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Reflections on the Efficacy of Pertussis Vaccines

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The literature on the protection imparted by conventional whole-cell pertussis vaccines was reviewed, and the extent to which the great variation in estimates of vaccine efficacy is attributable to methodologic problems in study design and analysis or to biologic features of the natural history of pertussis was explored. The protection against disease imparted by pertussis vaccines may be greater than that against infection. Estimates of vaccine efficacy from case-control studies are higher than those from studies of household secondary-attack rates; likewise, estimates of efficacy are higher when based on clinically severe or bacteriologically positive cases rather than simply on notified cases. Some of the reported differences in protection by different vaccines may be attributable to relations between the antigenic composition of the vaccine used and that of the circulating strain of *Bordetella pertussis*. Failure to consider age trends has sometimes led to spuriously high estimates of efficacy. Many biases can affect efficacy studies, and it is usually difficult to assess whether the net effect has been to underestimate or to overestimate "true" efficacy. The immunity imparted by conventional pertussis vaccines may be neither as solid nor as stable as that imparted by many live-virus vaccines. These issues must be considered during the evaluation of acellular pertussis vaccines.

The efficacy of pertussis vaccines is a subject of long-standing controversy, with particular relevance today. The controversy dates back to the first trials of pertussis vaccines, which were carried out during the 1930s. These were criticized as biased in favor of the vaccines because they were not randomized; vaccinated volunteers were compared with unvaccinated "nonvolunteers" [1, 2]. Although killed whole-cell pertussis vaccines were used increasingly in developed countries during the 1940s and 1950s (they were first recommended for routine use in all children in the United Kingdom in 1957), conflicting accounts of their efficacy have continued to be published. At least twice these reports have led to major policy changes. Evidence that the efficacy level of at least one of the pertussis vaccines used in the United Kingdom was only 20% during the mid-1960s led to a change in the required composition and concentration of British standard vaccines in 1968 [3]. In the late 1970s pertussis vaccines were totally withdrawn from use in Sweden because of evidence that their efficacy had fallen virtually to zero [4, 5]. To what extent the variation in published estimates of pertussis vaccine efficacy is due to methodologic problems in the studies or to poorly understood biologic factors remains unclear.

The recent development of a new generation of acellular pertussis vaccines has been stimulated in large part by continued dissatisfaction with the efficacy and safety of traditional whole-cell vaccines [6, 7]. The demonstration that a new vaccine is in fact more effective than one or another traditional product may not be easy, however, and efforts to assess new vaccines may well resurrect many of the problems confronted in studies of the killed whole-cell vaccines over the past several decades. It is thus particularly relevant that we now consider carefully the problems and controversies relating to the protective efficacy of pertussis vaccines.

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Estimation of Vaccine Efficacy

Table 1 summarizes the results of all published reports known to us on the efficacy of whole-cell pertussis vaccines [1, 4, 8–44]. Although the table may not include all reports actually in print, it should at least be representative of methods and results found in the literature. The vaccine efficacies (VE) reported here are calculated according to the con-

ventional definition: VE = the percentage reduction in risk attributable to vaccination among vaccinated individuals compared with similarly exposed unvaccinated individuals; that is, VE = $(R_{nv} - R_v)/R_{nv} = 1 - (R_v/R_{nv})$, where R_{nv} is the risk of pertussis in the unvaccinated group and R_v is the risk of pertussis in the vaccinated group.

Some publications provide several different estimates of vaccine efficacy, depending upon different case criteria, age groups, or vaccines. In some instances the vaccine efficacy given in table 1 was not calculated by the original authors but by us on the basis of data in the cited publication.

The table lists the studies in four groups according to the method used to derive vaccine efficacy: (*1*) controlled trials, in which there was random allocation of vaccine and placebo and active case detection to provide estimates of R_v and R_{nv}; (*2*) cohort studies, based on passive follow-up (i.e., notified cases) in populations in which vaccines were allocated or accepted on a nonrandom basis; (*3*) secondary attack rate studies, involving active detection of cases in households after the introduction of a primary case; and (*4*) case-control studies, in which vaccine efficacy was estimated through comparison of the vaccination status of ascertained cases with that of a control group (often the general population). In this case the vaccine efficacy is derived as illustrated in table 2 [45].

There is considerable variation in the estimates of vaccine efficacy presented in table 1. That this variation cannot be explained by sampling error alone is evident from the 95% confidence limits calculated by standard methods for relative risk analysis [46]. We now discuss some of the other factors that may underlie these differences.

Protection Against What?

What does it mean to say that a vaccine protects against pertussis? In surveying the literature we note that all published studies have used clinical criteria and thus that reported statistics reflect estimates of protection against clinical whooping cough rather than against infection with *Bordetella pertussis*. Looking deeper into this distinction, we find considerable evidence that conventional, killed, whole-cell pertussis vaccines are more effective in protecting against disease than in protecting against infection per se. Several observations support or are consistent with this contention.

First, many authors have reported that clinical pertussis is less severe in vaccinated than in unvaccinated individuals [1, 8, 12, 17, 18, 25, 26, 28, 47]. Indeed, we know of no study that has examined this question and failed to find this result, though the data are sometimes misleading if not broken down by age, as the most severe disease generally occurs in infants too young to have been vaccinated.

Second, it is widely accepted that the development of pertussis disease represents a two-stage process: an initial colonization or infection stage during which the organisms attach to and proliferate on the respiratory tract mucosa, and an invasive or toxic stage associated with cell damage attributed to toxic products of *B. pertussis* [7, 48, 49]. These two stages are mirrored in the immune response, in that the infection stage stimulates production of secretory IgA and the invasive stage stimulates production of IgG. Of particular interest is the recent finding by several workers that the immune response to conventional pertussis vaccines involves predominantly IgG, with little or no IgA component [50, 51], and that the titer of IgA antibodies to fimbrial hemagglutinin is inversely correlated with the persistence of *B. pertussis* infection in animal models [52]. This observation provides an immunologic rationale for the better protection offered by killed whole-cell pertussis vaccines against the later morbidity-associated stages than against the initial colonization stages of *B. pertussis* infection.

Third, pertussis epidemics appear cyclically, every 3 or 4 years in large populations (figure 1). The mechanism underlying these cycles is reasonably well understood, being a dynamic interaction between the entry of susceptibles into the population (mainly by births) and their depletion (mainly by infection or vaccination and conversion into immunes) [53, 54]. As each epidemic is touched off by the attainment of a critical density of susceptibles in the population (called the epidemic threshold and estimated at $\sim 3.5 \times 10^6$ for England and Wales), the interval between epidemics should reflect the rate of accumulation of susceptibles [55]. High birth rates and/or low uptake of immunizing vaccine should lead to a decrease in the interval between epidemics. Conversely, low birth rates and/or high uptake of immunizing vaccine should lead to an increased interval. On the other hand, if the vaccine were to protect against disease much more than against infection, one would predict that the amplitude of disease cycles would be affected by changes in vaccine uptake

Table 1. Summary of estimates of the efficacy of conventional pertussis vaccines as reported in the literature. (Note: Column entries apply to all cases in a given reference unless otherwise indicated. Explanatory footnotes appear at the end of the table.)

Type of study [reference]	Place	Year(s)	Measure*	VE (95% CL)†	Age (y) or birth year	Doses‡	Case definition§	VE publ‖	Vaccine
Controlled trial									
8	England	1946–1950	f	0.61 (0.41, 0.74)	0.5–5	3v0	D	No	Sauer
				0.69 (0.53, 0.80)					Glaxo
				0.72 (0.62, 0.79)					Glaxo
				0.86 (0.77, 0.92)					Michigan
				0.91 (0.85, 0.94)					Michigan
9	Norfolk, Va.	1938–1941	k′	0.70 (0.59, 0.78)	<6	2v0	D	No	Alum-precipitated
Cohort									
10	Faroe Islands,	1923	r′	~0	NS#	3v0	D	No	"2.2 × 10^{10} formalin killed"
	Denmark	1929	r′	0.24 (0.15, 0.31)			D		
		1919	r	0.94 (0.85, 0.97)			F		
11	Shetland, U.K.	1977–1978	r′	0.04 (−0.65, 0.44)	<16	3v0	D	No	Not stated
12	Peebleshire, U.K.	1964	r′	0.10	Preschool	3v0–2	C	No	Not stated
				0.68	Preschool		P		
				0.13	School		C		
				0.02	School		P		
13	Oxford, U.K.	1942–1944	r′	0.11 (−0.36, 0.42)	0.5–4	2v0	D	No	"4 × 10^{10} *H. pertussis* phenol killed"
14	England	1972–1974	r′	0.60 (0.55–0.65)	<6	3v0–2	N	No	Not stated
15	Camberwell, U.K.	1953–1954	r	0.66 (0.56, 0.74)	School entry	3v0	D	No	"PTAP or APT + 3 × 10^{10}
				0.87 (0.80, 0.91)			S		*H. pertussis*"
16	Shetland, U.K.	1977–1978	r′	0.68 (0.26, 0.86)	<4	3v0	N	No	Not stated
1	Michigan	1934–1937	r	0.80 (0.74, 0.85)	0.67–6	4v0	D	No	"7 × 10^{10} *H. pertussis* phenol and/or merthiolate killed"
17	21 AHAs,**	1978–1980	r′	0.84 (0.71, 0.91)	1979	3v0	D	Yes	"Triple"
	England			0.85 (0.80, 0.88)	1978				
				0.84 (0.81, 0.86)	1977				
				0.83 (0.81, 0.85)	1976				
				0.84 (0.82, 0.86)	1975				
				0.82 (0.80, 0.83)	1974				
				0.85 (0.83, 0.87)	1973				
				0.83 (0.82, 0.84)					
			r′	0.93	<6	3v0	B	Yes	"Triple"

(*continued*)

18	Karlskoga, Sweden	1956	f'	0.88 (0.75, 0.94) 0.96 (0.86, 0.99) 1.00 (0.85, 1.00)	<6	3–4v0	D S + M S	No	"Triple"
19	Central Glasgow, U.K.	1974	r'	0.89 (0.76, 0.95) 0.72 (0.49, 0.85) 0.67 (0.42, 0.81) 0.52 (0.04, 0.76) 0.68 (0.44, 0.81) 0.74 (0.49, 0.87) 0.61 (0.21, 0.81) 0.72 (0.63, 0.78)	1973 1972 1971 1970 1969 1968 1967	3v0–2	N	Yes	Not stated
20	Michigan	1932–1936	r'	0.91 (0.77, 0.97)	0.67–5	4v0	D	No	"7×10^{10} *B. pertussis* phenol or merthiolate killed"
21	Hertfordshire, U.K.	1978	r'	0.93 (0.82, 0.97) 0.94 (0.88, 0.97) 0.87 (0.80, 0.91) 0.88 (0.82, 0.92) 0.85 (0.77, 0.90) 0.89 (0.86, 0.91)	1977 1976 1975 1974 1973	3v0	N	Yes	Not stated
22	Hungary	1970–1973	r'	>0.97	>0.5	3v0	N	Yes	"$AlPO_4$-adsorbed DTP"
23	Nottinghamshire, U.K.	1977–1978	r'	1.00 (0.64, 1.00) 0.93 (0.73, 0.98) 0.83 (0.63, 0.92) 0.82 (0.61, 0.92) 0.88 (0.77, 0.94)	1976 1975 1974 1973	3v0–2	P	No	"Triple"
Secondary attack rate									
24	33 areas, U.K.	1966–1968	r'	0.16 (−0.10, 0.35) 0.22 (−0.23, 0.50) 0.17 (−0.10, 0.38)	<5 5–10	3v0	D	No	Glaxo
				0.53 (0.14, 0.74) 0.56 (−1.56, 0.92) 0.53 (0.10, 0.76)	<5 5–10	3v0	D	No	Wellcome
17	21 AHAs, England	1978–1980	r'	0.29 (−0.35, 0.63) 0.59 (0.42, 0.71) 0.52 (0.33, 0.66) 0.47 (0.24, 0.64) 0.50 (0.35, 0.61) 0.51 (0.42, 0.59)	0 1 2 3 4, 5	3v0	D	Yes	"Triple"
			r'	0.81	<5	3v0	B	Yes	"Triple"

(continued)

Table 1. (*continued*)

Type of study [reference]	Place	Year(s)	Measure*	"VE (95% CL)†	Age (y) or birth year	Doses‡	Case definition§	VE publ"	Vaccine
25	West Glamorgan, U.K.	1977–1979	r'	0.49 (0.26, 0.64) 0.21 (−0.24, 0.50) 0.41 (0.18, 0.58)	<5 5–9	V/Nv	D	Yes	Not stated
26	Michigan	1962	k'	0.54	<1->20	3/v0–2	D	No	"Triple"
27	United States	1979–1981	r'	0.55 (−1.66, 0.92) 0.74 (−0.04, 0.93) 0.64 (0.32, 0.90)	<1 1–4	≥3v0	N	"Yes"	"Formalin killed"
28	Southwest Thames, U.K.	1978	r'	0.58 (0.40, 0.70) 0.73 (0.47, 0.87)	<12	3v0	D D††	No	Not stated
29	New Zealand	1982	r'	0.59 (0.35, 0.73)	≤11	2v0–1	D	Yes	"Adsorbed triple"
30	Atlanta	1977	r'	0.54 (−0.54, 0.86)‡‡	<20	≥3v0	D	"Yes"	"Triple"
8	England	1946–1950	r'	0.66 (0.22, 0.86) 0.67 (0.40, 0.82) 0.74 (0.41, 0.88) 0.90 (0.76, 0.96) 0.91 (0.72, 0.97)	0.5–5	3v0	D	No	Glaxo Glaxo Sauer Michigan Michigan
31	Kurashiki, Japan	1975–1977	r'	0.68 (0.34, 0.84) 0.88 (0.09, 0.98) 0.69 (0.32, 0.86)	0–4 5–16	V/Nv	D	No	"Maeno-Tohama strain as source of vaccine"
32	United States	1979–1981	r'	0.82	<5	≥3v0	D	Yes	"Triple"
33	United States	1982–1983	r'	0.91 (0.86, 0.94)	0.5–9	≥3v0	D	Yes	Not stated
34	United States	1979	r'	0.93 (0.59, 0.99)	<5	3v0	D	Yes	"Triple"
35	Glasgow, U.K.	1978	r'	1.00 (−11.49, 1.00) 0.53 (0.19, 0.73) 0.21 (−0.65, 0.62) 0.45 (0.04, 0.69)	<1 1–5 6–15	3v0–2	D	No	Not stated
Case-control§§									
4	Sweden	1978	r'	0.00 (−0.24, 0.19)	1–6	3v0–2	B	No	Not stated
29	New Zealand	1982	r'	0.00 (−0.56, 0.36)	0.58–11	2v0–1	N	No	"Adsorbed triple"
35	Glasgow, U.K.	1978	r'	0.61 (0.39, 0.75)	1976	3v0–2	N	Yes	Not stated
36	Manchester, U.K.	1963–1964	r'	0.64 (0.55, 0.71) 0.80 (0.65, 0.89)	<5	3v0–2	N B	No	Not stated
37	Derbyshire, U.K.	1964–1974	r'	0.79 (0.72, 0.85)	<5	1–3v0	H	No	Not stated

(*continued*)

38	London, U.K.	1970–1979	k′	0.84 (0.78, 0.89)	School	3v0–2	N + H ‖‖	No	Not stated
39	Manchester, U.K.	1969–1971	r′	0.90 (0.77, 0.95)	1–3	3v0–2	B	No	"New vaccine, equally effective against all serotypes"
				0.29 (−0.45, 0.65)	4–10				"Old vaccine, mainly effective against strains containing antigen 2"
40	Michigan	1936–1941	r′	0.93 (0.47, 0.99)	0	V/Nv	N	No	Not stated
				0.91 (0.76, 0.97)	1				
				0.85 (0.70, 0.92)	2				
				0.85 (0.72, 0.92)	3				
				0.92 (0.82, 0.96)	4				
				0.81 (0.66, 0.89)	5				
				0.72 (0.49, 0.84)	6				
				0.80 (0.50, 0.92)	7				
				0.72 (0.11, 0.91)	8				
				0.61 (−1.89, 0.95)	9				
				0.84 (0.79, 0.87)					
41	11 sites, England and Wales	1965–1974	r′	0.94 (0.93, 0.95)	>1	3v0–2	H	No	Not stated
42	England	1974–1975	r′	0.95 (0.91, 0.97)	1.2–6	3v0–2	B	No	"Current [post-1968] vaccine"
43	Glasgow, U.K.	1969–1980	k′	0.95 (0.91, 0.97)	>0.5	3v0	H***	No	Not stated
32	United States	1979–1981	r′	0.96 (0.96, 0.97)	0.5–9	3v0–2	N	No	"Triple"
44	Birmingham, U.K.	1978–1979	r′	0.97 (0.78, 1.00)	"Children"	3v0–2	H	No	"Triple"

NOTE. Column entries apply to all cases in a given reference unless otherwise indicated.

* "Measure" codes refer to different methods of defining the population at risk or of selecting controls, as described elsewhere [45]: f = incidence rates R_v, R_{nv} (i.e., among vaccinated and unvaccinated individuals) calculated for period since vaccination, with person-time denominators; f′ = incidence rates R_v, R_{nv} calculated for period beginning at some time after vaccination, with person-time denominators for period under study; r = incidence rates R_v, R_{nv} calculated for period since vaccination, with initial numbers vaccinated and unvaccinated as denominators; r′ = incidence rates R_v, R_{nv} calculated for period beginning at some time after vaccination but with initial numbers vaccinated and unvaccinated as denominators (in the case-control context, this implies inclusion of past cases in the control group); k′ = case-control studies excluding past cases from control group.

† VE = vaccine efficacy, with 95% confidence limits (CL) where calculation was possible. Where appropriate, a summary VE value is given (under a rule).

‡ Data are expressed as the number of doses in the vaccinated group vs. that in the comparison group; e.g., the entry "3v0" refers to three doses in the vaccinated group vs. none in the comparison group. The entry "V/Nv" indicates that the comparison made was between those vaccinated and those not vaccinated.

§ Case definition codes are as follows: D = disease, severity not specified; B = bacteriologically positive case; N = notified case; F = fatal case; C = cough; P = paroxysm; H = hospitalized case; S = severe disease; M = moderate severity.

‖ "VE publ" indicates whether or not VE values were published in the paper cited. "Yes" in this column (inside quotation marks) indicates that the published VE differs from the age-standardized estimate given here.

NS = not stated in original publication.

** AHAs = area health authorities.

†† Index cases were bacteriologically positive.

‡‡ See table 6.

§§ All of the case-control studies used population controls except where indicated otherwise.

‖‖ Controls were matched for school, age, and sex.

*** Controls were measles cases.

Table 2. The case-control method of vaccine efficacy (VE) assessment.

	Pertussis cases	Control group
Vaccinated	A	B
Not vaccinated	C	D
Total	A + C	B + D

NOTE. The case-control method assumes that the selection of cases is independent of their vaccination status and that these cases can therefore be used to estimate the relative risk of pertussis among vaccinated and unvaccinated individuals. This estimate is obtained by comparison with the distribution of vaccination in a control group matched for age and other variables. VE = 1 − (AD/BC) [45].

to a much greater degree than would the frequency. This is in fact what has been observed in England and Wales over the past three decades [53].

Fourth, the literature contains several reports of the isolation of *B. pertussis* from asymptomatic individuals with a history of vaccination [26, 56, 57].

Implications of Ascertainment and Diagnostic Criteria

All published studies of pertussis vaccines have used clinical criteria to define pertussis. They have thus assessed protection against disease. There have been considerable differences in the actual criteria used in different investigations, however, and these differences have undoubtedly affected the numerical estimates of vaccine efficacy. The more important of these differences are described below.

The greater the clinical severity of cases accepted as pertussis, the higher should be (and have been) the estimates of vaccine efficacy. This relation is predicted by the evidence already presented that vaccines are more efficient in protecting against disease than against infection. Probably for this reason, case-control studies based upon hospitalized patients yield high estimates of vaccine efficacy (e.g., >95% in three studies of hospitalized patients in the United Kingdom [41, 43, 44]). Similarly, clinically severe cases are more liable to be bacteriologically positive than are mild cases (table 3), and it is consistently reported that the protective efficacy of vaccine is higher against bacteriologically proven cases than against the total number of cases or against bacteriologically negative cases [17, 42]. This relation would also lead to overestimates of vaccine efficacy among passively notified cases if there was a correlation between clinical severity and the probability that a physician both recognizes and notifies a case. It would not be surprising to us if there was indeed just such a correlation and if this situation had tended to raise estimates of vaccine efficacy in some cohort as well as case-control studies.

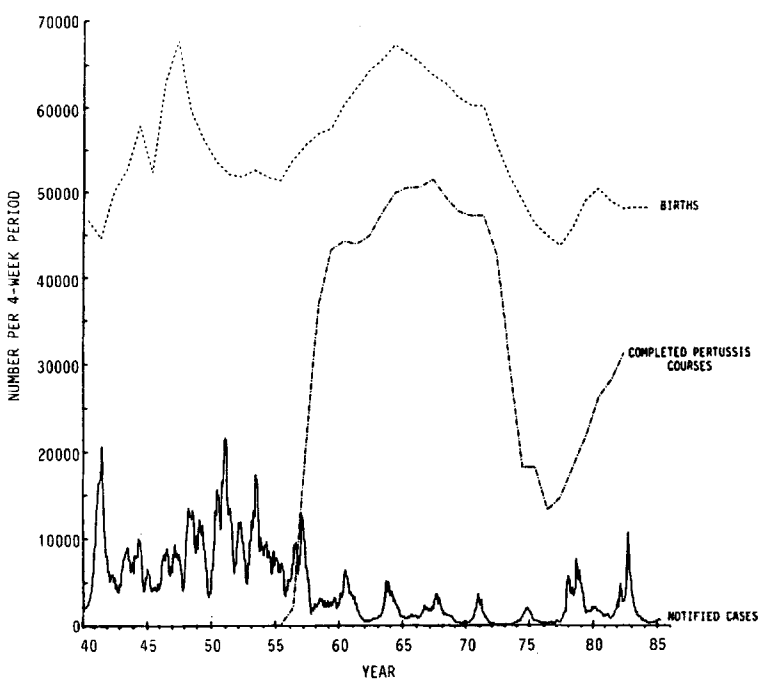

Figure 1. Numbers of notified pertussis cases, births, and completed pertussis vaccine courses (by cohort) in England and Wales per 4-week period, 1940–1984.

If a physician's knowledge of vaccination history influences the diagnosis, estimates of vaccine efficacy will be affected. In particular, if knowledge that a child has received pertussis vaccine reduces the index of suspicion that an illness is in fact pertussis, vaccine efficacy will be overestimated insofar as the observed risk of pertussis among vaccinees will be prejudicially reduced. It must be difficult for a physician to escape such a bias, in particular if he or she was responsible for the vaccination; a total avoidance of the bias would imply no faith in the protective properties of the vaccine. It is possible that this bias has influenced vaccine efficacy estimates derived in cohort and case-control studies based on notified disease. Studies of household secondary-attack rates are also subject to this bias unless the follow-up of household members is conducted without knowledge of vaccine status. None of the published household-contact studies has mentioned stringent measures to avoid such a bias.

There is also an important potential diagnostic bias in the opposite direction, in that the inclusion of illnesses that are not in fact due to *B. pertussis* will tend to reduce the observed estimate of pertussis vaccine efficacy. It is shown in figure 2 (and the appendix at the conclusion of this article) that if only *P*% of the apparent pertussis cases among nonvaccinees are in fact due to *B. pertussis*, and if the incidence rate of the condition that is mistakenly diagnosed as pertussis is not affected by pertussis vaccine, then the observed vaccine efficacy will be approximately *P*% of the "true value." This effect of nonspecific diagnoses is enhanced if the ascertainment (diagnostic sensitivity) of true cases is incomplete. Given the widely recognized difficulties in diagnosing pertussis [58], it is likely that this bias has affected many studies. It is an additional cause for the higher vaccine efficacies reported in studies restricted to bacteriologically confirmed cases.

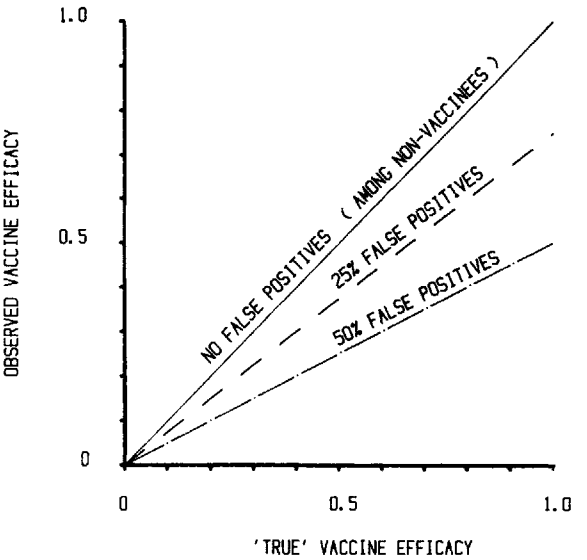

Figure 2. Diagram showing the impact of false-positive diagnoses on estimates of vaccine efficacy in cohort studies. If only *P*% of apparent pertussis cases among unvaccinated individuals represent true *Bordetella pertussis* infections, then the observed vaccine efficacy would be ~*P*% of the true value. This analysis assumes that the risk of false-positive diagnosis is independent of vaccination status and that ascertainment of true pertussis is complete. The relation shown is derived in the Appendix.

Table 3. Relation between bacteriologic status and number of paroxysmal coughs per day in cases of infection with *Bordetella pertussis*.

No. of paroxysms/day	No. positive for *B. pertussis*/ no. swabbed (% positive)*	
	DTP × 3	DT × 3
0	4/47 (9)	15/101 (15)
1–9	42/455 (9)	372/1,661 (22)
≥10	48/439 (11)	639/2,463 (26)
Total	94/941 (10)	1,026/4,225 (24)

NOTE. Data (kindly provided by Dr. E. Miller) are from the investigation by the Epidemiological Research Laboratory (Public Health Laboratory Service) of the efficacy of whooping cough vaccines in 33 areas of England and Wales [17].

* The association of bacteriologic positivity with an increased number of paroxysmal coughs per day is highly significant for individuals who received three doses of diphtheria-tetanus (DT) vaccine and for both groups considered together ($\chi^2 > 11$; $P < .005$). This association is not significant for individuals who received three doses of diphtheria-tetanus-pertussis (DTP) vaccine. Note also the implication of greater clinical severity (i.e., a higher proportion with >10 paroxysms) among persons not vaccinated against pertussis (DT recipients) than among those vaccinated (DTP recipients).

It is clear from this discussion that diagnostic and ascertainment criteria can affect the observed level of vaccine efficacy in different ways. The net effect of the different biases on any study is in general difficult to assess.

Implications of Distribution and Ascertainment of Vaccination

The calculation of vaccine efficacy assumes that the compared vaccinated and unvaccinated groups are equally exposed to infection. While this equal-

exposure condition can be assumed in a properly designed controlled trial, it may not be upheld in routine vaccination programs as investigated by cohort and case-control methods. (The special problem of exposure in secondary attack rate studies is discussed below.) If vaccine uptake within communities is nonrandom, or nonuniform, and if groups with high vaccine coverage are at low risk of exposure to infection, then studies will overestimate vaccine efficacy. If one grants that vaccine coverage is liable to be nonhomogeneous in most human societies, there are two reasons to suppose a bias in the direction proposed here. First, it is likely that vaccine uptake will be high in areas where overall medical services and hygiene are good. This pattern may be relevant to pertussis in that several authors have suggested that the disease is severest in less advantaged social classes [38, 59], among whom vaccine uptake is low [19, 60]. Second, insofar as high rates of vaccination may impart some indirect protection (herd immunity) to others in a neighborhood, this indirect effect will be directed preferentially—if ironically—towards vaccinated individuals (in the same neighborhood) rather than unvaccinated individuals (in other neighborhoods).

On the other hand, the nonuniform distribution of vaccination in a population introduces the potential for a bias against the vaccine in studies based upon notified cases. If the tendency to notify is a correlate of good public-health practice and hence is associated with high vaccine uptake, then there could be preferential reporting of cases in vaccinated individuals, leading to an underestimate of vaccine protection.

A related problem arises for cohort and case-control studies that depend on retrospective ascertainment of vaccination histories. Several studies have shown that parental recall or school records often disagree with the vaccination history as recorded in the clinic where vaccinations were actually given [61, 62]. Classification errors in vaccination status will in general tend to reduce estimates of vaccine efficacy unless there is a bias towards misrepresenting vaccinated patients as unvaccinated. Given problems in record keeping, there is probably a greater tendency for false-negative rather than false-positive recorded vaccination histories. Records will thus tend to underestimate vaccinations among cases and may inflate the vaccine efficacy observed in cohort studies that use vaccine uptake statistics for the total population in estimating denominators (e.g., the study by Church [21]). Case-control studies can in theory overcome this vaccination-ascertainment bias by using a group with disease not preventable by vaccination as controls [40]. If the control disease is itself preventable by vaccination, however, vaccine efficacy will be overestimated since such controls will tend to come from social groups with low vaccine uptake [43].

Differences Between Vaccines

It is possible that some of the differences shown in table 1 are attributable to differences in the composition and preparation of various vaccines. This situation is most clearly evident in the results of the early trials carried out by the Medical Research Council in the United Kingdom, during which it was found that vaccines prepared by the Michigan protocol were appreciably more effective than the others used [8]. Moreover, a significant difference was found between two vaccines used in the United Kingdom during the 1960s [24]. Unfortunately, in most investigations the vaccines used either have not been known or have not been specified.

It has been suggested that the fall in efficacy of pertussis vaccines in Sweden during the 1970s was due to a change in vaccine formulation at the beginning of the decade [4].

Despite considerable care taken by manufacturers to standardize their products, some residual batch variation is to be expected. This variation may apply more to pertussis than to other commonly used vaccines, particularly because the mouse protection test used to standardize such vaccines is recognized to be less precise than might be wished [63–65]. Although there may well be some variation between different batches of vaccine prepared by the same manufacturer, we expect that this variation is not a major source of the differences evident in table 1.

Variations in Wild *B. pertussis*

Several different antigenic types of *B. pertussis* are known to coexist in most populations. These are traditionally defined in terms of three major surface antigens, often called agglutinogens, found in combinations as strains or "serotypes" 1-2, 1-2-3, and 1-3. There is some evidence for strain specificity of vaccines. An increase in the proportion of strain 1-3 among circulating *B. pertussis* has been reported in several countries in past decades and has been attributed to widespread use of vaccines including in-

Table 4. Examples of recommended pertussis vaccination schedules in different countries and at different times.

Country (vaccine)	Period	Time or age of primary-course administration			Boosters
		First	Second	Third	
England and Wales (DPT)	1977–	3 mo old	6–8 w*†	4–6 mo*‡	None
	1967–	6 mo old	6–8 w	6 mo	None
	1961–	1–6 mo old	4–6 w	4–6 w	None
		9–12 mo old	4–6 w	18–21 mo old	None
United States (DPT)	1957–	<3 mo old	≥4 w	≥4 w	None
	1986	6–10 w old	6–8 w	6 mo old	15 mo of age and school entry
	1977–	6 w to 3 mo old	4–8 w	4–8 w	1 y after 3rd dose
	1966–	6 w to 3 mo old	4–6 w	4–6 w	1 y after 3rd dose
Czechoslovakia (DPT)	1984	9 w old	6 w	6 mo	3y and 6 y of age
Denmark (pertussis antigen alone)	1984	5 w old	9 w old	10 mo old	None
Sweden	1979–1985	Pertussis vaccination not recommended at all			

NOTE. The schedules cited here were selected solely to illustrate variations between countries and over time; they are not intended to be representative of vaccination schedules in the world today. DPT = diphtheria-pertussis-tetanus.

* An interval of only one month between doses is recommended during epidemic periods.

† Except for the Danish study, the intervals shown are those between the first and second doses.

‡ Except for values expressed as ages, the intervals shown are those between the second and third doses.

sufficient or no strain 1-3 component [12, 66–69]. The low reported efficacy of certain British pertussis vaccines during the mid-1960s was attributed in large part to this factor [24]. Although this contention of strain specificity has not been accepted universally [70], it was considered sufficiently compelling to warrant a change in composition (including the necessary inclusion of serotype 1-3 organisms) in British vaccines produced after 1968 [3, 24].

There is evidence that the immune response to the agglutinogen 2 component has been greater than that to the agglutinogen 3 component of several vaccines used in England and Wales [71, 72]. This difference may explain the high proportion of strain 1-3 organisms in some well-vaccinated communities. In this context it is of interest that the predominant serotype of *B. pertussis* in England shifted from 1-3 to 1-2 subsequent to the fall in vaccine uptake in the mid-1970s [73, 74]. Recent reports from Finland describe a situation opposite but complementary to that in England and Wales. In Finnish pertussis vaccines, agglutinogen 2 has proved less immunogenic than agglutinogen 3 and the vast majority of wild *B. pertussis* strains belong to the 1-2 serotype [75, 76]. Taken together, these reports from England and Finland argue strongly in favor of some degree of strain specificity for whole-cell pertussis vaccines.

The selective forces that determine the relative frequencies of the different serotypes of *B. pertussis* in unvaccinated populations are inadequately understood, as is the extent of natural cross-protection imparted by and between these serotypes. Whatever the selective forces are, they would be expected to vary over time and between different human populations; thus, they could be responsible for some of the observed differences in vaccine efficacy. What is more, the evidence that pertussis vaccines may in the past have selected for strains antigenically different from those in the vaccines argues for continued monitoring of the efficacy of vaccines used in routine programs.

Doses and Schedules

The recommended pertussis vaccination schedule has varied between countries and over time, as is illustrated in table 4. These varying schedules may well be responsible for some of the reported differences in vaccine efficacy (table 1).

There is evidence that for a maximal protective response to pertussis vaccines, the first dose should not be given until a child is at least 1 month of age, presumably because of interference from maternal antibody in the first month of life [65, 77]. Evidence

also supports an inverse relation between vaccine-induced IgG response and cord blood titer [51], but we have found no convincing data relating the age of initial vaccination to protection per se. Some studies on this topic have been seriously flawed—e.g., children vaccinated at an early age at urban welfare clinics have been compared with rural children vaccinated at later ages [78]. Given that the severity of clinical pertussis is also inversely related to age, the decision as to the optimal age for initial vaccination will vary between populations and will change in response to changes in the epidemiology of *B. pertussis*. The lower the risk of infection in the community (and in particular among young infants), the longer the initial vaccination may be delayed.

It is recognized that multiple doses of pertussis vaccines are required for an optimal immune response. A primary course of three doses, with intervals of 6–8 weeks between the first and second and 4–6 months between the second and third, is currently recommended in England and Wales. Although it was once believed that the final response was impaired if the interval between doses was too long, this is no longer thought to be true [79]. Few investigations have permitted estimates of the relative protection provided by one, two, or three doses of vaccine, but the few data available suggest a progressive increase in protection imparted by the three doses (table 5). Although boosters at 18 months and/or 5 years of age have been and are still recommended in some countries, we are aware of no data regarding their protective implications.

Duration of Protection

Pertussis has traditionally been considered a disease of children and was rarely diagnosed in adults before the introduction of vaccines. From this simple observation came the opinion that infection with the pertussis agent imparts lasting and solid protective immunity. We have thus been interested to note a number of recent publications on pertussis in adults [4, 80, 81]. Of course, these articles may reflect nothing more than the growth of the scientific literature in general. Alternatively, they may reflect merely a shift in the age distribution of pertussis cases and an increasing proportion of adult cases as the disease is effectively controlled among children. Age-specific notification data from England and Wales seem to support the latter interpretation (figure 3). On the other hand, several authors have recently expressed a concern that pertussis immunity may be only partial among adults, that they may carry repeated asymptomatic infections, and that such repeated infections may be necessary to maintain long-lasting protection against disease:

> [These observations] suggest that young adults with waning immunity and mild illness are a major reservoir for transmission of pertussis to infants. [80]
>
> This suggests the possibility that persisting immunity in vaccinated populations depends on subclinical or mild infections to booster waning immunity in later years. [70]
>
> Before pertussis vaccination was introduced whooping cough in adults was very uncommon. . . . The good immunity in adults may have been due to repeated natural booster doses through exposure to the disease. [4]
>
> We think that serologic responses in asymptomatic persons represent a natural booster phenomenon continuously occurring in relatives of patients with pertussis and thus maintaining herd immunity. [82]

The literature contains few data by which the du-

Table 5. Relation between the number of doses of pertussis vaccine administered and protection against clinical pertussis.

Type of study [reference]	Population studied	Protective efficacy (%)	
		1–2 doses	≥3 doses
Cohort [16]	Male	14	68
	Female	42	67
Cohort [21]	1-y-old*	73	93
	2-y-old	48	94
	3-y-old	53	87
	4-y-old	8	88
	5-y-old	50	85
Case-control [43]	Hospitalized patients 0–5 y old	33	95
Secondary attack rate [28]	Contacts of all index cases	37	58
	Contacts of all bacteriologically positive cases	60	73
Secondary attack rate [30]	1- to 5-y-old	56	55
	11- to 20-y-old	100	50
Secondary attack rate [56]	0- to 4-y-old	59	93

* Children were the ages listed in 1978.

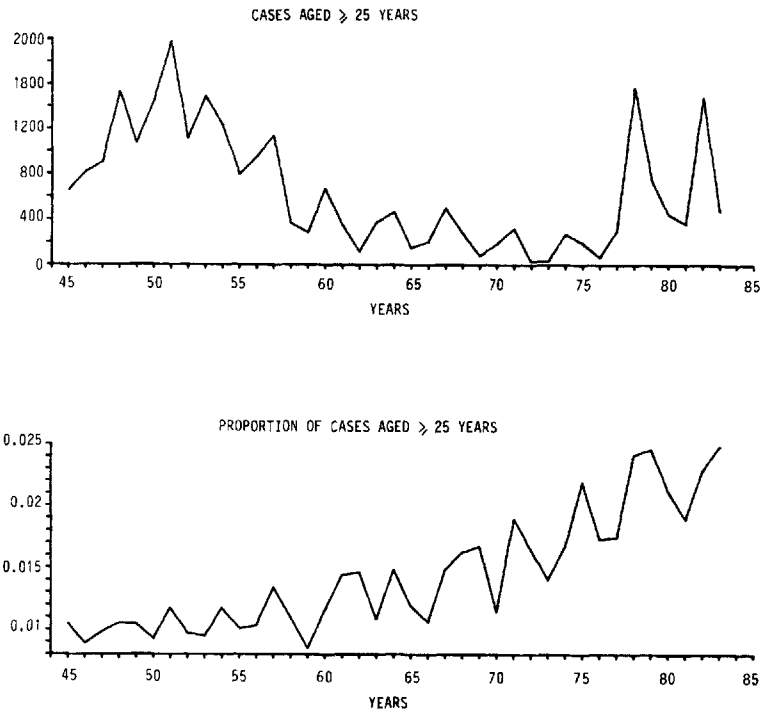

Figure 3. Absolute numbers and proportions of notified pertussis cases in persons ⩾25 years of age in England and Wales since 1945.

ration of vaccine-derived protection against pertussis can be assessed. A few studies give antibody titers by age, but the implications of such data for protection are not yet known [50].

In general, controlled trials of pertussis vaccines have not included a follow-up period sufficiently long for a determination of whether vaccine-derived protection wanes with time. On the other hand, several case-control and cohort studies provide data for groups of various ages or with various intervals elapsed since vaccination. Overall, these results indicate either stable vaccine efficacy [17] or a slight decrease with time [21, 25, 26, 40]. Table 5 includes data from a cohort study in Hertfordshire that may suggest a slight fall in protection imparted by three doses with age and time since vaccination [21]. Figure 4 shows the results of a classical case-control study; the findings are suggestive of a fall in efficacy with age and hence with the interval since vaccination [40]. (The original report did not present data by age at vaccination, and the trend in figure 4 may be confounded by selective allocation of vaccine to children without a history of prior pertussis.) Such observations of falling vaccine efficacy with time need not necessarily represent waning immunity. It has been pointed out elsewhere [45] that calculated efficacy will fall over time if a vaccine gives constant but relative protection (i.e., it reduces risk in all vaccinees but renders none totally immune for life) and if the efficacy estimates are based either upon cohort-study incidence risks calculated with initial population denominators (as in table 5) or upon case-control studies in which the control group is selected without regard to a history of pertussis (as in figure 4).

Protection Under Conditions of Household Exposure

Vaccine efficacy estimates derived in studies of household secondary-attack rates have in general been slightly lower than those obtained by other methods (table 1), despite the susceptibility of the former studies to diagnostic bias (as described earlier). The association of a low vaccine-efficacy rate with household contacts appears to be independent of diagnostic criteria: in a recent study by the Epidemiological Research Laboratory in the United Kingdom, the efficacy rate in the general population was found to be ~84% and ~93% for all cases and for bacteriologically proven cases, respectively, but only ~53% and ~81% for the same two case groups among household contacts (table 1) [17]. We may ask whether this finding reflects biologic mechanism or methodologic artifact.

If pertussis vaccines do indeed protect less well un-

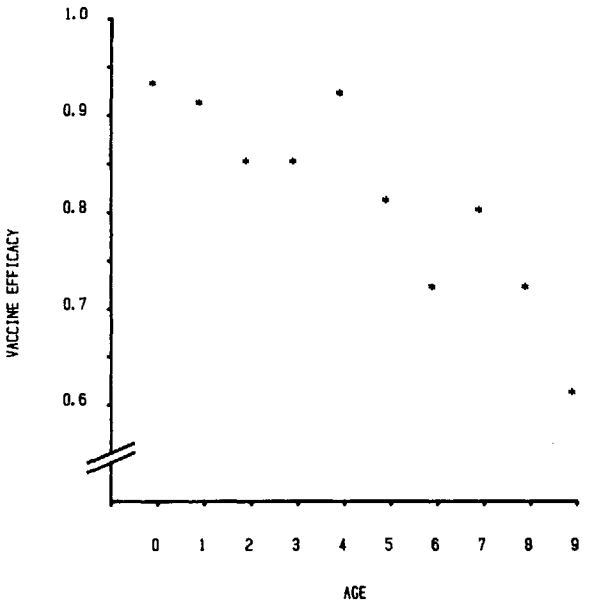

Figure 4. Estimates of pertussis vaccine efficacy by year of age (which is equal to the approximate time since last dose), as derived by a case-control method in which notified cases of measles, chickenpox, and scarlet fever were used as controls. Figure is based on data reported by Weiss and Kendrick in 1943 [40].

der conditions of household exposure than under other conditions, this pattern would suggest that vaccine-derived protection is dependent upon exposure level or challenge dose. Presumably, household exposure implies more frequent challenge with larger doses of *B. pertussis* than would normally occur outside the intimacy of a home environment.

It should also be recognized that the secondary attack rate method involves the study of highly selected populations—family contacts of ascertained cases—and that for several reasons this selection may introduce biases. First, the method requires information on both vaccinated and unvaccinated household contacts. If vaccine uptake is nonrandom, such that most or all members of some households are vaccinated and most or all members of the other households are not vaccinated, then most or all of the vaccinated individuals in the study will be included because of a prior vaccine failure in the household (i.e., the index case). Insofar as risk factors for vaccine failure—whether they be genetic, socioeconomic, or a reflection of the quality of the vaccine provider—are likely to be shared by members of a household, then the selection process involved in studies of secondary attack rates introduces a bias against the vaccine.

Second, studies of cases in which *B. pertussis* is introduced into a household by a vaccinated individual may be biased in favor of the vaccine. This statement is again based upon the assumption that vaccine uptake is nonrandom and thus that household contacts will in general share the vaccination status of the index case. Insofar as the clinical severity of pertussis is likely to be reduced in vaccinated individuals, the contacts of these individuals may be exposed to fewer bacilli than are the contacts of unvaccinated persons with the disease. This lower level of exposure should reduce the risk of infection preferentially among vaccinated contacts as a group and thereby increase the apparent efficacy of the vaccine. (The opposite could be argued if severely ill patients were somehow isolated from other household members.)

Third, the greater the number of pertussis cases in a family, the greater is the possibility that the family will be identified and included in a study. This ascertainment bias, favoring households with larger rather than smaller numbers of cases, is presumably against the vaccine since households in which the vaccine is working best would be selectively excluded from study. One way to lessen this bias is to restrict the analysis to cases with onset after the households have been identified and visited.

A detailed analysis of data from a large study of household secondary-attack rates in England has revealed higher vaccine efficacy when patients with index cases have not been vaccinated (consistent with the first point just discussed) and when retrospectively ascertained cases have been excluded (consistent with the second point) (P. E. M. Fine, J. A. Clarkson, and E. Miller, unpublished data).

There is a particularly interesting exception to the general rule of lower vaccine efficacy associated with household than with extrahousehold exposure. A direct comparison was made between these situations in the context of the first trials by the British Medical Research Council; no difference in vaccine efficacy was found (table 1) [8]. One possible explanation for this observation is that strain 1-2 of *B. pertussis* predominated at the time of these early trials, whereas the poor performance of vaccines under conditions of household exposure has been observed in periods when strain 1-3 predominated (e.g., as reported in [24]). On the other hand, because these trials were based entirely upon prospective follow-up, the finding of similar levels of vaccine efficacy in instances of household and extrahousehold ex-

posure may be interpreted as evidence that the low efficacy observed in some subsequent household studies reflects biases in the ascertainment of the households studied.

Age-Distribution Artifacts

Vaccine efficacy studies can be seriously in error if data are not analyzed separately for narrow age groups or are not otherwise standardized for age. An example of this error is shown in table 6, which presents data from a household secondary-attack rate study of the efficacy of pertussis vaccines [30]. The authors concluded that the overall rate of vaccine efficacy was 63%, but a close examination shows that the efficacy was lower than this figure in the only two age groups permitting an estimate. Insofar as the proportion of persons completely vaccinated will generally increase with age and the actual risk of pertussis in either vaccinated or unvaccinated groups will generally decrease with age (if for no other reason than that older individuals are more liable to have acquired natural immunity), a failure to take age into account will usually lead to overestimates of vaccine efficacy. Age standardization of the data shown in table 6 (by means of the Mantel-Haenszel method [46]) provides an overall efficacy estimate of 54%, considerably lower than that derived by crude analysis. The literature contains several other obvious examples of this bias [27, 31], and we suspect that many other studies presenting no data on age have been similarly affected.

Relation Between Serology and Protection

A serologic marker correlating strongly with protection would be useful for the measurement and monitoring of the efficacy of pertussis vaccines. Early investigations measured only agglutinin responses [71, 77, 83–85], but more recent studies have examined IgG and IgA responses to other specific components of *B. pertussis* [6, 50–52, 86, 87]. In general, seroconversion rates and titers increase with successive doses of vaccine and are higher if the vaccination course is initiated after 3 months of age, presumably because of blocking by maternal antibody in a proportion of younger infants. The implications of these results for protection are not yet clear. High agglutinin titers have been shown to correlate with protection in several studies involving the follow-up of children of known serologic status [83, 84, 88]; however, the observation that some children lacking agglutinins failed to contract clinical pertussis after exposure may indicate that the agglutinin response was itself a correlate of other "true" protective antibodies. The randomized controlled trials carried out by the British Medical Research Council in the 1950s included one acellular vaccine, "Pillemer's antigenic fraction," which was shown to provide a high level of protection against disease but to elicit almost no agglutinin response [64]. No recent investigators have succeeded in monitoring the serologic status of sufficient numbers of children to assess the protective implications of specific antibody types. On the other hand, the evidence that acellular vaccines containing few antigens may be protective against pertussis [7] may be a strong indication of which antibodies are important for protection. It may turn out that IgA antibodies to fimbrial hemagglutinin provide the main protection against infection and colonization, whereas IgG antibodies to lymphocytosis-promoting factor provide the main protection against systemic illness. The situation is still unclear.

Table 6. Pertussis vaccine efficacies as estimated by a study of household secondary-attack rates.

Age (y)	No. of cases/total no. of contacts (rate)		Vaccine efficacy (%)
	Vaccinated*	Unvaccinated	
<1	0/0 (. . .)	8/9 (0.89)	. . .
1–5	10/22 (0.45)	5/5 (1.00)	55
6–10	12/37 (0.32)	0/0 (. . .)	. . .
11–20	5/30 (0.17)	1/3 (0.33)	50
Total	27/89 (0.30)	14/17 (0.82)	63†

NOTE. Data are from [30].

* Three to five doses.

† The overall figure of 63% for ages 0–20 y is an overestimate because an increase in the proportion of individuals vaccinated and a decrease in pertussis risk occur simultaneously with age.

Discussion

From this review it is obvious that assessment of the efficacy of pertussis vaccines is by no means simple. The variety of difficulties encountered is such that it is often impossible to assess whether the net effect in any particular study has been to underestimate or to overestimate vaccine efficacy. Few publications have provided sufficient data or have been sufficiently critical in their analyses to allow such an assessment. On the other hand, some authors (e.g.,

Noah [14]) have been sufficiently aware of the problems to shy away from calculating vaccine efficacy and have been content to conclude only that the vaccine was providing statistically significant protection. In this context we admit having been less cautious than some of the original investigators in calculating the efficacy values cited in table 1. We believe that these calculations are justified, however, in that it is not enough merely to conclude that there is some protection—i.e., that a vaccine's efficacy is significantly greater than zero, as judged by statistical criteria. The fact that pertussis vaccine is generally given in combination with diphtheria and tetanus toxoids means a low marginal cost for the pertussis component and may justify the vaccine's use even at relatively low efficacy. However, given the cost of providing any vaccine and the inevitable—if low—risk of adverse effects, one may question whether it is worthwhile for a government to administer a pertussis vaccine whose efficacy against recognizable clinical pertussis is, say, <50% in a general population [89].

Although we have delineated the problems involved in defining protective efficacy and in clarifying that against which the vaccinee is protected (death, severe disease, mild disease, or infection), we hesitate to insist upon one or another criterion. Each has its place. If the objective of a control program is merely to reduce morbidity, then a high rate of coverage with a vaccine protecting only against disease may be considered satisfactory. In contrast, if herd immunity is considered desirable or if eradication of pertussis is contemplated then the concern must be over whether or not the vaccine protects against infection. It might also be useful to consider a third form of protection: that against infectiousness or transmissibility. Insofar as conventional pertussis vaccines appear to be particularly effective in protecting against bacteriologically positive disease, they may indirectly reduce transmission in a population—even if they do not protect against infection per se—by reducing the potential for transmission by those vaccinated individuals who do become infected. We recognize that this argument appears inconsistent with the unchanged periodicity of pertussis epidemics in England and Wales in recent years (see the above discussion, our earlier article [53], and the paper by Anderson and May [54]). Indeed, this is one of the unresolved problems relating to the population effects of pertussis vaccines.

In attempts to assess the efficacy of a vaccine currently in use, it may be useful to look beyond the confines of the data gathered in any particular study. If a vaccine is in widespread use, then we would expect its efficacy to be reflected in regional and national trends in pertussis morbidity. Thus, the dramatic decreases in notified pertussis cases both in the United States [90] and in England and Wales [3, 90] subsequent to the introduction of widespread vaccination have reasonably been cited as evidence of the effectiveness of the vaccines in use. Trends in pertussis-specific mortality may be less convincing evidence of vaccine effects, since the introduction of effective antibiotic therapy corresponded closely in time with the introduction of vaccines [91]. On the other hand, evidence that the efficacy of much of the pertussis vaccine used in England and Wales fell to only 20% during the mid-1960s [24] and then rose to 80% after the change in vaccine composition [17] is inconsistent with the notification trends illustrated in figure 1. Indeed, we suspect that the low efficacy values were in part due to the secondary attack rate methods used to derive the estimates.

In this context it is appropriate to note that several authors have recently recommended use of the household secondary-attack rate method for routine assessment of the efficacy of pertussis vaccines [30, 92, 93]. This approach has numerous methodologic difficulties and has often given estimates of vaccine efficacy lower than those obtained by other methods (P. E. M. Fine, J. A. Clarkson, and E. Miller, unpublished data). In a recent comparison of methods used to assess the efficacy of mumps vaccine, the highest estimates were obtained with the household secondary-attack rate method [61]. The low estimates of pertussis vaccine efficacy obtained by this method may indicate that challenge dose is more important and immunity less "absolute" in bacterial than in viral infections. There is evidence that immunity to some bacterial infections is dose dependent and can be overwhelmed by a sufficiently large challenge [94]—as, perhaps, during pertussis exposure within the intimacy of the home. Whatever the explanation, the relative simplicity of the household secondary-attack rate method should not be taken as a license for its uncritical application and interpretation.

We are impressed that several lines of evidence indicate that immunity to pertussis—in particular, the immunity derived through vaccination with killed whole-cell vaccines—is neither permanent nor sterile (i.e., protective against infection per se). It is unlike the immunity provided by live-virus vaccines, such as those for measles, mumps, or rubella. Con-

ventional pertussis vaccines appear to raise titers of IgG but not those of IgA, to protect against disease to a greater extent than against infection, to protect against low but not high levels of challenge, and to decrease in protective efficacy with time (as predicted by the model of relative but not absolute protection) [45]. All of these are attributes that those investigating the properties of new acellular vaccines would do well to keep in mind.

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Appendix

The effect of nonspecific (false-positive) diagnoses upon observed vaccine efficacy, as illustrated in figure 2, is derived below. If one assumes that x = the true incidence rate of pertussis in unvaccinated individuals, that y = the incidence rate of some other condition (or clinical form of a condition) that is mistaken for pertussis and that occurs with equal frequency among vaccinated and unvaccinated individuals, that E_t = the true efficacy of vaccine against pertussis, and that E_o = the observed efficacy of vaccine against pertussis, then

$$E_o = \frac{(x + y - xy) - (x(1 - E_t) + y - x(1 - E_t)\, y)}{(x + y - xy)}$$

$$= E_t \frac{x - xy}{x + y - xy} .$$

But the second-order term xy is in general trivially small, and thus

$$E_o \approx E_t \left(\frac{x}{x + y}\right),$$

which is the relation shown in figure 2. This argument assumes that all true cases are ascertained. If this assumption does not hold, then the observed vaccine efficacy is reduced even further [95].