# Commentary: Surveillance of Reactions to Biologicals

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Side effects after prophylactic vaccination are a delicate subject.

If there is a high incidence of an infectious disease and a newly developed vaccine against this disease becomes available, the public is primarily interested in the protective activity of the vaccine, and side reactions are accepted, as long as they are less severe than the disease. This is the best situation in which to start a study of side reactions. Each analysis of protective activity of a newly developed vaccine in the field should be combined with a study on its reactogenicity.

If, however, the disease is under control and vaccination is performed routinely in order to continue the existing favourable epidemiological situation, then the population is less inclined to accept side reactions.

A good example is the vaccination against pertussis. Twenty years ago the efficacy of the pertussis vaccine had been proven beyond doubt (*1* and *2*). Nowadays vaccines which give excellent protection are available, but several countries have recently abandoned pertussis vaccination because of the side reactions. In this situation a study to assess the reactogenicity of pertussis vaccine will be very difficult. Parents who are currently willing to have their child vaccinated might withdraw their consent when they are confronted with a study on side reactions. Therefore, the first factor to take into consideration when planning a study on side effects is the epidemiological situation in a country and the psychological effects it has on the population.

The Netherlands experienced a time with high pertussis mortality, but systematic vaccination of infants reduced it. At the end of 1962, with the introduction of DPT-Polio vaccine, it was decided to pay particular attention to side reactions because the mortality of the disease was zero, but some untoward reactions were reported.

The simplest way to collect certain data is through a questionnaire. In addition to information, one may also get the personal view of the addressee, the parents, or the doctor.

The complaints of the mother are influenced by her anxiety. Sometimes the child's crying makes her nervous; at another time she may accept a really serious situation but panics when the child refuses a feeding. A child with a temperature of 38°C is ill and shows signs of what is called in my country "general malaise." The diagnosis of this malaise is subjective. If, however, a fully documented case history is made of each reaction, other clinicians may agree. Therefore, each mother with a child who might have had a severe reaction after DPT-Polio vaccination was visited personally, and a complete case history was made of each reported side reaction.

When the different reactions which might occur were known, a study was started in one province to obtain information about their frequency. After some years it became evident that the most reliable reporting came from one town, the Hague and, in particular, from one baby clinic in the Hague. This study on such major reactions as shock and convulsions oc-

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curring up to 3 days after DPT-Polio vaccination revealed a frequency which was at the same time surprising and alarming (*3*), as shown in Figure 1.

This frequency was judged not to be acceptable; however, we did not want to abandon pertussis vaccination. Therefore, the amount of pertussis antigen added to the DPT-Polio vaccine was reduced, so that the final concentration per human dose was 10 IU instead of 16. However, the potency of the final vaccine still meets the potency requirements of WHO of 4 IU per human dose. This vaccine has now been in regular use for over one year, and during this period no serious side reactions have been reported neither from the baby-clinic in the Hague nor from the rest of the country.

The conclusion is that field studies on the reactogenicity of a vaccine should at least initially be confined to small geographic areas from which reliable information can be obtained. The quality of data is much more important than the quantity.

However favourable this situation is now, it should be stressed that the mechanism of reactions after pertussis vaccination is still unsolved. There is no objective criterion to measure the reactogenicity of different vaccines in man, nor has a relationship been established of the toxicity of different vaccines for animal and man. In order to obtain an objective criterion in man, a study was set up in that baby-clinic in the Hague. I now want to give you the experience obtained during that study on untoward reactions after DPT-Polio vaccination in which both a venous puncture and a heel puncture had to be performed.

**Input**

First, I fully informed each mother with a child who met the criteria for inclusion in the study about why the study was done, that her baby was to be vaccinated with the normal routinely used DPT-Polio vaccine, and further, that it was not an experiment but a controlled application. Then she was told how a venous puncture was to be performed and that—in case the first attempt was not successful—no second one would be made. Thereafter the mother was given all opportunity for questions. If she hesitated with her decision, she was never overruled.

If the mother was considering participation, a program for vaccination, clinical control, and bloodsampling was agreed upon; then she went home with her child still unvaccinated and a timetable for the next day. Therefore, the parents had ample time to make their final decision.

The conversation with the mother was carried on in the baby-clinic in the presence of the nurse who was to assist the next day. Although no signature was asked, this procedure was considered as an informed consent procedure. The mother could refuse directly or afterwards by telephone or just not re-appear the next day.

**Output**

The advantages of this time-consuming introduction were a personal relationship with the mother and a positive attitude of the parents towards participation. Refusal was exceptional. More than half of the fathers were present at the blood sampling. They showed much interest in the results. Several fathers even took a day off from work in order to be present. There were no rumours, no decline of the acceptance rate of vaccination in the baby-clinic, and we never reached the local papers.

**Results of the Study**

Two criteria were studied. The first criterion was the temperature 8 hours after vaccination. This simple information, easily obtained proved to be very reliable (Fig. 2).

There is a statistically significant difference in temperature 8 hours after vaccination with the DPT-Polio vaccine containing 16 IU and the vaccine with the reduced pertussis component. There was no difference in temperature in children vaccinated with DT-Polio vaccine and nonvaccinated children.

A second criterion was the plasma-insulin level at the same time, 8 hours after vaccination (Fig. 3).

There is a slight but significant elevation of

**Figure 1**

**Frequency of Shock and Convulsion after DPT-Poliovaccination**

| Period of observation | Estimated number vaccinated children | Number of reactions | |
|---|---|---|---|
| | | Shock | Convulsion |
| 1970–1974 | The Hague 28,000 | 8 = 1 : 3,500 | 13 = 1 : 2,150 |
| 1969–1974 | Z. Holland 190,000 | 11 = 1 : 17,270 | 6 = 1 : 31,660 |

**Figure 2**

**Temperature in °C, 8 Hours after Vaccination**

| Vaccine | Number | Mean temperature | Statistical test result[a] | |
|---|---|---|---|---|
| DPT-polio-16 | 11 | 38.3 | significant | significant |
| DPT-polio-10 | 15 | 38.1 | | |
| DT-polio | 9 | 37.4 | not significant | |
| control | 8 | 37.4 | | |

[a]Student's test, one-sided level of significance 5%.

**Figure 3**

**Plasma Insulin Level in µU/ML, 8 Hours after Vaccination**

| Vaccine | Number | Mean Level | Statistical test result[a] | |
|---|---|---|---|---|
| DPT-polio-16 | 14 | 13.5 | not significant | significant |
| DPT-polio-10 | 16 | 8.9 | | |
| DT-polio | 14 | 6.5 | not significant | |
| control | 10 | 7.1 | | |

[a]Student's test, one-sided level of significance 5%.

the plasma-insulin level 8 hours after vaccination with the DPT-Polio vaccine containing 16 IU.

The DT-Polio group does not differ from the control group; the insulin level of children vaccinated with the DPT-Polio vaccine with the reduced pertussis component lies in the middle. It does not differ significantly from the level in the group vaccinated with the 16 IU DPT-Polio vaccine or from the control group.

## CONCLUSION

It will be clear to you that I am not in favour of large comprehensive surveys of side reactions after vaccination. I do prefer initial small studies, taking into consideration the epidemiological situation in a country. The first requirement of each study should be informed parental consent; the first pursuit should be to establish objective criteria.

## References

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