Optimising Immunisation in Special Risk Groups

Nigel Crawford

Special Risk ‘Definition’

Patients who have:

– special immunisation requirements
  (e.g. children/adolescents with a chronic medical condition)
  and/or

– a suboptimal response to immunisation
  (e.g. due to impaired immunity)

Thesis: questions to address

• What are the additional vaccine requirements in ‘special risk’ groups?
  – What is the evidence base for these recommendations?
  – What about new vaccines? Immunogenicity studies?

• Are these vaccines recommended by subspecialist physicians?

• Are the special risk groups receiving them?

• Optimising protection through translation of guidelines into clinical practice

Studies

• Current special risk guidelines
  – Specialists recommendations
  – Adherence to guidelines [audits]

• Improving the evidence base
  – novel vaccine immunogenicity studies
    • 10 valent pneumococcal vaccine
    • 4 valent HPV vaccine

• Systematic reminders
  – RCT postcard immunisation reminder
Preterm Infants

- Relative immunodeficiency
- By 7 months
  - B cell numbers term equivalent
  - Decreased Lo, total Tcell and Th persist

- Other risk factors
  - Prolonged hospitalisation
  - Medications: Steroids
  - Chronic lung disease

Preterm Infants

- Mount protective responses to most vaccines
- Vaccinate according to **chronological** not gestational age
  - **Timeliness**
- Where response is suboptimal
  - "additional" doses recommended

Preterm risk VPD

- Pertussis
  - 50% cases in infants
  - LBW infants <2500 grams
  - RR 1.86 (95% CI 1.33-2.38)

- Invasive Pneumococcal Disease (IPD)
  - LBW c/w NBW infants RR 2.6 (P = 0.03)
  - PT c/w FT infants RR 1.6 (P = 0.06)

Routine schedule (2008)

- ...doses of ...vaccine...
**Additional doses recommended**

- Hep B vaccine (<32 weeks or <2000g)
  - extra dose 12 months

- Pneumococcal (<28 weeks or CLD)
  - 4th conjugate dose at 12 months
  - 23vPPV at 4-5 years

- Influenza vaccine (CLD, cardiac etc.)
  - >6 months
  - 2 doses in 1st year / 1 month apart
  - ½ dose if <3 years (0.25 ml)

**Paediatric cancer**

- Do childhood cancer survivors receive vaccination ‘boosters’ post chemotherapy?

- The following schedule was recommended (2007):
  - DTPa if <8 years of age (dTpa if ≥8 years of age)
  - IPV
  - MMR
  - Hepatitis B
  - 7vPCV
  - Hib (if <5 years or asplenia)
  - [meningococcal C; varicella]


**Paediatric cancer**

- Immunosuppressed
  - primary disease
  - treatment (chemotherapy and/or radiotherapy)

- Heterogeneous group
  - solid tumours: short intensive therapy
  - ALL 2-3 years of treatment
  - post bone marrow transplant
  - [separate guidelines]

**IBD and type 1 diabetes**

**Routine vaccines + additional:**

1. Annual trivalent influenza vaccine
   - underlying chronic disease

2. Pneumococcal vaccines
   - IBD higher risk of IPD (immunosuppressed)
   - Type 1 diabetes


**Special risk of IPD**

Diseases compromising immune responses

- Haematological malignancies
- HIV infection
- Renal failure, or relapsing or persistent nephrotic syndrome
- Down syndrome.
- Congenital immune deficiency
- Immunosuppressive therapy (including corticosteroid therapy ≥2 mg/kg per day of prednisolone ≥2 weeks; or radiation therapy)
- Splenic function compromise due to sickle haemoglobinopathies or congenital or acquired asplenia

Anatomical or metabolic abnormalities

- Cardiac disease associated with cyanosis or cardiac failure
- Insulin-dependent diabetes mellitus
- Proven or presumptive cerebrospinal fluid (CSF) leak
- Intracranial shunts and cochlear implants.
- Infant with chronic lung disease
- Cystic fibrosis
- ex-premature infants born at less than 28 weeks gestation

Australian Immunisation Handbook 9th edition p246

**Special risk of IPD**

If fall into one of these ‘special risk’ groups recommend:

- 4th dose PCV (pneumococcal conjugate vaccine)
  - 12 months of age or at diagnosis

&

- 23vPPV (polysaccharide vaccine)
  - @4-5 years of age
Physicians survey results

<table>
<thead>
<tr>
<th>Response rate</th>
<th>Recommendations as per guidelines</th>
<th>Personal immunisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Guide                  Other</td>
<td>Vaccine</td>
</tr>
<tr>
<td>Neonatologists</td>
<td>68% (96/111)           60% 8% 7% 1%</td>
<td>Vaccine</td>
</tr>
<tr>
<td>Paediatric Oncologists</td>
<td>56% (25/45)           60% 40% 97% post chemo</td>
<td>Vaccine</td>
</tr>
</tbody>
</table>


Audits of immunisation status

<table>
<thead>
<tr>
<th>No. participants</th>
<th>Median age (years)</th>
<th>Routine vaccines</th>
<th>Additional vaccines</th>
<th>Other vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm neonates</td>
<td>12 months</td>
<td>90% - 92%</td>
<td>20%</td>
<td>35%</td>
</tr>
<tr>
<td>Paediatric cancer</td>
<td>3-2.5 years</td>
<td>55%</td>
<td>47%</td>
<td>87%</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>13.2</td>
<td>88%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>15 (5.5 – 22.8)</td>
<td>90%</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

- *40% had primary course interrupted


Post chemo immunisations

Case study

- CB- Diagnosed ALL 2003
  – completed treatment June 2005
  – i.e. 3-6 years of age

- Family completed immunisation audit
  – CB now 11 years
    • Influenza vaccine
    • No other immunisations since 1 year of age
CB: Immunisation plan

- 6 vaccines @ clinic appointment
  - diptheria-tetanus-pertussis-polio [dTap-IPV]
  - conjugate pneumococcal vaccine [PCV7]
  - Hep B [adult dose]
  - varicella
  - measles-mumps-rubella
  - meningococcal C

- 2nd dose Hep B in 4/12; check MMR serology

Immunogenicity and safety of 10-valent pneumococcal vaccine in children and adolescents with leukaemia
National Immunisation Program

- PCV7 (Prevenar [Pfizer])
  - introduced NIP January 2005
  - catch-up to 2 years age (i.e. born Jan 2003)
- 3 + 0 dose regimen
  - 2, 4 and 6 months of age

Next generation vaccines

- PCV10 Synflorix ® (GSK): [Protein D NTHi]
- PCV13 Prevenar13™ [Pfizer (Wyeth)]

Oncology Guidelines

- At diagnosis haematological malignancy:
  - < 5 years of age completed 1st course
    - single PCV7 booster
  - Aged 6-9 years recommended
    - 2 doses of PCV7: 2 months apart
    - dose of 23vPPV 2 months later
  - ≥10 years of age
    - single 23vPPV

PCV10 study

Children and adolescents 0-18 years diagnosed with leukaemia

Group 1
- completed 1st PCV7 course
- 1 dose of PCV10

Group 2
- (incomplete course)
- 3 doses of PCV10 2 months apart

PCV10 STUDY

- Participants
  - 27 of 41 analysed [all ALL]
  - 23 RCH; 4 MMC
  - Age median 5.6 years [range 1.7-15.2 yrs]
  - 56% male 3 baseline serology only

- Groups
  - 22 Group 1 (previous PCV7)
  - 5 Group 2 (1 relapse post 2 doses)

- Treatment phase
  - 17/27 on maintenance therapy
### Pneumococcal GMC pre & post

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Baseline</th>
<th>Post Dose 1</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.12</td>
<td>0.18</td>
<td>0.68</td>
</tr>
<tr>
<td>4</td>
<td>0.06</td>
<td>0.49</td>
<td>0.0007</td>
</tr>
<tr>
<td>5</td>
<td>0.14</td>
<td>0.31</td>
<td>0.0003</td>
</tr>
<tr>
<td>6B</td>
<td>0.24</td>
<td>0.84</td>
<td>0.007</td>
</tr>
<tr>
<td>7F</td>
<td>0.09</td>
<td>0.31</td>
<td>0.001</td>
</tr>
<tr>
<td>9V</td>
<td>0.12</td>
<td>0.59</td>
<td>0.0008</td>
</tr>
<tr>
<td>14</td>
<td>0.38</td>
<td>2.5</td>
<td>0.0004</td>
</tr>
<tr>
<td>18C</td>
<td>0.10</td>
<td>0.64</td>
<td>0.003</td>
</tr>
<tr>
<td>19F</td>
<td>0.52</td>
<td>2.4</td>
<td>0.0012</td>
</tr>
<tr>
<td>23F</td>
<td>0.16</td>
<td>0.86</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

### PCV10: GMC above threshold

- **Group 1**:
  - Baseline vs Post Dose 1 vs Historical (post 3 infant doses)
  - GMC = geometric mean concentration

- **Group 2**:
  - Baseline vs Post Dose 1 vs Post Dose 2 vs Post Dose 3

### PCV10: ELISA & OPA*

- OPA = opsonophagocytic antibody

### Vaccine safety

- **5 day diary**
- **Local reaction**
  - 84% (21/25)
  - 19 tenderness; 2 induration/swelling
- **Systemic**
  - 44% (11/25)
  - 2 vomiting; 3 diarrhoea; 1 decreased appetite
  - 2 drowsiness; 2 irritability
  - only 1 fever > 38 degrees Celsius
Immunogenicity of a prophylactic quadrivalent HPV vaccine in females with special risk conditions

Cumulative incidence of HPV infection from time of first sexual intercourse

Time Line of Cervical HPV infections and progression to cervical cancer

Prophylactic HPV vaccines are L1 virus like particles (VLPs)

Quadrivalent vaccine efficacy
**National HPV Immunisation Program**

- Commenced April 2007
  - funded catch-up for women 12-26 years ended Dec 2008
- School Program:
  2007
  - Years 7, 10-12
  2008
  - Years 7, 9 & 10
  2009-
  - Year 7 only

**Evidence increased risk**


**HPV exposure risk**

- Paediatric cancer
  - female leukaemia survivors initiate sexual activity at the same age as healthy adolescents
- Rheumatology
  - 19.3 years (SD 3.9 years) higher than the general population at the time of the study (17 years)
  - 7.1% were sexually active before 16 years
  - 37.6% before transfer to adult care

**4vHPV [6,11,16,18] vaccine study**

- median age
  - 14.7 years [range 11.8 to 24.7]
- median time for 3 dose administration
  - 6.1 months [3.9 to 16.5 months]
- median time post serology
  - 1.4 months [0.9 to 23.2 months]

**HPV study**

<table>
<thead>
<tr>
<th>Special Risk Group</th>
<th>Number of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatric Rheumatological Diseases (PRD)</td>
<td>38</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease (IBD)</td>
<td>14</td>
</tr>
<tr>
<td>Paediatric cancer</td>
<td>10</td>
</tr>
<tr>
<td>Solid Organ Transplant Recipient (SOTR)</td>
<td>1</td>
</tr>
<tr>
<td>Chronic Renal Disease</td>
<td>1</td>
</tr>
</tbody>
</table>
### Post hoc analysis

<table>
<thead>
<tr>
<th>Immune category</th>
<th>No. participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 0</td>
<td>nil or NSAIDs only</td>
</tr>
<tr>
<td>Level 1</td>
<td>corticosteroids only or immunomodulator • Methotrexate • 6-MP • azathiothepine • cyclosporine • tacrolimus</td>
</tr>
<tr>
<td>Level 2</td>
<td>Biologic therapies (TNF blockers) or combination therapy of any level 1 medications</td>
</tr>
</tbody>
</table>

---

### JIA (n=28): combination therapies

<table>
<thead>
<tr>
<th>Medication or combination</th>
<th>No. participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 0</td>
<td>None</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1</td>
</tr>
<tr>
<td>Level 1</td>
<td>methotrexate</td>
</tr>
<tr>
<td></td>
<td>sulphasalazine</td>
</tr>
<tr>
<td>Level 2</td>
<td>Biologic alone</td>
</tr>
<tr>
<td></td>
<td>Biologic + methotrexate</td>
</tr>
<tr>
<td></td>
<td>Biologic + methotrexate + prednisolone</td>
</tr>
<tr>
<td></td>
<td>methotrexate + prednisolone</td>
</tr>
<tr>
<td></td>
<td>sulphasalazine + prednisolone</td>
</tr>
</tbody>
</table>

---

### Diminished response

- 1 non-responder
  - SOTR (renal)
  - Tacrolimus, mycophenolate; prednisolone

- 4 incomplete responders
  - Type 6 (PRD)
  - Type 18 (IBD x2; Paed cancer x1)
  - 3 of 4 > 16 years of age

---

### Immunogenicity GMT by HPV type compared with historical healthy controls*

<table>
<thead>
<tr>
<th>HPV type</th>
<th>log scale (mMu/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6</td>
<td>10</td>
</tr>
<tr>
<td>HPV 11</td>
<td>100</td>
</tr>
<tr>
<td>HPV 16</td>
<td>1000</td>
</tr>
<tr>
<td>HPV 18</td>
<td>10000</td>
</tr>
</tbody>
</table>

---

### Vaccine Safety

- Unsolicited
- One reported flare
  - 3 days post dose 3 4vHPV vaccine
    - lasted 6 weeks
  - very active background disease
    - on biologic and immunomodulator therapy
  - Nil change in medications
Postcard reminder RCT

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>648</td>
<td>466</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>62.8</td>
<td>56.9</td>
</tr>
<tr>
<td>Age (2.9 +/- 1.8)</td>
<td>2.8</td>
<td>+/- 1.8</td>
</tr>
<tr>
<td>Proportion &lt; 5yrs</td>
<td>81.5%</td>
<td>80.7%</td>
</tr>
<tr>
<td>No. appt (mean +/- SD)</td>
<td>1.4</td>
<td>2.3 +/- 1.8**</td>
</tr>
<tr>
<td>Clinic (% medical)</td>
<td>62%</td>
<td>60.1%</td>
</tr>
</tbody>
</table>

Minimising missed opportunities to vaccinate

- Immunisation status assessed at each healthcare contact
- Needs to be easily available to HCWs if parents unsure
- Only true medical contraindications should delay immunisations

Minimising missed opportunities to vaccinate

• ‘Window of opportunity before commencing immunosuppression

• Required vaccines should be administered simultaneously
  • avoid confusion and further missed opportunities

• All vaccinations should be recorded in the personal health record & ACIR

Publications

• Crawford NW, Buttery JP. Preterm infants immunisation. Paediatrics and Child Health. 2010; 20(6):297-301

Extra recommended free vaccines for babies born:

□ <28 weeks gestation: Pneumococcal conjugate vaccine and hepatitis B vaccine at 12 months and pneumococcal polysaccharide vaccine at 4 years
□ <32 weeks gestation and/or
□ <2000g birth weight: Hepatitis B at 12 months of age
□ underlying medical condition: Influenza vaccine annually, pneumococcal conjugate vaccine at 12 months and pneumococcal polysaccharide vaccine at 4 years

‘e’ health records

• Recommendations on discharge summary
  • Parents and GP

• Flag at outpatient appointments
  • Need resources to make sure immunisations can be administered
    • RCH Drop-in Centre
    • Monash Children’s Hospital

• Long term follow-up: transition to adult care
  • HPV vaccination: persistence and protection?
    • Adult physicians
      • All of life immunisation register

Thanks to my supervisors

Jim Buttery
Jenny Royle
Julie Bines
CHALLENGE

How can you best optimise immunisations in your patients?