Update on Pertussis – what should Asia do?

Peter McIntyre
National Centre for Immunisation Research and Surveillance
Sydney Childrens Hospital Network & University of Sydney
Australia
Pertussis incidence 1981-2009
Australia
Pertussis incidence rates – Asia

- Thailand
- China
- India


Incidence rates:
- 1981: Thailand - 51.4, China - 51.4
- 1991: Thailand - 8.6, China - 51.4
- 2001: Thailand - 3.4, China - 3.4
- 2008: Thailand - 3.8, China - 3.8
- 2011: Thailand - 3.0, China - 3.0
World Pertussis 1991 (n=430493)

- India: N=73520
- Nigeria: N=18685
- China: N=10679
- Canada: n=2724
- UK: N=6282
- US: N=2719
- Australia: N=337
- Other: N=315547

World Pertussis 2009 (n=120444)

- India: n=14237
- Nigeria: n=11281
- China: n=1612
- Canada: n=1667
- Australia: n=29545
- US: n=17000
- Other: n=44256
- UK: n=846
Update on Pertussis – what should Australia do?
The 3 big questions in pertussis

- **Aim of pertussis program?**
  - Prevent severe disease
  - Prevent all disease

- **How much severe disease?**

- **How can we best prevent severe disease?**
My 3 big answers

- Primary aim of pertussis vaccine program is to prevent severe disease
- Severe pertussis greatly reduced by vaccination
  - Measurement a problem
  - Setting crucial
- Best option for preventing severe disease?
  - It depends
The pertussis mountain

- Medically attended coughing illness
- Diagnosed pertussis
- Notified pertussis
- Hospitalised pertussis
- Pertussis deaths
- Cough illness
Pertussis deaths US 1938-40 - N=10,730
Pertussis death rates per million <5 years by decade 1926-35 to 2012 - Australia

Pertussis vaccine first became available in Australia in this decade

Deaths per million children under 5 years

Decade

Pertussis vaccine first widely used

Triple Antigen (DTP) vaccine first widely used
Pertussis deaths

- Difficult to measure
  - Death certificates?
  - Verbal autopsy?
  - Some characteristic features

- Probably underestimated
Evidence for underestimation of infant pertussis - UK

1. Intensive care admissions – London¹
   - 7/25 (28%) suspected on admission
   - 2/25 (8%) culture positive
   - 2 deaths

   - official statistics = 18
   - enhanced surveillance = 22
   - total (capture/recapture) = 46

¹ Crowcroft N. et al. Arch Dis Child 2003;88:802
Free vaccinations after whooping cough outbreak in Perth

Lucy Rickard
January 18, 2011

Whooping cough can be potentially

A worrying outbreak in which

government to offer free vaccinations in a bid to prevent

Eight babies die in Californian whooping cough outbreak

California health authorities are recommending that people be vaccinated against whooping cough.

12 to 17,” cautioned Lynette Mazur, a professor of paediatrics at the University of Texas Medical School, Houston.

California’s Department of Public Health is urging all Californians to ensure they are vaccinated against the disease, particularly if they are in contact with young children.

The roughly five year cyclical wave of infections is being made worse by a growing anti-vaccine movement that has led many parents to skip the standard childhood vaccinations. “We are seeing some of this in schools with very low immunisation rates, where parents have decided not to vaccinate their kids,” said Mitchell Katz, director of health for San Francisco.

Infants with immature immune systems are most at risk of death from the infection. But elderly people and people in poor health are also at risk of infection, because their protective antibodies are likely to have waned. However, Medicare, the federal health insurance programme for people aged over 65, doesn’t cover or reimburse for vaccination of adults against whooping cough because the clinical trials were conducted only in...
An Outbreak of Pertussis in Sarli Circle of Kurung-kumey District, Arunachal Pradesh, India

T Takum*, D Gara†, H Tagyung† and MV Murhekar*

From †Field Epidemiology Training Programme (FETP), National Institute of Epidemiology (ICMR), Chennai; ‡Directorate of Health Services, Government of Arunachal Pradesh; and §General Hospital, Naharlagun, Arunachal Pradesh, India.

**TABLE I** Incidence of Suspected Pertussis, Arunachal Pradesh, India, 2007

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Population*</th>
<th>No. of case-patients†</th>
<th>No. of deaths‡</th>
<th>Total case-patients</th>
<th>Attack rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 yrs</td>
<td>55</td>
<td>24</td>
<td>15</td>
<td>39</td>
<td>71</td>
</tr>
<tr>
<td>2-5 yrs</td>
<td>267</td>
<td>48</td>
<td>11</td>
<td>59</td>
<td>22</td>
</tr>
<tr>
<td>Male, No (%)</td>
<td>188 (58.4%)</td>
<td>31 (43.0)</td>
<td>13 (50)</td>
<td>44 (44.9)</td>
<td>23§</td>
</tr>
<tr>
<td>Tribe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangro</td>
<td>162</td>
<td>38</td>
<td>14</td>
<td>52</td>
<td>32</td>
</tr>
<tr>
<td>Ngishing</td>
<td>113</td>
<td>23</td>
<td>5</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Suhung</td>
<td>47</td>
<td>11</td>
<td>7</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>Overall</td>
<td>322</td>
<td>72</td>
<td>26</td>
<td>98</td>
<td>30</td>
</tr>
</tbody>
</table>

* The population denominators were estimated based on following assumptions: (a) 13% of the total population is under-fives (b) estimated number of infants = [Number of live birth - (No. of live birth X Infant mortality rate)] where No. of live birth = birth rate of the area X total population of the area. Birth rate and Infant mortality rate of the district during 2008 was 22/1000 population and 60/1000 live births respectively (c) sex ratio of the district = 901 females: 1000 males (2001 census); †Suspected case-patients among those attending medical camps; ‡Deaths as reported by local health workers and local administration; §Attack rate in females 40%.
Thailand experience different to India

- **DEATHS**: 2 deaths reported in the last 20 years
  - 2 years old in 1999, < 3 month old in 2003

- **OUTBREAK**: one outbreak in remote area in 2006
  (59 outpatient and 1 hospitalised case, no death)

1. Data courtesy of Dr Piyanit Tharmaphornpilas
Hospitalisation and intensive care
Cumulative percentage of pertussis hospitalisation in infants aged <1 year, Australia, 1995 to July 2008
Intensive Care – Infants

▪ Auckland, New Zealand 1991-2003²
  • 72 ICU admissions; 97% <12 months

- 5.2% died

- 10.3% survivors respiratory/neurological disability

1. Spokes et al NSW Public Health Bulletin 2010
2. Surridge et al Arch Dis Child 2007; 92: 970
Study of cough presentations to childrens hospital in Thailand

Poster presentation, European Society for Pediatric Infectious Diseases 2013
Piyarat Suntarattiwong et al.

• prospective study of outpatients and inpatients in 2011
• newborn – 18 years
  • cough for 7 with one of :
  • paroxysmal, whoop, post-tussive vomiting

……. 92% received DTP according to age, 47% < 1 year
……. 18 of 96 (18.8%) has rPCR positive for pertussis
……. 15 of positive rPCR cases are younger than 6 months
……. cyanosis more common in PCR + cases, 1/18 ventilated
Pertussis vaccine impact
Global Immunization 1980-2009, DTP3 coverage
global coverage at 82% in 2009

Source: WHO/UNICEF coverage estimates 1980-2009,
July 2010  Date of slide: 13 July 2010
Measuring pertussis - diagnostic tests

PCR
Serology
Clinical
Culture

Reimbursement for PCR tests
Pertussis notification rates and deaths, 1995-2010 Australia
Importance of disease severity in measuring vaccine effectiveness
Vaccine efficacy in relation to disease severity score
Senegal trial N=834 cases

1. Prezosi Clin Inf Diseases 2003; 37: 772
Efficacy of vaccines in Italian trial against increasing duration of cough

Greco et al NEJM 1996; 334: 341
Randomised trials – variation in DTPw efficacy

<table>
<thead>
<tr>
<th>Study location, year</th>
<th>Case definition</th>
<th>Vaccine</th>
<th>Cases</th>
<th>WHO [% efficacy (65% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GSK two-component (not licensed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stockholm, 1992</td>
<td>WHO</td>
<td>Tripacol™</td>
<td>159</td>
<td>59 (61, 66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Connaught DTwP</td>
<td>144</td>
<td>49 (37, 56)</td>
</tr>
<tr>
<td>Italy, 1993</td>
<td>WHO</td>
<td>Infanrix®</td>
<td>37</td>
<td>84 (76, 90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acelluvax™</td>
<td>36</td>
<td>84 (76, 90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Connaught DTwP</td>
<td>141</td>
<td>35 (14, 54)</td>
</tr>
<tr>
<td>Stockholm, 1993</td>
<td>WHO</td>
<td>GSK two-component (not licensed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not applicable/no data</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aceliavax™</td>
<td>21</td>
<td>RR 2.55 (1.55, 4.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dapacte®</td>
<td>13</td>
<td>RR 1.40 (0.78, 2.52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Welcome DTwP</td>
<td>15</td>
<td>RR 1.00</td>
</tr>
<tr>
<td>Gothenburg, 1994</td>
<td>WHO</td>
<td>Cerviva™</td>
<td>72</td>
<td>71 (63, 66)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trilava™</td>
<td>24</td>
<td>74 (61, 86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PMC-Fr-DTwP</td>
<td>7</td>
<td>92 (61, 97)</td>
</tr>
<tr>
<td>Erfurt, 1991</td>
<td>Modified WHO</td>
<td>Acel-Humune®</td>
<td>245</td>
<td>85 (77, 91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lederle DTwP</td>
<td>61.8</td>
<td>93 (68, 96)</td>
</tr>
<tr>
<td>Mainz, 1992</td>
<td>WHO</td>
<td>Infanrix®</td>
<td>7</td>
<td>89 (77, 98)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behring DTwP</td>
<td>1</td>
<td>93 (63, 100)</td>
</tr>
<tr>
<td>Munich, 1993</td>
<td>Modified WHO</td>
<td>Tripedia®</td>
<td>4</td>
<td>96 (63, 99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behring DTwP</td>
<td>1</td>
<td>98 (71, 100)</td>
</tr>
</tbody>
</table>

a Results are for a three-dose infant immunisation series; effects of any booster dose are not included. WHO efficacy results are based on the case definition closest to that of the WHO. Some of the WHO results were calculated from data provided in the referenced source; such results may represent crude, rather than adjusted, efficacies. WHO case definition: ≥21-day paroxysmal cough plus bacteriological, serological or epidemiological confirmation of *Bordetella pertussis*.

b Results are presented in relative risk instead of efficacy rates. No data are available for the GSK two-component vaccine as unblinding and boosting was necessary because of poor efficacy.

**DTwP** = diphtheria-tetanus-whole cell pertussis; **GSK** = GlaxoSmithKline; **PMC-Fr** = Pasteur Meneux Connaught-France; **RR** = relative risk.
Rapid waning immunity with acellular pertussis vaccines
Waning immunity acellular > whole cell vaccine in Senegal trial

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>General population (n = 626)</th>
<th>Population stratified by vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>[CI]_{95%}^{a}</td>
</tr>
<tr>
<td>Intensity of exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same compound</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Same kitchen</td>
<td>1.53</td>
<td>1.02–2.29</td>
</tr>
<tr>
<td>Same hut</td>
<td>1.62</td>
<td>1.07–2.48</td>
</tr>
<tr>
<td>Age at exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 18 ) months</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>19–29 months</td>
<td>1.37</td>
<td>0.94–1.99</td>
</tr>
<tr>
<td>( \geq 30 ) months</td>
<td>1.56</td>
<td>1.05–2.30</td>
</tr>
</tbody>
</table>

Risk factors for acellular and whole-cell pertussis vaccine failure in Senegalese children

Karine Lacombe\textsuperscript{a,b,*}, Abdoulaye Yam\textsuperscript{a}, Kirsten Simondon\textsuperscript{a}, Sybil Pinchinat\textsuperscript{a}, François Simondon\textsuperscript{a}
RESEARCH LETTER

Number and Order of Whole Cell Pertussis Vaccines in Infancy and Disease Protection

Sarah L. Sheridan, BMed, MApEpid
Robert S. Ware, PhD
Keith Grimwood, MB, ChB, MD
Stephen B. Lambert, MBBS, PhD

*Figure.* Pertussis Reporting Rates Between 1999 and 2011 by Primary Course of Pertussis Vaccination for Children Born in 1998

DTaP indicates diphtheria-tetanus-acellular pertussis; DTwP, diphtheria-tetanus-whole cell pertussis.

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Rapid waning of VE in adolescents who received all acellular vaccines from infancy – IDSA Oct 2013

139. Vaccine Effectiveness and Duration of Protection of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis among Adolescents, Washington State, 2012

Part of Session: 40. Adult and Pediatric Vaccines

ANNA M. ACOSTA, MD1, CHAS DEBOLT, RN, MPH2, AZADEH TASSLIMI, MPH2, MELISSA LEWS, MPH1, LAURIE STEWART, MS2, LARA K. MISEGADES, PHD, MS1, NANCY E. MESSONNIER, MD1, THOMAS A. CLARK, MD, MPH1, STACEY W. MARTIN, MS1 and MANISHA PATEL, MD, MSc1; 1Centers for Disease Control and Prevention, Atlanta, GA, 2Washington State Department of Health, Shoreline, WA

2012, Washington State declared a pertussis epidemic with a record 4,921 cases unexpectedly high disease incidence was observed in adolescents 13-14 years 2 or more years post-vaccination, VE declined to 41% (95% CI: 7-63%)
Waning vaccine effectiveness of 3 doses of DTPa in Australia

1. National case control study of pertussis notifications with controls from ACIR in press Pediatrics
Declining maternal immunity following re-introduction of pertussis vaccines – evidence from Sweden
Re-introduction of pertussis vaccination – the Swedish experience

1. Carlsson and Trollfors Vaccine 2009
Seroprevalence of pertussis antitoxin (anti-PT) in Sweden before and 10 years after the introduction of a universal childhood pertussis vaccination program

HANS O. HALLANDER, MIKAEL ANDERSSON, LENNART GUSTAFSSON, MARGARETHA LJUNGMAN and EVA NETTERLID
Strategies to reduce severe early infant morbidity

- **Indirect protection** of infant
  - Sibling vaccination – toddler, preschool, adolescent
  - “Cocooning” vaccination of adult contacts
  - General adult immunisation

- **Direct protection** of infant
  - Maternal immunisation in pregnancy
  - Newborn infant immunisation
Indirect protection

- **Sibling vaccination**
  - *Toddler and pre-school*
    - good evidence of indirect infant (<6 m) protection
  - *Adolescent*
    - limited indirect protection

- **Cocoon vaccination**
  - Funded programs with high uptake in Australia
  - Recent NSW evaluation found ~ 50% reduction in infant pertussis if vaccinated > 1 month prior to disease onset
Direct protection

- **Newborn vaccination**
  - 4 trials using acellular vaccine
  - High antibody after 2 doses
  - must be monovalent aP not DTPa
  - Large trial in Australia – 440 babies randomised

- **Maternal vaccination**
  - *High antibody for ~ 6 months; >baseline for ~ 5 years*
    - Active transport to newborn
  - *Recent UK maternal program*
Whooping cough vaccine a 'no-brainer' during pregnancy

Zoe was just four weeks old when she got whooping cough, and had to spend a month in hospital.

Women are understandably risk-averse during pregnancy and are advised to avoid all medication if possible. Now they are being offered a four-in-one vaccine to protect against whooping cough.
A Non-human Primate Model of Pertussis

Tod J Merkel
CBER, FDA
Key findings

- Infant baboons get sick and may die from pertussis
- Protected against symptoms by
  - Maternal pertussis vaccine during pregnancy
  - Neonatal vaccination – single dose (DTPw or DTPa)

BUT…..

- Vaccinated baboons still get infected by pertussis and still transmit pertussis to others
- Baboons who recover from pertussis infection do not get infected and do not transmit
Live attenuated pertussis vaccine?
Attenuated *B. pertussis* strain
BPZE1 (DNT- PTRE TCT-)

Bordetella pertussis
Chromosome

Summary

- Pertussis is complex
  - Varies by vaccine type, vaccine history in the population and how pertussis is measured

- Little data from less wealthy countries
  - Especially for more severe disease
  - May be little advantage for acellular vaccines or for boosters after 6, 10, 14 week doses

- Worldwide
  - Need better data on pertussis deaths and severe disease
  - Strategies targeting severe disease will vary by country-specific setting
What should Asia do?

- Gather more information about severe infant pertussis
- Assess level of maternal immunity
- Maintain use of whole cell vaccine if good coverage
- Early receipt of first 2 doses important
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