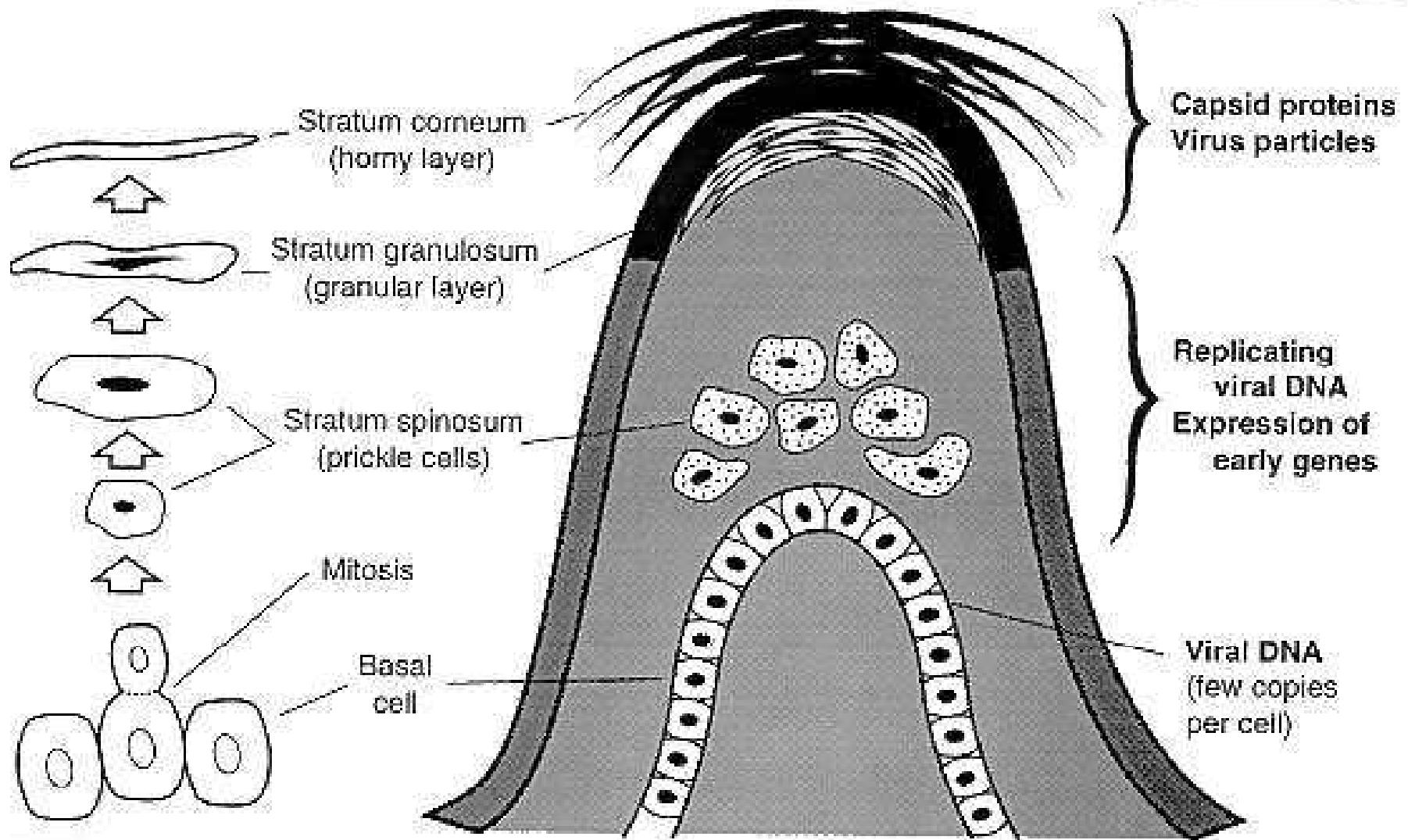
Doorbar J. Papillomavirus life cycle organization and biomarker selection. Disease Markers 23,297-313. 2007

Middleton K, Peh W, Southern S, et al. Organization of human papillomavirus productive cycle during neoplastic progression provides a basis for selection of diagnostic markers. J Virol 77(19),10186-10201. 2003

**Epidermal Cell
Differentiation Pathway**

Papilloma

Virus Life Cycle



PROTOCOL
研究计划

**A PHASE 1b, MULTICENTRE STUDY OF CICRVAX6
HPV 6L1 VLPs AS THERAPY FOR RECURRENT RESPIRATORY PAPILLOMATOSIS**

1b阶段CICRVAX6

HPV 6L1 VLPs 多中心研究治疗复发性呼吸道乳头状瘤病

SPONSOR
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**CENTRE FOR IMMUNOLOGY AND CANCER RESEARCH
UNIVERSITY OF QUEENSLAND
昆士兰大学免疫与癌症研究中心**

***** Professor Ian Frazer**

Gardasil

- Non-infectious quadrivalent vaccine
- Prepared from the purified virus like particles (VLP's) of the major capsid protein (L1)
- Of HPV types 6, 11, 16, 18
 - ➔ CIRCvax6 HPV L1 VLP
 - + Alum (aluminium potassium sulfate)
- B cell mediated Antibody response
 - i.e., prevention & not cure

CIRCVax6 HPV L1 VLP

- Non-infectious quadrivalent vaccine
- Prepared from the purified virus like particles (VLP's) of the major capsid protein (L1)
- Of HPV types 6, 11, 16, 18
 - ➔ CIRCVax6 HPV L1 VLP
 - Alum (aluminium potassium sulfate)
- T cell mediated immune response
 - i.e., “killer” cell response

Phase 1 trial of CIRCVax 6

- Study Design
- Inclusion criteria
- Exclusion criteria
- Immunogenic response

Recurrent Respiratory Papillomatosis (RRP)

- AIM
 - To evaluate the safety and tolerability profile of dose levels
 - To evaluate immunogenicity and efficacy as adjunct therapy for RRP

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- lengthen the time between surgical procedures
- effect not uniform

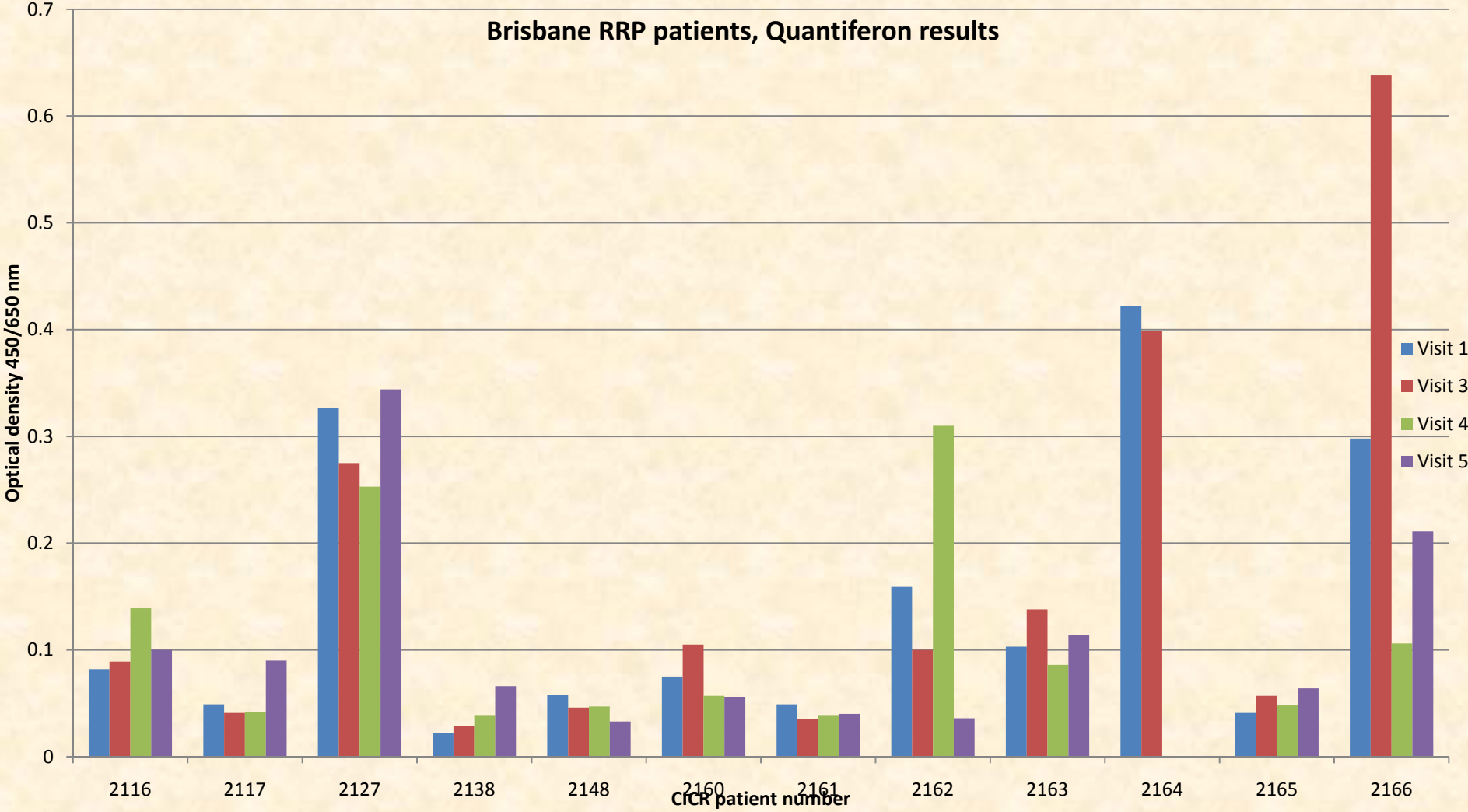
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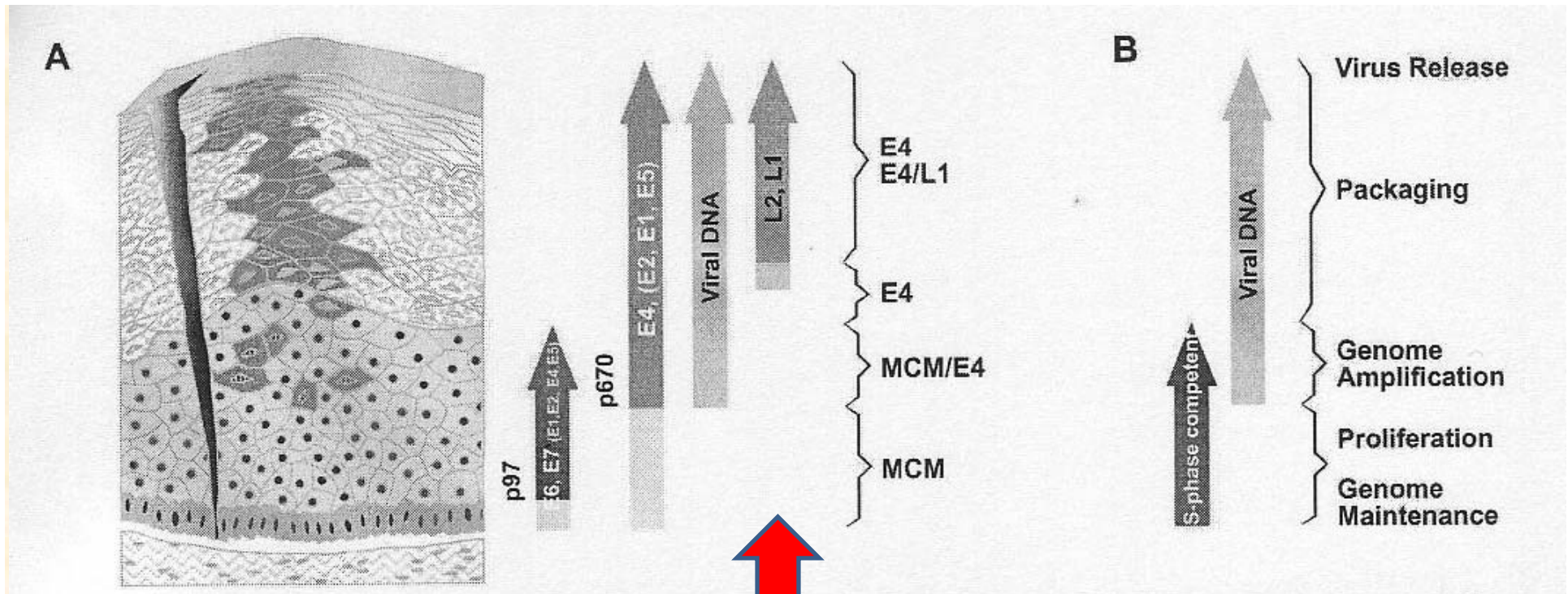
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RRP Quantiferon Assay

Brisbane RRP patients, Quantiferon results





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best job