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Acellular Pertussis Vaccines: Pertinent Issues

JOSEPH L MATHEW

Advanced Pediatrics Center, PGIMER, Chandigarh 160 012, India.
Email: jlmathew@rediffmail.com

The recent aggressive marketing of acellular pertussis vaccines and consequent queries from pediatricians prompt the following considerations.

FACTORS AFFECTING EFFICACY OF PERTUSSIS VACCINES

Efficacy of whole cell pertussis vaccines (wP) in humans correlates with (and hence is measured by) the 'mouse protection test', wherein vaccinated mice are challenged with live *B. pertussis.* This test does not work similarly with acellular pertussis vaccines (aP); hence antibody levels to various antigens are measured as a surrogate marker of efficacy. This difference between the direct as compared to indirect demonstration of efficacy of wP and aP respectively should be recognized, especially as there is considerable debate on whether antibody levels closely correlate with protective efficacy against pertussis.

The protective efficacy of wP has been proven by observing (*i*) reduction in disease burden with inception of vaccination program, (*ii*) resurgence of disease with decline in vaccination coverage, (*iii*) an almost reciprocal relationship between the attack rate during outbreaks and proportion of immunized children, and (*iv*) evidence that suggests herd immunity.

Maternally transmitted antibodies interfere with the immune response of infants to wP; this limits the age at which vaccination can be initiated. Maternal antibodies appear to have less impact on the immune response to aP. As for many other vaccines, the gap between doses (schedule of immunization) can also have an impact on efficacy.

EFFICACY

Although it is impractical to calculate efficacy of pertussis vaccines across various studies, the range usually quoted is 85-95% for wP and 75-90% for aP(1). It should be recognized that one or more products of both types would be outliers to this range; reiterating that all wP and all aP are not equivalent to each other.

Differences in efficacy among various aP depend on the overall impact of the number of antigenic components, quantity of each antigen and the manufacturing process. Thus the mere presence of more (or less) components cannot be used to assume efficacy (or otherwise); currently available aP are all deemed efficacious. Since data on head to head comparison between various aP are limited, it is difficult to determine which (if any) among the currently available products is superior.

SAFETY

wP often cause minor (but troublesome) side effects and rarely more serious adverse events. However, the relatively high incidence of the former is sometimes unacceptable to care-givers and care-providers; this is what prompted the development of aP. The incidence of frequent side effects (fever, erythema, swelling, fretfulness, drowsiness) is reported to be significantly less with aP as compared to wP. However, there is a very wide

TABLE I FREQUENCY OF SIDE EFFECTS WITH PERTUSSIS VACCINES

Event	Whole cell pertussis vaccine	Acellular pertussis vaccine	
	Average	Average	Range
Fever < 38.3°C	44.5%	20.8%	16-29.2%
Fever > 38.3°C	15.9%	3.7%	1.6-5.9%
Erythema	56.3%	31.4%	15-44 %
> 2.0 cm	16.4%	3.3%	1.4-5.9%
Swelling	38.5%	20.1%	7.5-24.2%
Drowsiness	62.0%	42.7%	29.4-52.2 %

TABLE II META-ANALYSIS OF SERIOUS ADVERSE EVENTS WITH PERTUSSIS VACCINES

Event	Frequency with aP	Frequency with wP	Pooled RR (95% CI)	Pooled Risk difference (95% CI)	Interpretation
High fever (>40°C)	227/99323 (0.23%)	996/96879 (1.03%)	0.18 (0.08-0.44)	0.02 (0.03-0.01)	RR is about 80% less with aP than with wP, but the absolute difference is 2%.
Seizures (within 48 h)	58/106204 (0.05%)	224/103474 (0.22%)	0.28 (0.13-0.61)	0.00 (0.00-0.00)	RR is about 72% less with aP than with wP, but the absolute difference is negligible.
Hypotensive-hyporesponsive episode	20/106204 (0.02%)	491/103474 (0.47%)	0.04 (0.01-0.19)	0.00 (0.00-0.00)	RR is about 96% less with aP than with wP, but the absolute difference is negligible.

aP: acellular pertussis vaccine; wP: whole cell pertussis vaccine; RR: relative risk.

range among various aP (***Table* I**); with varying frequencies for individual side effects. Therefore it is impossible to identify an aP with the most (or least) favourable adverse event profile. Meta-analysis of data from large randomized controlled trials(2-6), on serious adverse events shows that although the relative risk for some events is less with aP, the absolute risk difference is comparable to wP (***Table* II**) because such events are very rare with both.

COMBINATION WITH OTHER ANTIGENS

Combining wP or aP with diphtheria and tetanus toxoids does not adversely affect the efficacy of the three components. Combination of DwPT with conjugated Hib vaccine results in statistically significant, but clinically insignificant reduction in antibodies to Hib antigen. However DaPT-Hib combination results in much greater reduction in antibodies to Hib polysaccharide; to the extent that many such combinations are not used in North America, although most European countries do not regard this as clinically significant.

MAKING A RATIONAL CHOICE

Based on the above, there are no strong scientific grounds to urge either the Government of India or individual pediatricians to switch from wP to aP. The edge in terms of reduction in minor side effects must be balanced against slightly lower efficacy, equivalent frequency of serious adverse events and far greater cost.

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