Pneumococcal HUS
The NZ (Starship) Experience

Amanda Dickens

Starship Child Health

Te Whatu Ora
Health New Zealand
Te Toka Tumai Auckland

Starship
Child Health

Key Points

The past two years have been extraordinary for pneumococcal Haemolytic Uraemic Syndrome (SpHUS) in NZ children

Invasive Pneumococcal Disease (IPD) is on the up

Streptococcus pneumoniae serotype 19A was causing an almighty ruckus and was not covered by current vaccination schedule

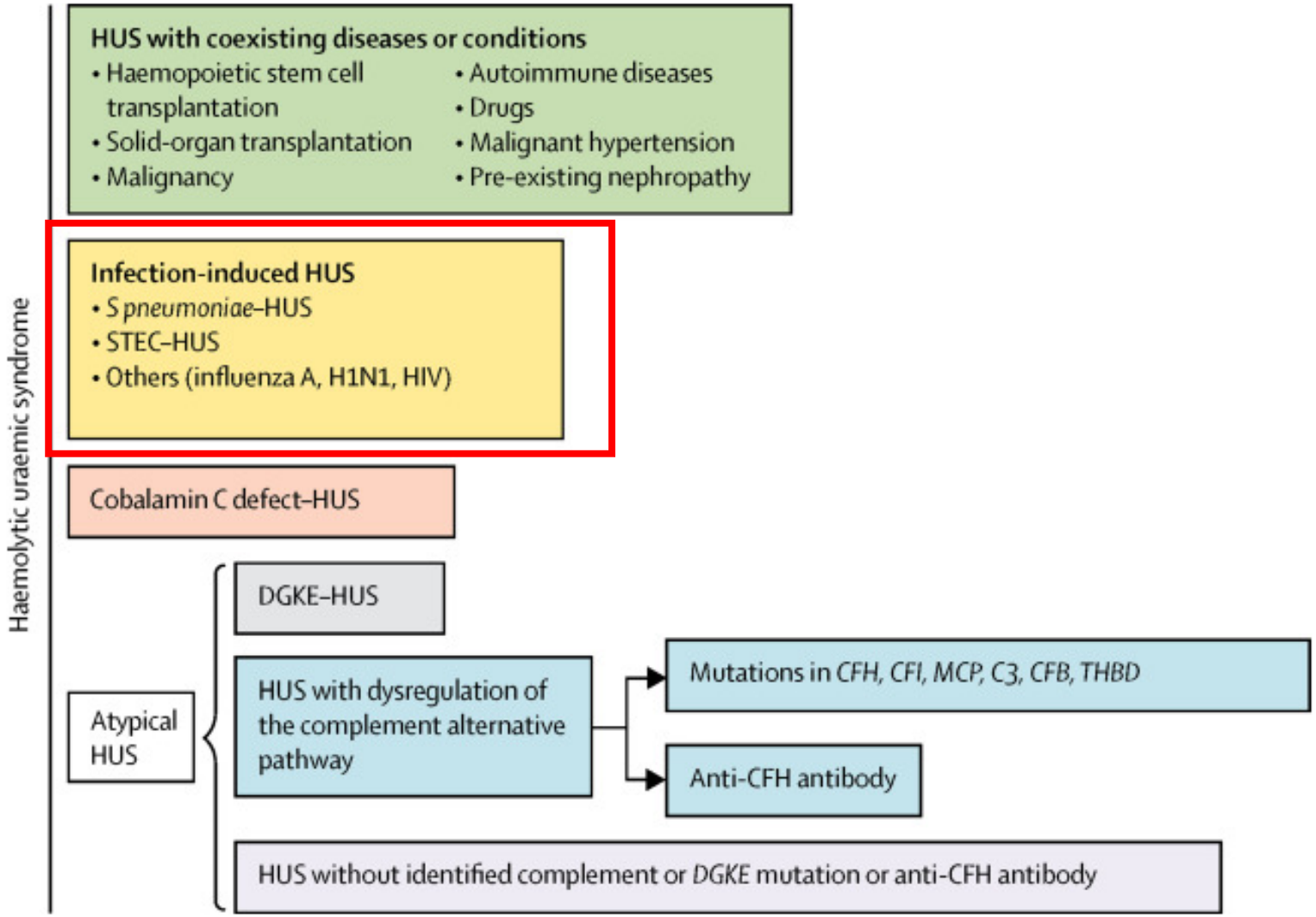

Haemolytic uraemic syndrome
HUS with coexisting diseases or conditions
• Haemopoietic stem cell transplantation
• Solid-organ transplantation
• Malignancy
• Autoimmune diseases
• Drugs
• Malignant hypertension
• Pre-existing nephropathy
Infection-induced HUS
• S pneumoniae–HUS
• STEC–HUS
• Others (influenza A, H1N1, HIV)
Cobalamin C defect–HUS
Atypical HUS
DGKE–HUS
HUS with dysregulation of the complement alternative pathway
Mutations in CFH, CFI, MCP, C3, CFB, THBD
Anti-CFH antibody
HUS without identified complement or DGKE mutation or anti-CFH antibody

Figure 1

A Case - Travellers from over the Tasman…

- R, A and K– arrived in Auckland from Perth early August,

- First holiday together as a Whanau – Night in Auckland before a few nights up North

- *‘This was the start to our horrible journey where we watched our son get sicker and sicker by the hour’*

	10/08/22 22:30
Urea	
Creatinine	66
Phosphate	
Magnesium	
Albumin	
Bilirubin	
Alkaline Phosphatase	
ALT	
Sodium	132
Potassium	5.3

	10/08/22 22:30
Haemoglobin	98
RBC	3.78
Haematocrit	0.29
Mean Cell Volume	77
Mean Cell Haemoglobin	25.9
RDW	13.8
Platelets	260
WBC	3.1
Neutrophils	0.7

Initial presentation 7 months old male infant

- Unremarkable BG, immunised to Aus schedule (*PCV13 incl*)
- Initial presentation non-specific viral like illness (*rhino/ enterovirus positive*)
- 2d later re-presentated poor feeding, O2 requirement, ?bronch → CXR LL pneumonia, FBC ~NAD, creatinine elevated 66, CRP 350
- IV cefuroxime started

Increasing oxygen requirement, increasing WOB

Gross haematuria

Blood culture strep pneumoniae positive

Bloods 2 days after presentation consistent with HUS

TF to Starship → worsening resp state, miserable → PICU

	10/08/22 22:30	11/08/22 13:48	12/08/22 14:10
Haemoglobin	**98**	**94**	**94**
RBC	**3.78**	**3.67**	**3.65**
Haematocrit	**0.29**	**0.28**	**0.27**
Mean Cell Volume	77	77	74

	10/08/22 22:30	11/08/22 09:12	11/08/22 13:48	12/08/22 09:33	12/08/22 14:10	12/08/22 21:38
Urea		**10.4**	**10.4**	**17.1**	**21.0**	**28.0**
Creatinine	**66**	**58**	**58**	**78**	**96**	**136**
Neutrophils	**0.7**		1.8		3.5	
Basophils	0.0		0.0		0.0	
Eosinophils	0.0		0.0		0.0	
Monocytes	0.7		0.9		**2.0**	
Lymphocytes	**1.6**		**1.8**		**2.7**	

PICU

- Intubated, L ICD inserted, urokinase administered, drain in for 4 days, I+V for 4 days
- Transfusions required for red cells and plt
- Anuric acute kidney injury, PD commenced
- Hypertension managed with isradipine
- Transaminitis, lipase 3 x ULN
- Managed on Ceftriaxone

On the mend

- Hospital admission = 26 days, PICU 5 days
- PD for 13 days
- Remained on antihypertensives most of the admission, ceased pre DC
- Total Abx duration 4 weeks
  - Note this will not be total duration for all empyemas
  - IV to oral switch would often be sooner if no CNS concerns
- Primary immunodeficiency work-up recommended
- Audiology review normal
- DC back to Aus for ongoing review – CKD
    - Cr 148
    - Renal feed 50%: Karicare 50%

Pneumococcal HUS

- 5% of total HUS cases in children
- Rate of HUS post Invasive pneumococcal infection reported as 0.4-0.6% Highest in < 2 years
- Most commonly with empyema – almost 3/4

Pneumococcal HUS is worse than STEC-HUS

- More severe renal and haematological disease
- Longer hospitalisation
- More often have long-lasting renal damage
- More transplants needed
- More death
  - Meningitis main driver BUT higher morbidity for SpHUS meningitis vs Sp meningitis alone

Who's most at risk of invasive pneumococcal disease?

- The **young** (highest incidence in kids <1) and the **old**
- Most frequent risk factors <5 = day-care, smoking in the household
- In NZ ~4 times higher in areas of highest social deprivation
- 4-5 times higher in Maori and Pacific peoples

The IPD back-drop:

Pre-vaccination

Pediatr Infect Dis J. 1994 Oct;13(10):873-8. doi: 10.1097/00006454-199410000-00005.

Invasive pneumococcal disease in a pediatric population, Auckland, New Zealand

L Voss [1], D Lennon, K Okesene-Gafa, S Ameratunga, D Martin

- 1984-1992
- <15yrs 22/100,000
- <5yrs 56/100,000
- Higher rates in Maori Pacific children

- 1994-1998, 27% Indigenous population in Australia
- Indigenous children <2 1534 per 100,000 in Central Aus
- Non-indigenous children 100/100,000

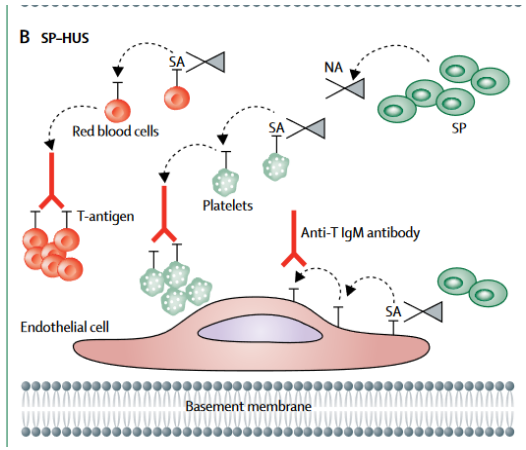
Management

- Management largely supportive and ***most*** of the time requires intensive care level support
- Kill the trigger
  - Key for INITIAL antibiotic choice is whether or not meningitis is present (may also include ‘too unwell to LP’)
  - Meningitis? Ceftriaxone and vancomycin until you know an MIC
  - Source control
- Blood pressure management
- Nutritional support
- Renal replacement therapy
- ?Plasma exchange
- ?Eculizumab (prevents generation of cytotoxic MAC complex)

So how does SpHUS happen?

Invasive pneumococcal disease in the Northern Territory of Australia, 1994-1998

Vicki L Krause MD, FAFPHM, DTMH, Susan J C Reid RN, BSc, MPHTM, Angela Merianos MPH, FAFPHM, MAE



The pathophysiology of Sp-HUS at the cellular and molecular levels remain ill-defined…

Neuraminidase important? Believed the amount and level of activity may influence development t of HUS (*think heavy bacterial loads i.e. empyema, subarachnoid….*) – NOT a sufficient explanation

Factor H? Pneumococcal surface protein C? Complement dysregulation? Who knows….

Thick vessel wells, lumina filled with platelet thrombi (partial or complete luminal obstruction), vascular endothelium detach, swelling and accumulation of material in sub-endothelial space

Agarwal, HS, Latifi SQ, Streptococcus Pneumonia – Associated Haemolytic uraemic syndrome in the Era of the pneumococcal vaccine. Pathogens 2021, 10, 727.

Empyema and SpHUS?

- IF neuraminidase plays a role in pathophysiology…….
  - Higher production from a heavy bacterial load in pleural space and subarachnoid space
  - More produced in a biofilm?
  - In Mice more neuraminidase produced in lung vs blood

The history of SpHUS

SpHUS history

- AKI (nephritis) associated with pneumococcal disease since 1872
- 1971 Fischer et al described the association of *S pneumoniae* and HUS
- Early reports 1977-1987 - 50% died, 67% CKD/hypertension.

Pediatr Nephrol (2008) 23:1951–1956
DOI 10.1007/s00467-007-0518-y

EDUCATIONAL FEATURE

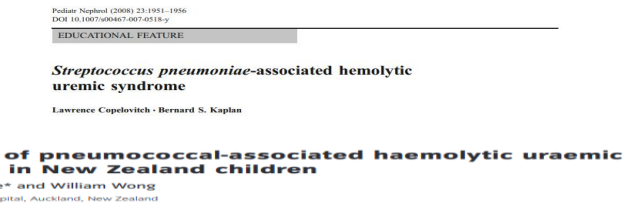
Streptococcus pneumoniae-associated hemolytic uremic syndrome

Lawrence Copelovitch · Bernard S. Kaplan

- Review of all cases reported in English literature to 2007
  - 85, of which 73 were children
- 72% pneumonia / empyema, 29% meningitis (some other sites)
- 12% died
  - 88% of deaths in the meningitis group
    - *pneumococcal meningitis* Mortality rate with HUS - 37%
    - *pneumococcal meningitis Mortality rate without HUS - 8-10%*
    - *pHUS with no meningitis Mortality rate* - 2% die
- 10% ESRF
- 16% CKD or hypertension

Prior NZ Experience
Pre vaccine era

Journal of Paediatrics and Child Health


Pediatr Nephrol (2008) 23:1951–1956
DOI 10.1007/s00467-007-0518-y

EDUCATIONAL FEATURE

Streptococcus pneumoniae-associated hemolytic uremic syndrome

Lawrence Copelovitch · Bernard S. Kaplan

Ten years of pneumococcal-associated haemolytic uraemic syndrome in New Zealand children

Chanel Prestidge* and William Wong

Starship Children's Hospital, Auckland, New Zealand

11 patients 1998-2007

Median age 8.5m

10/11 Maori or Pacifica

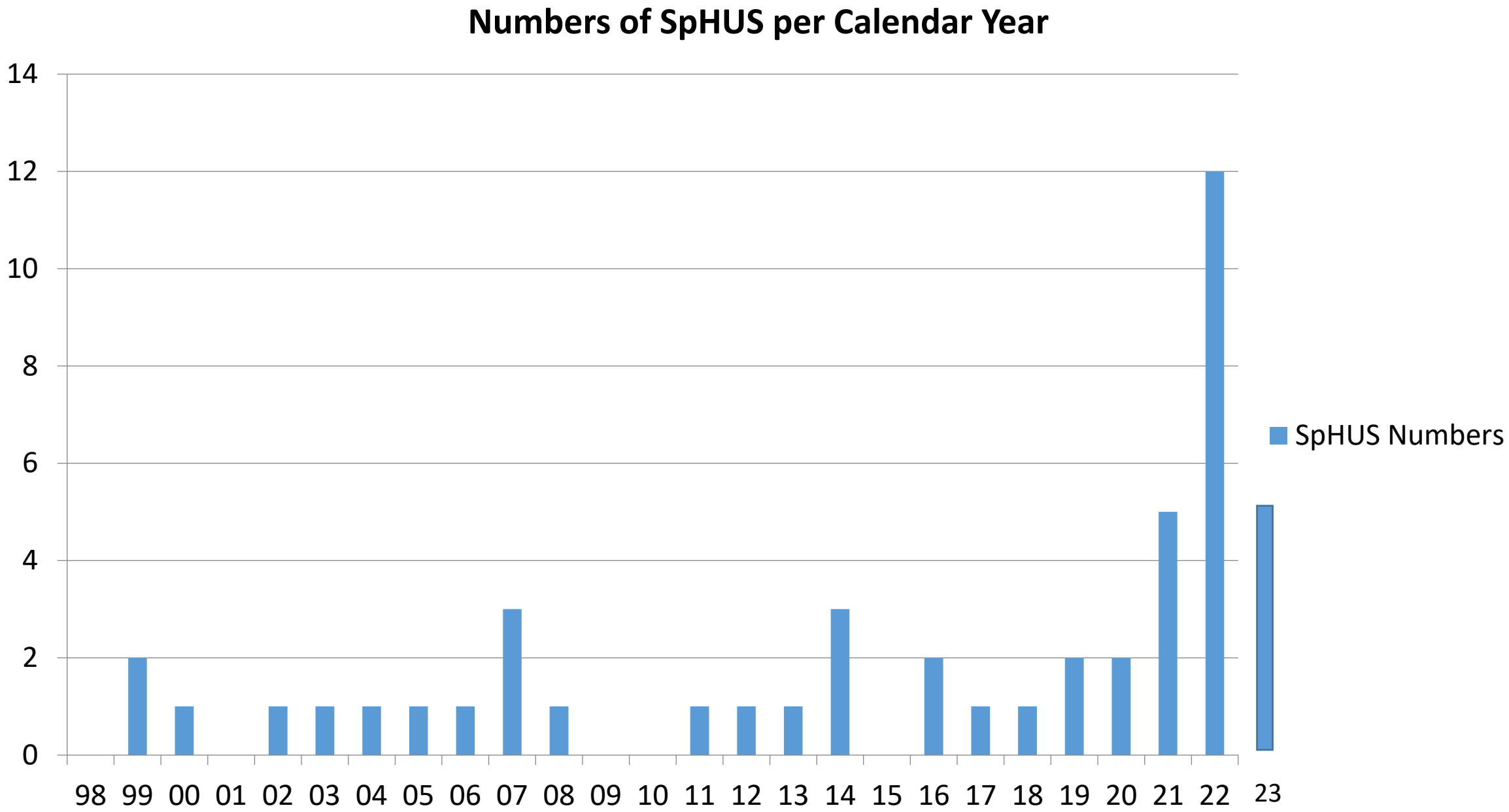
7/11 = pneumonia with effusion, 4/11 = meningitis

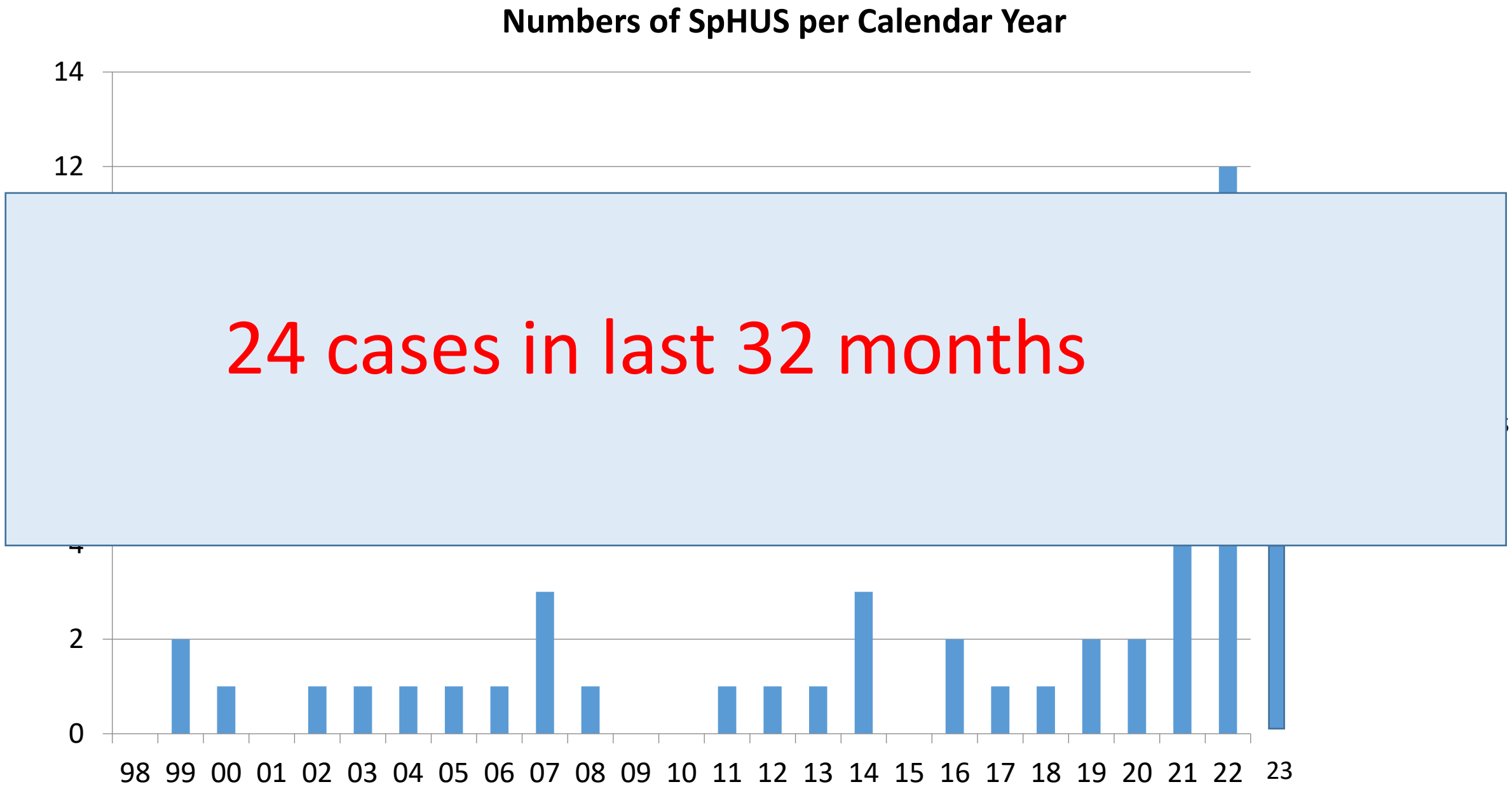
Outcomes

- 9 RRT for a median of 13 days
- 1 death
- 1 CKD 4 at discharge- transplant 6 yrs later
- 1 xCKD 2
- 1x proteinuria
- 3 survivors had neurological sequalae

	1998-2007 (pre-pneumo vaccine)	*1998 - 2019 (NZPSU data)*
Total number	11 over 10 years	24 over 22 years
IPD concurrent site of infection	Meningitis (4) Pneumonia and empyema (7)	Empyema (15) Pneumonia (3) Meningitis (6)
Age median (range)	8 mths (3-32months)	18 mths (4 – 51mths)
Sex	2/11 (F)	7/24 (F)
Renal replacement therapy (PD and/or CVVH)	11/11 median 13 days	20/24 median 13 (3-27)
Outcomes	ESKD then transplant @6 yrs Mild renal impairment@ 2 yrs Persisting proteinuria x2 @ 2 yrs	Since 2008…. CKD 3+ proteinuria x 1 (9yr) Proteinuria x 2
Other outcomes (IPD related)	1x death (meningitis) 1 sensorineural hearing loss 2x sensorineural hearing loss and profound neurodevelopmental delay	Since 2008…. 1 death

So what about the last 2(+) years?


Numbers of SpHUS per Calendar Year
14
12
10
8
6
4
2
0
98 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23
SpHUS Numbers


Numbers of SpHUS per Calendar Year
14
12
2
0
98 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 16 17 18 19 20 21 22 23
24 cases in last 32 months

Recent NZ SpHUS experience (20-22):

How frequent?

- Incidence of pneumococcal HUS 2020-2022:
  - Per 100,000 <2 years of age per year – 3.9/100,000
  - Per 100,000 <5yrs of age per year – 2.0/100,000
- Post IPD 2020-2022? (*Denominator = IPD notifications to ESR*)
  - 14 cases <2 = 10.9%
  - 18 cases <5 = 8.6%

Comparable incidences

Highest incidence in study period
= **0.25/100,000 <5 PCV7 period** -
0.08/100,000 <5 PCV13
Makwana et al, PIDJ, 2019

NZ 2021/22 =
2.6/100,000 <5 yrs

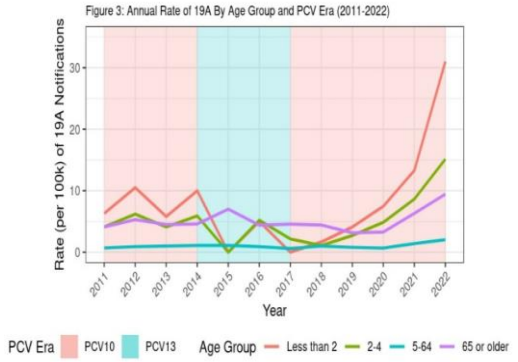
Most article introductions quote “0.4-0.6%”
Prestidge et al (NZ pre immunisation):
incidence post IPD 0.55% <2, 0.3% <5

HUS after IPD

NZ 2021/22
~10% post IPD

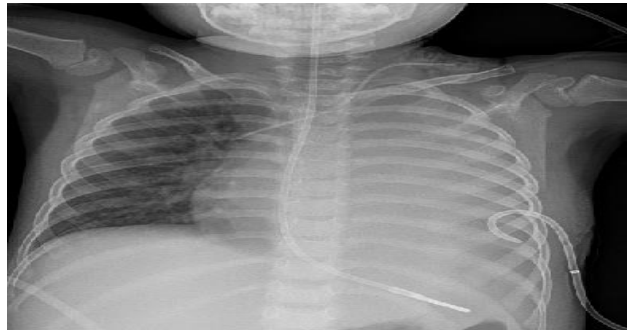
The 2020-2022 experience

6/19 Auckland
4/19 Waikato



PICU admission?
18/19
Median 7.5d (2-119)

18/19 Pneumonia
18/19 effusion or empyema
17/19 source control
2/19 meningitis (1 of these both pulmonary and CNS)



All serotypes are 19A

Pneumococcal Immunisation Status

- 4/19 completely unimmunised (~20%)
- 3/19 overdue 12m PCV boost
- 2 received 2 or more PCV13
  - vaccinated in Australia or during era of PCV13 in NZ

Ethnicity

- 11/19 identified as Māori – (2/11 un-immunised)
- 1 identified as Tongan + Samoan – (unimmunised)
- 1 identified as Samoan
- 6 NZ Pakeha, other European, Asian – (1/5 unimmunised)

The 2020-2022 experience

The kidneys

- 15/19 (~80%) required acute dialysis
- RRT median 10 days (2-45) – *for those who required acutely only*
- *2 needed PD post-discharge*
- 2 deaths
  - 1 complex clinical course, prolonged PICU admission on ECMO
  - 1 meningitis
- Of patients who did not die:
  - 1 renal transplant,
  - 1 in work up for transplant CKD 4/5 (2/19 = 11%)
- CKD –2 at CKD 3 with proteinuria

  1 Proteinuria alone (>50mg/mmol)

The 2020-2022/3 experience

The kidneys

- 18/24 (75%) required acute dialysis
- RRT median 10 days (1-45) – *for those who required acutely only – 2 needed PD post-discharge*
- 2 deaths
  - 1 complex clinical course, prolonged PICU admission on ECMO
  - 1 meningitis
- Of patients who did not die:
  - 1 renal transplant,
  - 1 in work up for transplant CKD 4/5 (2/19 = 11%)
- CKD –2 at CKD 3 with proteinuria
  - 1 Proteinuria alone (>50mg/mmol)

So what got us here?

The villain – Streptococcus pneumoniae

…estimated deaths associated with 33 bacterial genera or species across 11 infectious syndromes in 2019 using methods from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, in addition to a subset of the input data described in the Global Burden of Antimicrobial Resistance 2019 study…

Among children younger than 5 years, *S pneumoniae* was the pathogen associated with the most deaths.

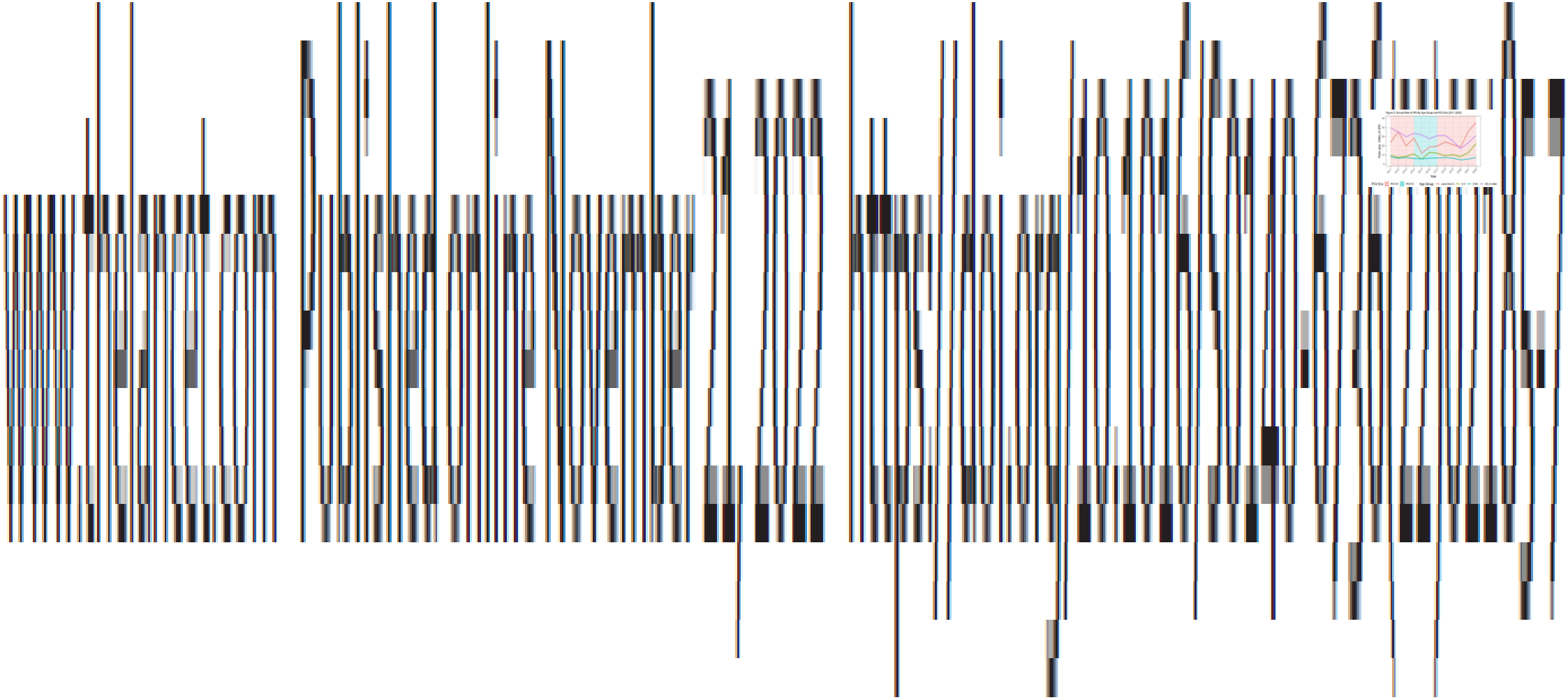
The villain– *Streptococcus pneumoniae*

- **Children**
  - higher burden in nasopharynx, 25-50% children colonised even post immunisation, major source to adults
  - Immunisation can change serotype but not carriage burden
- **Loves a virus** – URTIs correlated with new strain acquisition, increased receptors for pneumococci, viruses cleave sialic acid = sugary environment
  - “seen in ED x days ago with viral illness…”

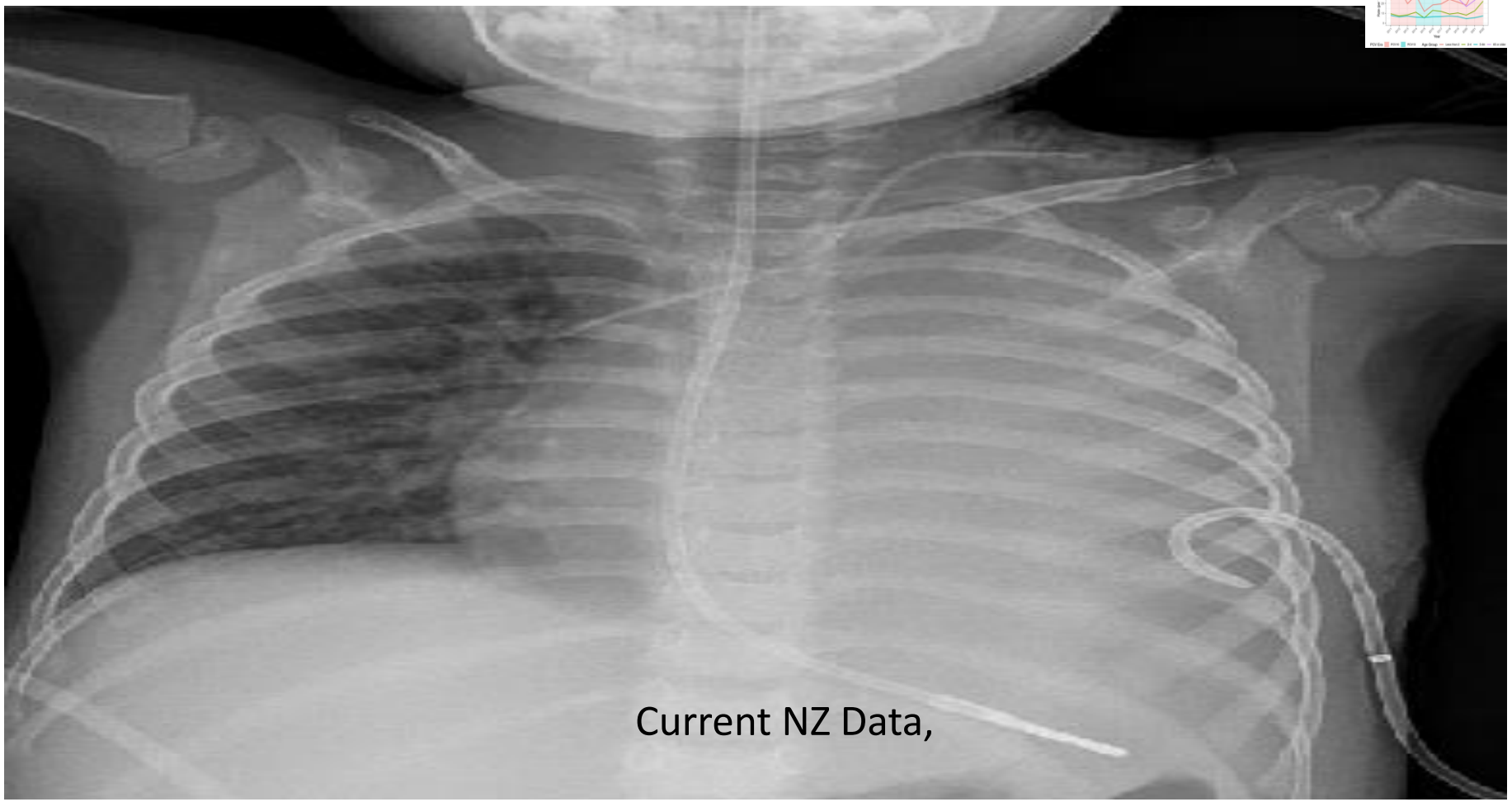
Vaccines work.
- A near 90% reduction in IPD under 2

Current NZ Data, Thanks to Andy Angelmyer (ESR).

Invasive pneumococcus rates are rising again



Pneumococcal serotype 19A



Vaccinations……

CURRENT ABSTRACTS

Increased Incidence of Invasive Pneumococcal Disease among Children after COVID-19 Pandemic, England

The Pediatric Infectious Disease Journal: December 2022 - Volume 41 - Issue 12 - p 988
doi: 10.1097/INF.0000000000003725

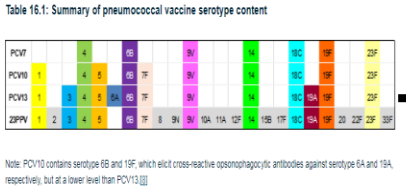
Prevenar 7

Synflorix PCV10

Prevenar 13

The IPD back-drop: Our vaccine time-course

PCV7 2008 → PCV10 2011 → PCV13 2014 → PCV10 2017



PCV7 2005 → PCV13 2011

PCV7 2006 → PCV13 2010

PCV7 2000 → PCV13 2010

19A – Not just an NZ phenomenon

Emergence of *Streptococcus pneumoniae* serotype 19A (Spn19A) in the pediatric population in Bogotá, Colombia as the main cause of invasive pneumococcal disease after the introduction of PCV10

Journal of Paediatrics and Child Health 45 (2009) 731–735

Clin Infect Dis. 2022 May 30;74(10):1859-1861. doi: 10.1093/cid/ciab766.

Invasive Pneumococcal Disease: Concerning Trends in Serotype 19A Notifications in New Zealand

Andrew Anglemyer [1 2], Andrea McNeill [1], Kara DuBray [3], Gerard J B Sonder [1 4], Tony Walls [5]

After a significant decrease during the PCV13 period, paediatric invasive pneumococcal disease incidence increased again during the PCV10 period. This observation mainly resulted from a **significant increase of serotype 19A cases.**

Dynamic changes in paediatric invasive pneumococcal disease after sequential switches of conjugate vaccine in Belgium: a national retrospective observational study

Stefanie Desmet, Katrien Lagrou, Chloé Wyndham-Thomas, Toon Braeye, Jan Verhaegen, Piet Maes, Steffen Fieuws, Willy E Peetermans, Sophie Blumental

Postvaccination Increase in Serotype 19A Pneumococcal Disease in Norway Is Driven by Expansion of Penicillin-Susceptible Strains of the ST199 Complex

Introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) into routine infant immunization programs worldwide resulted in serotype 19A becoming a leading cause of the remaining pneumococcal disease burden in vaccinated and nonvaccinated individuals

Streptococcus pneumoniae serotype 19A: worldwide epidemiology

Raul Isturiz, Heather L Sings, Betsy Hilton, Adriano Arguedas, Ralf-René Reinert & Luis Jodar

Pages 1007-1027 | Received 20 Jul 2016, Accepted 28 Jul 2017, Accepted author version posted online: 07 Aug 2017, Published online: 28 Aug 2017

Invasive pneumococcal disease in Western Australia: emergence of serotype 19A

C.M. Giele, A.D. Keil, Deborah Lehmann, P.G.

Streptococcus pneumoniae–Associated Hemolytic Uremic Syndrome: Classification and the Emergence of Serotype 19A

Pediatrics 2010;125:e174–e182

- 14 patients (1988-2009) with pneumococcal HUS ….
- **we highlight the emergence of serotype 19A subsequent to the introduction of 7-valent pneumococcal protein conjugate vaccine (Prevnar)**.
- This is the largest series of such subjects (to our knowledge) from a single center.

Other factors

?COVID pandemic

- Globally decrease in IPD rates during lock-down (2020)
- Decrease in viruses – esp RSV and flu, big drivers of IPD
- Impact on routine care visits and immunisations

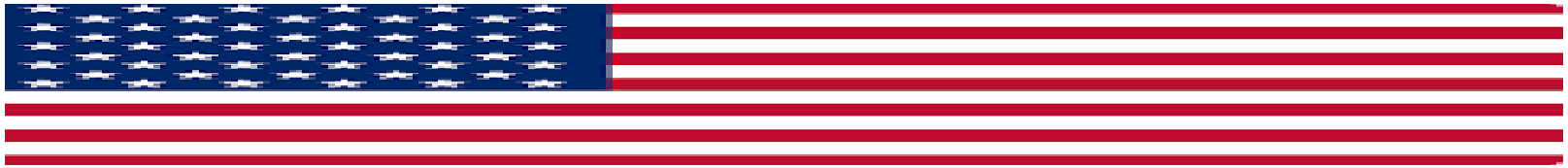
AUTHORS: Lawrence Copelovitch, MD and Bernard S. Kaplan, MB, BCh

Division of Nephrology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

…After lifting COVID-19 social restrictions, England experienced an increase in childhood IPD cases that exceeded prepandemic levels…

Vaccines work.
- A near 90% reduction in IPD under 2

Current NZ Data, Thanks to Andy Angelmyer (ESR).



Surveillance of pediatric parapneumonic effusion/empyema in New Zealand

Katherine Rix-Trott FRACP[1,2] | Catherine A. Byrnes FRACP, MD[1,3] | Catherine A. Gilchrist PhD[3] | Richard Matsas FRACP[2] | Tony Walls FRACP[4,5] | Lesley Voss FRACP[1] | Caroline Mahon FRACP[4] | Nigel P. Dickson MD[6] | Peter Reed DPhil[1] | Emma J. Best FRACP[1,3]

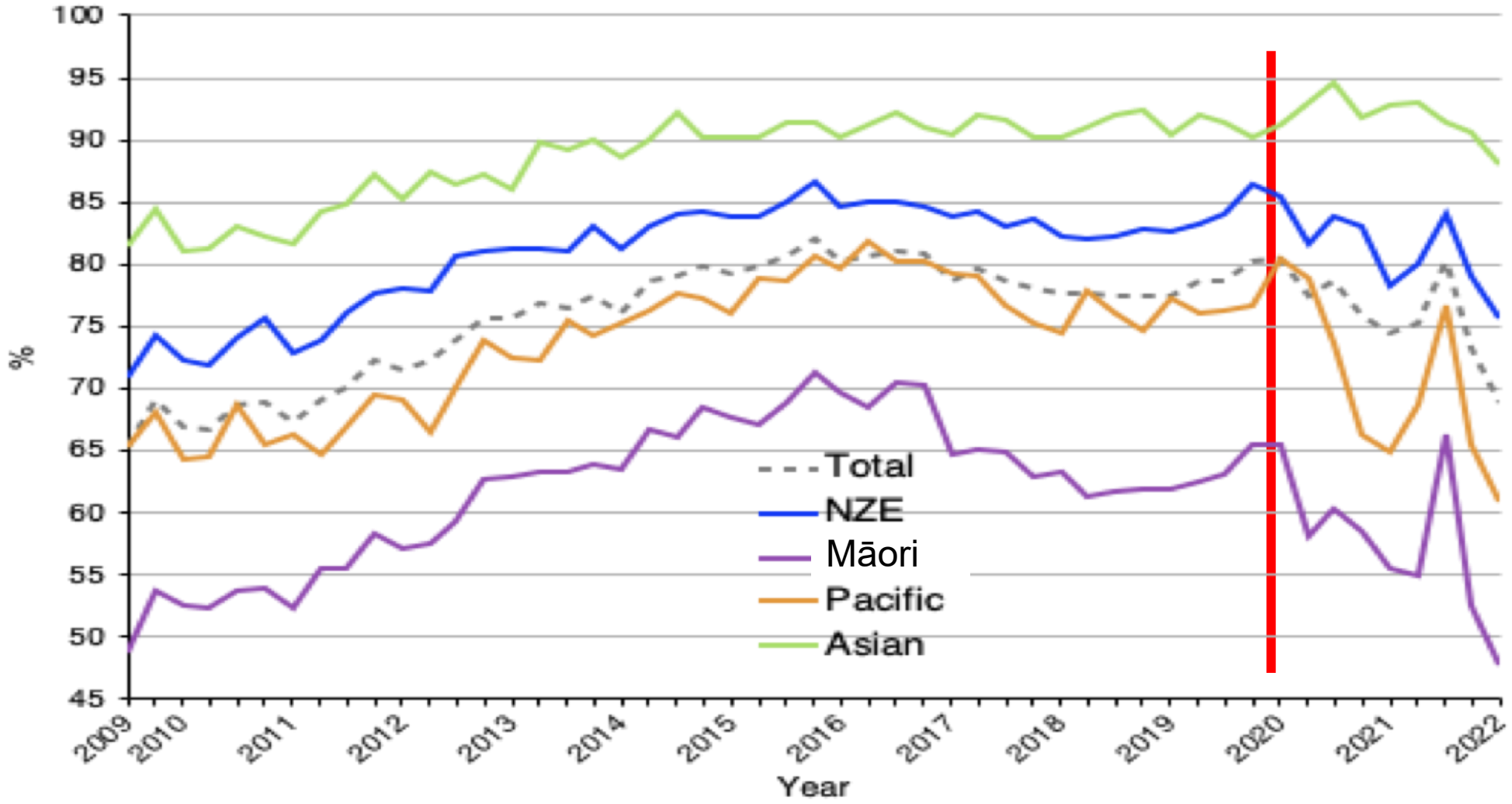
Prospective study 102 children <15 hospitalised parapneumonic effusion/ empyema, May 2014-May 2016

…**pneumococcal vaccination** was incomplete, with **only 61% fully immunized and 30% unimmunized**…

…Haemophilus influenzae type b vaccine uptake was near complete at 89/94 (95%)…

…**influenza** immunization only 3/78 (4%).

Immunisation coverage at 6 mths of age
ie: 2 or 3 doses of PCV received by age 6 mths



Impact of pandemic on immunisation coverage as health services under strain in many countries, however equitable timely coverage for Māori has never been achieved

Pediatric Pulmonology. 2021;56:2949-2957.

In summary

It has been a perfect storm of

- Immunisation delivery amongst Māori infants has always been inequitable and is now a national crisis[1]
- Re-direction of resources in the COVID environment
- The choice of PCV10 rather than PCV13
- Return of respiratory viral illness post lockdown

Have all contributed to lethal serotype 19A ‘escape’

1. New Zealand’s immunisation policy fails again and entrenches ethnic disparities, O Sincair, C Grant, NZMJ Sept 2021, vol 134, p92-95

So how does this compare to STEC-HUS in NZ?

ORIGINAL ARTICLE

Shiga Toxin Producing *Escherichia coli* Infections and Associated Haemolytic Uraemic Syndrome in New Zealand Children: Twenty Three Years of Epidemiology and Clinical Observations

William Wong, MB, ChB, FRACP*

Department of Paediatric Nephrology, Starship Children's Hospital, New Zealand

- 1998-2020 – 23 years surveillance – 226 patients
- Mean annual **incidence in children under 5** was around **2.5/100,000**
- **Acute dialysis** needed in **56%** for a median of 9 days
- Overall mortality 1.3% (exclusively severe cerebral injury)
- All dialysed patients recovered sufficient kidney function during the acute phase of their illness to become dialysis independent.
- One patient progressed to kidney failure requiring long term kidney replacement therapy (dialysis then transplant) during the study period.

SpHUS 2020/22 = 2.0/100,000 **<5 yrs (*2022 = 3.9/100,000*)**

SpHUS2020/22 = **15/19 required acute dialysis (~80%)**

Wong. Int J Pediatr Res 2022, 8:085

Family of baby spending first birthday in hospital with pneumococcal complications calls for vaccine switch

Nikki Macdonald · 05:00, Sep 13 2022

SUPPLIED

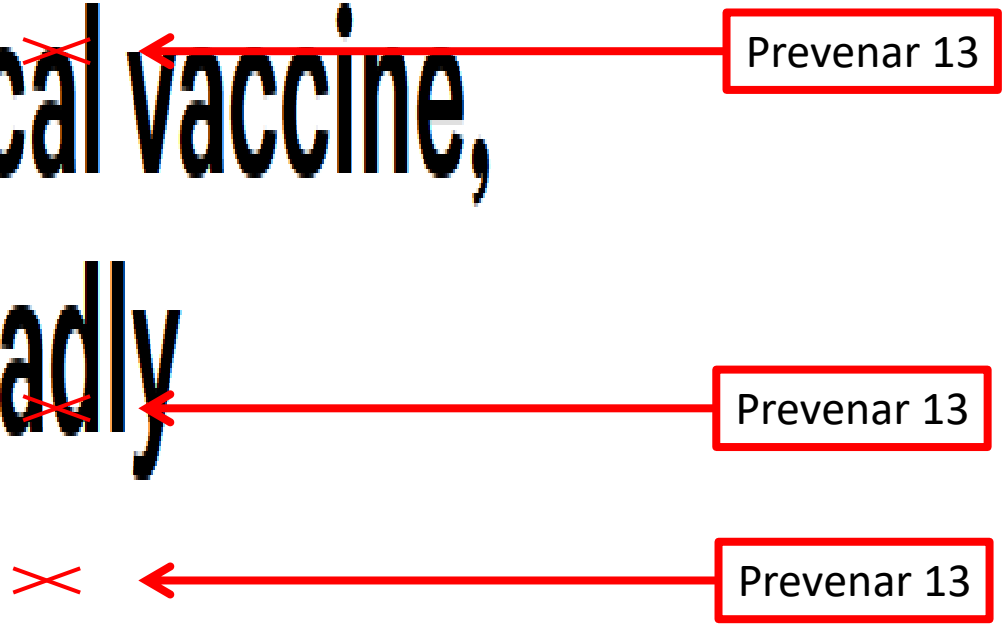
Pneumonia, sepsis and kidney failure: Rachael Van Mey Gaarden's daughter Eloise Swadel will spend her first birthday in hospital, after contracting pneumococcal disease. She wants Pharmac to fund a broader pneumococcal vaccine, to spare other families the same trauma.

'Heartbreaking': Parents of sick 11-month-old want greater meningitis awareness

Hannah Martin · 05:00, Nov 19 2022

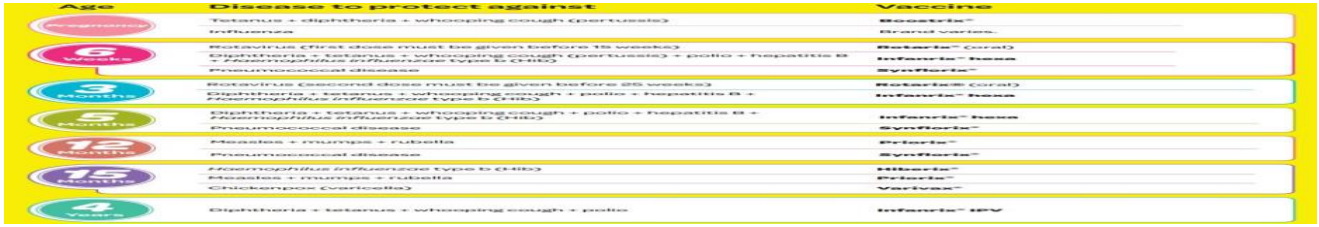
Images from Stuff NZ

Pharmac plans switch back to broader pneumococcal vaccine, following surge in deadly disease cases



Nikki Macdonald · 16:40, Sep 21 2022

Thank you any questions?



- Reviewed pHUS in children under 5 since PCV7 – 2006-2016
- Compared with PCV13 time period
- 54 cases total – (All SpHUS children were appropriately immunised bar one)
- Overall
  - 60% LRTI, 80% of which had empyema, 25% meningitis (a third abscess)
  - Case fatality rate 15%
    - Most of these meningitis (6/8), 40% of meningitis pHUS died
  - 45% of survivors who responded to questionnaire had “CKD” (46 survivors, 13/29 CKD)
  - Only 2/13 meningitis cases had a ‘normal outcome’
- In PCV13 period
  - Older cohort
  - Reduced incidence (0.25/100,000 peak in PCV7, to 0.08/100,000 in PCV13 era)
  - Most were non-PCV13 strains ie not as much 19A, BUT 19A the only PCV13 strain in the last 4 years of surveillance

Pneumococcal-related Hemolytic Uremic Syndrome in the United Kingdom
National Surveillance, 2006–2016
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BMJ Lawrence J, et al. Arch Dis Child 2018;103:957–961. doi:10.1136/archdischild-2017-313923

The Pediatric Infectious Disease Journal • Volume 38, Number 10, October 2019

- Australia, tertiary hospital, 1997-2016
- Increasing ***proportion*** of their HUS cases were pneumococcal related (INCLUDING PCV13 period – but small numbers…)
- 5/11 PCV13 immunised, 4 of these infected with a vaccine serotype, 2 of these 4 were 19A…
  - MAYBE reduced dialysis need??
  - 2/4 none, 2/4 short term dialysis 2-4 days
  - Those with non-vaccine strains and unvaccinated patients all needed dialysis, longer on average…
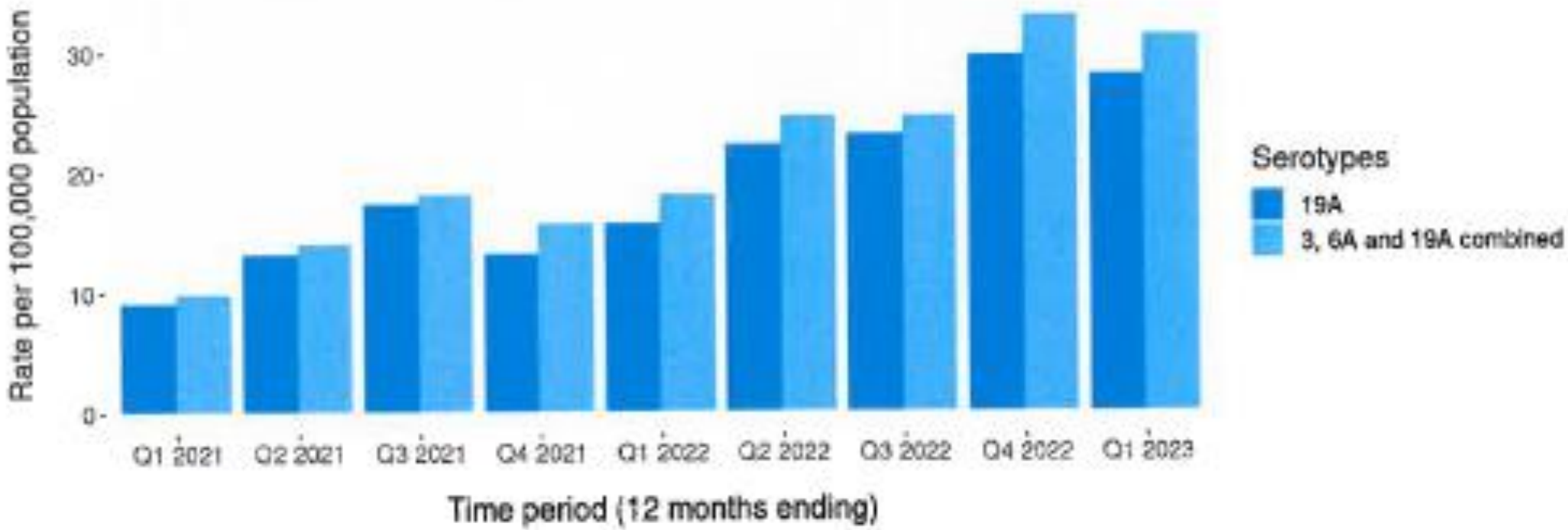
Figure 2: Quarterly IPD incidence rate per 100,000 children less than 2 years of age for the previous 12 months ending 31 March 2023