Pertussis vaccine in both children and adults

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Disclosure

I received research grants from GSK (hepatitis B vaccine) and Sanofi Pasteur (tetanus-pertussis-diphtheria vaccine)

I attended a GSK ad hoc Advisory Board meeting on the risk of convulsions associated with the Measles-Mumps-Rubella-Varicella vaccine for which my travel expenses were reimbursed
Outline

History of pertussis vaccines in Canada
Epidemiology of pertussis in Canada
Recommendations

• Vaccination of children, adolescents and adults
• Prevention of pertussis in infants
  • Cooconing strategy
  • Vaccination of pregnant women
  • Vaccination of pregnant women at each pregnancy
Pertussis vaccines

Whole cell pertussis vaccine

- Fluid (Connaught, Institut Armand Frappier)
  - Introduced in the 1940s
  - Combined with Diphtheria and tetanus
- Adsorbed
  - Introduced in the 1980s
  - Rapidly followed by a major resurgence of pertussis
  - Studies found the vaccine to be poorly protective
Acellular pertussis vaccines

- Were developed to improve safety (not efficacy) as a result of the UK controversy regarding chronic encephalopathy following pertussis vaccination in the 1970s
- Much less adverse events than whole cell vaccines
- As pertussis in adults was becoming increasingly recognized, adolescent/adult formulations (with lower antigen content) were developed
- Efficacy in short-term clinical trials was around 85%
  - Their introduction in Canada in 1997-1998 was expected to both reduce the pertussis burden and frequency of adverse events
Vaccination schedule

DTaP-Hib-Polio
• 2, 4, 6 and 18 months

DTaP-Polio or Tdap-Polio
• 4 to 6 years

Tdap
• 14 to 16 years (grade 9)
• Sometimes given in grade 6

Canadian Immunization Guide 2012
Adults (18 years and older)

All adults should receive one dose of Tdap vaccine if not previously received in adulthood.

In particular, adults who have not previously received Tdap vaccine in adulthood, and who anticipate having regular contact with an infant, should be prioritized to receive a dose of Tdap vaccine, ideally administered at least 2 weeks before contact with the infant.
Reported cases and incidence (per 100,000 person years) of pertussis in Canada, 1924 to 2012*.

*Case data for 1924 to 2008 was obtained from the Canadian Notifiable Diseases Surveillance System. Case data from 2009 to 2012 was obtained directly from P/T partners by CIRID and is preliminary. Data for 2012 was collected up to late July or early August, depending on the region. Population data was obtained from Statistics Canada July 1st annual estimates.
Incidence (per 100,000 person-years) of pertussis in Canada by age group and year, 1980 to 2012*.

*Case data for 1980 to 2008 was obtained from the Canadian Notifiable Diseases Surveillance System. Case data from 2009 to 2012 was obtained directly from P/T partners by CIIRD and is preliminary. Data for 2012 was collected up to late July or early August, depending on the region. Population data was obtained from Statistics Canada July 1st annual estimates.
Change in average pertussis incidence in Canada, 2002 to 2011.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Average Incidence (per 100,000 population)</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2002-2004</td>
<td>2009-2011</td>
</tr>
<tr>
<td>&lt;1</td>
<td>84.56</td>
<td>50.27</td>
</tr>
<tr>
<td>1 to 4</td>
<td>23.69</td>
<td>15.16</td>
</tr>
<tr>
<td>5 to 9</td>
<td>23.35</td>
<td>9.72</td>
</tr>
<tr>
<td>10 to 14</td>
<td>53.29</td>
<td>9.04</td>
</tr>
<tr>
<td>15 to 19</td>
<td>16.28</td>
<td>2.47</td>
</tr>
<tr>
<td>20 to 29</td>
<td>2.83</td>
<td>1.11</td>
</tr>
<tr>
<td>30 to 39</td>
<td>4.00</td>
<td>1.34</td>
</tr>
<tr>
<td>40 to 59</td>
<td>2.80</td>
<td>0.83</td>
</tr>
<tr>
<td>60+</td>
<td>1.00</td>
<td>0.30</td>
</tr>
<tr>
<td>All ages</td>
<td>10.05</td>
<td>3.07</td>
</tr>
</tbody>
</table>
FIGURE 1. Pertussis Hospitalization Incidence per 100,000 in Infants <1 year old (IMPACT), 1 to 16 years (IMPACT), and reported incidence in all ages in Canada, 1991–2004. Note:
**TABLE 1.** Characteristics of IMPACT Hospitalized Pertussis Cases by Type of Vaccine Routinely Used

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole-Cell Vaccine (%)</th>
<th>Acellular Vaccine (%)</th>
<th>Overall* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 1174</td>
<td>N = 842</td>
<td>N = 2096</td>
</tr>
<tr>
<td>Females</td>
<td>635 (54.1)</td>
<td>431 (51.2)</td>
<td>1111 (53.0)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 mo</td>
<td>307 (26.1)</td>
<td>328 (39.0)†</td>
<td>675 (32.2)</td>
</tr>
<tr>
<td>2–3 mo</td>
<td>401 (34.2)</td>
<td>361 (42.9)†</td>
<td>789 (37.6)</td>
</tr>
<tr>
<td>4–5 mo</td>
<td>188 (14.3)</td>
<td>86 (10.2)†</td>
<td>258 (12.3)</td>
</tr>
<tr>
<td>6–11 mo</td>
<td>152 (13.0)</td>
<td>41 (4.9)†</td>
<td>196 (9.3)</td>
</tr>
<tr>
<td>1–4 yr</td>
<td>111 (9.5)</td>
<td>24 (2.9)†</td>
<td>141 (6.7)</td>
</tr>
<tr>
<td>5–9 yr†</td>
<td>14 (1.2)</td>
<td>2 (0.2)†</td>
<td>16 (0.8)</td>
</tr>
<tr>
<td>10–16 yr</td>
<td>21 (1.2)</td>
<td>N/A</td>
<td>21 (1.0)</td>
</tr>
<tr>
<td>Death</td>
<td>10 (0.9)</td>
<td>6 (0.7)</td>
<td>17 (0.8)</td>
</tr>
<tr>
<td>Underlying conditions</td>
<td>111 (9.5)</td>
<td>61 (7.2)</td>
<td>181 (8.6)</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalitis</td>
<td>10 (0.9)</td>
<td>1 (0.1)†</td>
<td>11 (0.5)</td>
</tr>
<tr>
<td>Seizures (w/o encephalitis)</td>
<td>24 (2.0)</td>
<td>9 (1.1)</td>
<td>34 (1.6)</td>
</tr>
<tr>
<td>Mean days of hospitalization</td>
<td>8.0 (median = 5)</td>
<td>9.0 (median = 7)</td>
<td>8.6 (median = 6)</td>
</tr>
<tr>
<td>Mean days in ICU, N = 368</td>
<td>7.2 (median = 5)</td>
<td>6.6 (median = 5)</td>
<td>6.9 (median = 5)</td>
</tr>
</tbody>
</table>

N/A indicates not applicable: follow-up time insufficient for ACV in this age group.

*Overall includes 80 cases occurring during the transition year.

†Significant at $P \leq 0.05$.

‡Follow-up time is limited for ACV in this age group.

Bettinger et al PIDJ 2007;26: 31-5
### Table 1. Number and Percent of Pertussis Cases Reported to Public Health by Health Region in 2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Health Region 1</th>
<th>Health Region 2</th>
<th>Health Region 3</th>
<th>Health Region 4</th>
<th>Health Region 5</th>
<th>Health Region 6</th>
<th>Health Region 7</th>
<th>NB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>537 38%</td>
<td>126 9%</td>
<td>185 12%</td>
<td>190 13%</td>
<td>31 2%</td>
<td>314 22%</td>
<td>58 4%</td>
<td>1421</td>
</tr>
</tbody>
</table>
Number of doses of pertussis containing vaccine according to NB schedule for NB cases 0-18 years

Courtesy of the Office of the Chief Medical Officer of Health New Brunswick
Same epidemiological pattern elsewhere

Australia 2008-2011

United States
- California 2010
- Washington state 2012

Increasing incidence starting shortly after the pre-school booster dose
- Duration of acellular pertussis vaccines?
Pertussis notification rates for Western Australia and Australia, 1991–2011

Number and rate of pertussis notifications in Western Australia by age group, 2011

The highest notification rates during the 2008–2011 epidemic occurred in the 0–4, 5–9 and 10–14 years age groups.

Figure 2. Age specific pertussis notification rates per 100,000 population for the period 1991 to 2011.
California Pertussis Epidemic, 2010

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**Objective** In 2010, California experienced the highest number of pertussis cases in >60 years, with >9000 cases, 809 hospitalizations, and 10 deaths. This report provides a descriptive epidemiologic analysis of this epidemic and describes public health mitigation strategies that were used, including expanded pertussis vaccine recommendations.

![Diagram](image)

**Figure 3.** Number of pediatric pertussis cases* by age and vaccination status: California, 2010. *58% of cases with complete vaccine history data.
Number of Pertussis Cases Reported in WA State by Notification Week 2012 vs. 2013 YTD (3/23/13)

Additional cases may have occurred, especially in the most recent three weeks, that are not yet available to DOH.

http://www.doh.wa.gov/Portals/1/Documents/Pubs/348-254-PertussisUpdate.pdf
FIGURE 2. Number and incidence of confirmed and probable pertussis cases among persons aged ≤19 years, by patient age and vaccines received* — Washington, January 1–June 16, 2012

Abbreviations: DTaP = diphtheria and tetanus toxoids and acellular pertussis; DTwP = diphtheria and tetanus toxoids and whole-cell pertussis; Tdap = tetanus and reduced diphtheria toxoids and acellular pertussis.
Reported NNDSS pertussis cases: 1922-2012*

*2012 data are provisional.

SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System and 1922-1949, passive reports to the Public Health Service

http://www.cdc.gov/pertussis/surv-reporting.html
Reported pertussis incidence by age group: 1990-2012*

*2012 data are provisional.

SOURCE: CDC, National Notifiable Diseases Surveillance System and Supplemental Pertussis Surveillance System
FIGURE 3. Incidence of confirmed and probable pertussis among persons aged ≤19 years, by patient age and vaccines received* — National Notifiable Diseases Surveillance System, United States, January 1–June 14, 2012

Abbreviations: DTaP = diphtheria and tetanus toxoids and acellular pertussis; DTwP = diphtheria and tetanus toxoids and whole-cell pertussis; Tdap = tetanus and reduced diphtheria toxoids and acellular pertussis.

* Acellular vaccines (DTaP) replaced whole-cell vaccines (DTwP) for the 4th and 5th doses in 1992 and all 5 doses of the childhood series in 1997. Tdap was recommended for adolescents aged 11–12 years in 2006. Thus, all children aged ≤14 years are likely to have received acellular vaccines for the complete childhood series. Adolescents aged 15 years were born during a transition year from whole-cell to acellular vaccines for the childhood series. Adolescents aged ≥16 years received whole-cell vaccines for the first 3 doses, and acellular vaccines for the 4th and 5th doses.

† Ages during which the Advisory Committee on Immunization Practices recommends that specified vaccine doses be administered.
Waning Protection after Fifth Dose of Acellular Pertussis Vaccine in Children


Table 2. Waning of Effectiveness per Year after Fifth Dose of DTaP Vaccine.

<table>
<thead>
<tr>
<th>Group Compared with PCR-Positive Children</th>
<th>Odds Ratio for Pertussis (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR-negative controls</td>
<td>1.42 (1.21–1.66)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Matched controls</td>
<td>1.50 (1.13–2.00)†</td>
<td>0.005</td>
</tr>
</tbody>
</table>

After the fifth dose of DTaP, the odds of acquiring pertussis increased by an average of 42% per year.

Association of Childhood Pertussis With Receipt of 5 Doses of Pertussis Vaccine by Time Since Last Vaccine Dose, California, 2010

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Kathleen Winter, MPH
Kathleen Harriman, PhD, MPH, RN
John Talarico, DO, MPH
Nancy E. Messonnier, MD
Thomas A. Clark, MD, MPH
Stacey W. Martin, MSc

PERTUSSIS REMAINS A POORLY controlled vaccine-preventable disease in the United States, despite a well-established childhood vaccination program and high coverage.1 Although infants have substantially higher rates of pertussis compared with other age groups, data from the National Notifiable Diseases Surveillance System reflect a recent increase in the number of reported pertussis cases among children aged 7 to 10 years. In 2010, this age group had the second highest incidence of pertussis in the United States.2 The changing epidemiology raises important questions about possible waning protection from the childhood acellular pertussis vaccine series.

After the diphtheria, tetanus, and whole-cell pertussis (DTwP) vaccine was introduced in the late 1940s, a dramatic decline occurred in the number of reported pertussis cases. However, whole-cell vaccine was commonly associated with local adverse events (eg, redness, swelling, and pain at the injection site) and less commonly with more serious adverse events.3,4 These adverse events have limited the use of the whole-cell vaccine.

Context In 2010, California experienced its largest pertussis epidemic in more than 60 years; a substantial burden of disease was noted in the 7- to 10-year-old age group despite high diphtheria, tetanus, and acellular pertussis vaccine (DTaP) coverage, indicating the possibility of waning protection.

Objective To evaluate the association between pertussis and receipt of 5 DTaP doses by time since fifth DTaP dose.

Design, Setting, and Participants Case-control evaluation conducted in 15 California counties. Cases (n=682) were all suspected, probable, and confirmed pertussis cases among children aged 4 to 10 years reported from January through December 14, 2010; controls (n=2,016) were children in the same age group who received care from the clinicians reporting the cases. Three controls were selected per case. Vaccination histories were obtained from medical records and immunization registries.

Main Outcome Measures Primary outcomes were (1) odds ratios (ORs) for the association between pertussis and receipt of the 5-dose DTaP series and (2) ORs for the association between pertussis and time since completion (<12; 12-23, 24-35, 36-47, 48-59, or ≥60 months) of the 5-dose DTaP series. Logistic regression was used to calculate ORs, accounting for clustering by county and clinician, and vaccine effectiveness (VE) was estimated as $(1 - OR) \times 100\%$.

Results Among cases and controls, 53 (7.8%) and 19 (0.9%) had not received any pertussis-containing vaccines, respectively. Compared with controls, children with pertussis had a lower odds of having received all 5 doses of DTaP (OR, 0.11; 95% CI, 0.06-0.21), of which 95% CI, 79.4%-93.8%). When children were categorized by time since completion of the DTaP series, using an unvaccinated reference group, children with pertussis compared with controls were less likely to have received their fifth dose within the prior 12 months (19 [2.8%] vs 354 [17.6%], respectively; OR, 0.02; 95% CI, 0.01-0.04 [estimated VE, 98.1%; 95% CI, 96.1%-99.1%]). This association was even longer time since vaccination, with ORs increasing with time since the fifth dose. At 60 months or longer (n=231 cases [33.9%] and n=288 controls [14.3%]), the OR was 0.29 (95% CI, 0.15-0.54 [estimated VE, 71.2%; 95% CI, 65.2%-83.2%]). Accordingly, the estimated VE declined each year after receipt of the fifth dose of DTaP.

Conclusion Among children in 15 California counties, children with pertussis, compared with controls, had lower odds of having received the 5-dose DTaP series; as time since last DTaP dose increased, the odds increased, which is consistent with a progressive decrease in estimated vaccine effectiveness each year after the final dose of pertussis vaccine.

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www.jama.com

Author Affiliations are listed at the end of this article.
### Table 4. Odds Ratios for Pertussis Disease Associated With Receipt of 5 DTaP Doses and Estimated Vaccine Effectiveness for Each Year Following the Complete DTaP Series

<table>
<thead>
<tr>
<th>Estimated VE Model</th>
<th>Primary Analysis&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Secondary Analysis&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, No.</td>
<td>Controls, No.</td>
</tr>
<tr>
<td>Overall No. of doses</td>
<td>(n = 682)</td>
<td>(n = 2016)</td>
</tr>
<tr>
<td>5</td>
<td>629</td>
<td>1997</td>
</tr>
<tr>
<td>Time since fifth dose, mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>19</td>
<td>354</td>
</tr>
<tr>
<td>12-23</td>
<td>51</td>
<td>391</td>
</tr>
<tr>
<td>24-35</td>
<td>79</td>
<td>366</td>
</tr>
<tr>
<td>36-47</td>
<td>108</td>
<td>304</td>
</tr>
<tr>
<td>48-59</td>
<td>141</td>
<td>294</td>
</tr>
<tr>
<td>≥60</td>
<td>231</td>
<td>288</td>
</tr>
</tbody>
</table>

Abbreviations: IE, interval estimate; OR, odds ratio; VE, vaccine effectiveness.

<sup>a</sup>ORs and estimated VE, accounting for clustering by county and clinic.

<sup>b</sup>Median and 95% IE based on 200 random, iterative samples of n = 1029 controls and assuming an even distribution of controls in each age category from 4 to 10 years. When divided into “time since fifth dose” categories, the <12-month category captures a larger number of individuals (n = 230) since the fifth dose can be administered at ages 4, 5, or 6 years.

**Table 2. Vaccine Effectiveness, by Age**

<table>
<thead>
<tr>
<th>Age, Years</th>
<th>PPV, %</th>
<th>PCV, %</th>
<th>Effectiveness, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–7</td>
<td>91</td>
<td>86</td>
<td>41 (21–54)</td>
</tr>
<tr>
<td>8–12</td>
<td>89</td>
<td>86</td>
<td>24 (0–40)</td>
</tr>
<tr>
<td>13–18</td>
<td>89</td>
<td>62</td>
<td>79 (73–84)</td>
</tr>
<tr>
<td>2–18</td>
<td>90</td>
<td>81</td>
<td>51 (44–58)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PCV, proportion of cases fully vaccinated; PPV, proportion of the population fully vaccinated.
TABLE 1  Risk of Pertussis in Years 2–6 After Fifth Dose of DTaP, Minnesota and Oregon, 2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Minnesota RR (95% CI)</th>
<th>Oregon RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>2</td>
<td>1.9 (1.3–2.9)</td>
<td>1.3 (0.6–2.8)</td>
</tr>
<tr>
<td>3</td>
<td>2.6 (1.7–3.8)</td>
<td>1.5 (0.7–3.7)</td>
</tr>
<tr>
<td>4</td>
<td>3.2 (2.1–4.8)</td>
<td>1.7 (0.8–3.7)</td>
</tr>
<tr>
<td>5</td>
<td>6.1 (4.1–8.9)</td>
<td>2.6 (1.2–5.6)</td>
</tr>
<tr>
<td>6</td>
<td>8.9 (6.0–13.0)</td>
<td>4.0 (1.9–8.4)</td>
</tr>
</tbody>
</table>

RR, relative risk.
In Australia, children born in 1998 could have received a primary course consisting of only DTwP, only DTaP or a mixed schedule.

**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.

*Sheridan et al JAMA 2012;308:29-30*
<table>
<thead>
<tr>
<th>Table. Pertussis Reports Between 1999 and 2011 for Children Born in 1998 (N = 40 694)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Reports</td>
</tr>
<tr>
<td>Preepidemic (1999-2008) Pure course</td>
<td>13</td>
</tr>
<tr>
<td>DTAprimary course (n = 9827)</td>
<td>12</td>
</tr>
<tr>
<td>DTwP primary course (n = 22 956)</td>
<td></td>
</tr>
<tr>
<td>Outbreak (2009-2011) Pure course</td>
<td>110</td>
</tr>
<tr>
<td>DTAprimary course (n = 9827)</td>
<td>78</td>
</tr>
<tr>
<td>DTwP primary course (n = 22 956)</td>
<td></td>
</tr>
<tr>
<td>Mixed course First dose of DTA</td>
<td>12</td>
</tr>
<tr>
<td>First dose of DTwP (n = 6933)</td>
<td>42</td>
</tr>
<tr>
<td>Mixed course by No. of DTwP doses 1 dose of DTwP only</td>
<td>6</td>
</tr>
<tr>
<td>DTAprimary course (n = 549)</td>
<td></td>
</tr>
<tr>
<td>First dose of DTwP (n = 2501)</td>
<td>20</td>
</tr>
<tr>
<td>DTwP primary course (n = 429)</td>
<td>6</td>
</tr>
<tr>
<td>First dose of DTwP (n = 4432)</td>
<td>22</td>
</tr>
</tbody>
</table>

Abbreviations: DTA, diphtheria-tetanus-acellular pertussis; DTwP, diphtheria-tetanus-whole cell pertussis.
Summary

The resurgence of pertussis is occurring mostly in children and not in adults

If the protection of the acellular pertussis vaccine decreases within 5 years should we

• Reduce the interval between the pre-school booster and the adolescent Tdap booster?
• Reconsider whole cell vaccines?

Adults: If protection induced by a dose of Tdap in adults is as short-lived as in children should we reconsider this recommendation?

• A program requiring a dose every 5 years would probably not be feasible/acceptable/cost-effective
Infants

Infants are those most severely affected by pertussis (deaths, hospitalization)

• Average of one to two deaths per year in Canada, one death per 200,000 infants in the USA
Cocooning strategy

Strategy: to vaccinate parents to prevent pertussis in their infant

Number needed to vaccinate depends upon

- % of infection acquired from parents
- Absolute risk of hospitalization / intensive care unit admission
- Vaccine effectiveness (85%?)
# Cocooning

## Table 2. Summary of Published Studies: Percentage of Infants Infected by a Parent

<table>
<thead>
<tr>
<th>First Author (Country) [Ref]</th>
<th>Year</th>
<th>Number of Index Infants With Confirmed Pertussis, Setting, and Age</th>
<th>Method of Parental Diagnosis as Source and Defined Onset Before Index Infant</th>
<th>Identified Sources, Proportion (%)</th>
<th>Source of Infection in All Infants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Greeff (Netherlands) [23]</td>
<td>2006–2008</td>
<td>164 hospitalized, ≤6 months</td>
<td>PCR, culture, serology, cough onset ≥1 week prior</td>
<td>17%</td>
<td>41% (68/184 included in the analysis)</td>
</tr>
<tr>
<td>Wendelboe (4 countries) [24]</td>
<td>2003–2004</td>
<td>Hospital = 75; not in hospital = 20, ≤6 months</td>
<td>PCR, culture, serology, symptom onset 7–30 days prior</td>
<td>NA</td>
<td>52% (of 91 included in the analysis)</td>
</tr>
<tr>
<td>Kovalzik (7 countries) [25]</td>
<td>2001–2004</td>
<td>99 pediatric ICU, &lt;1 year</td>
<td>PCR, culture, serology, cough onset ≥7 days prior</td>
<td>10%</td>
<td>73% (64/88 included in the analysis)</td>
</tr>
<tr>
<td>Elliott (Australia) [26]</td>
<td>2001</td>
<td>140 hospitalized, &lt;1 year</td>
<td>Physician report of coughing contacts (source not otherwise ascertained)</td>
<td>11%</td>
<td>49%</td>
</tr>
<tr>
<td>Bisgard (US) [27]</td>
<td>1999–2002</td>
<td>774; 616 included in source analysis, hospital or outpatient, &lt;1 year</td>
<td>Report by parents of any contacts with cough illness and contact 7–20 days before; assigned to contact spending most time with index infant</td>
<td>15%</td>
<td>57% (352/616)</td>
</tr>
<tr>
<td>Bonmarin (France) [28]</td>
<td>1996–2005</td>
<td>1688 hospital or outpatient, &lt;6 months</td>
<td>Physician report based on clinical presumption</td>
<td>NA</td>
<td>47% (None identified = 24%; unspecified = 23%)</td>
</tr>
<tr>
<td>Halperin (Canada) [7]</td>
<td>1991–1997</td>
<td>1082 hospitalized, &lt;2 years (&lt;50% laboratory confirmed)</td>
<td>Cough ≥2 weeks</td>
<td>NA</td>
<td>29%–42%</td>
</tr>
</tbody>
</table>

### Table 3. Number Needed to Vaccinate to Prevent Serious Outcome in Infants (by Age Category in Months) Through Parent Pertussis Immunization

<table>
<thead>
<tr>
<th></th>
<th>No. Hospitalization/ICU Admissions</th>
<th>Infant Risk per 100 000 Hospitalization/ICU Admission</th>
<th>Percentage Attributed to a Parent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>35% NNV Hospitalization/ICU Admission</td>
</tr>
<tr>
<td>&lt;12 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Québec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005–2009</td>
<td>265/32</td>
<td>57/7</td>
<td>11 756/97 353</td>
</tr>
<tr>
<td>High hosp (2009)</td>
<td>87/13</td>
<td>89/13</td>
<td>7522/50 342</td>
</tr>
<tr>
<td>Low hosp (2007)</td>
<td>20/2</td>
<td>22/2</td>
<td>31 033/310 326</td>
</tr>
<tr>
<td>British Columbia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005–2009</td>
<td>71/14</td>
<td>33/7</td>
<td>20 177/102 325</td>
</tr>
<tr>
<td>High hosp (2005)</td>
<td>24/7</td>
<td>59/17</td>
<td>11 357/38 939</td>
</tr>
<tr>
<td>Low hosp (2007)</td>
<td>6/0</td>
<td>14/0</td>
<td>47 569/∞</td>
</tr>
</tbody>
</table>

For the period 2005–2009, the parental NNV to prevent one infant pertussis-related death would exceed 1 million at 35% parental attribution and at 55% would still approach that magnitude.
Cocooning strategy

Implementation difficult


Labor intensive and costly
Not yet shown to be effective
The Advisory Committee on Immunization Practice (ACIP) in the US has recommended that pregnant women who have not previously been vaccinated against pertussis receive pertussis-containing vaccine in the second half of pregnancy.

NACI’s current recommendation for pregnant women who have not previously received Tdap vaccine in adulthood is that Tdap vaccine should be administered immediately post-partum. In particular situations where potential benefits outweigh risks, such as during pertussis outbreaks, acellular pertussis-containing vaccine (Tdap) should be considered for pregnant women in the second half of pregnancy who have not previously received Tdap vaccine in adulthood. Pertussis vaccination in pregnancy is under review by NACI.
Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine (Tdap) in Pregnant Women and Persons Who Have or Anticipate Having Close Contact with an Infant Aged <12 Months — Advisory Committee on Immunization Practices (ACIP), 2011

Guidance for Use

Maternal vaccination. ACIP recommends that women’s health-care personnel implement a Tdap vaccination program for pregnant women who previously have not received Tdap. Health-care personnel should administer Tdap during pregnancy, preferably during the third or late second trimester (after 20 weeks’ gestation). If not administered during pregnancy, Tdap should be administered immediately postpartum.

Cocooning. ACIP recommends that adolescents and adults (e.g., parents, siblings, grandparents, child-care providers, and health-care personnel) who have or anticipate having close contact with an infant aged <12 months should receive a single dose of Tdap to protect against pertussis if they have not previously received Tdap. Ideally, these adolescents and adults should receive Tdap at least 2 weeks before beginning close contact with the infant.
Risk-benefit of an intervention

Benefit:
- Burden of disease (~ 1 death per 200,000 births)
- Effective intervention (no data)

Safety
- During the pregnancy
- In the infant (poorer response to the vaccine)
Safety of Tdap in Pregnant Women

In prelicensure evaluations, the safety of administering a booster dose of Tdap to pregnant women was not studied. Because information on use of Tdap in pregnant women was lacking, both manufacturers of Tdap established pregnancy registries to collect information and pregnancy outcomes from pregnant women vaccinated with Tdap. Data on the safety of administering Tdap to pregnant women are now available. ACIP reviewed published and unpublished data from VAERS, Sanofi Pasteur (Adacel) and GlaxoSmithKline (Boostrix) pregnancy registries, and small studies (7,8). ACIP concluded that available data from these studies did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine. Both tetanus and diphtheria toxoids (Td) and tetanus toxoid vaccines have been used extensively in pregnant women worldwide to prevent neonatal tetanus. Tetanus- and diphtheria-toxoid-containing vaccines administered during pregnancy have not been shown to be teratogenic (9,10). From a safety perspective, ACIP concluded that administration of Tdap after 20 weeks' gestation is preferred to minimize the risk for any low-frequency adverse event and the possibility that any spurious association might appear causative.
Safety

49 Tdap exposures from the Phase IV clinical trials, and one baby with a birth defect.

- 34 (69%) had no AEs,
- 10 (20%) had serious AEs (gestational diabetes, threatened labor, spontaneous abortion, preeclampsia, syncope/hypotension/bradycardia, pregnancy-induced hypertension, tuberculin test positive),
- 3 (6.1%) had non-serious AEs.

47 with known pregnancy outcomes

- 44 live births
- 1 unrelated congenital anomaly diagnosed prenatally pre-vaccination
- 2 spontaneous abortions, and 1 elective abortion.
Sanofi Pasteur vaccine registry

480 prospective spontaneous reports, 27 (6%) had serious AEs

• Spontaneous abortion, gestational diabetes, preterm labor, tubal rupture, preeclampsia, syncope/headache, ovarian cancer, labor complication

• 119 (25%) with known pregnancy outcomes,
  • 16 spontaneous abortions.

10 retrospective spontaneous reports, 2 serious AEs (2 spontaneous abortions)

Data are not yet available from GSK’s Boostrix® pregnancy registry.
Vaccine Adverse Event Reporting System (VAERS)

VAERS data from January 1, 2005 – June 30, 2010

129 reports after Tdap vaccines involved pregnant women.

- 6 were classified as “serious.”
- No maternal deaths [CDC/ISO unpublished data].
- 21 spontaneous abortions;
- 2 stillbirths
- 2 threatened abortion
- 1 preterm delivery
- Others
Pertussis Maternal Immunization
Clinical trials

NIAID (48 pregnant women + 32 non pregnant women)

Sanofi Pasteur (http://clinicaltrials.gov/show/nct00553228)

• 440 pregnant women vaccinated with Tdap or Td
• Primary Outcome Measures: (Immunogenicity not efficacy)
  Comparison of serum IgG antibody levels against PT, FHA, PRN, FIM between Tdap and Td groups [ Time Frame: birth, 2, 4, 6, 7, 12, and 13 months of age ]
• Secondary Outcome Measures: (safety)
  Safety of Tdap in pregnancy including pregnancy outcome and developmental assessment. [ Time Frame: developmental screening at 1 year of age ]

If an adverse event was occurring at a frequency of 1%, the sample size would be insufficient to properly detect it
Insufficient Safety Data

Sample size

- Eg: Preterm delivery (≈8% of pregnancy)
- If Tdap was causing premature labor in one out of 100 vaccinated mothers (1%), the sample size required to detect that increase (from the 8% baseline) would be >12000 per group. It would be larger if the adverse event is less frequent

Current data are grossly inadequate to evaluate safety during pregnancy
“In conclusion, killed vaccines are believed to be safe during pregnancy; however, it is difficult if not impossible to prove the safety of medication or vaccine use during pregnancy.

A very large sample size is required to detect rare adverse events, and most studies are too small to rule out a small to moderate increased risk.

In addition, exposures during pregnancy can cause a wide range of effects, including problems with development and risk for cancer. It is necessary to weigh the benefits with potential risks. Current data suggest that potential risks, if any, are likely to be small.”

Sonja Rasmussen, CDC

Interference with Infant Immune Response to Primary DTaP Vaccination

Several studies have suggested that maternal pertussis antibodies can inhibit active pertussis-specific antibody production after administration of DTaP vaccine to infants of mothers vaccinated with Tdap during pregnancy, referred to as blunting (12, 17). Because correlates of protection are not fully understood, the clinical importance of blunting of an infant’s immune response is not clear. Evidence suggests that any blunting would be short-lived because circulating maternal antibodies decline rapidly (12, 18). Circulating maternal pertussis antibodies might reduce an infant’s risk for pertussis in the first few months of life but slightly increase risk for disease because of a blunted immune response after receipt of primary DTaP doses. The benefit would be to reduce the risk for disease and death in infants aged <3 months, but the trade-off might be to increase the occurrence of pertussis in older infants; however, this group experiences a substantially lower burden of hospitalizations and mortality (National Notifiable Diseases Surveillance System, CDC, unpublished data, 2011).
One dose of vaccine currently very effective to prevent death

• Death occurs almost exclusively in unvaccinated infants.

• One dose of vaccine seems very effective to prevent death as incidence of pertussis death plummets after 2 months of age, before the 2\textsuperscript{nd} dose is administered
Number of deaths from pertussis among infants by month of life in the United States 1910-1912 and in Switzerland 1936-1944

Pertussis deaths in Japan 1975-1988

Because of fear of severe adverse events, infant pertussis vaccination was interrupted from 1975 to 1988 and replaced by vaccination starting at age 2 years.

During that period, 29% (49) of the 205 deaths occurred after one year of age.
Cost effectiveness

The program cost per QALY to save one year of perfect life for an infant with the pregnancy scenario is $415,442.

With the postpartum scenario (cocooning) it is $1,174,143. By adding the father, the cost per QALY rises to $2,154,170 and by adding the grandparent the cost rises to $5,418,427.

Updated Recommendations for Use of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) in Pregnant Women — Advisory Committee on Immunization Practices (ACIP), 2012

The 2011 Tdap recommendation did not call for vaccinating pregnant women previously vaccinated with Tdap. On October 24, 2012, ACIP voted to recommend use of Tdap during every pregnancy.
Studies on the persistence of antipertussis antibodies following a dose of Tdap show antibody levels in healthy, nonpregnant adults peak during the first month after vaccination, with substantial antibody decay after 1 year (8–10). Antibody kinetics in pregnant women likely would be similar.
Safety of Repeat Tdap Administration to Pregnant Women

In 2011, ACIP concluded that available data did not suggest any elevated frequency or unusual patterns of adverse events in pregnant women who received Tdap and that the few serious adverse events reported were unlikely to have been caused by the vaccine; at that time, a dose of Tdap for every pregnancy was not considered (9). Published data on receipt of 2 doses of Tdap and multiple doses of tetanus toxoid–containing vaccines were reviewed. Receipt of a second dose of Tdap at a 5- or 10-year interval in healthy nonpregnant adolescents and adults was well tolerated; injection site pain was the most commonly reported adverse event (9,17–20). The frequency of reported adverse events for the second dose was similar to the first dose in these same subjects and in naïve controls receiving Tdap for the first time. Of the few serious adverse events reported, none were attributed to the vaccine. Fever was reported in 2.4%–6.5% of recipients of a Tdap booster; the frequency of fever was similar to that in the same subjects after their first Tdap dose and in naïve controls (9,17–19). Studies on short intervals (i.e., within 21 days or ≤2 years) between receipt of tetanus and diphtheria toxoids (Td) and Tdap or Tdap-inactivated polio vaccine in healthy, nonpregnant adolescents and adults found no serious adverse events (21–23). Fever was reported in 1.7%–6.8% of subjects who received Tdap ≤2 years after Td; rates were comparable to the control group and to cohorts that received Tdap longer after receipt of Td (21,22). The number of subjects in these studies was small, and therefore, the findings do not rule out the possibility of rare but serious adverse events.
Maternal immunization

Major uncertainties

- No efficacy data
- Inadequate safety data
  - Pregnant women are generally considered a special risk population for which greater caution should be exerted
  - Would interference with the 1st dose of vaccine reduce the protection against death currently observed?

Certain: Enormous cost
Discussion

Acellular pertussis vaccine not protecting as long as expected

- Evidence of waning of immunity
- School-age children are the group most affected

Pertussis death in infants remains the priority

- The proposed solutions (maternal immunization and cocooning) may not be effective, may not be safe and will be very costly
Future

Elimination of this disease is impossible given the contagiousness of the disease and the efficacy of the vaccine.

We have to revisit the pertussis prevention strategy:

- We will have to tolerate some level of disease.
- Greater use of a poor vaccine may not be the solution.