Empyema in New Zealand
Declaration of conflicts

• Investigator led research in otitis media and nasopharyngeal carriage of pathogens funded by GSK

• Lead investigator in NZPSU empyema project
Outline

• NZ paediatric empyema incidence
  – Current data from greater Auckland

• Is NZ empyema different?
  – Microbiology and empiric antibiotic

• The NZPSU
Background

- Incidence of empyema in children has increased worldwide

- *S. pneumoniae* predominant causative organism in empyema in Europe/United States/Australia
  - Serotype 1 not covered by early generation conjugate pneumo vaccines
  - Post vaccine emerging serotypes 3 and 19A

- Increasing rates of *S. aureus* empyema noted in some centres (US)
  - +/- impact of MRSa

- Inclusion of 2009 pandemic data changing epidemiology

References:

Fletcher et al. Eur J Clin Micro Inf Dis 2014
Byington et al. Ped Inf Dis J 2006
Li et al. Pediatrics 2010
Grivalja et al Clin Inf Dis 2010
Ampofo et al 2010 Ped Inf Dis J
Annual hospitalization rates for empyema among children <5 yrs, United States 1996–2007

Reasons postulated

- Decreased primary care antibiotic prescribing
- Pre-hospital treatment with ibuprofen
- Delayed hospital presentation

- Changing microbiologic epidemiology &/or virulence
  - Impact of vaccination
  - *Pneumococcal vaccine & serotype replacement
  - *Staphylococcus aureus* virulence & emergent MRSa

*Introduction of national childhood PCV-7
What is the incidence of paediatric empyema in NZ?
N= 168
Mean age: 4.5 years
Primary discharge codes (J86–J86.9) likely represents minimum

Rate hospitalisations for empyema <15 yr old /100,000 (95% CI)

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>1992</td>
<td>0.4</td>
<td>(0.1 -1.2)</td>
</tr>
<tr>
<td>2001</td>
<td>0.8</td>
<td>(0.4-1.8)</td>
</tr>
<tr>
<td>2013</td>
<td>1.5</td>
<td>(0.9 – 2.6)</td>
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Increased Incidence of Pleural Empyema in Sth Auckland Children
Retrospective Review of Parapneumonic effusion (PPE) and Empyema 1998-2012

Caroline Mahon (Paed trainee)
presented at RACP congress 2014

Acknowledgement: Wendy Walker, Emma Best
Christian Coomarasamy, Dr Vandal, Peter Reid statisticians
Case Definitions

- Parapneumonic effusion (PPE)
  - Pleural effusion in association with pneumonia on formal CXR report
- Empyema
  - CT/USS showing complex fluid, loculation and/or $>1000 \times 10^6$ WCC on pleural tap and/or positive bacterial culture or positive ICT/PCR

N= 187 cases of PPE/empyema
- 104 criteria for empyema
- 83 cases of PPE
CMDHB empyema incidence children <15yrs, 1998 - 2012

Incidence rate increased by 13% per year from 1998 (p = 0.0001)

[Graph showing empyema incidence rates from 1998 to 2012 with peak incidence in 2009 labeled 'Pandemic H1N1', followed by PCV 10 vaccination in 2011-2012.]
Relative rates of empyema vs PPE do not vary over the 15 years of the study
RR 1.3 (CI 0.94-1.80) p=0.11
Introduction of conjugate pneumococcal vaccine – impact on childhood pneumonia

Consistent effect to lessen hospitalisation due to radiologically confirmed pneumonia

Reductions of 13-65% on all cause pneumonia

Pneumonia admissions for CMDHB resident children < 2y

Vogel, Trenholme, Best, Lennon, et al. NZMJ 2013

Impact of pneumococcal vaccine on hospital admission with LRI in children resident in South Auckland, NZ
So….

- High empyema incidence in Sth Auckland children
  - Now exceeds that seen in other countries
    - 10/100,000 <15yrs
    - 20/100,000 <4 yrs

- Empyema presentations increased 10x over 15 yrs
  (increase also reflected in national discharge data)
  - UK  3.7/100,000 (children<15yrs) & 3x increase
  - US   6/100,000 (children<15yrs) & 3x increase
  - Australia  0.4/100,000 - 1/100,000 & > 2x increase
    - further increase in 1-4yr olds empyema since PCV7 2006 -2010

- Quebec also report 10x increase in empyema1990-2007

Deceuninck et al. J Pediatric Inf Dis 2013
Peak incidence of empyema cases in 2009 - relates to H1N1 pandemic?

Empyema increase apparent before PCV7 introduction

Evidence of positive PCV7 vaccine impact in other areas - decrease radiologic & all-cause pneumonia in Sth Auckland

Ampofo K et al. Ped Inf Dis J. 2010;29:905-9
See H et al. Ped Inf Dis J. 2010;29:786-7
Pathogens of paediatric empyema in NZ—what’s our aetiology pie’?
NZ paediatric empyema: published data

- Retrospective review of empyema 2003-2008 @ SSH
- Identified 93 empyema cases (via hospital discharge data)
- Surgically managed empyema (n=62; VATS 55 or open thoracotomy 7), chest tube only (31)
  - 24/62 (39%) *S. aureus* (2/24, 8% MRSa)
  - 13/62 (21%) *S. pneumoniae*
  - 7/62 (11%) *S. pyogenes*
  - 18/62 (29%) no isolate

Audit of empyema & empiric antibiotics at SSH 2009 -2013

Aim

- To determine causative organisms (& susceptibilities) of empyema cases managed at SSH
- To review current first-line antibiotic recommendations

SSH empyema cases 2009 to 2013

- 150 cases identified via hospital discharge coding

Confirmed cases

- Positive culture from pleural fluid or pus in pleural space (microscopic or operative gross findings) or fibropurulent material on USS or CT

Acknowledgements: Cameron Burton (SHO), Neil Price (Surgeon)
Mode of infection: Paediatric empyema SSH 2009 -2013  (n=150)

- Pneumonia: 89%
- Disseminated Sepsis: 6%
- Other: 5%
- TB
- Lung abscess
Age: Paediatric empyema SSH 2009-2013

69% male, 31% female
Referring DHB: Paediatric empyema SSH 09-13

Auckland
CMDHB
WDHB
Nthland
Mid Cent
BOP
Waik
Hutt DHB
Lakes
Naki
Napier
Nel-Marl
Sthern
Tarawhiti
HB
CDHB
Sth CDHB
Hutt
Whang
CCDHB
Sthern
Hutt
Tarawhiti
HB
Whang
CDHB

2 cases referred from Pacific
Ethnicity: Paediatric empyema SSH 2009-2013

- Pacific: 32%
- Māori: 31%
- NZ European: 29%
- All other: 8%
Microbiology: Paediatric empyema SSH 2009-2013

- S.aureus 40%
- S.pneumoniae 26%
- S.pyogenes 6%
- H. influenzae 4%
- No pathogen 21%

12/61 (20%) MRSa
Microbiology: Paediatric empyema CMDHB
1998 - 2012 (n= 101)

Consistent increase in S.aureus empyema – now 50% of cases in Sth Auck

Byington et al. Clin Inf Dis 2002
Comparison: Microbiology for paediatric empyema 2001-2004, Paris

n= 78

Spneumoniae
Saureus
Spyogenes
No pathogen

Le Monnier et al CID 2006
Role of pneumococcal antigen detection in pleural fluid

- Empyema – pleural fluid proportion remain culture negative

*S. pneumoniae* antigen testing in kids

- YES - useful on pleural fluid
- NO - not useful on urine
  - (adult pneumonia only, children false positive results due to nasal carriage)

- When additional techniques (PCR/antigen) used *S. pneumoniae* most frequent pathogen in culture-neg empyema

Blaschke AJ et al. Ped Inf Dis J 2011; 30 (US)
Le Monnier et al. Clin Infect Dis 2006*
Usefulness of *S. pneumoniae* antigen detection directly on pleural fluid

**Table 1.** Review of Binax NOW *S. pneumoniae* assay performance for the diagnosis of pneumococcal empyema

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>No.</th>
<th>Study population</th>
<th>Age</th>
<th>Standard methods</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. [78]</td>
<td>Korea</td>
<td>Retrospective</td>
<td>62</td>
<td>Children</td>
<td>69 months (median)</td>
<td>Culture (blood or pleural fluid) or Positive PCR for <em>lytA</em></td>
<td>77</td>
<td>94</td>
</tr>
<tr>
<td>Picazo et al. [76]</td>
<td>Spain</td>
<td>Prospective</td>
<td>217</td>
<td>Children</td>
<td>&lt;15 years old</td>
<td>Culture (pleural fluid or CSF) or Positive PCR for <em>lytA</em></td>
<td>88</td>
<td>73</td>
</tr>
<tr>
<td>Strachan et al. [74]</td>
<td>Australia</td>
<td>Prospective</td>
<td>137</td>
<td>Children</td>
<td>4.9 years (mean)</td>
<td>Culture (blood or pleural fluid) or Positive PCR for <em>lytA</em></td>
<td>84</td>
<td>94</td>
</tr>
<tr>
<td>Martinon-Torres et al. [77]</td>
<td>Spain</td>
<td>Prospective</td>
<td>55</td>
<td>Children</td>
<td>6.5 years (mean)</td>
<td>Culture (blood or pleural fluid) or Positive PCR for <em>ply/uza</em></td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>Casado Flores et al. [79]</td>
<td>Spain</td>
<td>Prospective</td>
<td>76</td>
<td>Children</td>
<td>3.5 year (median)</td>
<td>Culture (blood or pleural fluid) or Positive PCR for <em>ply</em></td>
<td>88</td>
<td>71</td>
</tr>
<tr>
<td>Porcel et al. [75]</td>
<td>Spain</td>
<td>Retrospective</td>
<td>140</td>
<td>Adults</td>
<td>56 years (mean)</td>
<td>Culture (blood or pleural fluid)</td>
<td>71</td>
<td>93</td>
</tr>
</tbody>
</table>

PCR, polymerase chain reaction.

*The number includes 12 CSF (cerebrospinal fluid) samples.*
Audit: Empiric antibiotic recommendations for empyema - OK or not ?

$n = 101$

$S. aureus$ (n = 61)
  MRSa (n=12)

$S. pneumoniae$ (n= 19) 94% pen sensitive

$S. pyogenes$ (n= 9) 100% pen sensitive

$H. influenzae$ (n= 7) 83% sens amoxy, 100% sens to cef/co-amoxy clav

88% pathogens covered with empiric regimen of cefuroxime or co-amoxyclavulanic
Conjugate pneumococcal vaccine (PCV)

- What are the common serotypes causing empyema in NZ children

- Our unique pneumococcal schedule
  - given @6wks, 3mths, 5mths & 15mths

- PCV7 July 2008
- PCV10 July 2011
- PCV13 July 2014
Invasive *S. pneumoniae* serotypes in paediatric empyema greater Auckland region (n = 28) 1998 - 2012

PCV13 covers 89%
PCV10 covers 68%
PCV covers 36%
Pneumococcal Serotypes in Pediatric Empyema: 2001–2007, Utah (N=51)

>90% covered by PCV13

So our aetiology pie shows…

- **S. aureus** dominant pathogen for NZ paediatric empyema
  - accounts for >1/3 of cases;

- Appropriate empiric antibiotics choice = cefuroxime or co-amoxyclyclavulanate
  - +MRSA coverage for some areas

- Current vaccine PCV13 - likely good
  - Emergent invasive serotypes still possible
New Zealand and S.aureus

• More invasive?

• More resistant?

• More clonal?

• Just more generally?
• Rate of S. aureus infections in NZ – amongst highest reported in developed world
• Incidence rate for S. aureus SSTI - highest in age <5yrs and amongst Māori and Pacific peoples

*Williamson et al. Staphylococcus aureus Infections in New Zealand, 2000–2011*  
*Emerg Inf Dis 2014*
In New Zealand

MSSA infections increased significantly 2001 to 2011

MRSa did not increase — remained as a proportion at 12% of all Staph aureus infections
Invasiveness?

- Community onset invasive *S. aureus* disease in children at Starship 2007-2010
- Compare clonal complexes and virulence genes of *S. aureus* strains

- 2200 *S. aureus* isolates from children
- 163 children/isolates were invasive
  - 37 bacteraemia
  - 27 respiratory
- Compared to children with simple skin infections in same time period

Clinical and molecular epidemiology of community-onset invasive *Staphylococcus aureus* infection in New Zealand children

Non-metric multidimensional scaling of virulence genes in inv and non-inv *S.aureus* isolates based on Euclidean distances.
• High rates of PVL* (50% and 57%) in both non-invasive MSSa and invasive MSSa

• Marked ethnic differences in rates of invasive MSSa
  societal, environmental and host factors (barriers to healthcare access, household crowding, hygiene and nutrition).

*Panton-Valentine leukocidin

There are NZ specific questions..

- Is empyema increasing across the country or only in certain populations?

- More *S. aureus* – what is best management where pathogens are so different

- Actual contribution of *S. pneumoniae* with best diagnostic techniques

- Vaccine impact with newer generation pneumococcal conjugate vaccine
NZPSU empyema

- Commenced June 2014
  - 16 cases notified (3 months of data)
  - Feedback and cases welcome

Co-investigators:
Paediatric registrars: Kathy Rix Trott & Caroline Mahon
Paediatrician CMDHB: Richard Matsas
Paed ID: Lesley Voss and Tony Walls
Paed Resp: Cass Byrnes and Jacob Twiss
Paed Surgeons: James Hamill and Steve Evans
Microbiologist (ESR): Debbie Williamson
Figure 3. MRSA infection period-prevalence rates by district health board, 2013
Effect of 13-valent pneumococcal conjugate vaccine on admissions to hospital 2 years after its introduction in the USA: a time series analysis

Simonsen et al Lancet Resp Med May 2014
Pneumococcal serotypes paediatric empyema; Oz 2007–2009

- Of 53 +*S. pneumoniae* serotypes 2 (3.8%) covered by PCV7
- 51 (96.2%) had non PCV7 serotypes
  - 19A (n = 20; 36.4%)
  - 3 (n = 18; 32.7%)
  - 1 (n = 8; 14.5%)

*PCV10 covers 53%, PCV13 covers 90%*