

The Effect of Investigator Compliance (Observer Bias) on Calculated Efficacy in a Pertussis Vaccine Trial

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ABSTRACT. *Background.* In the course of a large pertussis vaccine efficacy trial we realized that investigator compliance could have a major impact on calculated vaccine efficacy.

Design. In our pertussis vaccine efficacy trial, the study investigators were to monitor illness in study families by telephone every 2 weeks. If a cough illness of ≥ 7 days duration was noted, the study child was to be evaluated. If the cough illness persisted for ≥ 14 days, the child was to be referred to a central investigator. For this report we analyzed study physician evaluation rates and rates of referral to the central investigators. Physician practices were separated into three compliance categories: high, intermediate, and low. We analyzed vaccine efficacy of an acellular pertussis component DTP vaccine (DTaP) and a whole cell pertussis component DTP vaccine (DTP) by compliance category. *Bordetella pertussis* infection was documented by culture of the organism in the study child or in a household contact or by a significant antibody response to pertussis toxin determined by enzyme-linked immunosorbent assay.

Results. Using a clinical case definition that included both mild and typical pertussis (cough illness ≥ 7 days duration) efficacy of DTaP vaccine was 40% (95% confidence interval [CI] = -3-65) in the high compliance category and 78% (95% CI = 65-86) and 75% (95% CI = 53-87) in the intermediate and low compliance groups, respectively. Similar, but less marked, differences in efficacy were noted with DTP vaccine recipients. Using a clinical case definition that required ≥ 21 days of cough with paroxysms, whoop, or vomiting (typical pertussis) the efficacy of DTaP vaccine was 69% (95% CI = 41-83) in the high compliance category and 86% (95% CI = 76-92) and 84% (95% CI = 64-93) in the intermediate and low compliance groups, respectively. In contrast, the efficacy of DTP vaccine did not vary by compliance category using this case definition. The attack rate in children vaccinated with diphtheria and tetanus toxoids vaccine (DT) was twofold less in low compliance physician practices when compared with the rates in high and intermediate groups. The DT/DTaP and DT/DTP fold-change differences were less in the high compliance group compared with the intermediate and low compliance groups.

Conclusions. Our data suggest that observer compliance (observer bias), can significantly inflate calculated

vaccine efficacy. It is likely that all recently completed efficacy trials have been effected by this type of observer bias and all vaccines have considerably less efficacy against mild disease than published data suggest. *Pediatrics* 1998;102:909-912; *observer bias, vaccine efficacy, acellular pertussis vaccine, whole cell pertussis vaccine, investigation compliance.*

ABBREVIATIONS. DTP, diphtheria-tetanus toxoids, whole cell pertussis vaccine, adsorbed; DTaP, diphtheria-tetanus toxoids, acellular pertussis vaccine, adsorbed; WHO, World Health Organization; PT, pertussis toxin; DT, diphtheria and tetanus toxoids vaccine; CI, confidence interval.

More than 3 years ago seven efficacy trials involving eight different acellular pertussis component (diphtheria-tetanus toxoids, whole cell pertussis vaccine, adsorbed [DTP] vaccines) (diphtheria-tetanus toxoids, acellular pertussis vaccine, adsorbed [DTaP] vaccines) were completed and the results of these trials have been published.¹⁻⁷ The eight vaccines in these seven trials were all different and reported efficacy of the products varied considerably. In preparing for our vaccine efficacy trial,^{1,8} we established a pertussis laboratory in Erlangen, Germany, and to test its functionality we asked physicians to send us nasopharyngeal specimens from children with cough illnesses regardless of whether or not they thought the children had pertussis.⁹ To our surprise many children from whom *Bordetella pertussis* was isolated did not have classic pertussis; specifically 47% coughed for 28 days or less and 26% coughed for 21 days or less. More recently we examined the duration of illness in 1548 culture positive unvaccinated children and found that 17.4% coughed for ≤ 3 weeks and 37.9% coughed for ≤ 4 weeks.¹⁰

In January 1991, an ad hoc World Health Organization (WHO) committee met to plan a universal case definition for the DTaP vaccine efficacy trials in infants that were being planned or were underway.¹¹ The WHO definition was: 21 days of paroxysmal cough plus positive culture or titer rise to pertussis toxin (PT), filamentous hemagglutinin, or fimbrial antigens by enzyme-linked immunosorbent assay or a household contact with a culture confirmed case. Examination of data from a previous Swedish efficacy trial completed more than 10 years ago in which a PT toxoid vaccine and a PT toxoid/filamentous hemagglutinin vaccine were evaluated, indicated that the use of a case definition similar to the WHO definition resulted in the removal of many cases of

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pertussis from the data set.¹² The percentage of cases removed in placebo recipients was similar to that which we would expect from our laboratory study data.^{9,10} Of more interest, however, was the fact that 76% of the cases in children who received the toxoid vaccine in the Swedish trial would be removed, therefore resulting in an inflated efficacy value.¹²

Infants and young children have 3 to 9 respiratory illnesses per year (depending on social factors such as day care) and 14% to 30% of these persist for 10 days or more.^{13,14} In most pertussis vaccine efficacy trials, the trigger for evaluation for possible pertussis is a cough illness of ≥ 7 days. Based on the respiratory illness rates it is apparent that a minimum of 42 children per 100 per year (42%) should be evaluated for possible pertussis. Because the attack rate in pertussis outbreaks of young children is $< 10\%$, it is apparent that many children without pertussis need to be studied to uncover all possible cases of pertussis.^{1,4-6}

Because of these facts, we hypothesized that observer compliance (observer bias) could markedly effect the results of all pertussis vaccine efficacy trials including those with double-blinding. Specifically, a less efficacious vaccine that prevents typical disease, but not mild disease, could be determined to be more efficacious than it is if the study personnel have a preconceived opinion as to what clinical pertussis is. This could lead to an a priori dismissal of mild cases as being other respiratory illnesses, and therefore, cultures and acute-phase sera not obtained or not obtained at the appropriate time and proper follow-up not performed. In this report, we examine the effect of study physician compliance, as a marker of observer bias, on efficacy in our cohort trial in Germany.

METHODS

The methods relating to the details of our efficacy trial have been presented in detail elsewhere.¹² Our trial was a longitudinal cohort, vaccine efficacy trial in which infants were vaccinated with the Lederle/Takeda acellular pertussis component DTP vaccine (DTaP), Lederle whole cell component DTP vaccine (DTP), or diphtheria and tetanus toxoids vaccine (DT).

The study was performed in 227 sites that were mainly pediatric office practices. From May 1991 through January 1993, healthy 2- to 4-month-old infants received a first dose of either DTaP or DTP in a double-blind, randomized manner or DT vaccine in an open arm of the trial after informed consent had been obtained from a parent. Second and third doses of DTaP and DTP were given at least 6 weeks after the preceding dose and the fourth dose at 15 to 18 months of age. DT recipients received a second dose at least 6 weeks after the first dose and the third dose at 15 to 18 months of age. The follow-up period ended December 15, 1994.

All cough illnesses in a vaccinee or a household member were to be reported by the parents to the study physicians. In addition, all study families were to be telephoned by the individual study physicians or their office personnel every 2 weeks. If a cough illness of ≥ 7 days duration without improvement was reported in any household member, a nasopharyngeal specimen for culture and an acute blood sample for serology were to be obtained. If the cough illness persisted for ≥ 14 days, the vaccinee or family member was to be seen by one of three central investigators from the central study center.

B pertussis infection was documented by culture of the organism in the study child or in a household contact or by the demonstration of a significant immunoglobulin G and immunoglobulin A antibody response to PT determined by enzyme-linked immunosorbent assay.

For this report we analyzed study physician reporting rates and rates of referral to the central investigators. We considered reporting rates to be an indicator of study physician compliance and a marker of their observer bias. We separated the physician practices into three groups based on their reporting and referral rates. The high compliance group were physician practices in which the reporting rate was ≥ 20 per 100 person years or the referral rate to the central investigators was ≥ 10 per 100 person years. The low compliance group were physician practices in which the reporting rate was < 10 per 100 person years and the referral rate to the central investigators was < 5 per 100 person years. The intermediate compliance group were physician practices that were not identified as either high or low.

RESULTS

Study Evaluation Rates

Overall, 10 271 children were enrolled in the study with 4273 receiving DTaP vaccine, 4259 receiving DTP vaccine, and 1739 receiving DT toxoids. During the follow-up period, 1824 children with cough illnesses were reported and 1245 children were evaluated by a central investigator. During the follow-up period, 22% of DT vaccinees and 17% of DTaP and DTP children were reported with cough illnesses. Rates of reporting per 100 person years by vaccine group were: DT, 13.1; DTaP, 8.4; and DTP, 8.5. Rates of central investigator evaluations per 100 person years by vaccine group were: DT, 9.5; DTaP, 5.7; and DTP, 5.7. The rate of total reports per 100 person years was 9.2 and of central investigator evaluations 6.3. The average reporting rates by high, intermediate, and low compliance groups were 21, 9.8, and 3.2 per 100 person years, respectively, and the central investigator evaluation rates by compliance group were 15, 6.4, and 1.8, respectively.

Because in our trial the DT group was unblinded (because blinding would have been unethical), it is possible that the findings by the evaluation group could be attributable to a specific physician compliance bias because of the unblinded group rather than a general bias because of a preconceived opinion as to what clinical pertussis is. In consideration of this, we looked for a correlation between the cough investigation rate and the percent of DT children in a physician study subject group. No correlation was found ($r = 0.06$).

Vaccine Efficacy by Study Physician Compliance Group

In Table 1, the efficacy of DTaP and DTP vaccines is presented by compliance category. Against laboratory confirmed *B pertussis* infection with cough of ≥ 7 days duration, the efficacy of DTaP was 40% (95% confidence interval [CI] = -3-65) in the high compliance group and 78% (95% CI = 65-86) and 75% (95% CI = 53-87) in the intermediate and low compliance groups, respectively. DTP vaccine efficacy using the same case definition was 73% (95% CI = 48-86) in the high compliance group and 83% (95% CI = 72-89) and 85% (95% CI = 68-93) in the intermediate and low compliance groups, respectively.

DTaP vaccine efficacy against laboratory confirmed typical pertussis was 69% (95% CI = 41-83) in the high compliance group and 17% and 19% higher in the intermediate and low compliance

TABLE 1. Percent Vaccine Efficacy by Investigator Compliance Category Against Mild and Typical and Typical Pertussis Attributable to *B pertussis**

Investigator Compliance Category†	Mild and Typical Pertussis (95% CI)‡		Typical Pertussis (95% CI)§	
	DTaP	DTP	DTaP	DTP
High	40 (3-65)	73 (48-86)	69 (41-83)	90 (75-96)
Intermediate	78 (65-86)	83 (72-89)	86 (76-92)	93 (85-96)
Low	75 (53-87)	85 (68-93)	84 (64-93)	93 (80-98)

Abbreviations: CI, confidence interval; DTaP, diphtheria-tetanus toxoids, acellular pertussis vaccine, adsorbed; DTP, diphtheria-tetanus toxoids, whole cell pertussis vaccine, adsorbed; PT, pertussis toxin.

* Positive *B pertussis* culture in subject or family member or a significant IgA or IgG rise to PT.

† High, reporting rate ≥ 20 per 100 person years or referral rate to central investigators ≥ 10 per 100 person years; low, reporting rate < 10 per 100 person years or referral rate to central investigators < 5 per 100 person years; intermediate, reporting rate or referral rate not identified as either high or low.

‡ ≥ 7 days of cough.

§ ≥ 21 days of cough with paroxysms, whoop, or vomiting.

groups, respectively. In contrast, the calculated efficacy of DTP vaccine against typical pertussis is similar for all three compliance categories (90% vs 93% and 93%).

Attack Rates by Investigator Compliance Category

Attack rates in DT, DTaP, and DTP vaccine recipients are presented by investigator compliance category in Table 2. As can be seen, the attack rate in DT vaccine recipients is ~2-fold less in low-compliance physician practices when compared with the rates in the high and intermediate compliance groups. The DT/DTaP fold-change is 1.66 in the high compliance group and 4.49 and 4.05 in the intermediate and low compliance groups, respectively. Similar differences between the high and intermediate and low compliance groups are noted with respect to DT/DTP. Specifically, the fold-change is 3.66 in the high compliance group and 5.85 and 6.44 in the intermediate and low compliance groups, respectively.

DISCUSSION

It is a general belief that efficacy trials with the most reliable data are those in which a double-blind

TABLE 2. Attack Rates* in DT, DTaP, and DTP Vaccine Recipients by Investigator Compliance Category

Investigator Compliance Category†	Attack Rates‡			DT/DTaP Fold Difference	DT/DTP Fold Difference
	DT	DTaP	DTP		
High	3.40	2.05	0.93	1.66	3.66
Intermediate	4.80	1.07	0.82	4.49	5.85
Low	1.74	0.43	0.27	4.05	6.44

Abbreviations: DT, diphtheria and tetanus toxoid vaccine; DTaP, diphtheria-tetanus toxoids, acellular pertussis vaccine, adsorbed; DTP, diphtheria-tetanus toxoids, whole cell pertussis vaccine, adsorbed.

* Per 100 person years.

† See Table 1.

‡ Case definition = ≥ 7 days cough plus *B pertussis* isolation in study subject or family member or significant IgA or IgG pertussis toxin antibody rise.

format has been followed.¹⁵ However, in two double-blind trials with very similar protocols the efficacy of the same lot of a whole cell DTP vaccine varied by 12% to 18%.^{5,6,16,17} In our efficacy trial in which the DT group was unblinded and was different in regard to several variables from the blinded DTaP/DTP group, we found that corrections for these variations had little or no effect on efficacy.¹

Relatively early in our trial we noted large differences in reporting rates of cough illnesses by study physicians. We recognized this as a physician compliance problem and we tried using our study newsletter and conferences to lessen the problem but without evidence of success. The total reporting rate of 9.2 per 100 person years is > 4 times less than the minimal predicted rate of cough illnesses meeting the criteria for study evaluation.

The efficacy calculations against mild and typical pertussis because of *B pertussis* infection in Table 1 supports our hypothesis except the lack of a linear relationship among the three compliance groups was at first surprising. However, we believe the interpretation is as follows: 1) the high responder physicians followed the protocol better than the other two groups; 2) the intermediate group followed the protocol but because of their bias (they knew pertussis) they were less careful in the work-up of less severe cases that were more likely to occur in DTaP and DTP recipients than in DT recipients; and 3) the low responder group followed the protocol poorly and passively and only worked-up study children when care was sought by the parents. This scenario is supported by the attack rate data in Table 2. The high compliance physicians found more cases in DTaP/DTP recipients than either of the other two groups. The lack of difference in efficacy in the intermediate and low compliance groups is explained by the similar DT/DTaP and DT/DTP fold differences despite the fact that more cases in DTaP and DTP vaccinees were noted in the intermediate group.

In our opinion, the type of observer bias that we have noted in our trial is likely to occur in all trials. Of the seven recent trials, three had limited criteria so that data relating to mild illness were not available^{3,7} or not comparable to our data.² In the other four trials (including our trial), data related to attack rates in DT vaccine recipients using a clinical case definition of cough ≥ 7 days and the typical pertussis definition (≥ 21 days of paroxysmal cough [WHO definition] or ≥ 21 days cough with paroxysms, whoop, or posttussive vomiting [our definition]) can be examined.^{1,4-6,16,17} As pointed out in the "Introduction," we would expect between 17% and 25% more cases in DT recipients when the case definition includes mild illness compared with the typical pertussis definition. When lesser percent differences are noted this would suggest that the study observers knew pertussis and were less likely to appropriately study mild illnesses. In the four trials, the percent of true cases removed with the use of the WHO case definition was: Göteborg, 4%⁴; Stockholm, 13%^{5,16}; Erlangen, 18%¹; and Rome, 20%.⁶ The Göteborg findings suggest considerable observer bias.^{4,17-19}

CONCLUSIONS

In summary, our data suggests that observer bias, (the observer knows pertussis) can significantly inflate efficacy findings and this can occur in blinded, as well as unblinded, trials. This bias can have a major effect on calculated efficacy and be far greater than confounding factors in unblinded studies such as factors relating to differences in DT families and DTP or DTaP families. It is likely that all recently studied DTaP vaccines have considerably less efficacy against mild disease than published data suggest.

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