Frequent symptoms after DTPP vaccinations

Petronella L Verschoor, Jeannette T Wilschut, Guus A de Jonge, Pieter J Kostense

Abstract

A prospective study of minor reactions after the four combined vaccinations for diphtheria, tetanus, pertussis, and poliomyelitis (DTPP) was performed in 540 infants in the Netherlands. An analysis was made of the symptoms observed by the infants' parents after 2026 inoculations. The aim was to assess the frequency, association, and risk of recurrence of minor reactions. These were designated as fever ($\geq 38.0^{\circ}\text{C}$), local reactions, crying, and other general symptoms (changes in sleeping or eating patterns, vomiting, drowsiness, fretfulness). Fever occurred after 67.7% of inoculations, one or more local reactions after 66.2%, and increased crying after 64.4%. After 80% of inoculations, one or more other general symptoms occurred. Only 4.4% of inoculations were followed by no minor reaction. Fever rarely occurred as an isolated symptom; it showed a significant association (i) with one or more local reactions, (ii) with increased crying, and (iii) with two or more other general symptoms. Chances of fever, redness at the inoculation site, and crying after inoculation increased with repeat inoculations if these reactions had occurred after preceding inoculation(s).

Since 1962 infants in the Netherlands have been vaccinated four times intramuscularly with a combined vaccine against diphtheria, tetanus, pertussis, and poliomyelitis (DTPP).¹ Injections are given at a minimum of three, four, five, and 11 months. The vaccine is prepared by the National Institute of Health and Environmental Protection (RIVM, Bilthoven). It contains diphtheria and tetanus toxoids, whole cell pertussis vaccine, and inactivated poliomyelitis vaccine in a medium containing aluminium phosphate. Administration occurs with the parents' permission and mainly at child health centres.

Frequent non-serious symptoms, known as minor reactions, and less common serious symptoms, the so called major reactions, are the undesirable side effects of these vaccinations.^{2,3} This paper reports on a prospective study of symptoms of the first type. It pays particular attention to four categories: fever, local reactions, crying, and other general symptoms within 48 hours after inoculation.

The aim of the study was to answer three questions:

(1) How frequently do minor reactions occur after DTPP vaccinations among healthy infants in the Netherlands?

(2) Is there an association between the different minor reactions that occur?

(3) How great is the risk of recurrence of minor reactions after subsequent DTPP inoculation?

Subjects and methods

STUDY POPULATION

A written request was sent to the parents of infants sequentially born between 1 March 1987 and 1 March 1988 in two medium sized towns (Amstelveen and Amersfoort) to participate in a study of the side effects of the four inoculations of the combined DTPP vaccine. The vaccinations were administered at 15 child health centres by physicians or nurses who knew the details of the study. Only infants who met the following conditions were enrolled into the study: birth weight not less than 2000 g; not suffering from neurological or internal diseases or defects; no fever ($< 38.0^{\circ}\text{C}$) at the time of inoculation; and at least one parent/guardian with adequate knowledge of Dutch.

METHODS

Parents who agreed by reply card to participate (62% of the parents asked) were visited at home by one of the two investigators (PLV, JTW) before the first vaccination. A number of data were collected at the visit (date of birth, birth weight, sex, general health). The observation forms were supplied in quadruplicate. The parents received a digital thermometer (Philips 5312M) and a transparent plastic ruler which measured the diameter of any redness at the injection site. The written information was also explained verbally.

The period of observation for each vaccination was four days, starting from the day before vaccination (day 0), the day of the vaccination (day 1), and the two subsequent days (day 2 and day 3). Day 0 served as a day of reference. Rectal temperature and any redness at the injection site were measured during four timed intervals per day (in the morning before the injection, 0–3 hours after the injection, 3–8 hours after the injection, and depending on the time of injection, in the evening). Further measurements were taken as the child's condition warranted.

On each observation day questions were also asked about the occurrence of swelling and pain at the injection site, about crying, and other general symptoms (changes in sleeping or eating patterns, vomiting, drowsiness, and fretfulness). Finally, data were collected on the time of vaccination, injection site, and use of any drugs.

Department of
Paediatrics,
Free University
Amsterdam

Petronella L Verschoor
Jeannette T Wilschut
Guus A de Jonge

Department of Theory of
Medicine,
Epidemiology and
Biostatistics,
Free University
Amsterdam
Pieter J Kostense

Correspondence to:
Petronella L Verschoor, MD,
van Lennepaan 3,
3818 VE Amersfoort,
The Netherlands.

Accepted 26 July 1991

After completion, the parents returned the observation form in a stamped, addressed envelope. Before DTPP4 the parents were telephoned. They were asked about the child's health and were reminded of their participation in the study.

After the forms were returned, the data were coded and entered into a computer. They were processed and analysed statistically with the use of the BMDP program. The association between minor reactions were tested by the χ^2 test for a 2x2 table and by the χ^2 test for trend in proportions. The risk of recurrence was assessed by multiple logistic regression analysis.

Results

There were 540 infants in the study, and 2026 complete and usable forms were returned (94% of the possible maximum). Four children were inoculated with DTPolio or with half doses of DTPP after a strong reaction to the previous vaccination. These forms have been excluded from the analysis. In 15 cases a fever ($\geq 38.0^{\circ}\text{C}$) was recorded before inoculation. These forms have also been excluded from the analysis. In 15 cases, infants received a measles, mumps, and rubella vaccination with the fourth DTPP vaccination (in different limbs). These forms were not excluded because these two different vaccinations do not interfere with each other. None of the participating children experienced convulsions, collapse, or encephalopathy.

FREQUENCY OF MINOR REACTIONS

One or more minor reactions were recorded by the parents after more than 95% of inoculations. Only 4.4% of inoculations were followed by no observable reaction. Table 1 lists the frequency of minor reactions observed on days 1, 2, and 3 (fever, local reactions, crying, and other general reactions) after each of the four DTPP vaccinations.

Fever $\geq 38.0^{\circ}\text{C}$ occurred after 67.7% of inoculations, high fever $\geq 39.0^{\circ}\text{C}$ after 9.9%, very high fever $\geq 40.0^{\circ}\text{C}$ after 0.6%. A fever of $\geq 40.5^{\circ}\text{C}$ was measured in three cases.

One or more local reactions occurred after 66.2% of vaccinations. A red area with a diameter exceeding 2 cm occurred in 19.3% of cases; after 2.5% of inoculations this red area had a diameter exceeding 8 cm. Redness,

swelling, and pain occurred together after 12.4% of inoculations.

Increased crying occurred after 64.4% of inoculations. In 13% of cases inconsolable crying occurred for more than one hour. After 80% of inoculations, one or more other general symptoms occurred. The most common reaction was a change in sleeping pattern. Excessive sleeping occurred much more frequently than sleep loss. A change in eating pattern generally meant eating less than usual.

Reactions by series number

Reactions were more frequent after the fourth inoculation (DTPP4) than after any of the preceding inoculations (see table 1). Differences in fever and local reactions were most marked. Also, reactions were generally stronger after the fourth inoculation. After DTPP4, 77.4% of children had a rectal temperature of 38.0°C or higher, while this was true for an average of 64.7% after the three preceding inoculations. After DTPP4 a temperature of 39.0°C or higher was measured in 14.8% of the children; after the three preceding inoculations the average was 8.4%.

The fewest reactions generally occurred after DTPP3. It was of note that the time at which local reactions started varied per series number. Later inoculations were followed by a later onset of reactions. After the first inoculation 92.3% of redness reactions started on the day of inoculation (day 1); after the fourth, only 57.2%. To a small degree the same pattern could be seen with swelling and pain.

ONSET AND DURATION OF MINOR REACTIONS

Minor reactions often started on day 1 (day of vaccination) or day 2, and generally disappeared by day 3. If children reacted with fever, it began within 24 hours of the inoculation in more than 91% of cases. If a swelling or a red area (>2 cm) developed at the injection site, more than three quarters of these reactions began on day 1. Pain also began on day 1 in more than 90% of cases. The onset of increased crying was in 82% of cases on day 1; for inconsolable crying lasting more than three hours this percentage was 77.4%. Other general symptoms began on day 1 in more than half of the cases.

The figure demonstrates that the highest percentages of reactions occurred on days 1 and 2. Crying occurred predominantly on day 1. On day 3 minor reactions occurred only in low percentages. For example, fever occurred on that day after 3.2% of inoculations. Inconsolable crying for more than three hours occurred on day 3 only in four cases. A red area (>2 cm) occurred on day 3 after 2.8% of inoculations, swelling after 10.1%, pain after 3.8%.

In some cases reactions persisted until after day 3. In 2.7% of all cases the reaction was fever. In nearly all these cases fever had disappeared within five days of inoculation. After 6.0% of inoculations there was a local reaction which persisted until after day 3. Half of these reactions had disappeared within five days. If not, there was generally a solid lump or

Table 1 Summary of minor reactions after four DTPP vaccinations, in percentages, per inoculation

Minor reactions	DTPP1 (n=536)	DTPP2 (n=523)	DTPP3 (n=501)	DTPP4 (n=466)	Total (n=2026)
Temperature					
38.0-38.9°C	58.4	57.2	53.3	62.7	57.8
≥ 39.0	7.1	9.8	8.3	14.8	9.9
Local reaction					
Redness >2 cm	19.4	16.1	13.0	29.6	19.3
Swelling	31.7	32.7	31.1	44.6	34.8
Pain	56.2	55.8	48.5	73.0	58.0
Crying					
Increased	62.1	67.1	56.9	71.9	64.4
Inconsolable					
1-3 hours	11.8	12.8	8.8	7.7	10.4
≥ 3 hours	2.4	3.2	2.4	2.4	2.6
Other general symptoms					
Sleeping changes	65.7	66.3	59.9	65.5	64.4
Eating changes	35.6	36.3	27.7	46.6	36.4
Vomiting	8.2	10.3	7.4	7.3	8.3
Drowsiness	29.1	30.0	26.5	43.6	32.0
Fretfulness	37.7	41.7	37.5	54.3	42.5

Minor symptoms on the day before DTPP vaccination (day 0), the day of the vaccination (day 1), and the two days after (day 2 and 3); data from 2026 vaccinations.

a haematoma. After 2.4% of inoculations, general symptoms persisted until after day 3.

Day before vaccination

Minor symptoms can also occur without inoculation. In order to get an impression of the frequency of these symptoms on a 'normal' day the parents filled in the questionnaire on the day preceding inoculation (day 0). It should be

noted that day 0 is not a completely arbitrary day. Given the fact that on the next day there were no contraindications to inoculation, the children were probably slightly healthier than on a completely arbitrary day.

In the figure percentages are given per day for all minor symptoms, starting from the day before inoculation. On day 0 all types of general symptoms occurred. However, on the day of inoculation (day 1) these 'reactions' occurred

Table 2 Summary of minor reactions after the fourth DTPP vaccination, per site of injection, in percentages

Minor reactions	Arm (n=213)	Leg (n=247)	p Value*
Temperature			
<38.0°C	18.8	25.1	0.1†
38.0-38.9°C	64.8	61.5	
≥39.0°C	16.4	13.3	
Local			
Redness >2 cm	46.5	15.8	<0.0001
Swelling	49.8	41.3	0.07
Pain	76.5	70.9	0.17
Combination	30.0	13.8	<0.0001
Crying			
Increased	72.3	72.9	0.9
Inconsolable			
1-3 hours	8.9	6.5	>0.5†
≥3 hours	2.3	2.4	
Other general symptoms			
Sleeping changes	66.2	64.4	0.7
Eating changes	46.0	47.0	0.8
Vomiting	6.1	7.7	0.5
Drowsiness	42.3	44.9	0.6
Fretfulness	56.3	53.0	0.5
Combination	3.3	3.2	0.98

* χ^2 test for 2×2 table, with exception of †.

† χ^2 test for linear trend, 1 df.

more frequently: fever 20 times more often, crying 10 times more often, other general symptoms twice to 15 times more often. On day 2 percentages of minor reactions were of the same order as on day 1. Figures show that most symptoms that occurred after a DTPP vaccination must be considered as reactions to the inoculation.

INFLUENCE OF SITE OF INJECTION

Vaccinations were given in the arm, upper leg, or buttock in 12.9%, 85.7%, and 1.3% of all inoculations respectively.

If the inoculation was given in the arm, it was in nearly all cases the fourth one. The fourth inoculation was given 213 times in the arm and 247 times in the leg. Our analysis includes data on whether the choice of the injection site at the fourth inoculation has an influence on the frequency of minor reactions.

Table 2 shows that after inoculation in the arm, redness occurs significantly more frequently than after inoculation in the leg. Also, fever and inconsolable crying occurred more frequently after inoculation in the arm, but these differences were not significant. No difference was observed in other general symptoms after arm and leg inoculations.

INFLUENCE OF SEX

There were 282 boys in the study, for whom 1061 forms were returned, and 258 girls for whom 965 forms were returned. There appeared to be no difference in the occurrence of minor reactions between boys and girls.

ASSOCIATIONS BETWEEN MINOR REACTIONS

The four categories of minor reactions were examined for associations. An association between two different symptoms was considered likely when they occurred more frequently after the same injection than might have been expected on the basis of chance. The association was analysed for each of the four inoculations separately, so that analyses were based on independent observations each time. Associations were considered only if they were assessed for each of the four vaccinations.

Fever seldom occurred as an isolated symptom; it showed a significant association with (i) one or more local reactions, (ii) with increased crying, and (iii) with two or more of the five general symptoms. Of the association between fever and local reactions, only the association between fever and pain at each of the four vaccinations was significant ($p<0.01$). In contrast to increased crying, no association existed between inconsolable crying for an hour or more and fever. Pain and increased crying were strongly related; this applied also to the subgroup of inconsolable crying for at least one hour.

RISK OF RECURRENCE

Chances of fever, redness, and crying after DTPP vaccination increased if these symptoms occurred after preceding inoculation(s). Depending on the series number, chances increased roughly by a factor 1.5 to 3. With high fever ($\geq 39.0^\circ\text{C}$), severe redness (>8 cm), and inconsolable crying for more than one hour, chances of recurrence increased most, by a factor of approximately five.

Discussion

All recorded general symptoms occurred in varying frequency on the day before inoculation. This study shows, however, that the great majority of symptoms that occur after DTPP vaccination must, indeed, be considered as reactions to that inoculation.

Minor reactions occurred frequently. In this study only 4% of all vaccinations were not followed by a reaction within 48 hours. Fever ($\geq 38.0^\circ\text{C}$) occurred after 68% of inoculations, local reactions after 66%, increased crying after 64%, and other general symptoms (including changes in sleeping and eating patterns, and fretfulness) after 80%.

Serious symptoms occurred rarely. After 2026 vaccinations no collapse, convulsion, or other neurological complications occurred. A temperature of $\geq 40.0^\circ\text{C}$ occurred 12 times (0.6%), in three cases $\geq 40.5^\circ\text{C}$. It should be noted, however, that the definitions of serious and non-serious symptoms are still a matter of discussion. This applies particularly to fever and crying. In the USA a temperature of $>40.5^\circ\text{C}$ or persistent screaming for more than three hours was until recently a contraindication to further inoculation with pertussis vaccine.⁴ In the Netherlands these reactions are not considered as contraindications.⁵ In four children with, in total, six changed inoculations, however, the normal vaccination programme was changed as a result of a strong reaction to a previous DTPP. Three children continued to be vaccinated with DTPolio after a strong local reaction (in one child) or high fever $\geq 40.0^\circ\text{C}$ (in two). One child was vaccinated several times with half a dose of DTPP after a strong crying reaction after DTPP1.

In the literature we find a considerable variation in the reported incidence of reactions after DTP(P) vaccinations. Factors relevant to the interpretation of the data include the composition of the vaccine (in the Netherlands

there is only one combined vaccine against diphtheria, tetanus, pertussis, and poliomyelitis), vaccination schedules and ages, series number, definitions of possible reactions, and the manner and frequency of observation.

In our study, a large number of children reacted with fever. In the only other Dutch study, approximately 23% of children experienced a temperature of $\geq 37.5^{\circ}\text{C}$. It should be noted, however, that in that study there were no fixed times of measurement.⁶ In other studies, the percentage of children with a fever of $\geq 38^{\circ}\text{C}$ varies between 46.5%² and 66%.⁷ The percentage of subjects with high fever is also high in our study: 9.9% at $\geq 39.0^{\circ}\text{C}$. In other studies, the figure varies between 3% at $\geq 39.4^{\circ}\text{C}$, 4.2% at $> 38.9^{\circ}\text{C}$,³ and 6.1% at $> 39.0^{\circ}\text{C}$.² Differences in the definition of high fever complicate the comparison of these figures and may partly explain variations.

In our study, paracetamol or aspirin was administered to the child after 11% of vaccinations. These drugs can influence temperature, pain, and associated behavioural reactions. Half of the cases were related to the fourth vaccination. Generally, drugs were administered only after occurrence of a reaction and not prophylactically. Other studies report much higher percentages of drug intake after inoculation. Barkin (Denver, USA) mentions the use of drugs in 65% of cases³ and Long (New York, USA) in 75% of cases.⁷ The less frequent use of antipyretics in our study may partly explain the rather high frequency of fever recorded.

As to local reactions, there are no notable differences between our results and those from others. Cody *et al* found local reactions after 64% of vaccinations,² Barkin and Pichichero after 72%,³ and Swaak after 63%.⁶ Only Long *et al* found a much higher incidence (85%).⁷

DTPP4 inoculations were given both in the arm and the leg; thus it was possible to compare the two injection sites. A remarkable difference was found. Redness, fever, and inconsolable crying for more than an hour occurred more frequently after inoculation in the arm; the difference in redness was significant. It is, therefore, worth considering administering DTPP4 in the leg.

Frequency of local reactions was different between sequential inoculations. After the fourth inoculation local reactions occurred more frequently than after the three preceding inoculations. The difference in redness, however, was caused by the fact that DTPP4 was often given in the arm. There was very little difference in the occurrence of redness between the fourth and the preceding inoculations in children who were vaccinated exclusively in the leg.

Baraff *et al* studied the effect of the injection site for DTPertussis 1, 2, and 3 (primary vaccinations) and compared the anterior mid thigh, the upper lateral thigh, and the buttock.⁸ Local swelling, pain, and fever occurred less frequently after immunisation in the buttock than in the thigh. Persistent crying, however, occurred more frequently after inoculation in the buttock. None of the three injection sites, however, were associated with an

overall lower frequency of reactions. Baraff assumed, therefore, that general reactions are not related to the degree of local reaction. In our study, however, an association was found between fever and pain after each of the four inoculations.

In this study, reactions occurred more frequently after DTPP4 (administered at the age of 11 months in the Netherlands), than after any of the three preceding inoculations. This was found in other studies also.^{2 3 6 7} In our study, these differences were most noticeable for fever and local reactions (table 1). In this regard it may be noted that paracetamol/aspirin was administered more frequently after DTPP4 than after DTPP1, 2, or 3. Inconsolable crying showed a different pattern: this reaction decreased after repeated inoculations.

In a study of 772 children the incidences of fever $\geq 39.0^{\circ}\text{C}$, continuous crying for more than half an hour, and a red area exceeding 2.5 cm were compared with the same reactions after the previous inoculation.⁸ The incidence of these reactions was two to three times higher in children who had experienced a similar reaction after the preceding inoculation; but these differences were not significant except for redness. In our study, the occurrence of high fever ($\geq 39.0^{\circ}\text{C}$), severe redness (> 8 cm), and inconsolable crying for one hour or more increased significantly, approximately by a factor of five, in children with the same symptoms after preceding inoculation(s).

As this study shows that symptoms occur very frequently after DTPP vaccinations, we strongly suggest that the parents of the vaccinees be well informed about the nature, frequency, and risk of recurrence of these predominantly non-serious reactions.

In assessing the importance of minor reactions, they should be measured against the great benefits of these vaccinations. However, because minor reactions occur frequently and tend to cause discomfort, they (as well as major reactions) should be included in the assessment of new DTPP vaccine formulations.

This study was made possible by a grant from the Praeventiefonds (Prevention Fund).

- 1 Wezel AL van, Steenis G van, Hannik CA, Kapsenberg JG, Hofman B, Cohen H. Bereiding en toepassing in Nederland van geïnactiveerd vaccin tegen poliomyelitis anterior acuta (Preparation and administration of inactivated vaccine against anterior acute poliomyelitis in the Netherlands). *Ned Tijdschr Geneesk* 1979;123:466-74.
- 2 Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclark CR. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatrics* 1981;68:650-60.
- 3 Barkin RM, Pichichero ME. Diphtheria-pertussis-tetanus vaccine: reactogenicity of commercial products. *Pediatrics* 1979;63:256-60.
- 4 Advisory Committee of Immunization Practices. Diphtheria, tetanus, and pertussis: guidelines for vaccine prophylaxis and other preventive measures. *MMWR* 1985;34:405-25.
- 5 Rümke HC. Contra-indicaties tegen vaccinaties in het Rijks-vaccinatieprogramma (Contraindications to vaccination in the National Vaccination Programme). *Ned Tijdschr Geneesk* 1989;133:1975-7.
- 6 Swaak AJ. Reacties op DKTP-vaccin; reacties van zuigelingen op de 1e, 2e, 3e en 4e inenting met DKTP-vaccin (Reactions to DTPP vaccine; reactions of infants to vaccination 1, 2, 3 and 4 of DTPP vaccine). *Medisch Contact* 1980;35:1061-4.
- 7 Long SL, Deforest A, Smith DG, *et al*. Longitudinal study of adverse reactions following diphtheria-tetanus-pertussis vaccine in infancy. *Pediatrics* 1990;85:294-302.
- 8 Baraff LJ, Cody CL, Cherry JD. DTP-associated reactions: an analysis by injection site, manufacturer, prior reactions, and dose. *Pediatrics* 1984;73:31-6.