Better the Devil You Know?

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Tuesday 13th September 2011

The Case of Master NA – Introduction

ROYAL CHILDREN'S HOSPITAL

- 10 month old boy presents to RCH ED
- Background:
  - Elective LUSCS at term
  - No significant past medical history
  - Immunisations up to date
  - Normal developmental progress
  - 2 older siblings; well

The Case of Master NA – Introduction

- Presenting complaint:
- Unwell for 4 days
  - Initial coryza
  - Bilateral discharging ears (green pus)
  - No improvement with cephalexin then cotrimoxazole
  - Increasingly lethargic
  - Vomiting

The Case of Master NA

- Examination:
  - Unwell, lethargic, photophobic
  - Temp 39.1; HR 160; RR 44; BP 100/60; SaO_2 100%
  - Pus in ear canals
  - Cardiovasc / resp / abdo exam normal
  - Neurological exam not documented

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The Case of Master NA

- Investigations:
  - Hb 102 WCC **16.7** (N **11.52**, L **1.50**, bands **2.84**, ITR **0.22**), PLT 237
  - UEC normal – Na 140. LFT normal
  - CRP **250**
  - VBG: pH **7.32**, lactate **4.3**, bicarb **21**, glucose 6.1
  - Blood culture and ear swabs pending

The Case of Master NA

- Started IV benzylpenicillin for perforated otitis media

- Reassessed – more unwell

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The Case of Master NA

- Cerebrospinal fluid:
  - 12 erythrocytes
  - 111 white cells
    - 96 polymorphs
    - 15 lymphocytes
  - Protein: 1.89
  - Glucose: 1.1
  - Gram stain: Gram positive cocci resembling streptococci.

The Case of Master NA

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- What would you start him on?
  - Cefotaxime alone
  - Penicillin & cefotaxime
  - Vancomycin & cefotaxime
  - Vancomycin & cefotaxime & rifampicin

The Case of Master NA

- Progress:
  - Cefotaxime commenced
  - No corticosteroids given
- Day 1
  - Ongoing fever, irritability, lethargy, fluctuating conscious state, neck stiffness
- BC & CSF: alpha haemolytic streptococci

The Case of Master NA

- Progress – Day 2:
  - Ongoing fever but improving conscious state

- CSF culture:
  - *Streptococcus pneumoniae*
    - Penicillin MIC: 2.0 mg/L
    - Cefotaxime MIC 1.0 mg/L

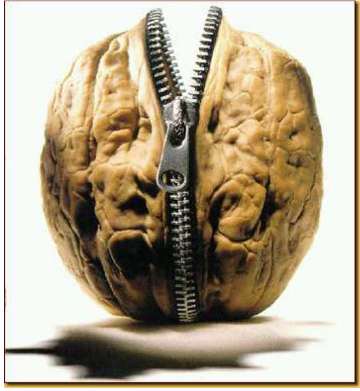
Streptococcus pneumoniae – Microbiological Aspects OLD CLSI break points

	Sensitive	Intermediate	Resistant
Penicillin (pre-2008) (all clinical syndromes & routes of administration)	≤ 0.06	0.12 – 1	≥ 2
Cefotaxime (pre-2003)	≤ 0.5	1	≥ 2

Streptococcus pneumoniae – Microbiological Aspects NEW CLSI break points

	Sensitive	Intermediate	Resistant
Penicillin			
Meningitis	≤ 0.06	----	≥ 0.12
Non-meningitis	≤ 2	4	≥ 8
Non-meningitis (oral)	≤ 0.06	0.12 - 1	≥ 2
Cefotaxime			
Meningitis	≤ 0.5	1	≥ 2
Non-meningitis	≤ 1	2	≥ 4

Streptococcus pneumoniae – The Changes in a Nutshell



- EUCAST: same breakpoints (for meningitis)
- Penicillin for pneumococcal meningitis
  - Same sensitivity cut-off ($\leq$ 0.06)
  - No intermediate zone
  - Lower resistance breakpoint ($\geq$ 0.12)
- Cefotaxime for pneumococcal meningitis
  - No changes
  - Changes only for non-meningitis isolates

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Rationale for change in breakpoints

- Rising MICs in community acquired pneumonia → change in physicians' practice
  - newer / broader / more costly drugs
  - *but* penicillin not clinically failing / no difference in outcomes
- Breakpoints raised for non-meningitis indications
- Effect: worldwide (SENTRY) data: 68% susceptible → 93% susceptible

Weinstein, M. P., K. P. Klugman, et al. (2009) "Rationale for revised penicillin susceptibility breakpoints versus Streptococcus pneumoniae: coping with antimicrobial susceptibility in an era of resistance."CID 48(11): 1596-1600.

Back to The Case of Master NA

- CSF isolate of *Strep. pneumoniae*:
  - Penicillin MIC = 2.0 mg/L → RESISTANT
  - Cefotaxime MIC 1.0 mg/L → intermediate

- Blood culture isolate of *Strep. pneumoniae*
  - Penicillin MIC = 4.0 mg/L → RESISTANT
  - Cefotaxime MIC = 2.0 mg/L → RESISTANT

- ID referral!

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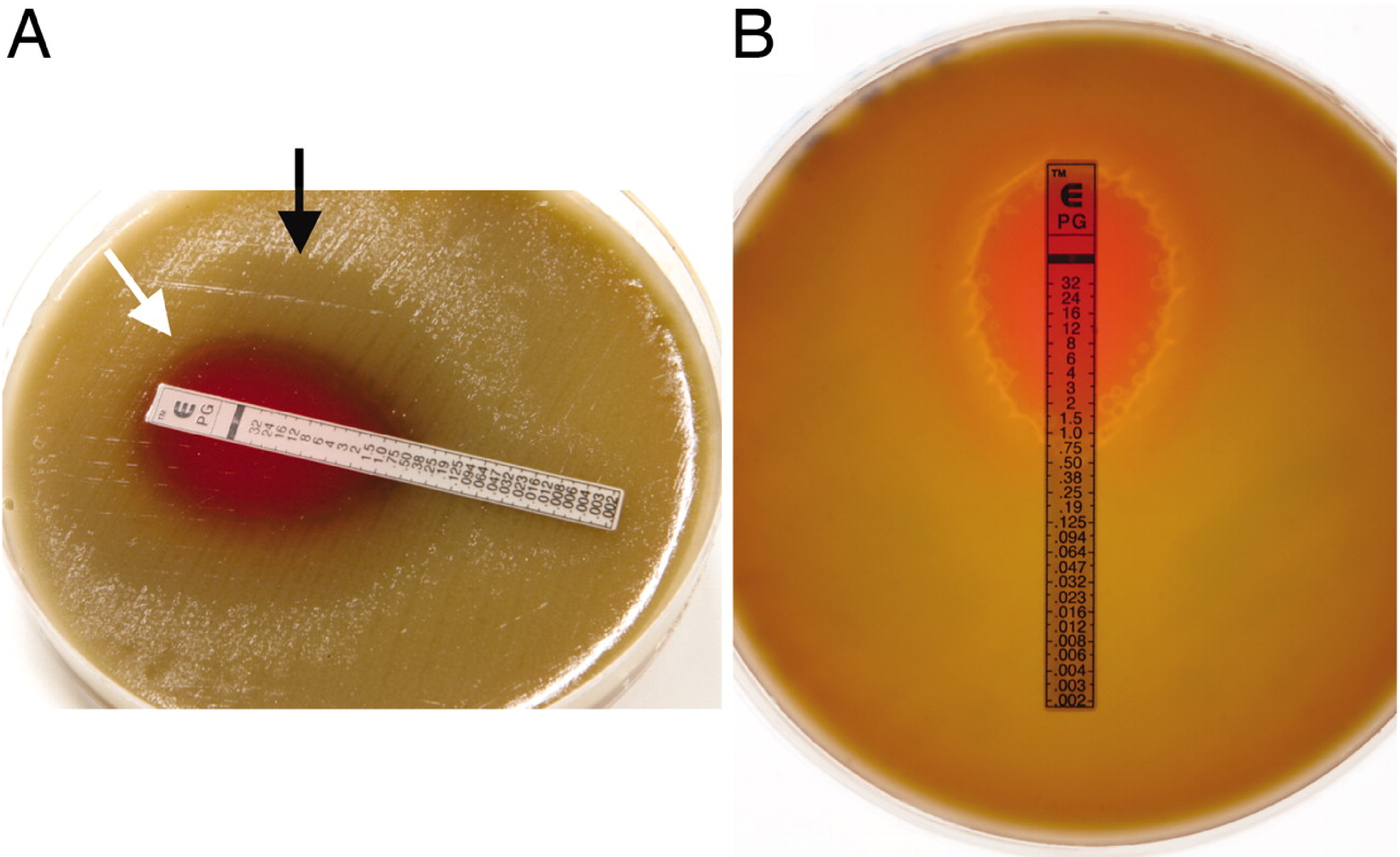

Morand, B. and K. Mühlemann (2007). "Heteroresistance to penicillin in Streptococcus pneumoniae." Proceedings of the National Academy of Sciences 104(35): 14098-14103.

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The Case of Master NA

- Day 2
  - Penicillin ceased; Cefotaxime continued
  - Vancomycin started 15 mg/kg Q6h
- Day 4-6
  - Ongoing marked clinical improvement
  - Vancomycin trough levels 7, 9 then <5! (target 15-20)
  - Despite dose increased sequentially:
    - 22.5 mg/kg → 25 mg/kg → 28 mg/kg

The Case of Master NA

- Day 6 eventful!
- New fever 38.1
- Focal seizures
- MRI brain & lumbar puncture under GA
- Unwell in recovery post GA: vomiting, increased secretions, desaturation requiring CPAP

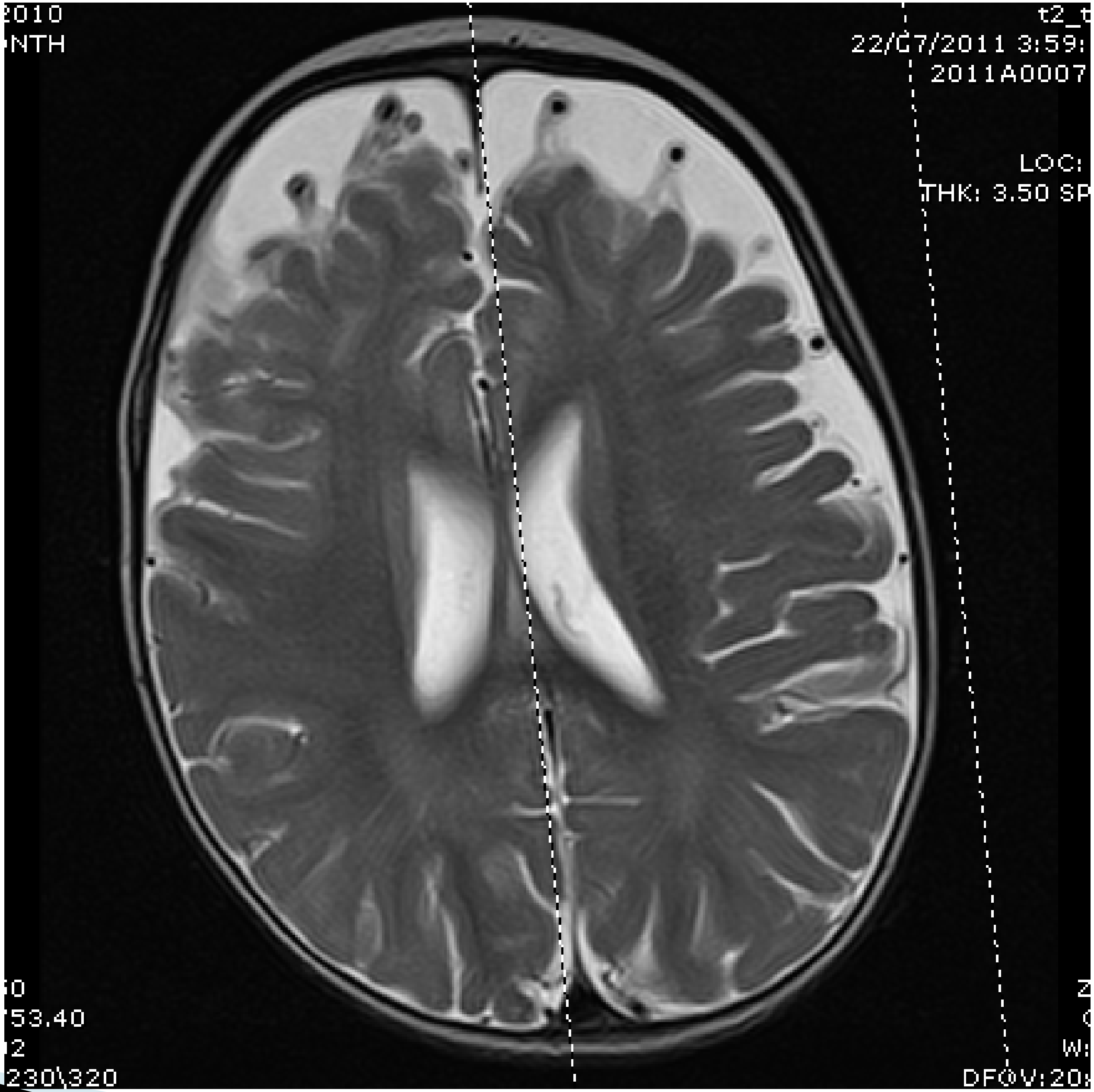
The Case of Master NA

- Friday afternoon at 5 o'clock: ID team called to review in recovery
- What shall we do now?
- Are we failing therapy?
- No MRI or LP results

- Thoughts??

The Case of Master NA

- Changed vancomycin to IV linezolid
- Rpt CSF:
  - 12 red blood cells,
  - <u>116</u> leukocytes (← 111)
    - <u>36</u> polymorphs (← 96)
    - <u>80</u> lymphocytes (← 15)
  - Protein <u>1.43</u> (←1.89)
  - Glucose 2.6 (← 1.1)
  - No organisms on Gram stain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THK: 3.50 SP
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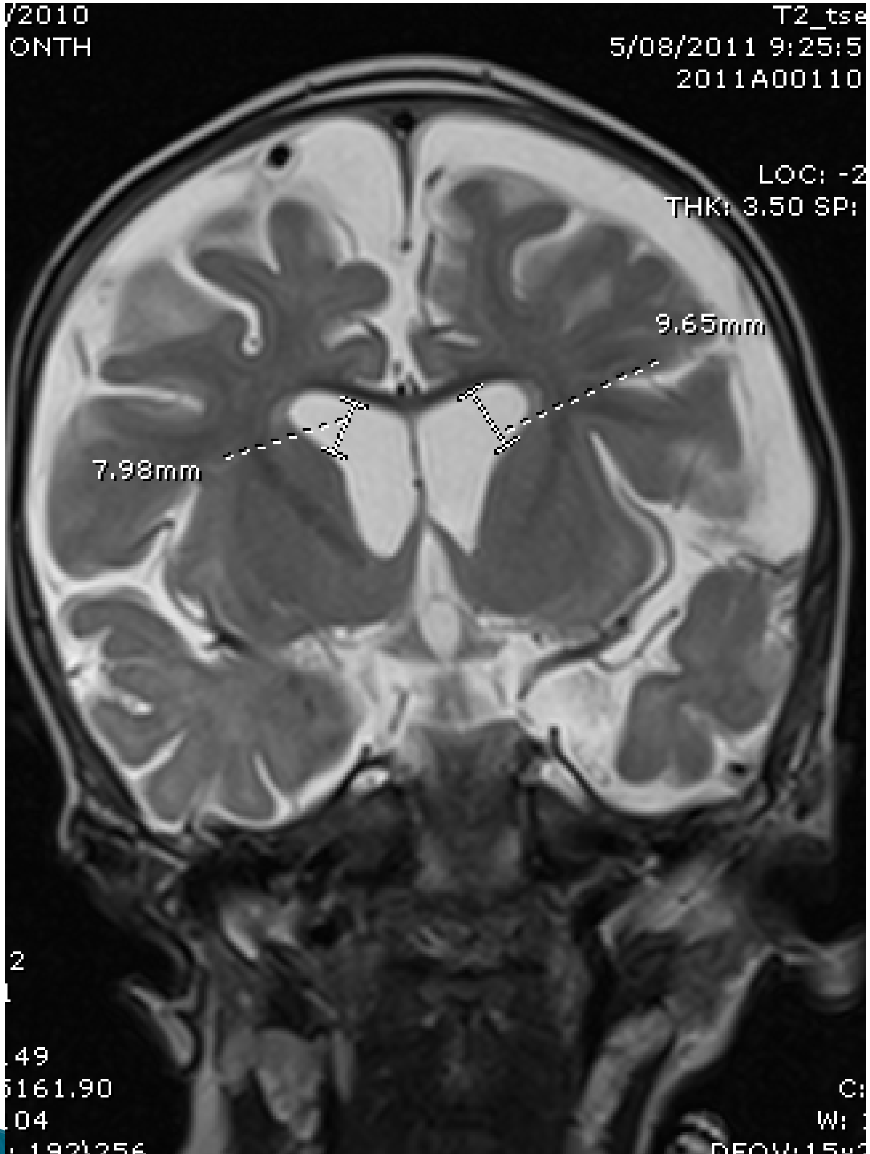
The Case of Master NA

- Neurosurgical opinion requested
  - Not for surgical management
- Day 11 – 19
- Ongoing low grade fevers (stopped ~ day 14)
- Excellent clinical improvement
  - back to normal self
  - no further seizures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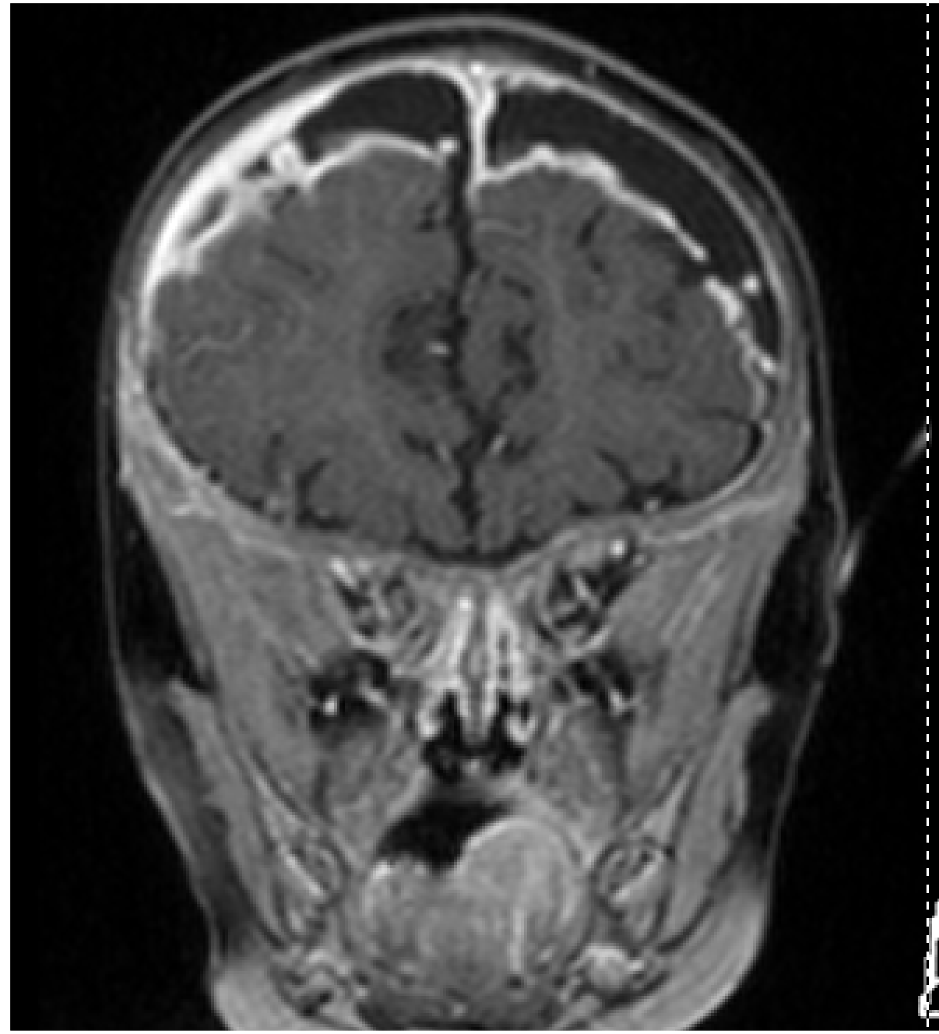

Summary: Master NA

- 10m boy with penicillin- & cephalosporin-resistant pneumococcal meningitis complicated by seizures & bilateral subdural collections on IV linezolid (BD) and cefotaxime (TDS)
- Now completely well but persistent changes on MRI
- Day 17 of effective treatment (vanc → linezolid)

Issues

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- How many children are we going to see like N.A.?
- What does this mean for our empirical treatment of suspected or proven bacterial meningitis?
- What is the optimal treatment of cephalosporin-resistant pneumococcal meningitis?

Impact of conjugate vaccines on pneumococcal disease

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- Increasing penicillin & cephalosporin resistance in Australia 1990s
- 7vPCV universal vaccination:
  - USA children < 2 yrs since 2000
  - Australia:
    - Indigenous children July 2001
    - all children January 2005

Collignon, P. J. and J. D. Turnidge (2000). "Antibiotic resistance in Streptococcus pneumoniae." Medical Journal of Australia 173 Suppl: S58-64.

Roche, P. W., V. Krause, et al. (2008). "Invasive pneumococcal disease in Australia, 2006." Communicable Diseases Intelligence 32(1): 18-30.

Williams, S. R., P. J. Mernagh, et al. (2011). "Changing epidemiology of invasive pneumococcal disease in Australian children after introduction of a 7-valent pneumococcal conjugate vaccine." Medical Journal of Australia 194(3): 116-120.

Impact of conjugate vaccines on antibiotic resistance in pneumococcal disease

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- Most clinically significant drug resistance confined to seven serotypes: 6A, 6B, 9V, 14, 19A, 19F, & 23F
- 7vPCV offers some cross-protection of vaccine-related serotypes → 6A, but not 19A
- Herd immunity reduces DRSP carriage & disease
- Antibiotic pressure on non-vaccine strains in serotype replacement leads to increasing DRSP
- IPD strains less resistant than carriage

Dagan, R. and K. P. Klugman (2008). "Impact of conjugate pneumococcal vaccines on antibiotic resistance." The Lancet Infectious Diseases 8(12): 785-795.

Impact of conjugate vaccines on pneumococcal disease

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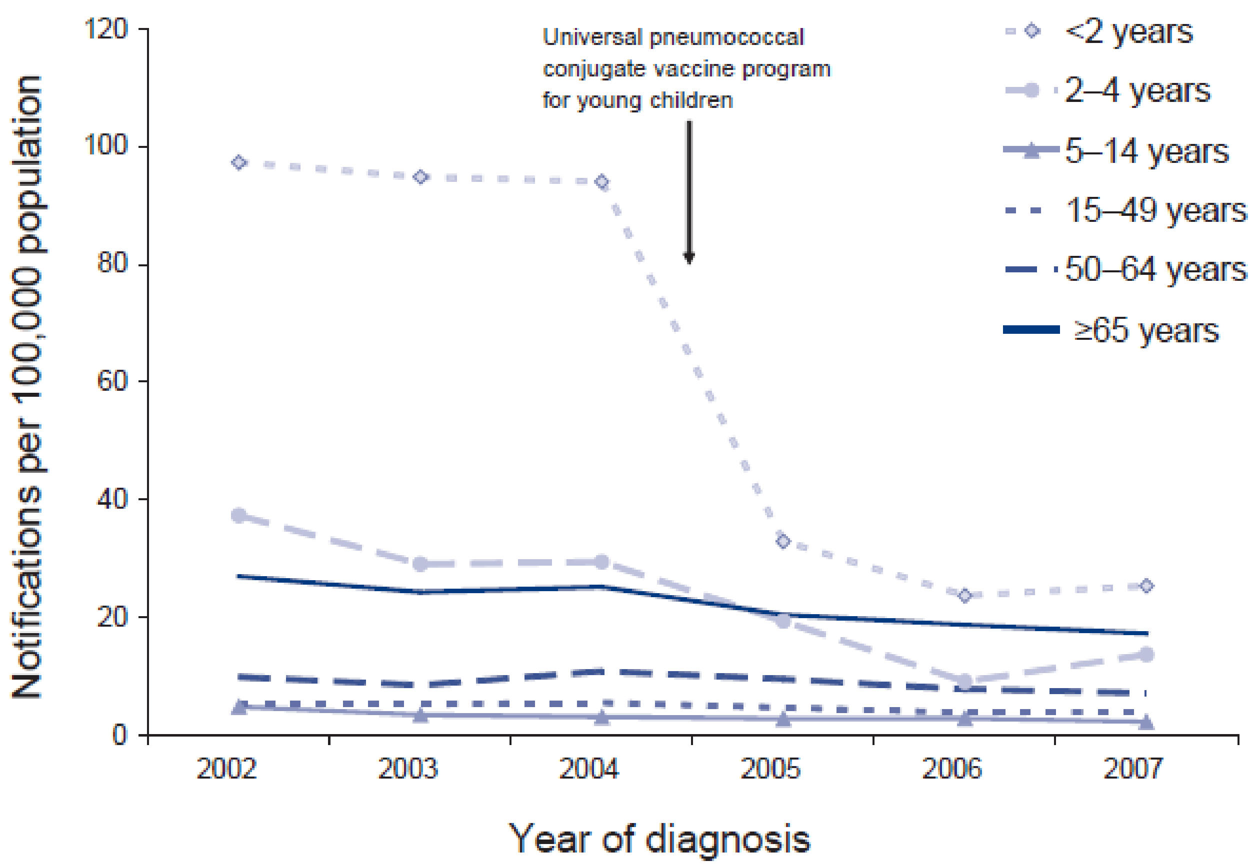
Figure 3.10.2: Pneumococcal disease notification rates, Australia, 2002 to 2007,* by age group and year of diagnosis



Chiu, C., A. Dey, et al. (2010). "Vaccine preventable diseases in Australia, 2005 to 2007." Communicable Diseases Intelligence 34 Supp: S1-167.

Impact of conjugate vaccines on pneumococcal disease

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Table 3.10.2: Average annual notification rates and percentage change in notification rates of invasive pneumococcal disease, Australia, 2006–2007 compared with 2002–2004, by age group

Age group (years)	Average rate 2002–2004*	Average rate 2006–2007†	Change‡ (%)
<2	95.4	24.6	–74
2–4	31.9	11.4	–64
5–14	3.8	2.6	–32
15–49	5.5	3.9	–28
50–64	9.8	7.5	–23
65+	25.5	18.0	–29
All ages	11.8	7.0	–40

* Average age-specific rate per 100,000 population. Notifications where the date of diagnosis was between January 2002 and December 2004.

† Average age-specific rate per 100,000 population. Notifications where the date of diagnosis was between January 2006 and December 2007.

‡ Percentage change in the average notification rate of 2006–2007 compared with the average notification rate of 2002–2004.

Chiu, C., A. Dey, et al. (2010). "Vaccine preventable diseases in Australia, 2005 to 2007." Communicable Diseases Intelligence 34 Supp: S1-167.

Impact of conjugate vaccines on antibiotic resistance in pneumococcal disease

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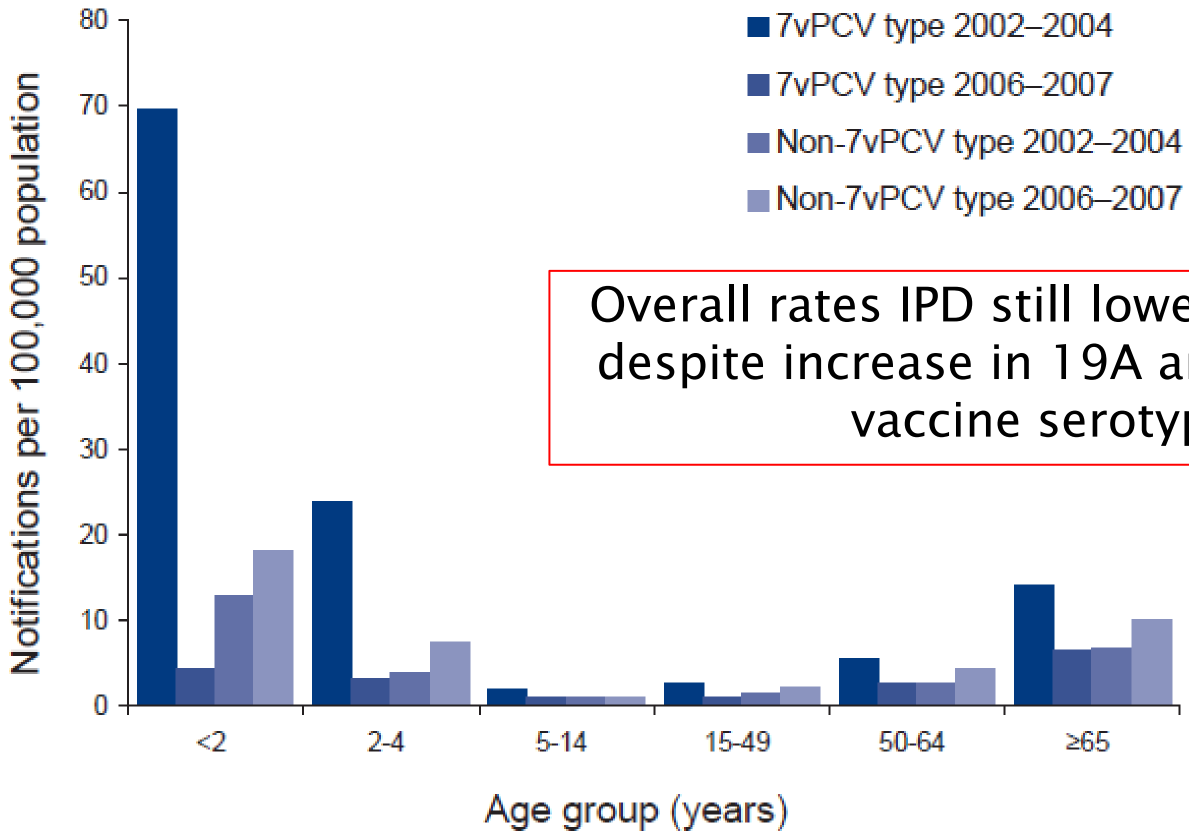
Figure 3.10.4: Notification rates of IPD cases with serotypes contained in the 7-valent pneumococcal conjugate vaccine (7vPCV),* versus notification rates for other non-7-valent serotypes,† Australia, 2006–2007 compared with 2002–2004, by age group



Overall rates IPD still lower post-7vPCV, despite increase in 19A and other non-vaccine serotypes

IPD 0–4yrs

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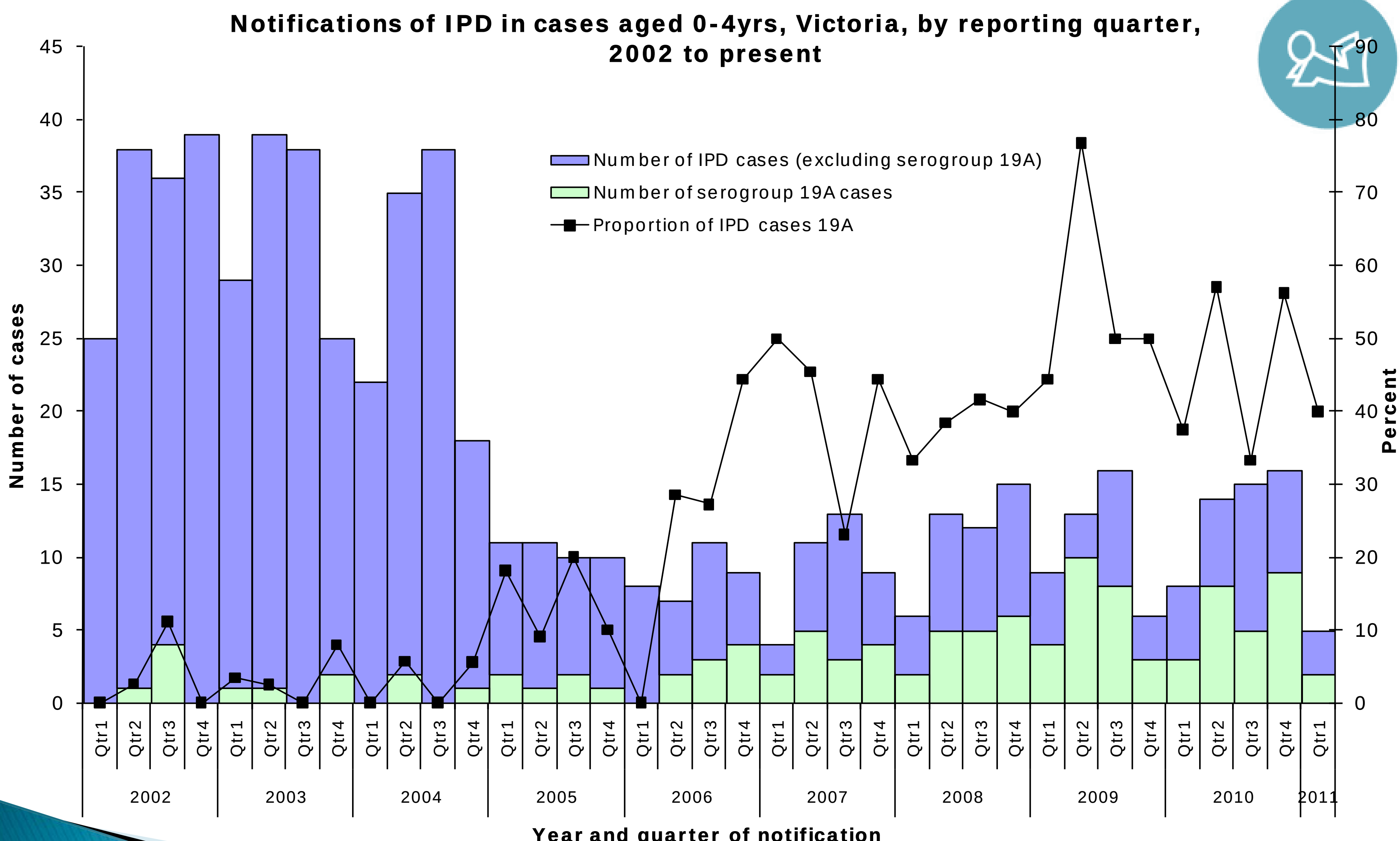
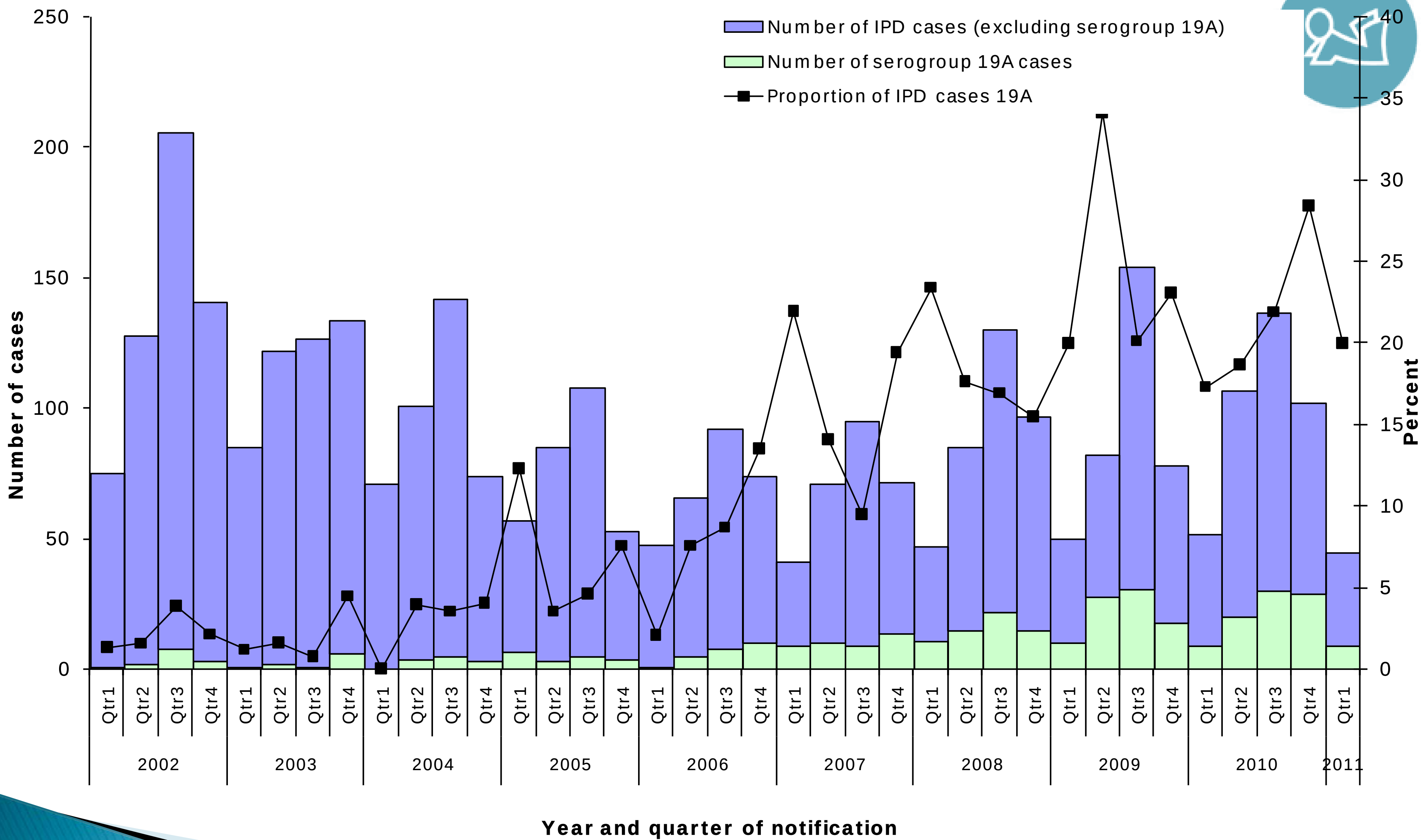


Courtesy of Lucinda Franklin & Michael Batchelor – Department of Health. Reproduced with permission.

All IPD cases, proportion serogroup 19A



Courtesy of Lucinda Franklin & Michael Batchelor – Department of Health. Reproduced with permission.

Pneumococcal antibiotic susceptibility data, Australia

Table 9. *Streptococcus pneumoniae* susceptibility to penicillin and ceftriaxone/cefotaxime, Australia, 2006, by state or territory

Antibiotic	Description	State or territory								Australia
		ACT	NSW	NT	Qld	SA	Tas	Vic	WA	
Penicillin	Resistant	0	15	1	12	1	0	3	0	32
	Intermediate	1	29	4	26	14	0	21	16	111
	Sensitive	17	450	50	220	86	40	237	108	1,208
	Total tested	18	494	55	258	101	40	261	124	1,351
	% reduced susceptibility	5.6	8.9	9.1	14.7	14.9	0.0	9.2	12.9	10.6
Ceftriaxone	Resistant	0	6	0	2	0	0	1	0	9
	Intermediate	0	11	1	3	2	0	4	0	21
	Sensitive	18	348	43	231	40	39	172	125	1,016
	Total tested	18	365	44	236	42	39	177	125	1,046
	% reduced susceptibility	0.0	4.7	2.3	2.1	4.8	0.0	2.8	0.0	2.9

Roche, P. W., V. Krause, et al. (2008). "Invasive pneumococcal disease in Australia, 2006." Communicable Diseases Intelligence 32(1): 18-30.

Penicillin - All age groups VIC

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011#	Total
Total isolates	476	474	434	349	298	273	278	341	351	376	154	3804
Isolates with susceptibility data	415	431	407	348	297	272	277	339	346	375	152	3659
Sensitive	392	390	355	319	259	247	257	299	310	334	132	3294
Intermediate	19	27	45	27	33	23	20	39	20	11	3	267
Resistant	4	14	7	2	5	2		1	6	9	2	52
Not categorised^									10	21	15	46
% non-susceptible	6%	10%	13%	8%	13%	9%	7%	12%	8%	5%	3%	9%

Penicillin by Age group

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011#	Total
Children under 5 years of age												
Sensitive	145	114	110	94	26	27	34	39	29	46	19	683
Intermediate	6	6	10	7	9	7	5	4	8	2	-	64
Resistant	2	3	3	-	2	-	-	1	-	2	-	13
Not categorised^	-	-	-	-	-	-	-	-	2	1	2	5
Not reported *	14	8	4	-	1	-	-	1	1	-	-	29
Total of isolates	167	131	127	101	38	34	39	45	40	51	21	794
%Non-susceptible	5%	7%	11%	7%	30%	21%	13%	11%	21%	8%	-	10%

Courtesy Marion Easton MDU

Cefotaxime / ceftriaxone - All age groups

VIC

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011#	Total
Total isolates	476	474	434	349	298	273	278	341	351	376	154	3804
Isolates with susceptibility data	245	291	308	322	282	248	260	317	339	357	142	3111
Sensitive	243	284	300	313	277	243	255	312	333	351	139	3050
Intermediate	2	3	7	9	2	5	5	4	4	5	1	47
Resistant	-	4	1	-	3	-	-	1	1	1	-	11
Not categorised^	-	-	-	-	-	-	-	-	1	-	2	3
% non-susceptible	1%	2%	3%	3%	2%	2%	2%	2%	1%	2%	1%	2%

Cefotaxime / ceftriaxone - By age group

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
Children under 5 years of age												
Sensitive	93	84	97	95	35	32	36	42	36	46	19	615
Intermediate	1	-	1	1	1	1	-	1	1	2	-	9
Resistant	-	1	-	-	1	-	-	-	-	-	-	2
Not reported *	73	46	29	5	1	1	3	2	3	3	2	168
Total of isolates	167	131	127	101	38	34	39	45	40	51	21	794
%Non-susceptible	1%	1%	1%	1%	5%	3%	-	2%	3%	4%	-	2%

Courtesy Marion Easton MDU

Cefotaxime / ceftriaxone - All age groups

RCH

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011#	Total
Total isolates	40	52	41	39	16	20	8	16	16	21	11	280
Isolates with susceptibility data	27	44	35	36	16	20	7	16	15	21	11	248
Sensitive	26	44	35	36	15	18	7	15	13	20	11	240
Intermediate	1	-	-	-	-	2	-	1	2	1	-	7
Resistant	-	-	-	-	1	-	-	-	-	-	-	1
% non-susceptible	4%	-	-	-	6%	10%	-	6%	13%	5%	-	3%

Cefotaxime / ceftriaxone - By age group

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011#	Total
Children under 5 years of age												
Sensitive	26	40	32	33	9	13	6	11	10	12	6	198
Intermediate	1	-	-	-	-	1	-	-	1	1	-	4
Resistant	-	-	-	-	1	-	-	-	-	-	-	1
Not reported *	13	6	6	3	-	-	1	-	1	-	-	30
Total isolates	40	46	38	36	10	14	7	11	12	13	6	233
% non-susceptible	4%	-	-	-	10%	7%	-	-	9%	8%	-	2%

Courtesy Marion Easton MDU

Empiric treatment at RCH

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Age	Antibiotics	Steroids
>2 months	Cefotaxime 50 mg/kg (2 g) iv 6H	Dexamethasone 0.15 mg/kg, iv 6H
4 weeks-2 months	Cefotaxime 50 mg/kg (2 g) iv 6H, Benzylpenicillin 60 mg/kg iv 4H and Gentamicin	Dexamethasone 0.15 mg/kg, iv 6H
< 4 weeks	Cefotaxime 50 mg/kg (2 g) iv 6H, Benzylpenicillin 60 mg/kg iv 12H (wk 1 of life) 6-8H (wk 2-4 of life), Gentamicin	No

Antibiotics

- Cefotaxime can be substituted with Ceftriaxone 100 mg/kg (max 2gm) iv daily
- Chloramphenicol may be used in children with a type 1 hypersensitivity to cephalosporins.

- Empiric use of Vancomycin: The prevelence of pneumococcal resistance to penicillin and 3rd generation cephalosporins has reduced signficantly since the introduction of vaccination, such that empiric use of vancomycin is not currently recommended for *S pneumoniae* meningitis in Victoria.

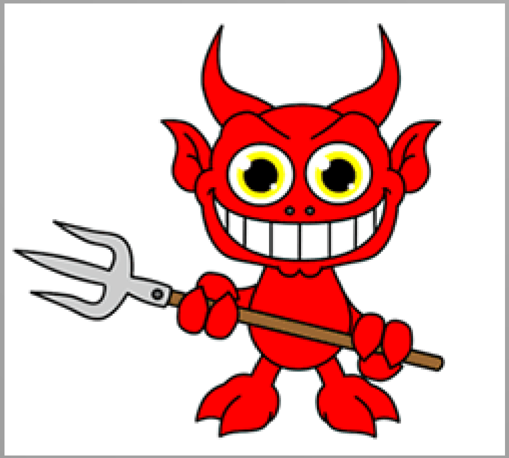
- Continue empiric treatment until cultures are known to be negative or an organism and its sensitivity pattern are known. A positive culture result with sensitivities should lead to narrower spectrum treatment:

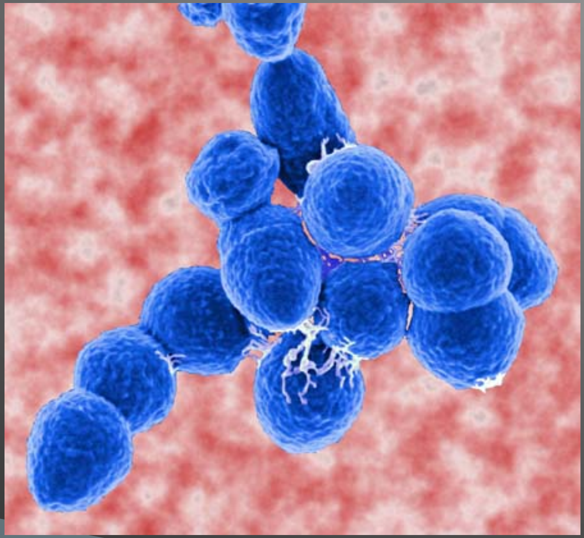
The future?

- 13vPCV replaced 7vPCV from 1st July 2011
- 6 additional serotypes including 19A

- Heading for another decline in antibiotic resistance?

Treatment of cephalosporin-resistant pneumococcal meningitis





Treatment of Cephalosporin-Resistant Pneumococcal Meningitis

- Choice of antibiotics for meningitis influenced by:
  - CSF penetration
  - Bactericidal activity
  - Pharmacodynamics
    - Time dependent killing
    - Concentration dependent killing

Treatment of Cephalosporin-Resistant Pneumococcal Meningitis

- CSF penetration increased / improved by:
  - Meningeal inflammation
  - High drug lipid solubility
  - Low molecular weight
  - Low serum protein binding
  - Minimal ionisation and physiological pH
- Bactericidal activity reduced by:
  - Low pH, high lactate, high CSF protein

3rd generation cephalosporins in treatment of cephalosporin-resistant pneumococcal meningitis

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- CSF penetration 4.8 ± 3.5% (J Ped (1983) 102 (1) 134-7)
- T > MIC must be 95-100% to achieve CSF sterilisation in ceph-R disease
- High dose (300 mg/kg/day) may be effective in cef-I disease (case series)
- Case series level & in vitro data – failure of CSF bacterial killing → Not safe to use alone

•Klugman, K. P., I. R. Friedland, et al. (1995). "Bactericidal activity against cephalosporin-resistant Streptococcus pneumoniae in cerebrospinal fluid of children with acute bacterial meningitis." Antimicrobial Agents & Chemotherapy 39(9): 1988-1992.
•Lutsar, I., A. Ahmed, et al. (1997). "Pharmacodynamics and bactericidal activity of ceftriaxone therapy in experimental cephalosporin-resistant pneumococcal meningitis." Antimicrobial Agents & Chemotherapy 41(11): 2414-2417.
•Viladrich, P. F., C. Cabellos, et al. (1996). "High doses of cefotaxime in treatment of adult meningitis due to Streptococcus pneumoniae with decreased susceptibilities to broad-spectrum cephalosporins." Antimicrobial Agents & Chemotherapy 40(1): 218-220.

4^{th} generation cephalosporins

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- Equivalent or superior to 3^{rd} generation cephalosporins for pen-R but ceph-S strains
- Better T>MIC in CSF than ceftriaxone
  - pts w shunt + hydrocephalus + uninflamed meninges
- Cephalosporin cross -resistance

Saez-Llorens, X. and M. O'Ryan (2001). "Cefepime in the empiric treatment of meningitis in children." Pediatric Infectious Disease Journal 20(3): 356-361.

Hameed, N, and Tunkel A (2010). "Treatment of Drug-Resistant Pneumococcal Meningitis". Curr Infect Dis Rep 12:274-281

Glycopeptides: Vancomycin

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- Commonly used
- Synergistic w CTX in animal models
- Decreased / unreliable CSF penetration in presence of corticosteroids
  - Circumvented by adequate doses: 60 mg/kg/day in a study in children
- Tolerance an emerging problem
- Teicoplanin – less clinical experience

Friedland, I. R., M. Paris, et al. (1993). "Evaluation of antimicrobial regimens for treatment of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis." Antimicrobial Agents & Chemotherapy 37(8): 1630-1636.
Hameed, N, and Tunkel A (2010). "Treatment of Drug-Resistant Pneumococcal Meningitis". Curr Infect Dis Rep 12:274-281
Fernandez, A., C. Cabellos, et al. (2005). "Experimental study of teicoplanin, alone and in combination, in the therapy of cephalosporin-resistant pneumococcal meningitis." Journal of Antimicrobial Chemotherapy 55(1): 78-83.

Rifampicin

ROYAL CHILDREN'S HOSPITAL

- Good CSF penetration
- Effective monotherapy but rapid emergence of resistance = CTX + rif = CTX + rif + vanc > CTX + vanc
- Combination with vanc &/or ceftriaxone
- Recommended for delayed clinical / bacteriological response or CTX MIC > 4
- ? Antagonism of beta-lactams

Lee, H., J.-H. Song, et al. (2004). "Evaluation of a triple-drug combination for treatment of experimental multidrug-resistant pneumococcal meningitis." International Journal of Antimicrobial Agents 23(3): 307-310.
Hameed, N, and Tunkel A (2010). "Treatment of Drug-Resistant Pneumococcal Meningitis". Curr Infect Dis Rep 12:274-281
Doit, C. P., S. P. Bonacorsi, et al. (1994). "In vitro killing activities of antibiotics at clinically achievable concentrations in cerebrospinal fluid against penicillin-resistant Streptococcus pneumoniae isolated from children with meningitis." Antimicrobial Agents & Chemotherapy 38(11): 2655-2659.

Linezolid in drug-resistant pneumococcal meningitis

- Oxazolinidone antibiotic
- Protein synthesis inhibitors; 50s ribosomal subunit
- Bacteriostatic; time-dependent killing; significant post-antibiotic effect
- 100% oral bioavailability
- VD 0.5 – 0.6 L/kg (TBW); 31% protein bound
- Variable estimates of CSF penetration:
  - 70-80% (humans; VP shunts; uninflamed meninges)
  - 18-38% in rabbit meningitis models

•Cottagnoud, P., C. M. Gerber, et al. (2000). "Linezolid against penicillin-sensitive and -resistant pneumococci in the rabbit meningitis model." Journal of Antimicrobial Chemotherapy 46(6): 981-985.

•Hachem, R., Afif, C., Gokaslan, Z. & Raad, I. (2001). Successful treatment of vancomycin-resistant Enterococcus meningitis with linezolid. European Journal of Clinical and Microbiological Infectious

•Diseases 20, 432-4.

•MacGowan, A. P. (2003). "Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections." Journal of Antimicrobial Chemotherapy 51 Suppl 2: ii17-25.

Linezolid in drug-resistant pneumococcal meningitis

- Minimal bactericidal activity *in vitro*
- Inferior to ceftriaxone for pen-S disease & to ceftriaxone + vancomycin for pen-R disease in rabbits
  - better than ceftriaxone alone for pen-R
- Very limited clinical data in humans – case series
  - Neurosurgical use – VRE, MRSE, MRSA

Cottagnoud, P., C. M. Gerber, et al. (2000). "Linezolid against penicillin-sensitive and -resistant pneumococci in the rabbit meningitis model." Journal of Antimicrobial Chemotherapy 46(6): 981-985.
Faella, F., P. Pagliano, et al. (2006). "Combined treatment with ceftriaxone and linezolid of pneumococcal meningitis: a case series including penicillin-resistant strains." Clinical Microbiology & Infection 12(4): 391-394.
Ntziora, F. and M. E. Falagas (2007). "Linezolid for the treatment of patients with central nervous system infection." Annals of Pharmacotherapy 41(2): 296-308.

Carbapenems

- Imipenem: highly effective *in vitro / vivo*; risk of seizures in children
- Meropenem: despite susceptibility in vitro, therapeutic failure against CTX-resistant strains
  - Rabbit model – Poor bacterial killing even when CSF conc >> MIC
  - Limited clinical experience

Friedland, I. R., M. Paris, et al. (1993). "Evaluation of antimicrobial regimens for treatment of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis." Antimicrobial Agents & Chemotherapy 37(8): 1630-1636.

Wong, V. K., H. T. Wright, Jr., et al. (1991). "Imipenem/cilastatin treatment of bacterial meningitis in children." Pediatric Infectious Disease Journal 10(2): 122-125.

Fluoroquinolones

- eg moxifloxacin, levofloxacin, trovafloxacin gatifloxacin, others
- Good CSF penetration (moxifloxacin 50-85%)
- Excellent in vitro activity against *Strep. pneumoniae*
- Clinical efficacy & synergy w other agents in animal models
  - Levo + CTX >> vanc + CTX
- Promising but human data lacking
  - RCT trovafloxacin + CTX +/- vanc
    - Equivalent; not superior
      - ?hepatotoxic

Hameed, N, and Tunkel A (2010). "Treatment of Drug-Resistant Pneumococcal Meningitis". Curr Infect Dis Rep 12:274-281
Saez-Llorens, X., C. McCoig, et al. (2002). "Quinolone treatment for pediatric bacterial meningitis: a comparative study of trovafloxacin and ceftriaxone with or without vancomycin.[Erratum appears in Pediatr Infect Dis J 2002 Mar;21(3):270]." Pediatric Infectious Disease Journal 21(1): 14-22.

The effect of steroids on antibiotic therapy of DRSP meningitis

- CSF penetration
  - ↓ vancomycin
  - ↔ ceftriaxone and rifampicin
- Bacterial killing in CSF
  - ↓ vancomycin alone, ceftriaxone alone
  - ↔ vanc + ceftriaxone combination at CTX MIC 1.0 but ↓ at CTX MIC 4.
  - ↔ rifampicin

Paris, M. M., S. M. Hickey, et al. (1994). "Effect of dexamethasone on therapy of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis." Antimicrobial Agents & Chemotherapy 38(6): 1320-1324.

The Case of Master NA

ROYAL CHILDREN'S HOSPITAL

- Decision at this point:
- Once daily teicoplanin and ceftriaxone plus oral rifampicin
- Total duration 4 weeks from date of commencement of vancomycin
- (11 days from discharge date)

- Seen in clinic – neurologically normal; doing very well

Key points

- IPD due to cephalosporin-resistant *Streptococcus pneumoniae* is uncommon in Australia 7vPCV era
  - May increase with Abx pressure on non-vaccine serotypes
- Usual therapy vanc + cefotaxime / ceftriaxone may result in treatment failures
  - (? + effects of corticosteroids)
- Rifampicin and anti-streptococcal fluoroquinolones are promising adjuncts

Thank you

Questions?