Pertussis: a critical appraisal (2)

Aan de Minister van Volksgezondheid, Welzijn en Sport

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Op 12 november 1999 verzocht de Minister van Volksgezondheid, Welzijn en Sport de Gezondheidsraad om een advies waarin de recente ontwikkelingen met betrekking tot kinkhoest worden beschreven en waarbij tevens wordt ingegaan op de stand van wetenschap sinds het uitbrengen van het advies 'Pertussis: a critical appraisal' in 1997.

Het advies 'Pertussis; a critical appraisal (2)', dat door de commissie Kinkhoest is opgesteld, bied ik u - gehoord de Beraadsgroep Infectie en Immuniteit - hierbij aan.

w.g.
prof. dr JJ Sixma

Pertussis: a critical appraisal (2)

to:

The Minister of Health, Welfare and Sport

No. 2000/14, The Hague, June 28, 2000

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Executive summary

In 1997 a Health Council Committee produced a report entitled “Pertussis a critical appraisal”. This report was an initial response to the epidemic of whooping cough in 1996 and 1997. Possible explanations were discussed. Due to the fact that many children with the disease had a history of vaccination, special attention was given to the whole-cell vaccine against whooping cough. The intention was that the conclusions of this 1997 report should be reviewed after a given period of time. In this second report special attention is devoted to the efforts to modify the current whole-cell vaccine with a greater immunogenicity and to study the protection given by the vaccine. Introducing, again, revaccination against whooping cough at the age of four years is expected to have an important effect on the incidence of the disease and should be effected as soon as possible. In view of adverse reactions the Committee prefers an acellular vaccine for this revaccination. For the primary vaccination during the first year of life the development of a combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis vaccine should be given priority.

Samenvatting

In 1997 stelde een commissie van de Gezondheidsraad een advies op onder de titel Pertussis: a critical appraisal (kinkhoest: een beoordeling). Dit advies gaf een eerste bespreking van een epidemie van kinkhoest die zich voordeed in 1996 en 1997. Mogelijke verklaringen van deze epidemie werden besproken. Omdat veel kinderen die aan de ziekte leden tegen kinkhoest gevaccineerd waren, werd daarbij in het bijzonder aandacht gegeven aan de kwaliteit van het heelcel vaccin gericht tegen kinkhoest. In dit advies werd het voornemen uitgesproken om de conclusies na verloop van enige tijd nog eens te bezien. In het voorliggende (tweede) advies wordt met name aandacht gegeven aan de pogingen om het bestaande heelcel vaccin om te vormen tot een grotere immunogeniteit en aan de bescherming die door het vaccin gegeven wordt. Van herinvoering van de revaccinatie tegen kinkhoest op de leeftijd van vier jaar wordt een belangrijk effect verwacht op de incidentie van de ziekte. Deze revaccinatie dient zo spoedig mogelijk te worden ingesteld. Bij deze revaccinatie wordt aan het gebruik van een acellulair vaccin de voorkeur gegeven, dit in verband met de kans op bijwerkingen. Ten behoeve van de vaccinatie in het eerste levensjaar dient aan de ontwikkeling van een gecombineerd difterie, tetanus, acellulair pertussis, geïnactiveerd poliomyelitis vaccin grote prioriteit gegeven worden.

Chapter 1

Introduction

Since 1996 there has been an increase in the incidence of reported pertussis in the Netherlands. The peak incidence is in the age group 5-9 years, but there are also many cases in the age groups 1-4 years, 10-14 years and ≥ 20 years. Most patients in the age group 1-15 years were children who had been vaccinated against pertussis.

In 1997 the Health Council's Standing Committee on Infectious Diseases and Immunology consulted a working party of experts and produced an advisory report entitled 'Pertussis: a critical appraisal' (GR97). The most important recommendations were:

- to improve the acquisition of clinical and microbiological data from pertussis patients
- to improve the Dutch whole-cell pertussis vaccine
- to investigate the potential benefits of a booster vaccination with acellular pertussis vaccine at four years of age
- to further the plans to introduce an acellular pertussis vaccine for the vaccination in the first year of life.

The Standing Committee recommended a re-evaluation of the situation at some point in the future. The present report is the result of this re-evaluation. A Committee was installed by the President of the Health Council. This Committee met during a two day conference and had fruitful and stimulating discussions with a group of staff members from the National Institute for Public Health and the Environment (RIVM). The following presentations were held:

- Epidemiology of pertussis in the Netherlands (JFP Schellekens)
- Comparison of whole-cell and acellular vaccines in four year old children: the 'Apeldoorn' study (WAM Berbers)
- Pertussis vaccines: current concepts and RIVM developments (M Thalen)
- Variations in *B. pertussis* antigens and its immunological relevance (FR Mooi)
- Summary of RIVM activities on improvement of DTP-IPV-vaccine (diphtheria, tetanus, pertussis, inactivated poliomyelitis-vaccine) (BAM van der Zeijst).

The request from the Minister of Health, Welfare and Sport for this re-evaluation is presented in Annex A. The membership of the Committee is presented in Annex B.

Chapter 2

The current situation on pertussis in the Netherlands

2.1 Epidemiology/surveillance

Following a long period of relatively low incidence of pertussis (Hof98, Mel96) the Netherlands experienced an epidemic from autumn 1996 till spring 1997 especially among children in the age group 4-7 years. Many of the patients concerned had been vaccinated against pertussis (GR97, Mel97). Until 1999 the scheme of vaccination against pertussis was 3, 4, 5, 11 months. In the second half of 1997 and in 1998 the incidence of pertussis declined, but it increased again in 1999 (Mel00b, Nep99a). In the third quarter of 1999 the total number of pertussis notifications was 2223, as compared with 925 (1998), 856 (1997) and 1522 (1996) in former third-quarter periods.

Surveillance data in the Netherlands are based on notifications to the Health Care Inspectorate, laboratory data from the National Institute of Public Health and the Environment (RIVM), isolation of *Bordetella pertussis* strains from regional public health laboratories and national registration of hospital admissions and of deaths (Nep99b). Cases are ascertained using both positive one-point serology (high titre in the first serum sample) and positive two-point serology (fourfold increase or more in antibody-titre) (Mel00a). Since 1997, data from the Netherlands Paediatric Surveillance Centre (NSCK) have also been available (Nep99b).

There are several epidemiological pitfalls and bias factors when comparing the surveillance data. For example criteria for notification and case-definitions have changed

during the surveillance period. However, the Committee feels that there is a definite increase since the mid 90's and there is an important public health problem.

The age-specific distribution of pertussis notifications in 1999 shows a peak incidence in the age group 5-9 years. Most patients in the age group 1-15 years were children who had been vaccinated against pertussis. The real number of cases is higher than the number of notifications, but difficult to estimate precisely. The circulation of *Bordetella pertussis* in the population can roughly be estimated by measuring the serum IgG-PT (immunoglobulin G anti-pertussis toxin) levels in blood samples. An increased level of IgG-PT is an indication of a recent (re)infection with *Bordetella pertussis* (Mel00a). Based on the results of a recent study by the RIVM, the number of re-infections can be estimated at between 1000 and 5000/100 000 population per year (Mel00a).

The efficacy rate of the pertussis whole-cell vaccine used in the Netherlands appears to have been low for at least a number of years and surveillance data show that a decline in this rate had already started in 1994 (Mel00b).

The Committee concludes that the present vaccination programme against pertussis (annex c) does not apparently provide sufficient protection, particularly not to children in the age group 1-10 years.

2.2 Antigenic variants in B pertussis strains

Bordetella pertussis, the aetiological agent of whooping cough, produces many virulence factors. A number of these factors: pertussis toxin, filamentous haemagglutinin, pertactin and fimbriae, are proteins involved in intoxication or adhesion processes to host tissues and are critical antigens responsible for inducing immunity to *B. pertussis*. Results obtained in experimental studies with animals showed that these antigens are effective in preventing *B. pertussis* infections. The resurgence of pertussis experienced during recent years in countries with a long tradition in pertussis vaccination (not only the Netherlands but also the United States, Canada and Australia) evoked discussions as to whether or not vaccination had affected the genetic structure of *B. pertussis* and had resulted in antigenic shifts (Moo98). The results of recent studies indicate a shift in the structure of strains isolated over successive time periods and a divergence in the pertussis toxin and pertactin proteins between vaccine strains and clinical isolates (Mas99, Moo96, Mor98).

The Committee recognises the potential importance of the findings of *B. pertussis* strains which are structurally different from the vaccine strains. There is only some indirect

evidence (in animals) of immunological consequences with the currently used RIVM whole-cell vaccine. However, the apparent mismatch between vaccine strains and cultured circulating strains has thus far not resulted in proven clinical consequences for humans. Therefore, the Committee feels that it is too early to suggest that the decline of vaccine efficacy since 1994 and the increased incidence of pertussis since 1996 are related to antigenic changes of *B. pertussis* over time. The Committee possesses no convincing evidence that the mutations of strains directly result from vaccination pressure, since other countries where the same mutations occurred do not have the same vaccination pressure. There the vaccines continue to give satisfactory protection against all circulating strains (Mas99).

The monitoring of further developments is important. The RIVM has a leading position in this field of research and should be strongly supported in continuing this work.

2.3 The '96 improved RIVM whole-cell pertussis vaccine

The RIVM is continuously working to improve the quality of its pertussis vaccine, in accordance with the recommendations made by the working party in 1997 (GR97). An improved vaccine was introduced in 1997. Till 1996 the pertussis vaccine, (called RVP93) was cultured in 350 litre containers. In 1996 the culture volume was enlarged. The so called RVP96 vaccine is now cultured in 1000 litre containers. This vaccine was tested in a booster vaccination trial on four year old children (Ber99). The results of this so called Apeldoorn study are discussed later on in this report.

RIVM is engaged in further improving the manufacture of the whole-cell pertussis vaccine, for example, culturing the two vaccine strains in a chemically well defined and stable medium (the so called THIJS-medium).

2.4 Booster vaccination at four years of age

Recently RIVM studied the immunogenicity and adverse effects of three commercial acellular pertussis vaccines and the '96 improved RIVM whole-cell vaccine combined with diphtheria, tetanus and poliomyelitis vaccine as a booster in a randomised controlled study in four year old children after primary vaccination with whole-cell vaccine (WCV): the Apeldoorn study (Ber99). The immune response of the children in this study (each group 21-24 children) is a reflection of the composition of the vaccines which had different concentrations of pertussis antigens.

The number of participants who responded with a fourfold increase in the immune response (IgG antibody titre) to the pertussis antigens: pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) was clearly higher in the groups with the acellular vaccines (except for one of those vaccines which did not contain pertactin). Only 45 percent of the children with whole-cell vaccine had a fourfold increase in PT titre. For the acellular vaccines this percentage was at least 90. The incidence of adverse events in the recipients of the whole-cell pertussis vaccine was much higher (factor 4-12) than in the acellular pertussis vaccine recipients. Systemic and local reactions — both of minor importance — were prominent in the WCV recipients, both in frequency and in duration.

The Committee feels that the results of this Apeldoorn study demonstrate that a booster pertussis vaccination at four years of age with acellular vaccine has preference above a booster with WCV.

Chapter 3

The follow up of recommendations made in the 1997 report

The Committee evaluated the follow-up of recommendations made in the first report on the subject (GR97):

1 *Improvements to the collection of clinical and microbiological data from the epidemic are needed*. The Committee notes that the present pertussis surveillance system in the Netherlands is of a high quality, is an example for other countries and has been improved since 1997 (Nep99a, Nep99b).

2 *The current vaccine should be improved*. At the end of 1997 an improved pertussis whole-cell vaccine was introduced by the RIVM (Moo00). The results were compared with three acellular vaccines in the Apeldoorn study (see 2.4) (Ber99).

3 *The bacterial strains used should be compared with those used in the French vaccine (which originally used the same parental strains); this may indicate ways in which the vaccine can be improved*. The Dutch whole-cell vaccine parent strains 509 and 134 were sent to the Institut Pasteur in Paris and compared with the French vaccine parent strains. The DNA patterns were similar, but not identical. The French whole-cell vaccine is produced by Pasteur Merieux Connaught. Additional information is not available.

4 *Expression of the various pertussis antigens should be identified as part of the in process-control procedures performed during preparation of the vaccine*. The improved 1996 Dutch whole-cell vaccine — as used in the Apeldoorn study — still has a low concentration of pertussis toxin (PT) and filamentous haemagglutonin (FHA) as compared with the acellular vaccines. The in-process control procedures have been improved (Ber99, Moo00).

5 *An investigation should be conducted into the potential benefits of a booster vaccination using an acellular pertussis vaccine, to be given at the age of four. If this could be shown to be of genuine benefit then a suitable immunisation programme should be introduced*. A randomised controlled study with whole-cell and three acellular pertussis vaccines had been completed (Apeldoorn study, see 2.4) (Ber99).

6 *It is recommended that the current primary vaccination scheme is left unchanged, since any changes would have limited value*. In 1998 the Dutch primary immunisation scheme was been changed: the first vaccination against diphtheria, pertussis, tetanus, poliomyelitis and *Haemophilus influenzae* type b is now given at the age of two months instead of three months (GR99). The main reason for this change was the fact that many children received their first three vaccinations later than on the intended 3, 4 and 5 months of age. This leads to a delay in the building up of immunity against particularly *B. pertussis* and *Haemophilus influenzae.*

7 *The introduction of an acellular pertussis vaccine for primary vaccination should go ahead as planned and start with field studies*. Little progress has been made between 1997 and 2000.

8 *A re-evaluation should be carried out after a period of 9-12 months, by which time the cause of the epidemic may have become clear*. This re-evaluation took place at the end of January 2000. The results are presented in this report.

Chapter 4

Recommendations

4.1 Data collection

The Committee feels that the current surveillance programmes should be continued. There is a need for more precise data on the number of vaccination doses that each child receives, so that the efficacy rate of the primary vaccination and of the booster vaccination at the age of four years can be more accurately calculated. Also more data on the circulation of *B pertussis* in the population is needed. The Committee suggests that such surveillance studies should be carried out in conjunction with future vaccine trials. In these studies also *B pertussis* strains should be collected and analysed.

4.2 The booster vaccination at four years of age

The Committee strongly recommends a booster vaccination at four years of age with an acellular pertussis vaccine. It is difficult to assess the health benefits of such a booster vaccination, but a considerable reduction in the number of pertussis cases in the age group 5-9 years can be expected. Another effect will be a general decrease in the circulation of *B. pertussis*. Mathematical modelling studies are needed to analyse more accurately the latter effect. Further reduction of the circulation will be accomplished by efficacious primary vaccination in the first year of life. There is no proof of an increased risk for disease in unvaccinated young children due to transmission from adults (parents) as a result of the booster at four years of age.

The booster vaccination at four years has to be performed with a registered acellular vaccine. The Committee prefers a vaccine with three or more immunogenic components. These vaccines in general have better efficacy than one- or two-component vaccines, although some exemptions exist (Hal99, Kle96, Sim97). The combination of an acellular vaccine given with the now used diphtheria-, tetanus-, poliomyelitis (DT-IPV) vaccine at four years will make a second injection necessary. There are no real objections to this in view of the very low frequency of adverse effects of the acellular vaccines, as was shown in the Apeldoorn study (Ber99) and many studies from abroad (Hal99, Oli97, Sim97, Wil96). A second injection could be avoided by using a combined commercial vaccine. The Committee does not prefer that option.

The Committee does not recommend the use of the RIVM-whole-cell pertussis vaccine for the booster, in view of the adverse effects and the low antibody response as compared with the acellular vaccines (Ber99).

4.3 The primary vaccination with pertussis vaccine in the first year of life

The Committee strongly supports the RIVM-plans for the future of primary pertussis vaccination. It is the Committee's understanding that there will be three tracks of development:

- development of a combined DT-polio acellular pertussis vaccine
- development of a new DT-polio whole-cell pertussis vaccine
- development of a pertussis vaccine made based on genetically modified strains in view of the mutation findings.

The Committee emphasises that a direct approach to tackle the pertussis problem in the Netherlands would be the introduction of an effective and safe pertussis vaccine to be administered in the first year of life. High priority should be given to developing a combined DT-polio acellular pertussis vaccine (track a) as soon as possible. An acellular vaccine should be incorporated that has been proven to be safe and efficacious in clinical trials. In the long term such a primary vaccine can also be used for the booster vaccination at four years of age. The Committee strongly feels that in this way it will be possible to reduce the pertussis problem in the Netherlands to an acceptable level as well as solving the current public health problem.

In the Committee's opinion, the development of a new DT-polio and whole-cell pertussis combined vaccine (track b) should not be given any priority. It will be difficult to assess the efficacy of such a vaccine compared to the combined acellular vaccine.

In future, it may be possible that a new effective whole-cell vaccine will be developed with minimal adverse effects, based on genetically modified strains. The Committee believes that track c is a long term approach.

The Committee acknowledges the great expertise in RIVM in the field of *B pertussis* mutations. Further research is needed and RIVM — which has a leading position internationally — should be strongly supported in continuing this research.

4.4 The vaccination scheme

The Committee recommends that the current vaccination scheme in the Netherlands, dating from January 1999, be retained. In this scheme the vaccinations in the first year of life (including pertussis vaccine) take place at 2, 3, 4 and 11 months of age. As mentioned before, a booster pertussis vaccination at four years of age should be implemented in conjunction with the current DT-Polio booster.

The Hague, 28 June 2000,
for the Committee

J Sekhuis, arts
scientific secretary

Professor dr HKA Visser,
chairman

Literature

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A The request for an advisory report

B The Committee

C Vaccination scheme of the National Vaccination Programme since 1 January 1999

Annexes

Annex **A**

The request for an advisory report

The President of the Health Council of the Netherlands received the following letter, dated 12 November 1999, from the Minister of Health, Welfare and Sport.

On 30 June 1997, following a whooping cough epidemic in the Netherlands, the Health Council produced a report, at my request, entitled “Pertussis: a critical appraisal”, being an assessment of an earlier report, (“Whooping cough epidemic 1996-1997. Present position, possible causes and responses”), produced by the National Institute of Public Health and Environment (RIVM). In your report, you indicated that you would eventually like to issue a re-evaluation of your findings. In response to your report, improved quality assurance arrangements were introduced for the present cellular whooping cough vaccine and a number of studies were carried out. For example, circulating pertussis strains have been investigated and a study to determine the value of administering acellular booster vaccinations to four-year-olds has been carried out. Field studies involving the use of a DT-IPV vaccine containing an acellular whooping cough vaccine and improved cellular component have also been prepared.

In view of the developments that have taken place in this field, I would like you to review the conclusions of your earlier report in the light of the latest scientific thinking. In particular, please indicate whether booster immunisation of four year olds using acellular vaccine may be expected to provide better protection and what the health benefits are likely to be, bearing in mind the other measures already taken. The short-term and long-term effects of such revaccination on the transmission of *B. pertussis*, especially to unvaccinated infants, should also be addressed.

Please take the following into consideration:

- the reduction in the age at which vaccination under the National Immunization Programme is carried out by one month, with effect from 1999
- the present epidemiological situation with regard to whooping cough
- the report by the RIVM entitled ”A randomized controlled study with whole-cell or acellular pertussis vaccines in combination with regular DT-IPV vaccine and a new poliomyelitis (IPV-Vero) component in children 4 years of age in the Netherlands”.

Minister for Health, Welfare and Sport
(signed)
Dr E Borst-Eilers

Annex **B**

The Committee

- HKA Visser, *chairman*
  emeritus professor of paediatrics, Erasmus University Rotterdam (the Netherlands)
- Ph Duclos
  epidemiologist; World Health Organisation, Geneva (Switzerland)
- J Huisman
  emeritus professor of epidemiology and control of infectious diseases, Rotterdam (the Netherlands)
- JWM van der Meer
  professor of internal medicine, Catholic University Nijmegen (the Netherlands)
- P Olin
  paediatrician; Swedish Institute for Infectious Disease Control, Solna, Stockholm (Sweden)
- CH Wirsing von König
  professor of microbiology; Institute for Hygiene and Laboratory Medicine; Krefeld (Germany)
- JK van Wijngaarden, *advisor*
  Inspectorate for Health Care, The Hague (the Netherlands)
- J Sekhuis, *scientific secretary*
  Health Council, The Hague (the Netherlands)

The Committee consulted the following scientific staff members from the National Institute of Public Health and the Environment (RIVM), Bilthoven (the Netherlands):

- WAM Berbers
- G Elzinga
- FR Mooi
- JFP Schellekens
- BAM Van der Zeijst

Annex **C**

Vaccination scheme of the National Vaccination Programme since 1 January 1999

age	vaccinations
2 months	DTP-IPV[a] –1 + Hib[b]-1
3 months	DTP-IPV –2 + Hib-2
4 months	DTP-IPV –3 + Hib-3
11 months	DTP-IPV –4 + Hib-4
14 months	MMR[c]-1
4 years	DT-IPV[d] -5
9 years	DT-IPV –6 + MMR-2

[a] DTP-IPV: Diphtheria toxoid, Tetanus toxoid, Pertussis vaccine, Inactivated Polioviruses

[b] Hib: Haemophilus influenzae type b

[c] MMR: Measles, Mumps, Rubella

[d] DT-IPV: Diphtheria toxoid, Tetanus toxoid, Inactivated Polioviruses