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Effects of pertussis vaccination on transmission: vaccine efficacy for infectiousness

Marie-Pierre Préziosi [a,b,*], M. Elizabeth Halloran [b]

[a] *Niakhar Project, Institut de Recherche pour le Développement, Dakar, Senegal*
[b] *Department of Biostatistics, Rollins School of Public Health, Emory University, 1518 Clifton Road NE, Atlanta, GA 30322, USA*

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Abstract

We estimated the effect of pertussis vaccination on reducing transmission from vaccinated breakthrough cases from a comprehensive follow-up of a community of 30,000 residents in Niakhar, Senegal. Using a wide spectrum of case definitions, vaccine efficacy was estimated as 1 − the ratio of secondary attack rates (SAR) in all households with cases during the calendar year 1993, a pertussis epidemic year. Vaccine efficacy for infectiousness (VEi) was 85% (95% confidence interval (CI), 46–95%) for children vaccinated with three doses of a whole-cell (WC; 94%) or an acellullar (6%) pertussis vaccine, with pertussis defined as a cough ≥21 days with paroxysms confirmed by culture, serology, or contact with a culture-confirmed person. It was high for all case definitions. Partial vaccination reduced infectiousness. Pertussis vaccination is highly effective in reducing transmission from vaccinated breakthrough cases.

Keywords: Whooping cough; Pertussis vaccine; Disease transmission

1. Introduction

Pertussis incidence continues to increase in infants, adolescents, and adults in the United States and in other developed countries [1,2]. In the developing world, millions of cases occur annually [3]. A better understanding of transmission of the disease is needed to define and to promote vaccination policy [1–4].

Whether vaccination reduces transmission of *Bordetella pertussis* is a critical and long-debated issue. Vaccination had been thought not to alter circulation of the bacteria in the population, because the interepidemic period of whooping cough did not appear to vary with level of vaccine uptake [5]. Analyses of more extensive datasets provided evidence that the dynamic behavior of pertussis had changed after widespread vaccination, with synchronization of epidemics and an increased interepidemic period [6]. These latter results support the conclusion that pertussis vaccination decreases circulation of the bacteria.

Recent studies suggest that pertussis vaccination reduces transmission. Disease incidence in infants too young to be protected directly by vaccination decreased as population vaccine coverage rose [7–9]. In a large randomized vaccine trial, incidence of pertussis in parents and younger siblings of vaccinated children was lower than in parents and siblings of unvaccinated children [10]. However, no studies have estimated the efficacy of vaccination in reducing transmission from vaccinated compared with unvaccinated cases. We have analyzed data from a population with active surveillance of pertussis to estimate the efficacy of pertussis vaccination both in reducing infectiousness of vaccinated breakthrough cases (VEi) and in protecting vaccinated susceptibles (VEs) as measured by the reduction of person-to-person transmission [11,12].

2. Methods

Active population surveillance has been conducted since 1983 in Niakhar, a sub-Saharan rural community of 30 villages. The community is very homogeneous, composed of Sereer peasant families, living in compounds, the residential unit for extended families. As part of many research components [13,14], pertussis has been under prospective and active surveillance, and pertussis vaccine studies were conducted in the 1990s in accordance with the Helsinki Declaration [15,16]. As a result, for each child, information was

* Corresponding author. Tel.: +1-404-712-0804; fax: +1-404-727-1370.
E-mail address: mprezio@sph.emory.edu (M.-P. Préziosi).

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available not only on pertussis illnesses and vaccinations but also on contacts, permitting an analysis examining the effect of pertussis vaccination on transmission.

As previously described [9,16], pertussis was endemic, with epidemics every 3–4 years. Trained and supervised field workers used structured questionnaires to report cases on an annual basis. In 1988, they started to report potential cases weekly to experienced physicians who assessed each illness. In addition, during pertussis vaccine trials 1990–1996, physicians collected biological samples from consenting suspected cases in the entire population, defined as having a cough lasting 8 days or more. Nasopharyngeal aspirates were drawn to isolate *B. pertussis* (*Bp*) or *Bordetella parapertussis* (*Bpp*) and to detect *Bp* DNA via polymerase chain reaction (PCR). Blood samples (S), acute (S1) and convalescent (S2) sera, were drawn to measure IgG titers to PT or FHA by enzyme-linked immunosorbent assay (ELISA) [16,17]. Erythromycin chemoprophylaxis was not used except for young infants (under age 6 months) living in the same compound with a suspected pertussis case.

Before introduction of the Expanded Program on Immunization (EPI) in 1987, pertussis vaccine coverage was below 10% [9]. Thereafter, infants received the following pertussis vaccines: diphtheria and tetanus toxoid-whole-cell (WC) or acellular (AC) pertussis vaccine-inactivated poliomyelitis vaccine (DTP_{wc}-IPV; Tetracoq, or DTP_{ac}-IPV; Tetravac, Aventis Pasteur, Lyon, France) [14,16]. The benefits of vaccines are highly regarded within the community and refusals of vaccination did not exceed 5% of all children eligible for EPI [15]. As a result, the population vaccine coverage rose steadily to reach 77 and 19% in 1993, among children under 5 and 5–14 years of age, respectively [9]. All vaccine doses were documented and extensive checks were performed [9,16].

2.1. Eligibility of transmission units, cases, and contacts

The transmission unit was the compound, within which it was assumed that susceptibles were exposed to infection by the first case in the unit. The compound is the "home", the residential unit where individuals make privileged contacts and where random mixing is a reasonable assumption. Any compound with onset of suspected pertussis cases in 1993 was included. We focused on the calendar year 1993, a pertussis epidemic year, to better achieve homogeneity in exposure, case detection and ascertainment, and availability of diagnostic tools. All children less than 15 years old were actively surveyed. Older residents were included only if they became suspected cases. The first case in the unit is the primary or index case. A potentially infectious contact was defined as living in the same compound during the period of infectiousness of the index case. Assuming a minimum duration of 6 days for the incubation period [18], a case was a co-primary if its onset of cough was <7 days of that of the first or index case. Thus, eligible contacts were all children under 15 years of age present in the compound not defined as index or co-primary cases. In addition, they had to have no previous history of pertussis to be included in the main analysis. To allow for uncertainty in duration of both infectiousness and incubation periods, a secondary case was defined as a suspected case whose date of onset was ≥ 7 days of that of the index case and less than a variable cut-off period, specifically none, 56, 42 or 28 days. Indeed, if one considers infectiousness to be negligible 35 days after the beginning of the symptoms [11] and a maximum period of incubation of 21 days [18], secondary cases could occur until $35 + 21 = 56$ days after the date of onset of the index case. In our setting, 90% of the suspected secondary cases in 1993 occurred within 56 days of the date of onset of the first case in their unit.

Compounds were excluded from further analysis if there were no eligible contacts or suspected co-primary cases were present. For each case definition, a compound was selected into the main analysis if the index case satisfied that case definition. Contacts were considered cases only if they also met that same case definition. To assess solely the effect of variation in the index case definition (i.e. the exposure) and to obtain estimates when data were sparse due to restrictions of the case definition, a second analysis was performed, where only the case definition of the index case varied and all the contacts who met the key case definition were considered cases. A dose of vaccine was taken into account 28 days after its administration. Children were classified as unvaccinated (0 dose), partially vaccinated (1 or 2 doses), fully vaccinated (3 doses). For the main analysis, only compounds with an unvaccinated or a fully vaccinated index case were selected, and only contacts with 0 or 3 doses were considered.

2.2. Case definition

A spectrum of case definitions was used to assess the validity of the results, as pertussis vaccine efficacy can vary with the definition used [16,19–23]. Each definition had two components as outlined in Table 1. Combining the five clinical and eight laboratory criteria yielded 40 case definitions, including the WHO 1991 case definition [24]. A *key* case definition, indicated in Table 1, was similar to the latter, except that it included for the laboratory component, serology decreases in addition to increases [17]; for the clinical component, it required cough with paroxysms instead of continuous paroxysmal cough, as recently recommended [3].

2.3. Statistical analysis

The traditional or non-parametric secondary attack rate (SAR) was estimated as the number of cases in the contacts divided by the number of contacts exposed to an infectious case. The VE measures were estimated as 1 − the ratio of SARs in the relevant comparison groups. Vaccine efficacy for susceptibility (VEs) was defined as the relative reduction in SAR in vaccinated contacts compared to unvaccinated contacts [11]. Vaccine efficacy for infectiousness (VEi) was

Table 1
Pertussis case definition: a combination of two components

A clinical case definition (five syndromes of rising severity)	A laboratory confirmation criterion (eight criteria of rising specificity[a])
1. Cough ≥21 days	1. None
2. Cough ≥ 21 days with paroxysms	2. bacterio+ or sero+ or epilink+ ← key definition
3. Physician's clinical diagnosis	3. Bacterio+ or seroi+ or epilink+
4. Paroxysmal cough ≥21 days	4. Bacterio+ or sero+ or (epilink+ and PCR+)
5. Paroxysmal cough ≥21 days with whoops	5. Bacterio+ or sero+
	6. Bacterio+ or seroi+ or (epilink+ and PCR+)
	7. Bacterio+ or seroi+
	8. Bacterio+

[a] Definitions of the components of the laboratory criteria: bacterio+, *Bp* isolated from nasopharyngeal aspirate; sero+, significant (100% S2/S1) increase or decrease in PT or FHA antibodies; seroi+, significant increase in PT or FHA antibodies; PCR+, PCR positive for *Bp* on aspirate; epilink+, presence of a case bacterio+ within 28 days in the same compound.

defined as the relative reduction in SAR when exposed to vaccinated compared to unvaccinated cases [12]. Total vaccine efficacy (VEt) was defined as the relative reduction in SAR when both the infectious case and the contact are vaccinated compared to if both are unvaccinated [12]. For VEi, one unstratified (for contacts with 0 or 3 doses combined) and two stratified (separately for contacts with 0 or 3 doses) versions were computed. Similarly, for VEs, one unstratified (for index cases with 0 or 3 doses combined) and two stratified estimates (separately for index cases with 0 or 3 doses) were computed. Unless otherwise indicated, results presented are unstratified estimates.

To look at the effect of partial vaccination, we computed VEi for 1, 2 or 3 doses versus 0 dose in the index case, and for all combined vaccine status in the contacts. To assess possible bias resulting from misclassification of susceptibles, analyses were also performed using all exposed children as eligible contacts, regardless of previous history of pertussis.

To take into account possible correlation within compounds, estimates were also obtained by fitting a logistic model to the data using generalized estimating equations and transforming back to the probability (SAR) scale [25]. The model was fit using proc GENMOD in SAS software with an exchangeable working correlation matrix [26]. To obtain appropriate estimates for the confidence intervals, Bias-Corrected and accelerated bootstrap CIs [27] for both methods were computed using 2000 bootstrap samples with compounds as the sampling unit [28]. The bootstrap is a databased simulation method for statistical inference, in which each bootstrap sample is analyzed to obtain a new point estimate. The histogram of the 2000 bootstrap sample estimates approximates the distribution of the estimator. Here, we report the model-based VE estimates.

3. Results

3.1. Population selection

During 1993, physicians identified suspected cases (cough ≥8 days) widespread throughout the study area, including 518 of 1800 compounds, in 28 of the 30 villages. Of the 4629 residents under 15 years of age in the 518 compounds, 27% had participated in the vaccine trials. Of the 518 compounds, 340 (66%) were selected for analysis as follows. Compounds were excluded if there were co-primary cases ($n = 155$, i.e. 30%) or no eligible contacts ($n = 23$, i.e. 4%). Thus, a total population of 3021, 99% under age 15 years, was selected, composed of 340 suspected index cases and 2681 contacts of whom 2006 had no history of pertussis and thus, were eligible for the main analysis. Among the latter, 41% (814) became suspected secondary cases.

Index cases in 152/340 compounds (45%) met the key case definition. Among those, 110 index cases (72%) had 0 or 3 doses, and finally 109 compounds with at least one contact with 0 or 3 doses were eligible (Table 2). The overall SAR for the key definition was SAR = (20 + 134)/(194 + 444) = 24%, and SAR = (6 + 93)/(194 + 444) = 16%, using no or a 28-day cut-off period for secondary cases, respectively. Data were too sparse to stratify by vaccine type. Only 7 (6%) index cases and 126 (20%) susceptibles had received an acellular vaccine.

Table 2
Pertussis vaccine efficacy for infectiousness using the key case definition: cough ≥21 days with paroxysms and bacterio+ or sero+ or epilink+[a]

Population selected for analysis			Pertussis vaccine efficacy for infectiousness (VEi %) (95% CI)[b]
Compounds	109		
Index cases 3 or 0 doses	30	79	
Contacts exposed to 3 or 0 doses	194	144	
Cases exposed to 3 or 0 doses			
With no cut-off period[c]	20	134	67 (20–85)
With a 28-day cut-off period[c]	6	93	85 (46–95)

[a] bacterio+, *Bp* isolated from nasopharyngeal aspirate; sero+, significant (100% S2/S1) increase or decrease in PT or FHA antibodies; epilink+, presence of a case bacterio+ within 28 days in the same compound.

[b] CI, confidence interval (bootstrap method: Bias-Corrected and accelerated).

[c] Cut-off: criterion for determining secondary cases, interval between onset of the index case and the secondary cases in the compound.

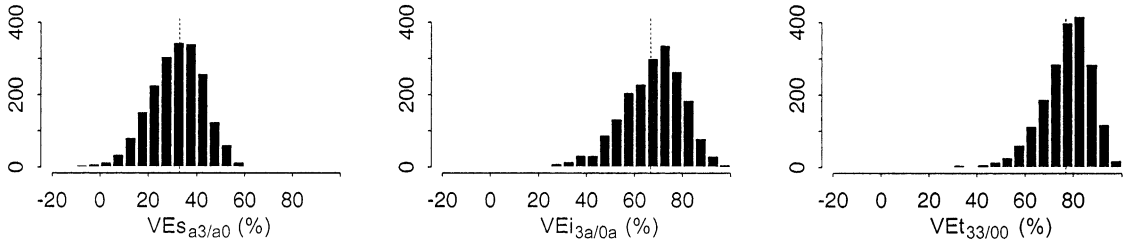

Fig. 1. Histograms of 2000 bootstrap estimates of vaccine efficacies for pertussis: for susceptibility (VEs), infectiousness (VEi), and total (VEt). Vaccine efficacy parameters are computed as 100 × (1 − model-based SAR ratio). The following SARs are used in the VE estimates: for $VEs_{a3/a0}$, a3 = all (0 and 3 doses) index cases to 3 doses contacts and a0 = all-to-0 doses; for $VEi_{3a/0a}$, 3a = 3 doses to all and 0a = 0 doses-to-all; and for $VEt_{33/00}$, 33 = 3-to-3 doses and 00 = 0-to-0 doses. The point estimate from the data is at the dotted line. All cases meet the key case definition with no cut-off.

3.2. Vaccine effects on person-to-person transmission

VEi was significantly very high for the key definition: 85% (95% CI: 46–95%) with a 28-day cut-off and 67% (95% CI: 20–85%) for no cut-off period for secondary cases, respectively (Table 2). Histograms of the 2000 bootstrap estimates of VEs, VEi, and VEt were plotted for the key case definition with no cut-off period for secondary cases (Fig. 1). The unstratified VEs point estimates were 33 and 34%, with no or a 28-day (not shown) cut-off period for secondary cases, respectively. The unstratified VEi point estimate was high (67%), and all bootstrap estimates were well above 0. The VEt point estimates were 77 and 89%, with no or a 28-day (not shown) cut-off period for secondary cases, respectively.

In the 152 compounds with index cases meeting the key case definition, 79 (52%), 25 (16%), 17 (11%) and 31 (20%) index cases had received 0, 1, 2, and 3 doses, respectively. The estimated VEi was −47% (95% CI: −128–23%), 48% (95% CI: 3–76%) and 83% (95% CI: 50–93%) for 1, 2, and 3 doses, respectively, with a 28-day cut-off period for secondary cases.

3.3. Distributions of gender and age

No effect of gender on vaccine efficacy was found. As previously reported [9], the SAR was slightly higher among females: 27.4% versus 20.4%, relative risk of 1.34 (95% CI: 1.01–1.78) for the key definition. Males were more frequent among index cases (59%), but the SARs were identical in those exposed to either gender (24%).

The age distribution of cases and contacts appears in Table 3, with the time since vaccination. Among index cases, the median age was 10 and 4 years for 0 and 3 doses, respectively (Table 3), 7 and 6 years for 1 and 2 doses, respectively. No model-based estimates and confidence limits adjusting for age could be computed due to collinearity of age and vaccine status, and sparse data. However, non-parametric VEi point estimates were still high when stratifying on age of the index case: VEi = $100 \times (1 - \{(2/82)/(5/31)\}) = 85\%$ for <4 years versus VEi = $100 \times (1 - \{(18/112)/(129/413)\}) = 49\%$ for ≥4 years of age.

3.4. Sensitivity analysis

For each of the 40 case definitions, the number of eligible compounds differed (Table 4). Numbers decrease moving right (rising biological specificity) or down (rising clinical severity) in Table 4. The maximum number of compounds included was 246, the minimum 22.

The VEi estimate corresponding to each selected population in Table 4 appears with its 95% confidence limits in Table 5.

VEi point estimates were high for each case definition. However, due to small numbers in the more restrictive categories, the precision of some estimates could not be computed accurately. Indeed, point estimates were 100 in some of them since there were no secondary cases with 3 doses meeting these definitions (lower right corner of Tables 4 and 5). High point estimates were still obtained in the second analysis (using the key definition for all secondary cases), though confidence limits could still not be properly computed. VEi rose as the cut-off period for secondary cases became shorter from none to 28 days (Table 5). Results

Table 3
Age and time since vaccination among cases and contacts

Cases and contacts	No.	Age (years)		Time since vaccination (years)	
		Median	Q1–Q3	Median	Q1–Q3
Total cases[a]					
0 dose	189	8.9	6.1–10.6		
3 doses	126	4.0	2.3–4.9	3.3	1.8–3.9
Index cases[a]					
0 dose	79	9.7	7.8–11.7		
3 doses	31	4.2	3.7–5.6	3.4	3.2–4.7
Secondary cases[a]					
0 dose	110	7.4	4.1–10.0		
3 doses	95	3.8	2.1–4.7	3.0	1.6–3.8
Non-cases[b]					
0 dose	226	7.0	2.3–10.7		
3 doses	379	2.9	1.7–4.5	2.3	1.0–3.5

Q1–Q3, first and third quartiles.
[a] Meeting the key case definition.
[b] Contacts not meeting the key case definition.

Table 4
Population selected for analysis: number of compounds, cases, and contacts for each case definition

Compounds, cases and contacts per clinical case definition	Cut-off[a] (days)	Laboratory confirmation criterion													
		None		Bacterio or sero or epilink		Bacterio or seroi or epilink		Bacterio or sero or epilink and PCR		Bacterio or sero		Bacterio or seroi or epilink and PCR		Bacterio or seroi		Bacterio	
≥21 days of cough																	
Compounds		246		142		109		130		120		93		82		51	
Index cases 3 or 0 doses		84	162	41	101	28	81	38	92	36	84	24	69	21	61	16	35
Contacts exposed to 3 or 0 doses		463	792	234	533	174	432	212	459	177	400	150	343	114	284	98	147
Cases exposed to 3 or 0 doses	None	121	381	73	256	64	217	39	170	35	136	17	106	10	66	5	19
	28	77	230	41	170	37	145	24	118	20	91	9	79	2	45	0	13
≥21 days of cough with paroxysms																	
Compounds		152		*109*		89		101		93		78		69		44	
Index cases 3 or 0 doses		42	110	*30*	*79*	21	68	29	72	28	65	20	58	18	51	13	31
Contacts exposed to 3 or 0 doses		256	563	*194*	*444*	148	381	177	381	145	324	131	303	98	246	82	135
Cases exposed to 3 or 0 doses	None	22	163	*20*	*134*	19	121	10	95	10	75	7	65	7	40	4	11
	28	8	111	*6*	*93*	5	83	2	68	2	50	1	49	1	27	0	7
Physician's clinical diagnosis																	
Compounds		137		109		89		100		92		76		67		42	
Index cases 3 or 0 doses		32	105	28	81	20	69	27	73	26	66	18	58	16	51	11	31
Contacts exposed to 3 or 0 doses		204	524	186	445	145	378	169	379	137	322	126	297	93	240	77	129
Cases exposed to 3 or 0 doses	None	15	142	15	120	14	109	9	84	9	66	6	59	6	36	4	10
	28	4	100	4	87	3	79	2	63	2	48	0	46	0	27	0	7
≥21 days of paroxysmal cough																	
Compounds		105		86		73		81		75		66		59		36	
Index cases 3 or 0 doses		23	82	19	67	15	58	18	63	17	58	14	52	12	47	7	29
Contacts exposed to 3 or 0 doses		158	409	141	354	111	299	124	310	92	268	94	243	61	201	45	107
Cases exposed to 3 or 0 doses	None	5	74	5	65	5	57	0	50	0	42	0	35	0	23	0	7
	28	3	57	3	53	3	47	0	42	0	34	0	30	0	18	0	6
≥21 days of paroxysmal cough with whoops																	
Compounds		58		33		44		48		44		38		34		22	
Index cases 3 or 0 doses		12	46	11	12	8	36	10	38	9	35	7	31	6	28	5	17
Contacts exposed to 3 or 0 doses		111	251	106	235	84	200	89	191	57	173	67	148	35	130	33	67
Cases exposed to 3 or 0 doses	None	4	28	4	25	4	21	0	18	0	16	0	13	0	10	0	2
	28	2	20	2	20	2	17	0	15	0	13	0	11	0	8	0	2

The key case definition is shown with italic values. Bacterio, *Bordetella pertussis* (*Bp*) isolated from naso-pharyngeal aspirate; sero, significant increase or decrease in PT or FHA antibodies (100% S2/S1); seroi, significant increase in PT or FHA; epilink, presence of a case bacterio+ within 28 days in the same compound; PCR, positive on aspirate for *Bp*.

[a] Cut-off: criterion for determining secondary cases, interval between onset of the index case and the secondary cases in the compound.

Table 5
Pertussis vaccine efficacy for infectiousness (VEi) per case definition, ordered by rising severity and specificity

Clinical case definition	Cut-off[a] (days)	Laboratory confirmation criterion							
		None	Bacterio or sero or epilink	Bacterio or seroi or epilink	Bacterio or sero or epilink and PCR	Bacterio or sero	Bacterio or seroi or epilink and PCR	Bacterio or seroi	Bacterio
≥21 days of cough	None	44 (21–59)	33 (−2 to 57)	22 (−20 to 55)	43 (6–68)	36 (−12 to 64)	59 (8–84)	65 (−13 to 89)	66 (−4 to 95)
	28	39 (11–60)	40 (−6 to 65)	30	47	40	69	87	100/81[b]
≥21 days of cough with paroxysms	None	71 (39–88)	*67* (*20–85*)	58 (7–84)	75 (26–91)	71 (20–88)	70 (−1 to 90)	56 (−44 to 85)	39 (−109 to 80)
	28	83 (43–95)	*85* (*46–95*)	84 (33–95)	92[c]	90[c]	91[c]	87[c]	100/92[b,c]
Physician's clinical diagnosis	None	72 (40–88)	68 (28–85)	63 (17–85)	72 (34–89)	68 (23–87)	74 (13–93)	61 (−57 to 88)	31[c]
	28	89 (72–97)	88 (69–97)	89	90	88	100/88[b]	100/84[b]	100/92[b]
≥21 days of paroxysmal cough	None	90[c]	87[c]	84[c]	100/76[b,c]	100/71[b,c]	100/68[b,c]	100/60[b,c]	100/53[b,c]
	28	91[c]	90[c]	87[a]	100/93[b,a]	100/91[b,a]	100/91[b,a]	100/86[b,a]	100/100[b,a]
≥21 days of paroxysmal cough with whoops	None	72[c]	67[c]	54[c]	100/88[b,c]	100/83[b,c]	100/83[b,c]	100/74[b,c]	100/87[b,c]
	28	78[c]	78[c]	72	100/91[b]	100/87[b]	100/88[b]	100/78[b]	100/100[b]

The key case definition is shown with italic values. Estimates are VEi % (95% CI). VEi, vaccine efficacy for infectiousness; CI, confidence interval (bootstrap method: Bias-Corrected and accelerated); bacterio, *Bordetella pertussis* (*Bp*) isolated from naso-pharyngeal aspirate; sero, significant increase or decrease in PT or FHA antibodies (100% S2/S1); seroi, significant increase in PT or FHA; epilink, presence of a case bacterio+ within 28 days in the same compound; PCR, positive on aspirate for *Bp*.

[a] Cut-off: criterion for determining secondary cases, interval between onset of the index case and the secondary cases in the compound.

[b] Second analysis: estimate computed with the key case definition as the definition for all secondary cases.

[c] 95% CI was not included because >5% of bootstrap samples failed to converge.

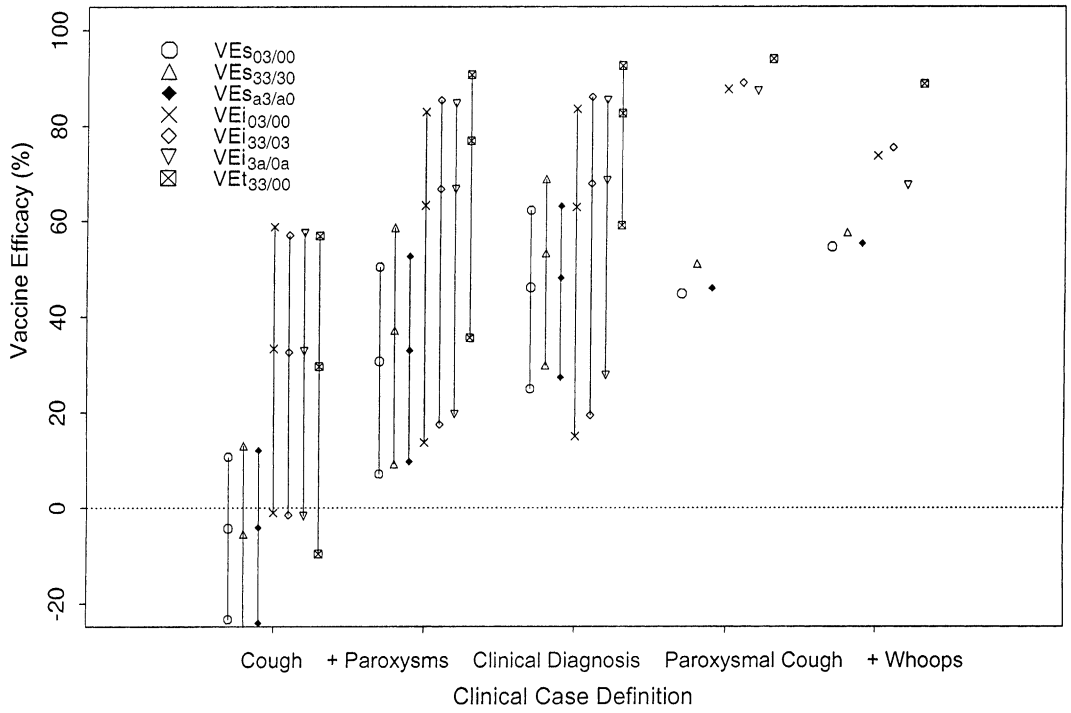

Fig. 2. Vaccine efficacies for pertussis per case definition in rising order of clinical severity. The model-based point estimates are plotted with their 95% confidence interval (bootstrap method: Bias-Corrected and accelerated). The bootstrap confidence intervals are not included if ≥5% of the sampled estimates did not converge. VEs, VEi, and VEt denote vaccine efficacy for susceptibility, infectiousness, and total, respectively. VE measures are subscripted with the SAR subscripts that went into their estimation. For instance, $VEi_{33/03} = 1 - SAR_{33}/SAR_{03}$. Ordered subscript pairs in the SAR indicate the vaccine status of the index case, and that of the contacts: 0 dose, or 3 doses, or all (0 and 3 doses), respectively. For example, SAR_{03} indicates the SAR from an unvaccinated case to a vaccinated contact with three doses of vaccine. An "a" for "all" in a subscript indicates that either the index cases or the contacts were not stratified by vaccine status. All cases meet the key laboratory confirmation criterion (i.e. bacterio+ or sero+ or epilink+) and the indicated clinical case definition with no cut-off period for secondary cases (i.e. successively: cough ≥21 days, cough ≥21 days with paroxysms, physician's clinical diagnosis, paroxysmal cough ≥21 days, and paroxysmal cough ≥21 days with whoops).

with intermediate cut-off values (56 and 42 days) were consistently between those extremes (not shown). VEi point estimates showed a rising trend with clinical severity with an initial step going from the first relatively non-specific definition to more specific syndromes (Table 5 and Fig. 2). Analyses using all exposed as eligible contacts, regardless of pertussis history, yielded similar results.

Stratified VEi and VEs estimates were nearly the same (Fig. 2). VEs estimates increased with clinical severity (Fig. 2). For example, with the key confirmation criterion and no cut-off period for secondary cases, estimates rose from −4% (95% CI: −24–12%) for "≥21 days of cough" to 33% (95% CI: 10–53%) when "with paroxysms" was required.

4. Discussion

These results provide direct evidence of the high efficacy of pertussis vaccination in reducing infectiousness in children fully vaccinated with three doses. The effect is invariant over a wide spectrum of case definitions and positive even in children vaccinated with two doses. The results explain previous [5,29] and confirm more recent findings [6–10]. In a context where further randomized studies are difficult to consider [16,19–23], this is additional evidence that pertussis vaccination can provide substantial indirect beneficial effects in a population [30,31]. It could be a convincing argument to motivate individuals to get vaccinated [4]. There are plausible biological mechanisms whereby vaccination could reduce transmission. *Bp* has extremely complex, well-adapted mechanisms to modulate virulence expression and invasive properties and to disrupt host functions [32–34]. Vaccination could decrease inherent transmissibility by affecting virulence regulation and host-pathogen interactions.

Estimates of VEs obtained here were consistent, although slightly lower, with those obtained earlier in the same setting with a similar case definition [16]. Indeed, the latter were estimated only from the population of young children included in the clinical efficacy trial whereas here we considered the entire population under age 15, and a waning effect could possibly be at work.

Unvaccinated index cases were older than those with three doses, as expected in any population with a vaccination program targeted at young children. However, VEi estimates remained positive when stratified by age of the index case.

The field study was not specifically designed for our research question and is open to the usual biases in observational studies. Essential among those, ascertainment bias is likely not a critical issue here since surveillance was active, with a low threshold for case detection and participation of experienced physicians. Misclassification biases related to previous or current illness, vaccine status, or exposure could have occurred. To deal with some of these issues and as a sensitivity analysis to test the robustness of the results, we systematically estimated VE using different assumptions: a broad spectrum of case definitions, two definitions of eligible contacts, and four definitions of secondary cases. In addition, in presenting Bias-Corrected and accelerated bootstrap CIs, we chose those with the most conservative lower bound [28].

If these biases were present here, the striking estimates of VEi we obtained would likely be underestimates of the true effect on infectiousness. Indeed, vaccine doses would more likely have been omitted than extra doses recorded, causing underestimation of VEi. There would likely be more omissions of previous illnesses in vaccinated children, leading to overestimation of VEs but with no effect on VEi. Similarly, current disease would likely be under-diagnosed more in vaccinated than in unvaccinated children [35], and bacteriological and serological confirmation are more likely negative in vaccinated than in unvaccinated cases [17,36]. But any omitted vaccinated breakthrough cases are probably either equally or less infectious than diagnosed cases, potentially resulting in an overestimation of VEs, but with no effect or an underestimation of VEi.

Also, one might argue that the effect is on disease, not infection, transmission. Indeed, there could be inapparent or unrecognized infections in either children or adults. The latter, long recognized [37], appear to play an increasing role in pertussis transmission in countries that have been vaccinating for decades [38,39]. Even if we assume that subclinical infections and more cases than diagnosed occurred, observing such a positive VEi would be altogether improbable if vaccination did not alter transmission of infection [28]. Future studies measuring infection are warranted to assess the relation between severity of symptoms and infectiousness and to establish the role of asymptomatic or mild cases in transmission.

In conclusion, vaccinated breakthrough pertussis cases are clearly and consistently less contagious than unvaccinated cases.

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References

[1] Centers for Disease Control and Prevention. Pertussis—United States, 1997–2000. MMWR CDC Surveill Summ 2002;51:73–6.
[2] Campins-Marti M, Cheng HK, Forsyth K, et al. Recommendations are needed for adolescent and adult pertussis immunisation: rationale and strategies for consideration. Vaccine 2001;20:641–6.
[3] World Health Organization, Department of Vaccines and Biologicals. In: Proceedings of the Pertussis Surveillance: A Global Meeting. Geneva, 16–18 October 2000. Geneva: WHO; 2001. p. 1–40.
[4] Orenstein WA. Pertussis in adults: epidemiology, signs, symptoms, and implications for vaccination. Clin Infect Dis 1999;28(Suppl 2): S147–50.
[5] Fine PE, Clarkson JA. The recurrence of whooping cough: possible implications for assessment of vaccine efficacy. Lancet 1982;1: 666–9.
[6] Rohani P, Earn DJ, Grenfell BT. Impact of immunisation on pertussis transmission in England and Wales. Lancet 2000;355:285–6.
[7] Miller E, Gay NJ. Epidemiological determinants of pertussis. Dev Biol Stand 1997;89:15–23.
[8] Taranger J, Trollfors B, Bergfors E, et al. Mass vaccination of children with pertussis toxoid-decreased incidence in both vaccinated and nonvaccinated persons. Clin Infect Dis 2001;33:1004–10.
[9] Preziosi MP, Yam A, Wassilak SG, et al. Epidemiology of pertussis in a West African community before and after introduction of a widespread vaccination program. Am J Epidemiol 2002;155:891–6.
[10] Trollfors B, Taranger J, Lagergard T, et al. Immunization of children with pertussis toxoid decreases spread of pertussis within the family. Pediatr Infect Dis J 1998;17:196–9.
[11] Kendrick PL, Eldering G, Borowski A. A study in active immunization against pertussis. Am J Hyg 1939;29:133–53.
[12] Halloran ME, Struchiner CJ, Longini IM. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. Am J Epidemiol 1997;146:789–803.
[13] Garenne M, Cantrelle P. Three decades of research on population and health: the Orstom experience in rural Senegal, 1962–1991. In: Das Gupta M, Aaby P, Garenne M, Pison G, editors. Prospective community studies in developing countries (International studies in demography). Oxford: Clarendon Press; 1998. p. 233–52.

[14] Aaby P, Samb B, Simondon F, et al. Divergent mortality for male and female recipients of low-titer and high-titer measles vaccines in rural Senegal. Am J Epidemiol 1993;138:746–55.
[15] Preziosi MP, Yam A, Ndiaye M, Simaga A, Simondon F, Wassilak SG. Practical experiences in obtaining informed consent for a vaccine trial in rural Africa. N Engl J Med 1997;336:370–3.
[16] Simondon F, Preziosi MP, Yam A, et al. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. Vaccine 1997;15:1606–12.
[17] Simondon F, Iteman I, Preziosi MP, Yam A, Guiso N. Evaluation of an immunoglobulin G enzyme-linked immunosorbent assay for pertussis toxin and filamentous hemagglutinin in diagnosis of pertussis in Senegal. Clin Diagn Lab Immunol 1998;5:130–4.
[18] Benenson AS. Pertussis, Parapertussis (whooping cough). In: Benenson AS, editor. Control of communicable diseases manual. 16th ed. Washington: American Public Health Association; 1995. p. 347–51.
[19] Trollfors B, Taranger J, Lagergard T, et al. A placebo-controlled trial of a pertussis-toxoid vaccine. N Engl J Med 1995;333:1045–50.
[20] Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. N Engl J Med 1996;334:341–8.
[21] Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med 1996;334:349–55.
[22] Schmitt HJ, von Konig CH, Neiss A, et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. JAMA 1996;275:37–41.
[23] Stehr K, Cherry JD, Heininger U, et al. A comparative efficacy trial in Germany in infants who received either the lederle/takeda acellular pertussis component DTP (DTaP) vaccine, the lederle whole-cell component DTP vaccine, or DT vaccine. Pediatrics 1998;101:1–11.
[24] WHO, Division of Communicable Diseases. In: Proceedings of the WHO Meeting on Case Definition of Pertussis. Geneva, 10–11 January 1991. Geneva: WHO; 1991. p. 1–40.
[25] Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika 1986;73:13–22.
[26] SAS Institute. I. SAS Software Version 8.1 for the Unix operating system (SunOS). Cary (NC): SAS Institute Inc.; 1999.
[27] Efron B, Tibshirani RJ. An introduction to the bootstrap. New York: Chapman & Hall; 1993.
[28] Halloran ME, Preziosi MP, Chu H. Estimating vaccine efficacy from secondary attack rates. JASA 2003 [in press].
[29] Fine PE, Clarkson JA. Reflections on the efficacy of pertussis vaccines. Rev Infect Dis 1987;9:866–83.
[30] Cherry JD. Acellular pertussis vaccines—a solution to the pertussis problem. J Infect Dis 1993;168:21–4.
[31] Schneerson R, Robbins JB, Taranger J, Lagergard T, Trollfors B. A toxoid vaccine for pertussis as well as diphtheria? Lessons to be relearned. Lancet 1996;348:1289–92.
[32] Parton R. Review of the biology of *Bordetella pertussis*. Biologicals 1999;27:71–6.
[33] Bassinet L, Gueirard P, Maitre B, Housset B, Gounon P, Guiso N. Role of adhesions and toxins in invasion of human tracheal epithelial cells by *Bordetella pertussis*. Infect Immunol 2000;68:1934–41.
[34] Diehn M, Relman DA. Comparing functional genomic datasets: lessons from DNA microarray analyses of host-pathogen interactions. Curr Opin Microbiol 2001;4:95–101.
[35] Cherry JD, Heininger U, Stehr K, Christenson P. The effect of investigator compliance (observer bias) on calculated efficacy in a pertussis vaccine trial. Pediatrics 1998;102:909–12.
[36] Hallander HO. Microbiological and serological diagnosis of pertussis. Clin Infect Dis 1999;28(Suppl 2):S99–S106.
[37] Cherry JD. Pertussis in the preantibiotic and prevaccine era, with emphasis on adult pertussis. Clin Infect Dis 1999;28(Suppl 2):S107–11.
[38] Nelson JD. The changing epidemiology of pertussis in young infants. The role of adults as reservoirs of infection. Am J Dis Child 1978;132:371–3.
[39] Wirsing VKC, Postels-Multani S, Bock HL, Schmitt HJ. Pertussis in adults: frequency of transmission after household exposure. Lancet 1995;346:1326–9.