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# Vaccination against pertussis

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To the Minister of Health, Welfare and Sport

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Subject : Submission of advisory report on vaccination against pertussis  
Your reference : GZB/GZ 2.108.780  
Our reference : 2061/HH/693-L1  
Appendices : 1  
Date : 7 April 2004

Minister,

In a letter dated 29 September 2000, your predecessor requested the advice of the Health Council of the Netherlands concerning the future of the National Vaccination Programme. In that context, I hereby submit the advisory report entitled 'Vaccination against pertussis'. The advisory report was drawn up by the National Vaccination Programme Review Committee. It was checked by the Standing Committee on Immunology and Infectious Diseases, and by the Standing Committee on Medicine.

This topic was the subject of previous reports in 1997 and 2000. The fact that yet another Health Council advisory report on this topic is now required only serves to emphasize the complexity of the subject matter. The Committee has also provided further clarification concerning various ambiguities and gaps in the scientific knowledge. The Committee has also produced clear advice concerning the vaccination of infants with an acellular pertussis vaccine. I fully endorse that advice. Like the Committee, I believe that Dutch citizens must be able to feel confident that the vaccines used in the National Vaccination Programme meet strict requirements with regard to effectiveness and safety.

While this advisory report confines itself to the vaccination programme in the Netherlands, I would like to draw your attention to another aspect that was briefly raised by the Committee. There has been a sharp decline in the number of vaccines available to developing countries. Furthermore, an increasing number of those that are still available are too expensive for many Third World countries. This problem has also been identified by the World Health Organization. The threat that it poses in such countries is not restricted to the control of pertussis alone, it also involves other diseases targeted by the basic vaccination. This observation may well be significant in terms of Dutch policy in the area of development cooperation.

Yours faithfully,  
(signed)  
Prof. JA Knottnerus



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# Vaccination against pertussis

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to:

the Minister of Health, Welfare and Sport

No. 2004/04E, The Hague, 7 April 2004

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The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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# Contents

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## Summary 9

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- 1 Introduction 13
  - 1.1 Antecedents 13
  - 1.2 Request for advice 14
  - 1.3 Method 15
  - 1.4 Structure of the advisory report 15
- 
- 2 Increasing incidence of pertussis in the Netherlands and elsewhere 17
  - 2.1 The history of pertussis vaccination 17
  - 2.2 Epidemiology in the Netherlands 20
  - 2.3 Epidemiology in other countries 27
  - 2.4 Comparison 28
- 
- 3 Causes of the increase 31
  - 3.1 Waning immunity 31
  - 3.2 Reduced effectiveness of the vaccine 35
  - 3.3 Conclusion 42
- 
- 4 Vaccine selection criteria 43
  - 4.1 Effectiveness 44
  - 4.2 Adverse effects 46
-

4.3	New data on the immunology of pertussis	51
4.4	The importance of national vaccine production	56
4.5	The availability of specific combined vaccines	57
<hr/>		
5	Assessment of scenarios for the vaccination of infants	59
5.1	Reference scenario	59
5.2	Temporary purchase of quantities of pertussis vaccine	61
5.3	Temporary purchase of existing DTP/Hib vaccines	62
5.4	Time at which a booster can be administered	63
5.5	Efficiency of the preferred scenario	63
5.6	Conclusion	65
<hr/>		
6	Assessment of additional measures	67
6.1	Vaccinating mothers and reducing the vaccination age	67
6.2	Vaccinating older children and adults	69
6.3	Conclusion	70
<hr/>		
7	Dilemmas and recommendations	71
7.1	Five dilemmas	71
7.2	Recommendations	73
<hr/>		
	Literature	77
<hr/>		
	Annexes	85
A	Request for advice	87
B	The Committee and the experts consulted	89
C	Composition, antibody response, effectiveness and adverse effects of combined vaccines against pertussis	93
<hr/>		
	Addendum Estimate of adverse effects by Dutch Cochrane Centre	95



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# Summary

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## Question posed

In this advisory report, the National Vaccination Programme Review Committee addresses the measures needed to improve pertussis vaccination in the Netherlands. The Health Council previously issued advisory reports on pertussis vaccination in 1997 and 2000.

## Increasing incidence of pertussis in the Netherlands

Since 1996, the number of cases of pertussis in the Netherlands has increased, even though virtually all children have been immunised against this disease. Currently, four to eight thousand cases of pertussis are reported each year, mainly in young vaccinated children. Between 250 and 500 children are admitted to hospital in connection with pertussis. Since 1996, eight deaths at least have occurred as a result of pertussis.

Increases have also been observed in other countries. However, there are significant differences in terms of the ages of the patients in question. Elsewhere, the increase primarily affects adults, older children and infants who have either not yet been vaccinated or have not completed their course of vaccination. In the Netherlands, the 1996-1997 epidemic affected people in all age groups, including young children who had been vaccinated.

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## Causes of the increase

What is the reason for the increase seen in the Netherlands? Given the age range of pertussis patients, it is unlikely that a change in the vaccine is responsible. This is because the first effect of any change in the vaccine (arising from production problems, for example) would be an increased incidence in recently vaccinated young children. Only later would other age groups gradually follow suit.

A more plausible explanation is that the vaccine's effectiveness has been impaired by selection of non-vaccine-related strains of the pertussis bacterium in the Netherlands. To the best of our knowledge, this problem has not been encountered in other countries. The Netherlands' unique position in this respect may be due to the specific characteristics of the vaccine used here. This contains low levels of the major antigens pertussis toxin and pertactin.

In the Netherlands, as in various other countries, there is a general phenomenon at work that contributes to the increased incidence of this disease. The vaccination of young children leads to a decline in the circulation of *Bordetella pertussis* within the population. As a result, older children and adults are exposed to the bacterium less often. Immunity, which would otherwise be boosted by early re-exposure, then starts to wane. Subsequent reinfection then results in a greater incidence of disease among older children and adults. This in turn means that infants who have either not yet been vaccinated or have not completed their course of vaccination are also at greater risk of infection. This model of waning immunity is in keeping with epidemiological and immunological findings. Observers throughout the world consider it to be the best explanation for the changing epidemiology of pertussis at international level.

## Advisory report

The Committee has considered a range of scenarios for improving the protection of young children. It recommends a scenario involving the fastest possible transition to the use of an acellular, combined DTPPHib vaccine (against diphtheria, tetanus, pertussis, polio and infections with *Haemophilus influenzae* type b). It is anticipated that this will substantially reduce the present incidence of pertussis cases in young children. This option is also better than the current whole-cell vaccine in terms of the balance between efficacy and adverse effects.

Whole-cell pertussis vaccines rarely or never cause serious adverse effects with lasting physical effects. Also, the frequency of so-defined 'highly unpleasant adverse effects' is relatively small, about 1.4 percent. With use of acellular vaccines, however, these reactions occur in only 0.3 percent of cases on average. It is estimated that switch-

ing to an acellular vaccine will lead to more than 8000 fewer cases of highly unpleasant adverse effects per annum, and to many fewer instances of 'other adverse effects'.

Until the Netherlands Vaccine Institute is capable of producing an acellular, combined vaccine, the Committee recommends that an alternative source of supply be used. The Committee feels that Dutch citizens must be able to feel confident that the vaccines used in the National Vaccination Programme meet strict requirements with regard to efficacy and safety. The Committee recommends that various measures be taken in connection with the temporary suspension of DTPPHib vaccine production by the Netherlands Vaccine Institute. The aim is to retain expertise and to avoid jeopardising the long-term prospects for independent vaccine production in the Netherlands.

Besides effective infant vaccination, additional measures are needed to ensure that babies who have either not yet been vaccinated or have not completed their course of vaccination are better protected against pertussis. However, the context of this advisory report precluded exhaustive discussions of such measures. The Committee nevertheless recommends that research be carried out into the sources of infections in very young infants in the Netherlands. The Committee will further explore these additional measures, such as targeted vaccination for specific groups of older children and adults, in the context of a subsequent advisory report.

Finally, the Committee recommends that support be given to fundamental research into the immunology of pertussis. This would benefit the development of future pertussis vaccines.



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# Introduction

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## 1.1 Antecedents

In 1996, there was a marked increase in the number of cases of pertussis in the Netherlands. With reference to this, on 7 May 1997 and 28 June 2000, the Health Council produced advisory reports on vaccination against this disease for the Minister of Health, Welfare and Sport.<sup>1,2</sup> The Council concluded that the vaccination schedule in use at the time provided children with insufficient protection against pertussis. However, the limitations of the available data meant that the Council was unable to identify the precise cause of this upsurge. Nevertheless, it did make a number of recommendations. Partly as a result of the Council's advice:

- pertussis surveillance was redoubled;
  - the minimum strength of the pertussis component of the DPTP (Diphtheria + Pertussis + Tetanus + Polio) vaccine was boosted from 4 to 7 International Units per human dose (introduced in December 1997);
  - changes were made to the production process to increase the amount of pertussis toxin in the vaccine (introduced at the start of 1998);
  - the age at which it is recommended that the first vaccine be administered was reduced from three months to two months (introduced on 1 January 1999), and
  - a booster using an acellular vaccine, at the age of four years, was introduced on 1 July 2001.
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The Council also recommended that high priority be accorded to the development of a DPTP vaccine with an acellular pertussis component. Any such vaccine would have to be based on the vaccine which was produced formerly by the National Institute of Public Health and the Environment (RIVM) and which is currently produced by the Netherlands Vaccine Institute (NVI). This would involve replacing the cellular pertussis component with an acellular pertussis vaccine that has been shown to be both safe and effective. The vaccine in question would be supplied by an industrial partner. The Council attaches great importance to research into variants of the bacterium, *Bordetella pertussis*, in the Netherlands. It recommends that this research effort be given additional support.

The number of cases of pertussis was still at an elevated level at the end of 2003, with epidemic peaks every two to three years (the latest being in 2001). Nevertheless, the first effect of the acellular pertussis vaccine booster given at age four, which was introduced in 2001, seems to have appeared. Strengthening of the cellular vaccine at the start of 1998 may have produced a slight improvement in the vaccine's effectiveness. However, pertussis still produces a considerable disease burden, particularly among infants who are too young to be eligible for vaccination.

The cellular vaccine is still used as the basic vaccination for infants. The NVI has encountered delays in its attempts to develop a new combined vaccine with an acellular pertussis component, in collaboration with industrial partners. Originally planned for 2004, the introduction of this vaccine has now been deferred until 2007.<sup>3</sup>

These are the most important developments that have taken place since the second advisory report was published in the year 2000. Meanwhile, new views have been published on the workings of the innate immune system which are of relevance to vaccination against pertussis. The National Vaccination Programme Review Committee felt that this was sufficient reason for it to re-evaluate vaccination against pertussis.

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## 1.2 Request for advice

This advisory report falls within the scope of the Minister of Health, Welfare and Sport's broad request for advice concerning the National Vaccination Programme (NVP; see annex A). The report was drawn up by the National Vaccination Programme Review Committee, which was established by the President of the Health Council on 13 June 2001. The Committee will continue to advise on issues relating to the NVP for a period of five years (annex B).

With regard to this advisory report, the Committee addressed the following principal question:

- What measures are needed to reduce the number of cases of pertussis in children aged five or less?

In order to answer this question, it was necessary to explore six individual sub-issues:

- 1 What trends can be seen in the number of cases of pertussis in the Netherlands and elsewhere?
- 2 What are the causes of the increase in the number of cases of pertussis in the Netherlands and elsewhere?
- 3 When assessing vaccination scenarios, what criteria does the Committee use?
- 4 How does the Committee judge the relative merits of possible vaccination scenarios?
- 5 Which particular vaccination scenario does the Committee recommend?
- 6 What other measures does the Committee recommend?

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### **1.3 Method**

Before answering the question, the Committee first explored the scientific literature. It also organised hearings to which it invited representatives of the pharmaceutical industry, the National Institute of Public Health and the Environment (RIVM) and the Netherlands Vaccine Institute (NVI). The Committee also consulted a number of experts, both at home and abroad (annex B). The objective of these hearings and consultations was to obtain the widest possible range of views on a number of points. These involved possible interpretations of the scientific data, as well as the causes of the increase in the number of pertussis cases in the Netherlands and elsewhere. Other points were the safety and effectiveness of vaccination scenarios, as well as the current and future availability of vaccines.

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### **1.4 Structure of the advisory report**

Chapter two charts recent developments in the incidence of pertussis, in the Netherlands and elsewhere. The chapter concludes with a comparison of the increase, which in some countries has been both less pronounced and of a different character than that seen in the Netherlands. In chapter three, an attempt is made to identify the causes of the increase, both in the Netherlands and elsewhere. Two causes are examined: 1) waning immunity among older children and adults and 2) changes in the incidence of various bacterial strains, which have impaired the vaccine's effectiveness. In the Netherlands, genetic variants may well be involved in the upsurge in pertussis. Elsewhere in the world, there is little evidence of this. In chapter four, the Committee specifies the criteria that it uses to assess vaccination scenarios, and how it weighs these criteria against one another.

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Chapter five continues in a similar vein, assessing scenarios for the vaccination of infants. However, more will be needed to halt the current upsurge. Accordingly, chapter six explores the options for vaccinating older children and adults. Chapter seven opens with a summary of the dilemmas encountered by the Committee in the course of its deliberations. Finally, the latter part of the chapter lists all of the Committee's recommendations concerning vaccination and the need for further research.



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## Increasing incidence of pertussis in the Netherlands and elsewhere

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### 2.1 The history of pertussis vaccination

Pertussis is a highly infectious disease of the respiratory system, which is caused by the bacterium *Bordetella pertussis*. Particularly in very young children, the course of the disease can be very serious and sometimes even fatal. The disease is characterised by bouts of coughing. During these attacks, individuals gasp for air, producing a characteristic ‘whooping’ sound. The attacks can be so severe that children are at risk of suffocating. The disease has a very protracted course. This explains one name for the disease, one-hundred-day cough.

Pertussis was first described as a distinct disease in the sixteenth century. Prior to that, the clinical picture may have been seen as an aspect of influenza. However, there is no escaping the fact that this disease has a highly characteristic clinical picture. It is therefore conceivable that it did not exist before that time, and that the pertussis pathogen jumped the species barrier, from an animal reservoir to humans, at some time in the sixteenth century.

In addition to *Bordetella pertussis*, the related bacterium *Bordetella parapertussis* can also cause the disease. The latter is responsible for about four percent of all cases of pertussis in the Netherlands.<sup>4</sup>

Cherry estimates the number of cases of pertussis in the United States, before the introduction of vaccination, at 872 per 100 000 individuals per annum. The majority of such cases involved children below five years of age. In fact, almost entire cohorts of younger

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children probably became ill. On average, 7300 children died of pertussis each year in the US. However, that number had already started to fall before the introduction of antibiotics and vaccines.<sup>5</sup>

The first crude vaccines appeared soon after Bordet and Gengou succeeded in culturing the bacteria in 1906. In 1914, one of the first vaccines was admitted for use in the United States. The era of large-scale vaccination in the United States was ushered in following the introduction of the first combined diphtheria, pertussis and tetanus toxoid vaccine (DPT) in 1948.

From about 1950 onwards, many countries introduced vaccination programmes to protect children from pertussis. Prior to the introduction of large-scale vaccination, severe cases of pertussis were almost entirely restricted to children below five years of age. Accordingly, vaccination was introduced for the protection of these young children.

Infants in the Netherlands have been vaccinated against pertussis since 1953. The vaccine used for this purpose was a DPT vaccine produced by the former National Institute of Public Health (RIV). At the start of the twentieth century, pertussis was still responsible for about 1000 deaths each year in the Netherlands. At the start of the 1950s, prior to the introduction of vaccination, this had declined to well over one hundred deaths per annum. According to official figures, there were still 30 deaths as a result of pertussis in 1955. The total for the entire period from 1964 to 1995 was just six.<sup>6</sup> While the instances of morbidity and mortality caused by pertussis had been in decline since the start of the twentieth century, vaccination programmes accelerated this process still further.

From the very start, the development of vaccines with a good balance between efficacy and adverse effects has presented major challenges.

Indeed, the history of vaccination against pertussis includes numerous vaccines that were only moderately efficacious. This was the case in Sweden in the late 1970s,<sup>7</sup> for example. The same is true of the United Kingdom before the highly effective Evans-Wellcome vaccine was adopted in 1982<sup>8</sup> and of Canada at the start of the 1990s.<sup>9</sup> In Norway, during the latter half of the 1990s, there was an epidemic upsurge in pertussis. It is not clear whether this resulted from a decline in the vaccine's effectiveness. It was claimed that the cellular vaccine in use at the time provided good protection for children of up to five years of age. In 1998, however, it was replaced with an acellular vaccine.<sup>10</sup> Comparative studies have found marked variation in the efficacy of vaccines.<sup>11</sup> In most cases, nothing is known about the underlying causes of such vaccine failures. They might be due to vaccines which are just moderately efficacious, to production problems (which was probably the case in Sweden), or to changes in the bacterium which cause the vaccine to be less effective. The latter possibility, involving genetic variants, is discussed in subsection 3.2.

Traditional pertussis vaccines are produced from killed, whole bacterial cells containing a great many antigens. One drawback is that they have a relatively high incidence of adverse effects. Attempts have therefore been made to modify the production process such that the vaccine contains only low levels of those substances that are considered to be responsible for the adverse effects. One common problem here is the lack of certainty about which substances are beneficial to immunity and which give rise to adverse effects. Even where a clear distinction can be made, it is still very difficult to remove the harmful substances from the vaccine while retaining the beneficial substances.

As recently as 1970, research carried out at RIV indicated that histamine-sensitising factor (HSF) was responsible for the adverse effects. An HSF-free vaccine was subsequently prepared.<sup>12</sup> However, it later emerged that HSF is synonymous with pertussis toxin, which is vital to the protective effect of the vaccine. The HSF-free vaccine was never introduced into the general population. Nevertheless, the vaccine that is now being used also contains low levels of pertussis toxin. The French cellular vaccine is based on the same bacterial strains as the Dutch vaccine. Differences in production methods were probably responsible for the fact that the French vaccine generates higher levels of anti-pertussis-toxin antibodies than its Dutch counterpart. The same applies to the anti-pertactin antibody levels generated by both vaccines. Pertactin, like pertussis toxin, is probably important for effective protection against pertussis.

While there was marked variation in the effectiveness of cellular vaccines, the incidence of pertussis during the 1970s had declined to such low levels that the spotlight shifted to the adverse effects of the vaccines. The pros and cons of vaccination became the subject of public debate in several countries. In 1979, for example, this resulted in the suspension of the general vaccination programme in Sweden. In Britain too, there was a sharp decline in the level of vaccination. This led to a steep rise in the number of pertussis cases, and to the deaths of 36 children.<sup>13,14</sup>

The poor acceptance of cellular vaccines in some countries helped to promote the development of a new type of vaccine. No longer based on killed whole bacteria, but on their protein components, these are known as acellular vaccines. These acellular vaccines contain various combinations of pertussis toxin (PT), pertactin (PRN), filamentous haemagglutinin (FHA) and fimbriae (FIM). They cause fewer adverse effects than cellular vaccines.<sup>7</sup> Large-scale studies have demonstrated that good acellular vaccines are about as effective as good cellular vaccines. Most western countries have now switched to acellular vaccines. The Netherlands still uses a cellular vaccine.

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## 2.2 Epidemiology in the Netherlands

### Situation up to 1966

The vaccination level in the Netherlands in 1958 was estimated at 60 percent. By 1962 this had risen to about 90 percent.<sup>15</sup> The current vaccination level is estimated to be 96 percent.\* The vaccine was highly effective until 1996 (table 4, below). Between 1964 and 1996, there were only a few isolated fatalities as a result of pertussis infections. There were only six cases during this entire period.<sup>6</sup>

### Epidemic of 1996-1997

In 1996, the incidence of pertussis in the Netherlands suddenly turned into an epidemic. Figure 1 gives a clear picture of this increase:

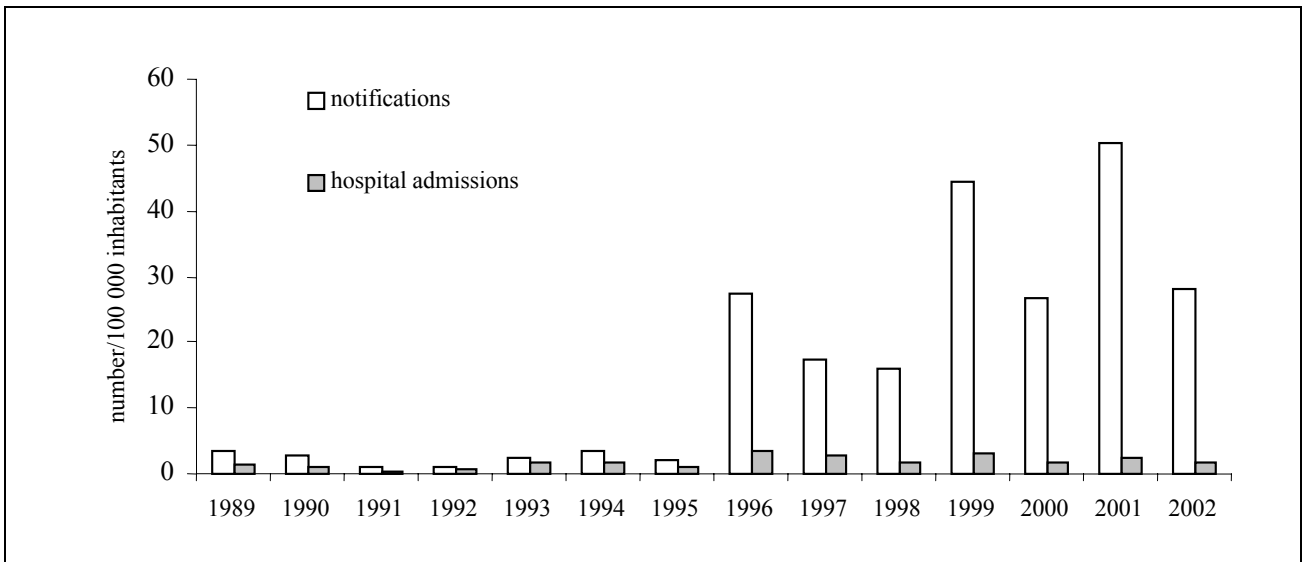


Figure 1 Incidence of pertussis per 100 000 head of population, on the basis of notifications and hospital admissions, Netherlands, 1989-2002 (source: RIVM).

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\* Diphtheria, pertussis, tetanus and polio vaccine (DTP) has a vaccination level of 97 percent. It is estimated that one percent of parents opt for the DTP combined vaccine, without a pertussis component.

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The exact figures are shown in table 1:

*Table 1* Absolute number of pertussis notifications and hospital admissions as a result of pertussis, and the relationship between these two figures, Netherlands, 1989-2002 (source: RIVM).

Year	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Hospital														
Admissions	221	157	82	101	288	276	162	513	436	282	509	247	397	261
Notifications	523	397	145	160	346	519	341	4231	2671	2508	6980	4229	8030	4504
Relationship	0.42	0.40	0.57	0.63	0.83	0.53	0.48	0.12	0.16	0.11	0.07	0.06	0.05	0.06

Detailed descriptions and analyses of this epidemic have already been published.<sup>16-19</sup> It was not possible to account for the increase in terms of changes in the method of registration. The pertussis cases in question satisfied a strict case definition, one which incorporated typical pertussis symptoms as well as laboratory confirmation. In other words, this was a genuine epidemic. In addition, the vast majority of cases involved vaccinated children. It therefore seems that the vaccine's effectiveness underwent a sudden decline.

In 2003, the number of pertussis cases was still elevated relative to the period prior to 1996. It seems that, since 1996-1997, there has been an increase every two to three years. The epidemic years were 1996, 1999 and 2001. This pattern is reflected in both notifications and hospital admissions.

#### Increase per age group

What is the distribution of pertussis cases by age group? Table 2 classifies the post-1996 incidence by age group. The table shows that the post-1996 increase occurred in all age groups. The increase was relatively small among children below one year of age (four times), but relatively large in the 10-14 and 15-19 age groups (20 times).

The elevated incidence in young children, with a peak at ages four to six, is anomalous. In other countries, such as Australia, the United States and the United Kingdom, the peak generally occurs at a later stage.<sup>20-23</sup> Only the Canadian epidemic of the early 1990s had a comparable age range.<sup>9</sup>

*Table 2* Age-specific incidence of pertussis notifications per 100 000, 1989-2002 (source: RIVM).

Age (years)	1989-1995	1996	1997	1998	1999	2000	2001	2002
0	36.9	160.4	112.0	69.7	153.7	104.6	181.6	105.4
1-4	12.0	152.4	90.1	91.9	186.4	124.8	211.1	82.2
5-9	12.6	162.0	84.0	93.4	254.0	145.8	302.4	155.7
10-14	3.8	57.1	33.0	28.7	94.5	45.1	93.3	62.0
15-19	0.5	10.3	8.4	5.4	28.1	14.1	27.3	25.4
≥ 20	0.3	4.4	4.6	3.5	12.8	8.4	15.1	10.1
Total	2.3	27.1	17.1	16.0	44.2	26.6	50.2	28.0

### Increase in mortality

Following the introduction of vaccination in 1953, mortality in the Netherlands due to pertussis was virtually zero. However, there have been eight such deaths since 1996, almost exclusively (seven cases) in children who had either not yet been vaccinated or had not completed their course of vaccination (source: Central Bureau of Statistics). The mortality among these very young infants indicates an increased circulation of bacteria in the population. Research carried out abroad revealed that some cases of pertussis that result in the death of very young infants are not recognised as such.<sup>24,25</sup>

### Influence of booster vaccination since 2001

A booster, using an acellular vaccine, was introduced for four-year-old children in July 2001. It was anticipated that any associated effects would not become apparent before 2002 (figure 2). In 2002, the age-specific incidence among children of up to four years of age was indeed substantially lower than in 2001. However, since 2001 was an epidemic year, it would be more appropriate to compare the incidence in 2002 with that of the year 2000. When this is done, it can be seen that there is a specific drop in incidence among three- and four-year-olds. The incidence in all other age-groups was slightly higher in 2002 than in the year 2000.

### Hospital admissions

Figure 3 shows the number of individuals, sorted by age, that had to be admitted to hospital in connection with pertussis for the epidemic year 2001 and for 2002. The majority of the hospital admissions involved children below the age of six months who had either not yet been vaccinated or had not completed their course of vaccination.

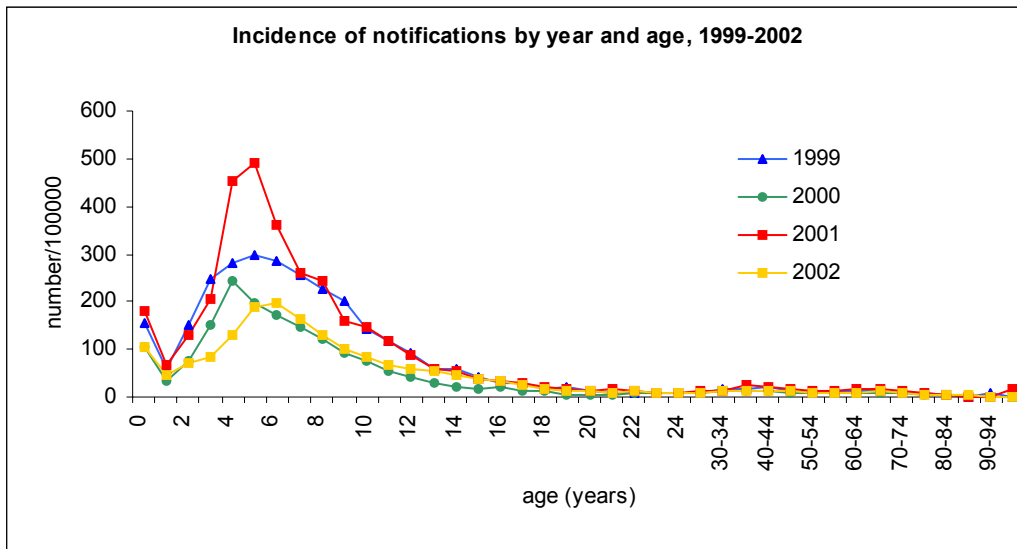


Figure 2 Age-specific incidence for notifications in 1999-2002 (source: RIVM).

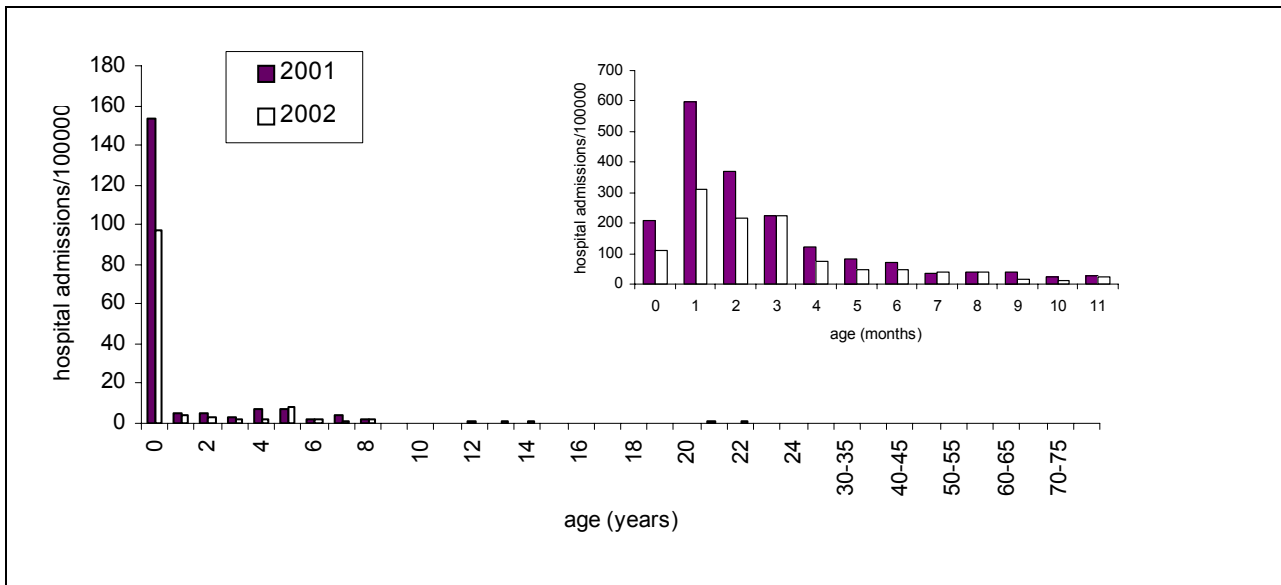


Figure 3 Absolute number of hospital admissions, sorted by age (in years and months) per 100 000 for the age group in question, the Netherlands 2001 and 2002 (source: RIVM).

Table 3 shows the number of hospital admissions for a series of successive years, calculated per 100 000 individuals in an age category. The table shows that, in 2002, the frequency of hospital admissions involving children below one year of age was still elevated in comparison to the figure for the period from 1989 to 1995. The frequency in

children aged from one to four had stabilised. The frequency in children aged from five to nine was still relatively high.

*Table 3* Age-specific incidence of pertussis-related hospital admissions per 100 000 1989-2002 (source: RIVM).

Age (years)	1989-1995	1996	1997	1998	1999	2000	2001	2002
0	66.2	184.0	150.9	99.8	189.3	91.7	153.6	97.5
1-4	4.9	11.6	12.4	7.1	10.3	4.9	5.0	3.1
5-9	1.3	4.9	3.4	2.2	2.5	1.4	3.3	2.7
10-14	0.4	1.2	0.5	0.4	1.2	0.5	0.1	0.4
15-19	<0.1	0.3	0.0	0.1	0.2	0.0	0.0	0.0
≥ 20	<0.1	<0.1	0.1	0.1	0.1	0.05	0.04	0.05
Total	1.2	3.3	2.8	1.8	3.2	1.6	2.5	1.6

### Vaccine effectiveness

While the effectiveness of Dutch pertussis vaccine has not been compared to that of other vaccines in the context of formal trials, it has been established at the level of the population. Table 4 contains estimates of vaccine effectiveness for one- to four-year-olds for the period from 1981 to 2002, calculated using the screening method.\* For the purposes of comparison, estimates are given for the DPT vaccine used in Britain. Estimates calculated on the basis of the screening method are imprecise. While the exact figures must be interpreted cautiously, it is certainly possible to detect trends. Up until 1993, the vaccine was highly effective. After that, there was a marked decline. Interestingly, it seems that there was another decline in vaccine effectiveness in the mid-1980s.

In table 5, the estimates for the Dutch vaccine were calculated separately for one- to four-year-olds. From 1999 to 2002, vaccine effectiveness in one-year-old children was estimated at between 63 and 78 percent, following a marked dip in the preceding period. During 2002, the vaccine's estimated effectiveness among three-year-olds was only 54 percent, while the screening method revealed no effect among four-year-olds. It is therefore likely that the vaccine only provides short-lived protection.

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\*  
Vaccine effectiveness= 
$$\frac{\text{attack rate among non-vaccinated individuals} - \text{attack-rate among vaccinated individuals}}{\text{attack-rate among non-vaccinated individuals}} \times 100$$

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*Table 4* Vaccine effectiveness against pertussis in 1-4-year-olds, determined using the screening method, on the basis of notifications, percentage (95% confidence interval) for the NVI's DPTP vaccine and for Evans-Wellcome's DPT vaccine (sources: <sup>16, 23, 62, 26</sup>).

Year	Name of vaccine	
	NVI DPTP	Evans-Wellcome DPT
1981	99 <sup>a</sup>	
1982	98 <sup>a</sup>	
1983	96 <sup>a</sup>	
1984	95 <sup>a</sup>	
1985	85 <sup>a</sup>	
1986	76 <sup>a</sup>	
1987	72 <sup>a</sup>	
1988	92 <sup>a</sup>	
1989	95 <sup>a</sup>	93 (89 – 95)
1990	95 <sup>a</sup>	
1991	95 <sup>a</sup>	
1992	89 <sup>a</sup>	
1993	96 (93 – 97)	
1994	79 (69 – 86)	
1995	71 (47 – 83)	96 (92 – 98)
1996	51 (36 – 61)	93 (89 – 95)
1997	cannot be determined	89 (84 – 92)
1998	17 (-18 – 41)	
1999	17 (-7 – 35)	
2000	10 (-23 – 34)	
2001	18 (16 – 55)	
2002	39 (16 – 55)	

<sup>a</sup> 95% confidence interval not calculated

Further discussions of the Dutch vaccine's effectiveness, and comparisons with other vaccines, can be found in section 4.1.

Table 5 Estimate of the vaccine's effectiveness (%) sorted by age, on the basis of notifications, calculated using the screening method at a vaccination level of 96%, Netherlands, 1993-2002 (source: RIVM).

Age (years)	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
1	94	78	92	31	30	38	63	78	73	63
2	92	58	42	63	-	32	22	52	46	41
3	95	97	60	38	-	10	-	-	-	54
4	85	77	71	-	-	-	7	-	-	-

- = cannot be determined

Figure 4 shows the vaccination status (as recorded via the Dutch Paediatric Surveillance Unit) for a selected group of children, below the age of 12 months, who were admitted to hospital in connection with pertussis. As anticipated, in the case of children below the age of three months, those involved had either not yet been vaccinated or had not completed their course of vaccination. In contrast, older children with pertussis have generally completed their course of vaccination.

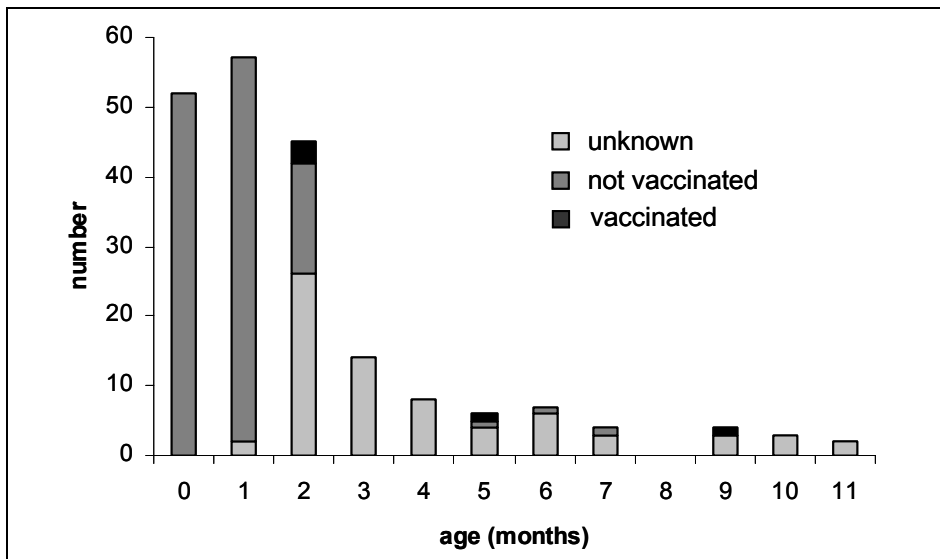


Figure 4 Number of children below the age of 12 months admitted to hospital in connection with pertussis, sorted by vaccination status and age, 2001 and 2002 (age in months) (source: Dutch Paediatric Surveillance Unit, RIVM)

## Conclusion

To summarise, since 1996 four to eight thousand cases of pertussis have been reported each year in the Netherlands, mainly in young children. Each year, between 250 and 500 children are admitted to hospital in connection with pertussis. These cases of the disease

involve 'genuine' pertussis, diagnosed in accordance with strict criteria. Since 1996, eight deaths at least have occurred as a result of pertussis. The reported figure of eight cases represents a minimum, because the actual mortality is conceivably higher. This is because pertussis is not considered as a possible cause of disease in every case of respiratory distress. Since 1994 there has been a substantial decline in the effectiveness of the Dutch vaccine.

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### 2.3 Epidemiology in other countries

Pertussis has a world-wide distribution. In those countries where both the vaccination level and socio-economic standards are low, pertussis causes a considerable burden of disease, as well as high mortality. Senegal, for example, introduced large-scale vaccination in 1986. Previously, the annual rate of pertussis infection among the under-fives was 183 out of every 1000 children, and mortality was 2.8 percent. Six years after the introduction of a vaccination programme, the number of cases had declined by 46 percent. Interestingly, there was also a marked drop among infants who had either not yet been vaccinated or had not completed their course of vaccination. This phenomenon indicates the presence of group immunity.<sup>27</sup> The same phenomenon was observed following the re-introduction of infant vaccination in Sweden, in 1996. Prior to 1996, the frequency of pertussis among Swedish 0 to 4-year-olds was 50 to 60 per 1000. Three years after the introduction of vaccination, this frequency had fallen to 6 per 1000.<sup>28</sup>

Vaccination has therefore resulted in a considerable reduction in the number of cases of pertussis. Recently, however, an increase has once again been seen at international level. That increase primarily affects older children, adults and very young infants who have either not yet been vaccinated or have not completed their course of vaccination. Canada was the only other country in which the peak in pertussis cases involved individuals of an age comparable to that seen in the Netherlands. Following the switch to a better vaccine in 1997-1998, this peak gradually shifted to an older age group.<sup>9</sup>

It is also interesting, of course, to review the epidemiology of pertussis in those countries that share a border with the Netherlands. The surveillance of pertussis in the Flemish community of Belgium (hereafter referred to as Flanders) differs from that in the Netherlands, and is generally less active. Fourteen cases of pertussis were reported for 1997, which represented a slight increase with respect to the preceding years. The majority of these cases were in children who had either not yet been vaccinated or had not completed their course of vaccination. With regard to the pertussis epidemic in the Netherlands, an active approach was made to sixty-two GPs and four hospitals in six municipalities in border regions. This revealed only two previously unknown cases.<sup>29</sup> More recent information reveals no evidence that Belgium is facing a pertussis problem

of comparable scope to that seen in the Netherlands (Van Damme, written communication 2004).

Pertussis policy in Germany is characterised by marked regional variation. Unlike East Germany, the former West Germany carried out no general vaccination between 1975 and 1991. Although vaccination had been generally recommended from 1991 onwards, this had little effect on uptake. Following the registration of acellular vaccines in 1995, however, there was a large increase in vaccination level. Pertussis is not a notifiable disease in Germany, so there is little in the way of epidemiological data.<sup>30</sup>

## 2.4 Comparison

It is difficult to compare epidemiological data on pertussis from different countries, given the enormous variation of their respective registration systems. As a result, any comparison of data derived from notifications is seldom worthwhile. However, one country where such a comparison is worthwhile is the United Kingdom. The effective surveillance in that country reveals a lower frequency of pertussis cases than in the Netherlands.<sup>23</sup>

Another useful exercise is to compare the frequency of hospital admissions in specific age groups. It is estimated that, in 1999, the frequency of admissions to hospitals throughout Finland involving pertussis in children aged less than twelve months was 135 per 100 000 (extrapolation based on a verbal communication from J Mertsola, 2003). This is reasonably similar to the frequency seen in the Netherlands. The Committee is not aware of data for France and the United Kingdom that is comparable to the hospital admission figures for the Netherlands. Tables 6 and 7 compare the Netherlands, Canada and Sweden in terms of the number of pertussis-related hospital admissions.

*Table 6* Hospital admissions per 100 000 for the age group in question, in the Netherlands and Canada (British Columbia), 1990-2000<sup>a</sup>.

country	age	year						
		1990	1993	1996	1997	1998	1999	2000
the Netherland	< 1 jaar	61	115	184	151	100	189	92
Canada	< 1 jaar	191	208	230				111
the Netherland	1-4 jaar	2.7	6.3	11.6	12.4	7.1	10.3	4.9
Canada	1-4 jaar	15	16	17				4

<sup>a</sup> No data for the omitted years. Source: RIVM

The comparison of data in table 6 shows that, at the start of the 1990s, the frequency of pertussis-related hospital admissions in Canada was much higher than in the Netherlands. In the period just prior to the year 2000, however, the frequency seen in the Netherlands roughly doubled. Conversely, the frequency in Canada halved during this

The net effect was that the frequency in both countries was about the same. There was a major epidemic in Canada during the early 1990s. This was followed by a switch to an acellular, five-component vaccine (Pediacef) in 1997-1998. By the year 2000, however, this new vaccine had still not been administered to every child aged four and below. Nevertheless, the effect of the introduction of that new vaccine was already visible. It is anticipated that this will have increased still further since then.<sup>9</sup>

*Table 7* Hospital admissions per 100 000 for the age group in question, in the Netherlands and Sweden, 1997-2002. Source: Sweden: Olin, written communication 2003; Netherlands: De Greeff, written communication 2003.

age (in months)	the Netherland	Sweden
2	317	148
3-5	141	78
6-12	16	8
>12	0.5	0
all ages	2.2	unknown

As stated, Sweden resumed vaccination against pertussis in 1996, after the programme had been suspended for 17 years. During the post-1996 period, there was a marked decline in the frequency of pertussis.<sup>28,31</sup> From 1997 to 2002, the frequency of pertussis-related hospital admissions in the Netherlands was approximately twice that in Sweden.



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## **Causes of the increase**

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In recent years, an increased incidence of pertussis has been reported both in the Netherlands and elsewhere. In this chapter, the Committee discusses some possible explanations for this increase. Section 3.1 deals with the gradual waning of immunity in the rest of the population, following the vaccination of young children. Immunity, it seems, is not permanent. This mechanism accounts for the world-wide increase in young children who have either not yet been vaccinated or have not completed their course of vaccination, older children, and adults. However, this explanation cannot account for the increase seen in the Netherlands. This is because all age groups are affected, including young children who had been vaccinated. Accordingly, another explanation is explored in section 3.2. This involves the possibility that the pressure of large-scale vaccination has resulted in the selection of non-vaccine related strains, which cause the specific Dutch vaccine to become less effective.

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### **3.1 Waning immunity**

#### The duration of protection

The pertussis epidemic is a puzzle whose pieces are only just starting to fall slowly into place. Little is known about the natural course of infection with *Bordetella pertussis*. This is because, prior to the recent development of modern diagnostic methods, people were unable to distinguish between the various stages of infection and disease.

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Before the introduction of vaccination, there was a widely held belief that the immunity derived from natural infection conferred lifelong protection. This was because, at that time, pertussis in older children and adults was seldom reported. There probably were some cases of the disease among adults, but these were not always correctly diagnosed.

We now know that protection against pertussis is of only limited duration, whether this is derived from a natural infection or as a result of vaccination.<sup>32</sup> The decline in immunity over time is referred to as 'waning immunity'.

The exact duration of protection acquired through natural infection is not known. Most authors assume that the protection acquired through natural infection lasts longer than that conferred by vaccination. However, there is no experimental evidence to support this hypothesis. There are two reasons for believing that the protection acquired through natural infection may last longer than that conferred by vaccination. Firstly, there is the fact that the body responds to natural infections by producing additional antibodies that exert their effect via mucous membranes (immunoglobulin A, also referred to as IgA). In addition, the immune response induced by a natural infection in an unvaccinated child is probably more potent than that generated by vaccination. However, it is an established fact that individuals can suffer reinfection several years after an initial natural infection.<sup>33</sup> Wirsing von König has given a figure of 15 years for the duration of protection against pertussis afforded by a natural infection.<sup>34</sup> However, the study on which his estimate is based was carried out on a population with a vaccination level of just a few percent. Given that low level of vaccination, the infection would certainly have been endemic. In practice, therefore, immunity would have been repeatedly boosted. Accordingly, the average duration of protection acquired through natural infection is almost certainly less than the 15-year period suggested.

When vaccination against pertussis was first introduced, old notions concerning the lifelong immunity supposedly conferred by natural infection led people to believe that the protection provided by vaccination was also either long-term or lifelong. From 1950 to 1980, vaccination against pertussis in western countries was generally highly effective, which appeared to confirm this idea. Various studies have demonstrated, however, that the average duration of protection derived from vaccination is about 6-8 years.<sup>34</sup> The use of some cellular vaccines may result in a longer period of protection than when acellular vaccines are used.<sup>28,31.</sup>

### Immunity before and after the introduction of large-scale vaccination

The immunity conferred by vaccination generally protects an individual against pertussis for about 6 to 8 years. Only by coming into contact regularly with the bacterium can individuals maintain an effective level of immunity once this initial period of protection

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has elapsed. If so, their immunity is restored to an effective level, an effect known as 'boosting'. Improved diagnosis has shown that infections with *Bordetella pertussis*, with or without accompanying symptoms, occur in all age groups. Hardly surprising, given that pertussis is highly infectious.

While vaccines primarily provide protection against disease, they also prevent infections that would not necessarily cause illness. There is evidence that the protection against infection generally lapses before the protection against disease. This is because infection and disease are not based entirely on the same mechanisms. Infection is particularly dependent on the bacterium's ability to bind to, and colonise, mucous membranes. Disease is more dependent on the virulence factors that the bacterium releases into the bloodstream and the extent of lung invasion. Various components of bacterial cells are involved in this. It is not known whether different vaccines provide different degrees of protection against infection or disease.

The course of immunity against pertussis in the population before and after the introduction of large-scale vaccination can be reconstructed as follows. Prior to 1950, vaccination levels were insignificant. Accordingly, all young children (80% of the cohorts) became infected before that time. A large proportion of these children went on to develop pertussis, which was associated with a considerable burden of disease and mortality. Before the introduction of vaccination, this facilitated the distribution of the bacterium, which in turn boosted the immunity of older children and adults. Waning immunity meant that older children again became susceptible, only to be boosted by natural infection at a point in time when the protection against infection had waned, while the protection against disease was still largely intact. That pattern repeated itself for the rest of their lives.

As a result, pertussis in adults was rarely seen prior to the introduction of large-scale vaccination. Regular contact with the bacterium protected most adults from the disease. During the first few months of life, infants probably enjoyed a degree of protection through the transfer of antibodies from mother to child. Further protection was provided by group immunity.

Vaccination curtailed the spread of the bacterium from toddlers to older children and adults. Many infections still occur in adolescents and adults. Figures for the Netherlands and other western countries show an attack-rate of around eight percent per annum. However, one net effect of large-scale vaccination has been a decline in infection pressure.

Since vaccinated populations have a lower infection pressure, reinfection occurs at a relatively late stage, at a point in time when the protection against disease has also waned. In such cases, infections will more often be accompanied by symptoms of per-

tussis. In turn, the latter has implications for the spread of the bacteria, which is associated with specific clinical symptoms.

### Development of the current situation

Our current understanding of the duration of protection and the importance of boosting can fairly easily account for the epidemiology of pertussis in western countries.

The large-scale vaccination of infants and toddlers has been gradually introduced since 1950. This has had the effect of dramatically reducing the incidence of pertussis in the vaccinated age groups. Moreover, group immunity has caused this effect to impinge on the age groups above and below them. Mass vaccination has reduced the infection pressure.

Once the period of protection has elapsed, vaccinated children again became susceptible. Initially, this does not cause any problems, since vaccination of the younger age groups, coupled with widespread immunity among adults, means that there is a high degree of group immunity. As vaccinated cohorts age, however, the immunity conferred by natural infection is 'flushed' out of the population. As a result, older children and adults become exposed to a risk of infection.

This leads to a relatively high incidence of pertussis among older children and young adults. Around 10 to 30 percent of adults with long-lasting periods of coughing or attacks of bouts of coughing can be shown to have suffered a recent infection by *Bordetella pertussis*.<sup>34</sup> The occurrence of pertussis among older children and young adults also represents a risk of infection for infants who are too young to have been vaccinated or to have completed their course of vaccination. Unlike those living in situations where natural infection prevails, most young mothers have low levels of antibodies as a result of the low infection pressure. While the importance of maternal antibodies is generally still a matter of debate, in this particular situation they almost certainly make no significant contribution to the protection of very young infants.

### Conclusion

The conclusion is that waning immunity provides a possible explanation of the observed upsurge of pertussis. The vaccination of infants and young children provides good protection against pertussis. One effect of protecting young children is that older children and adults are exposed to the bacterium less often. As a result, the natural boosting that is required for the maintenance of immunity is postponed. This in turn leads to waning immunity among older children and adults. The model conforms with the epidemiological and immunological findings. It is seen by international observers as the best explanation of the changing epidemiology of pertussis at international level.<sup>34-37</sup>

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## 3.2 Reduced effectiveness of the vaccine

By itself, waning immunity cannot fully account for the situation in the Netherlands. Another factor is the reduced effectiveness of the vaccine as a result of the appearance of variants of the bacterium, which have different genetic characteristics. The Committee first discusses what is currently known about this phenomenon, on the basis of research findings. It goes on to explore the suggestion that changes in the bacterial population are responsible for the upsurge of pertussis in the Netherlands.

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### 3.2.1 Research into genetic variants

#### The Netherlands

Mooi *et al* found that all of the bacterial strains occurring in the Netherlands in the 1950s, like the vaccine strains, were characterised by pertactin type 1 (prn1) and pertussis toxin type ptxS1B. During subsequent years, these were gradually replaced by different variants. From 1990 to 1996, 90 percent of patients tested were found to be infected by a strain other than the vaccine type.<sup>38</sup> The researchers formulated the hypothesis that the gradual replacement of vaccine-related bacterial strains by non-vaccine related strains was induced by vaccination pressure. They claimed that the upsurge of pertussis in the Netherlands resulted from the replacement of vaccine-related bacterial strains by bacterial variants with different genetic characteristics (genetic variants).

Incidentally, unlike viral diseases such as influenza, the appearance of genetic variants which have implications for vaccine effectiveness has never before been demonstrated for a bacterial disease. Immunity against bacteria is generally complex, probably involving a simultaneous response to several different components of bacterial cells. Accordingly, any changes will not easily lead to the loss of protective immunity.

However, Mooi *et al* have presented the following arguments to underscore the importance of genetic variants as an explanation for the pertussis epidemic in the Netherlands. Antibodies against pertactin play an important part in immunity.<sup>39-42</sup> Pertactin variants of the vaccine type were found more often in unvaccinated patients than in those who had been vaccinated.<sup>38</sup> The antibodies generated by bacteria or vaccines containing different pertactin variants have been shown to be type specific. Cross-reacting antibodies against other variants were only generated to a very limited extent.<sup>43</sup> One particular mouse model showed that vaccine effectiveness was influenced by variation in pertactin.<sup>39</sup> The pertussis epidemic of 1996-1997 was accompanied by the appearance of bacterial variants characterised by a different pertussis-toxin promoter gene and enhanced virulence (Mooi, written communication 2003). Details of the latter have yet

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to be published. Following publication, it is important that other researchers determine whether comparable changes to this gene have also occurred in other countries.

Mooi *et al* initially formulated their hypothesis to account for the 1996 pertussis epidemic in the Netherlands. They wondered whether the appearance of genetic variants might also help to account for the upsurge in pertussis in other parts of the world.<sup>44,45</sup> Their results and hypothesis have caused a great deal of controversy. After all, if the hypothesis is correct, it means that the current generation of vaccines may provide less protection against the bacterial strains that are currently in circulation. Every vaccine currently in common use, both the older cellular vaccines and the recently developed acellular vaccines, is based on bacterial strains that circulated in the population during the 1950s and 1960s. However, the genetic characteristics of major components of the *Bordetella pertussis* strains found in the population (such as pertussis toxin and pertactin) have changed since the introduction of mass vaccination. A reduction in vaccine effectiveness, resulting from the appearance of genetic variants, may go some way towards explaining the increased frequency of pertussis in many countries.

## Abroad

Has Mooi *et al*'s hypothesis been confirmed by studies in other countries? This is generally not the case.

Among their other findings, the following foreign studies play down the importance of genetic variants as a general explanation of the changing epidemiology of pertussis. Pertactin variants similar to those in the Netherlands have been found in Finland and Italy. Yet Finland had not experienced any pertussis epidemics, even though its high vaccination pressure was comparable to that in the Netherlands. While Italy had no general vaccination programme against pertussis whatsoever.<sup>46,47</sup>

For more than thirty years the French have been using a cellular vaccine which is based on the same two bacterial strains as the Dutch vaccine. From 1991-2001, as in the Netherlands, most pertussis patients were found to be infected with the ptxS1A and prn2 strains of the bacterium, whose characteristics differed from those of the vaccine strains. Throughout this period, however, the frequency of pertussis remained roughly constant.<sup>48</sup>

Surprisingly, every bacterial strain characterised in the United Kingdom from 1990 to 1999 was of the same ptx type as the cellular vaccine used there. An analysis of the genetic variants that occurred from 1940 to 1999 gave rise to the suggestion that the composition of the bacterial population was continuously changing. This would involve the possible expansion of certain types during periods of low vaccination levels, and the elimination of the least 'fit' strains when vaccination levels started to rise again.<sup>53</sup>

In the US it was also possible to study the genetic changes that had occurred over an extended period of time. The ptxS1B and prn1 variants were dominant from 1935 to 1975, later giving way to ptxS1A and prn2. Given the large numbers of vaccines in use, it was impossible to study any association between these changes and specific vaccines.<sup>54</sup> Similar changes in the *Bordetella pertussis* population were also reported in countries such as Germany, Argentina and Poland.<sup>49-51</sup> There are no indications that changes in the bacterial population in any of these countries have led to a significant decline in the vaccine's effectiveness.

To summarise, foreign researchers and observers have generally been unable to confirm that genetic variants are playing a significant part in the upsurge of pertussis.<sup>52-54</sup> However, this could be countered by the observation that few others have studied the appearance of genetic variants, and its implications for vaccine effectiveness, in as much detail as Mooi *et al.* Particularly since the latter used an experimental design which was also capable of detecting more minor, relative effects. While most such studies involved bacterial strain typing, only the research by Mooi *et al* and two other studies investigated the effect of strain variation on vaccine effectiveness. Guiso *et al* found that Infanrix, a three-component, acellular pertussis vaccine, provided protection against all of the strains in circulation. However, they did not determine the relative degree of protection against vaccine-related strains and other strains.<sup>52</sup> Gzyl *et al* opted for a quantitative determination of the degree to which mice were able to clear the bacteria after nasal exposure. This group alone found, like Mooi *et al*, that bacterial strains with pertactin or pertussis toxin variants which differed from those of the vaccine strain were less readily eliminated than those with the same characteristics as the vaccine strain.<sup>55</sup>

## Analysis

Before the role of the genetic variants can be properly identified, two questions must be answered. Firstly, were the observed genetic changes in the pertussis bacterium partly induced by vaccination? Secondly, do the changes have any repercussions for vaccine effectiveness?

The answer to the first question is probably an affirmative. Studies in the Netherlands, the US and the United Kingdom have shown that considerable genetic variation existed prior to the introduction of large-scale vaccination. The introduction of vaccination was followed by a decline in genetic diversity, due to the elimination of those variants that had been incorporated into the vaccine. The general picture from studies in other countries also involves the selection of non-vaccine-related bacterial strains. These strains seem to have a certain immunological advantage. However, the immunology of *Bordetella pertussis* infections is not governed solely by the immune response to the above-mentioned pertactin and pertussis-toxin genes. This is shown, for example, by the

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occurrence of pertactin variants in the very different circumstances pertaining in Finland and Italy. It is also evident from the persistence of vaccine-related ptxS1A in the United Kingdom, in spite of the fact that a highly effective cellular vaccine is used in that country.

The second question is whether the observed genetic changes have caused the world-wide upsurge of pertussis. In general, the answer to this question is negative. On the basis of these international studies, the Committee has concluded that there is firm evidence that vaccination against pertussis can lead to the selection of bacterial strains whose genetic characteristics differ from those used in the vaccine. This involves selection for relevant characteristics that are capable of conferring an immunological advantage on the bacterial strains in question, and which may be associated with the extent to which these strains can cause disease.

In general, any immunological advantage appears to be limited, possibly as a result of immunity against other relevant components of the bacterium. Researchers in other countries have yet to find convincing evidence of reduced vaccine effectiveness. In this context, the above-mentioned pertactin variants were already circulating through the populations of Sweden and Italy by the time major trials into the effectiveness of acellular pertussis vaccines took place in those countries. In those trials, the efficacy of good acellular vaccines was estimated at 80-85 percent.

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### 3.2.2 *Development of the current situation in the Netherlands*

What implications do the findings concerning genetic variants hold for the current situation in the Netherlands? In addition to the part played by changes in the bacterium, the Committee addresses the possibility of changes in the vaccine caused, for instance, by modifications to the production process.

#### Verdicts of previous advisory reports

In previous advisory reports, the Health Council has addressed the possible causes of the 1996 epidemic and of the subsequent upsurge in the number of pertussis cases.<sup>1,2</sup> In its 1997 advisory report, the Committee cited as a possible cause the appearance of *Bordetella pertussis* strains with different genetic characteristics to those strains used in the vaccine. This mainly involved variants of pertactin, one of the bacterium's surface proteins. Pertactin (PRN) and pertussis toxin (PT) are bacterial antigens which are considered to be critically important for the establishment of protection. It was the failure of the Dutch vaccine to generate adequate antibody levels against these very proteins which would have created the conditions in which such variants could arise and spread.

At that time, this was the basis for the Committee's recommendation that the production process be modified to increase the amount of pertussis toxin in the vaccine.

In the advisory report which it published in the year 2000, the Committee confirmed its previous recommendations. However, by that time it had become clear that the variants found in the Netherlands also occur in countries where the use of other vaccines creates different types of selective pressure. This observation, together with the absence of any evidence of reduced vaccine effectiveness in those countries, meant that the Committee was unable to reach a final verdict at that time.

### Changes in the bacterium

As an explanation of the epidemic, the appearance of genetic variants is an appealing concept. This involves the selection, by vaccination pressure, of certain bacterial variants within the population. These variants differed from the strains used in the vaccine, which was therefore less effective at providing protection against them. This is a familiar phenomenon in viruses, whose genetic material is relatively simple. However, this has never before been seen in bacteria, whose genetic material is much more complex. Now that it can take stock of matters, the Committee is forced to conclude that the results are far from unambiguous.

Mooi *et al* have shown that antibodies generated during inhalation experiments in mice, in response to the various pertactin variants of *Bordetella pertussis*, confer type-specific protection. The differences are relative since, while these antibodies clearly offer better protection against the types that generated them than against other types, there is also some cross-reaction. At the same time, however, other researchers showed that bacterial strains with the pertactin and pertussis toxin variants that were claimed to be responsible for the epidemic in the Netherlands had long been present in countries where there were no epidemic upsurges (Finland, Britain). The escape variant hypothesis is also challenged by several cases which cannot be accounted for by vaccination pressure (Italy, Britain).

It is fascinating to compare Aventis' cellular vaccine against the vaccine produced by the Netherlands Vaccine Institute. These vaccines are both based on the same two seed strains. Unlike the NVI's product, however, the French vaccine does generate a strong antibody response against pertussis toxin. The difference can probably be explained by a feature of the NVI's vaccine production process which was introduced at that time in an attempt to reduce the vaccine's adverse effects.<sup>12</sup> For more than 30 years, this was the only pertussis vaccine used in France. Throughout that period, the vaccine remained unchanged. However, the bacterial strains in the population appeared to have been gradually replaced by strains whose pertussis toxin and pertactin variants differed from those contained in the vaccine. Nevertheless, there is no evidence that the French

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vaccine has lost any of its efficacy over the course of time.<sup>48-56</sup> The Committee suspects that a comparative study of the French and Dutch vaccines would contribute to an improved understanding of protective immunity in pertussis.

In most countries, the bacterium appears to have derived only a slender selective advantage from the development of pertactin and pertussis toxin variants. This is not significant enough to have a major adverse impact on vaccine effectiveness. Almost without exception, international observers have concluded that the development of bacterial strains with the pertactin and pertussis toxin variants in question has no implications in terms of vaccine effectiveness.

However, use of the Dutch vaccine probably involves a relatively large selective advantage. This is because that vaccine generates very few antibodies against pertussis toxin and pertactin, two of the most important pertussis antigens.

### *Changes in the vaccine*

At that time, in compliance with a request by the board of RIVM, Cohen investigated an alternative explanation for the vaccine's reduced effectiveness, involving changes in the vaccine (and in its production process).<sup>57</sup> The report revealed that, in several cases, the strength of the basic product/vaccine had fallen below the four IU required by the WHO. Particularly when the vaccine from the lot in question was stored for a relatively long period of time before being administered, this could have produced insufficient levels of protection.

After subjecting the Cohen report to a further critical analysis, the Committee had a number of questions which it submitted to the NVI. The central question was whether changes in the production process, involving the culture of seed strains (including changes to the duration of the process) and scaling up, were adequately monitored.

The Committee notes that the NVI's production methods have undergone a process of professionalisation in recent years. Over the course of time, vaccine production has undergone some radical changes. One example is the scale involved. Initially, 70-litre vats were used, however the bacteria are now cultured in vats with a capacity of 1000 litres. Looking back, it is difficult to assess the extent to which past production problems might have been involved in the post-1994 decline in the effectiveness of pertussis vaccine. The Committee is unaware of any specific evidence in this regard.

### **Analysis**

However, an analysis of the epidemiological data does yield one specific item of evidence concerning the cause of the 1996 epidemic. In chapter 2 it was shown that the sudden upsurge in the number of pertussis cases affected all age groups (table 2). If this was

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caused by a change in the vaccine, you would expect a gradual increase in the incidence of pertussis, starting in young, recently vaccinated children. The fact that the epidemic occurred suddenly, across all age groups, strongly suggests that the change occurred in the bacterium, rather than in the vaccine.

The epidemic of the mid-1980s also affected all age groups. This came at the end of a period (1976 to 1984) in which an attempt was made to reduce the vaccine's adverse effects by reducing its strength from 16 to 10 IOU/HD (international opacity units per human dose).

An interaction between the bacteria and the vaccine used in the Netherlands may account for the findings in this country. The vaccine generates low levels of antibodies against two of the three major pertussis antigens, pertactin and pertussis toxin. Escape variants therefore enjoy a substantial advantage, compared to situations in which a strong immune response is generated. Accordingly, the risk that more virulent bacterial strains will be selected is greater here than in other countries.

This hypothesis is consistent with the findings on the 1996-1997 epidemic. It can also account for the epidemic upsurge of the mid-1980s. The use of reduced strength vaccine, from 1976 to 1984, facilitated the appearance of genetic variants. Mathematical modelling of the epidemic also points to a change in the bacterium as the most plausible explanation.<sup>58</sup> Once the vaccine was returned to its original strength, its effectiveness was restored and the epidemic upsurge faded away.

However, this situation was not to last. There was another decline in the vaccine's effectiveness at the start of the 1990s. In addition to the pertactin and pertussis toxin variants, the 1996-1997 epidemic also involved changes to the pertussis toxin promoter gene, which codes for one of the bacterium's virulence factors. The resultant increase in virulence led to a major pertussis epidemic.

It therefore seems likely that a combination of three different factors led to the current situation in the Netherlands. One was a relatively weak vaccine. Another was the selection of genetic variants of pertactin and pertussis toxin which had a relatively limited immunological advantage. Lastly, there was a mutation in the pertussis toxin promoter gene. This situation is specific to the Netherlands. It is substantially different from situations involving the use of vaccines which, even though they may be based on the same seed strains, nevertheless generate strong immunity against pertussis toxin and pertactin.

Switching to one of the latter vaccines would be expected to improve the situation in the Netherlands. The problems encountered in the Netherlands, which are due to the appearance of genetic variants and more virulent bacterial strains, are probably directly associated with the type of vaccine in use here.

This combination of genetic variants, virulent strains, and the vaccine in use in the Netherlands also resolves the apparent contradiction between the findings of studies in the Netherlands and those carried out elsewhere.

However, the possibility cannot be excluded that other countries have in the past encountered problems with their vaccines that were comparable to those in the Netherlands, or that they will do so in the future. To date, no such situation has been documented.

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### **3.3 Conclusion**

The Committee concludes that waning immunity provides a plausible explanation for the increased world-wide incidence of pertussis. In the Netherlands, unlike the situation elsewhere, there is also evidence that the upsurge in pertussis mainly results from the appearance of genetic variants and of more virulent bacterial strains. The age-specific incidence data obtained during the 1996-1997 epidemic can best be explained in terms of a change in the bacterium which led to reduced vaccine effectiveness in all age groups.

The Netherlands' unique position in this respect may be due to the specific characteristics of the vaccine used here. This contains low levels of the major antigens pertussis toxin and pertactin. Switching to another vaccine would be expected to improve the situation in the Netherlands.

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## Vaccine selection criteria

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The general principles of the National Vaccination Programme have already been discussed by the Committee in a previous advisory report, as have the criteria to be met by vaccines for admission to the programme.<sup>59</sup> Pertussis is potentially a serious disorder, especially in young children. The Committee therefore takes the view that it was justifiable to include vaccination against pertussis in the National Vaccination Programme.

In view of the fact that vaccination against pertussis has become less effective here, people in the Netherlands want to know what measures need to be taken to improve its effectiveness. In this chapter, the Committee provides a summary of the criteria which it has reviewed in the course of its investigation. This includes an indication of the weight assigned to each criterion.

In the case of pertussis, two criteria that were reviewed in detail were effectiveness (section 4.1) and adverse effects (4.2). These criteria carried more weight than the others. In section 4.3 the Committee addresses the extent to which novel insights in the field of immunology should contribute towards the assignment of weight. In section 4.4, consideration is given to the importance of retaining expertise and national vaccine production. Another consideration that influenced the Committee's recommendations, however, was the availability of specific combined vaccines for inclusion in the NVP. This is dealt with in section 4.5. The Committee employs the general principle that any discomfort caused to children by the vaccination programme should be within acceptable limits, and preferably as little as possible. One of the implications of this criterion is that the number of injections should be kept to a minimum. This criterion is applied when considering various scenarios in chapter 5. Efficiency is also a criterion for the

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inclusion of a vaccination in the NVP. The efficiency of vaccination against pertussis is discussed in section 5.6.

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## 4.1 Effectiveness

### Evaluation method

A vaccine's effectiveness is, of course, a vital consideration when reaching a decision regarding its use. Ideally, vaccine efficacy should be evaluated in standardised, well designed and blinded trials.<sup>32</sup> Data on the frequency of pertussis in various countries is often reviewed in the course of discussions about the effectiveness of the vaccines that they use. Nevertheless, the Committee feels that such data is not suitable for evaluation purposes. This is primarily because surveillance systems differ enormously from one country to another, which makes it difficult to compare frequency data. Even if the comparison were to be restricted to much more sharply defined groups (such as data on hospital admissions in specific age groups), the epidemiology of pertussis is still too complex and too dependent on local factors for a verdict to be reached concerning the effectiveness of the vaccines used.

When evaluating the various vaccines, the Committee made an assumption regarding the data on vaccine efficacy against pertussis and on adverse effects. It assumed that data on DPT combined vaccines (against diphtheria, pertussis and tetanus) is equally applicable to DPTP/Hib combined vaccines from the same manufacturer (which are also effective against poliomyelitis and *Haemophilus influenzae* type b). Data on composition, antibody response, efficacy and adverse effects is summarised in tables 1-4 in annex C.

### Results

Large-scale trials in Italy (1992) and Stockholm (1993) were critically important for evaluating the efficacy and adverse effects of acellular vaccines.<sup>60,61</sup> In the Italian trial, two acellular combined vaccines (Infanrix and Acelluvax) and a cellular combined vaccine manufactured by Connaught were compared to a placebo. The vaccine efficacy of Infanrix was estimated at 84 percent (95% confidence interval 76-89), while that of Acelluvax also came to 84 percent (76-90). At 36 percent (14-52), the efficacy of the cellular vaccine was quite low. In the Swedish trial, the acellular combined vaccines Pediacel, Infanrix and SKB-2 were compared to a cellular vaccine manufactured by Evans-Wellcome. This was not a placebo-controlled trial, so vaccine efficacy can only be estimated relative to a comparative vaccine. Compared to the cellular vaccine, the relative risks of pertussis were 0.85 (0.41-1.79) for Pediacel, 1.38 (0.71-2.69) for Infan-

rix and 2.3 (1.5-3.5) for SKB-2. Twenty one and a half months into the follow-up study, it emerged that Pediacel provided even better protection against pertussis than the cellular vaccine from Evans-Wellcome, which generally performs very well.

Three and five years into the follow-up study, however, there was evidence that this acellular vaccine provided less effective protection over the longer term than the cellular vaccine.<sup>28,31</sup> After five years, the incidence of pertussis in the group of children that had received the Evans-Wellcome vaccine was 32 per 100 000 (95%-betrouwbaarheidsinterval 21-43). The figure for Pediacel was 56 (42-71) per 100 000.

Jefferson *et al* have carried out a meta-analysis of 49 randomised, controlled trials into the efficacy and adverse effects of cellular and acellular pertussis vaccines.<sup>7</sup> This analysis revealed a marked variation in the efficacy of cellular vaccines, which ranged from 37 to 92 percent. The efficacy of acellular vaccines was dependent on the number of protein components. Vaccines with one and two components had an efficacy of 67-70 percent, while the figure for vaccines with three or more components was 80-84 percent.

Unlike cellular vaccines, acellular vaccines suffer from the limitation that they are probably ineffective against pertussis caused by *Bordetella parapertussis*. In the Netherlands, this bacterium accounts for about four percent of all cases of pertussis.<sup>4</sup>

No comparative-trial data is available for the cellular vaccine used in the Netherlands. In cases such as this, efficacy can only be evaluated at population level. Vaccine effectiveness can be estimated using the screening method mentioned in chapter 2. This method is less reliable than a direct comparative study, in the form of a trial.

However, other countries also use the screening method to measure vaccine effectiveness. In Britain, for example, this approach was used to estimate vaccine effectiveness in children aged 1 to 4. This value was 93 percent in 1989 (95% confidence interval 89-95), 96 percent in 1995 (92-98), 93 percent in 1996 (89-95) and 89 percent in 1997 (84-92). For details see table 4 in chapter 2.<sup>23,62</sup> The relatively low level of protection in 1997 was probably associated with the epidemic upsurge in pertussis which occurred in that year. Vaccine effectiveness from then until the end of 2002 was estimated to be about 90 percent (Miller, written communication 2003). In the United States too, vaccine effectiveness was determined using the screening method. From 1992 to 1994, vaccine effectiveness was estimated at 90 percent (88-92) in children aged about two to four who had received four doses of vaccine.<sup>63</sup> Throughout the period of the investigation, both countries primarily used cellular pertussis vaccines.

Vaccine effectiveness in the Netherlands, as determined using the screening method, was high during the early 1980s (more than 90 percent for one- to four-year-olds; see table 4 in chapter 2). It declined somewhat during the mid-1980s. This reduction was accompanied by an increase in pertussis notifications. At the time, this was seen as an artefact of changes in the case definition.<sup>17,64,65</sup> As in the 1996-1997 epi-

demid, the increase seen from 1984 to 1986 affected all age groups.<sup>65</sup> During the second half of the 1980s, vaccine effectiveness was restored. The temporary decline in vaccine effectiveness was probably due to the fact that a lower vaccine dose was used from 1976 to 1984. The estimate for 1993 was 96 percent (95% confidence interval 93-97). Effectiveness subsequently underwent a rapid decline until, in 1996, it was just 51 percent. In 1997, workers using this method were actually unable to find any protective effect at all.

As a result of the 1996-1997 epidemic, there was a critical evaluation of DTP vaccine production at the NVI. In order to increase the level of pertussis toxin in the vaccine, a slightly different production process was introduced in December 1997. As pointed out in chapter 2, there is only limited evidence that this has contributed to the slight increase in vaccine effectiveness. From 1999 to 2000, screening-method estimates of vaccine effectiveness in 1-year-old children varied from 63 to 78 percent. However, it seems that the vaccine only provides short-lived protection. During 2002, the vaccine's estimated effectiveness among three-year-olds was only 54 percent, while the screening method no longer showed any effect among four-year-olds (table 5 in chapter 2). Estimated vaccine effectiveness for the entire group of one- to four-year-olds was 39 percent. Part of this can be attributed to the acellular vaccine booster that was introduced on 1 July 2001. If the calculation of vaccine effectiveness is restricted to children aged from one to three and a half (who are known not to have received a booster), then the resultant estimate of vaccine effectiveness is 29 percent.

Thus there is no data regarding a direct comparison. The Committee nevertheless feels that the above-mentioned points can justifiably be interpreted as showing that several vaccines, including both cellular and acellular types, are more effective than the Dutch pertussis vaccine.

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## **4.2 Adverse effects**

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### **4.2.1 Evaluation method**

Vaccine safety, like vaccine efficacy, should ideally be evaluated in well designed, controlled and randomised trials. Studies of a vaccine's effectiveness and of its side effects, which are usually combined, are part of the assessment for admission to the market. Various pitfalls inherent to the methodology for investigating the safety of vaccines can cause the frequency and severity of adverse effects to be either overestimated or underestimated.<sup>66,67</sup> Following admission to the market, postmarketing surveillance can take the form of a system for registering adverse effects. In some cases, this can serve as an alternative to extensive clinical trials, especially in the case of uncommon adverse effects.

The major trials in Italy and Sweden, together with the meta-analysis of a large number of randomised and controlled trials by Jefferson *et al*, have provided the most scientifically reliable data on adverse effects to pertussis vaccines.<sup>11,60,61</sup> As with effectiveness, there is no data from direct comparisons of adverse effects for the vaccines used in the Netherlands. The Committee assumes that the safety profile of the Dutch cellular vaccine is comparable to the general pattern for cellular vaccines.

The Netherlands has a system for the postmarketing surveillance of adverse effects associated with vaccines used in the NVP. The register is maintained by RIVM, which provides annual reports on this topic.<sup>69</sup> To date, all severe or unusual symptoms and all symptoms involving permanent impairments have been submitted to a Health Council committee (Committee on adverse effects following immunisations under the National Vaccination Programme).<sup>68</sup> Not only are virtually all young children vaccinated several times, but the reported symptoms and disorders also occur in unvaccinated individuals of this age. Special expertise is therefore required to determine whether there is an actual connection between the vaccination and the reported disorder. Due to the lack of data from comparative trials on the adverse effects of the Dutch pertussis vaccine, the Committee sets great store by this registration. However, it feels also that it is important to point out the limitations of registration. This is a passive system, in which data collection only occurs in conjunction with a notification. Notifications regarding severe post-vaccination disorders are expected to be reasonably complete. However, it is anticipated that notifications of less serious or transient post-vaccination symptoms will be far from complete.

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#### 4.2.2 *Classification of adverse effects, by severity*

There is no generally accepted international classification of adverse effects. Nor is there consensus regarding the question of which post-vaccination symptoms should be assessed as severe. The Health Council's Committee on adverse effects following immunisations under the National Vaccination Programme does not use a strict criterion, instead it evaluates the assessment of all notifications submitted to the RIVM regarding deaths, all symptoms involving permanent impairments and all unusual symptoms. Notifications concerning only high and/or long-lasting fever, febrile and afebrile convulsions, persistent, inconsolable screaming, hypotonic hyporesponsive episodes or abscess formation are not evaluated, unless special aspects of the notification indicate a need to do so.<sup>68</sup> This does not detract from the fact that notifications which are not assessed as serious can nevertheless be very worrying and distressing both to the child in question and its parents.

Given the lack of a generally accepted classification system for adverse effects, by severity, the Committee has used a system of its own. It defines the concept of 'serious

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adverse effect' as 'death', 'serious neurological symptoms' or 'adverse effects of vaccination, with permanent physical impairments. The Committee also distinguishes 'highly unpleasant adverse effects', which include adverse effects that can be very worrying and distressing both to the child in question and its parents, but which do not involve permanent physical impairments'. This second category includes febrile convulsions, hypotonic hyporesponsive episodes, and persistent, inconsolable screaming. All adverse effects that do not fall within the first or second categories are grouped into the category of 'other adverse effects'. These include symptoms associated with the injection site, such as pain, swelling or redness, fever and high fever, malaise, poor appetite, vomiting, drowsiness, and grogginess.

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### 4.2.3 Results

#### General

The adverse effects associated with the DPTP/Hib combined vaccine, which is used for the basic vaccination for infants, are primarily caused by the pertussis component. The register of side effects produced by vaccines used in the NVP, which is maintained by RIVM, shows that in 2001 there were 1034 notifications of possible adverse effects following DPTP/Hib vaccination. These mainly involved systemic reactions (427 children), hypotonic hyporesponsive episodes (273), discoloured legs (173) and persistent, inconsolable screaming (49). Fifty eight to one hundred percent of these notifications (dependent on the category) were thought to involve a possible or probable link with vaccination. In 2001, the notifications for all vaccines (which of course includes vaccines other than the DPTP/Hib vaccine) involved 10 cases of epilepsy, 55 cases of atypical seizures, 56 cases of febrile and afebrile convulsions, 1 case of encephalitis and 7 deaths. In none of the cases of epilepsy, encephalitis or death was a link to vaccination considered to be possible or probable. However, such a link was considered possible or probable in 44 cases of atypical seizures (80 percent) and 45 cases of febrile convulsions (80 percent).<sup>69</sup>

#### Serious adverse effects

The issue of whether cellular pertussis vaccines can give rise to serious neurological adverse effects, such as encephalopathy has, in the past, been the subject of considerable debate. The fact is that initial claims concerning the frequency of such serious neurological adverse effects have not been corroborated. Improvements in research methodology led to a decline in the frequency at which such serious adverse effects might occur.

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Since 1987, there have been no further reports in the Netherlands of serious neurological adverse effects possibly arising from pertussis vaccination.<sup>69</sup>

Another important question is whether epilepsy can develop as a result of vaccination (including pertussis vaccination). This issue has been the topic of a large body of research. This research has shown that there is no reason to assume the existence of a connection between vaccination (including pertussis vaccination) and afebrile convulsions, epilepsy, and West Syndrome.<sup>70-72</sup>

West Syndrome, which is also known as infantile spasms, is an epileptic syndrome that occurs in young children. It is associated with characteristic, anomalous electroencephalogram traces and developmental stagnation.

This is a highly heterogeneous syndrome. In the majority of cases, further examination reveals one of several other disorders on which the syndrome might be based. The prognosis is usually poor.

In 85 to 90 percent of cases, this syndrome develops during the first year of life. This is, of course, the same period in which the DTP/Hib vaccinations are given. The latter makes it difficult to investigate a possible causal relationship between vaccination and West Syndrome.

While no causal relationship was found in the case of West Syndrome, there was a relationship in terms of time. This is also known as a temporal shift. What this means is that, soon after vaccination, there is an increased risk of an attack which will subsequently be recognised as the first manifestation of West Syndrome. Later after vaccination the risk actually declines, so on balance there is no increase.<sup>73,74</sup> As mentioned, the clinical picture usually develops during the first year of life. The incidence of West Syndrome is between 1 child in 2000 and 1 child in 6000.<sup>114,115</sup> This frequency shows good correspondence with an estimate of the Dutch situation (WFM Arts, verbal communication 2004). In the Netherlands, around 200 000 babies are born each year. Accordingly, from 35 to 100 children will be diagnosed with this clinical picture in the same period. In some of these cases, the first manifestations of the disease (usually convulsions) will be induced (but not caused) by vaccination. The exact nature of the trigger mechanism in such cases is still unknown. It is conceivable, but not proven, that a reaction to the vaccination (such as fever) could serve as a trigger. If this is indeed the case, then the incidence of syndrome development following (but not as a result of) vaccination could be reduced by the use of less reactogenic acellular vaccines.

### Highly unpleasant adverse effects

The authoritative meta-analysis carried out by Jefferson *et al* found the following frequencies for cellular vaccines: convulsions 4/6780 (0.06 percent), hypotonic hyporesponsive episodes 14/6780 (0.21 percent), more than two hours of inconsolable

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screaming 81/6851 (1.2 percent).<sup>11</sup> The Committee assumes that these frequencies are also applicable to the Dutch vaccine.

Compared to cellular vaccines, there were strong indications that acellular vaccines less often give rise to febrile convulsions (odds ratio for three-component vaccines 0.15 (95% confidence interval 0.02-1.22), odds ratio for four-component vaccines cannot be measured) and hypotonic hyporesponsive episodes (odds ratios 0.38 (0.23-0.63) and 0.76 (0.47-1.21) respectively). Compared with a diphtheria-tetanus-vaccine or placebo, more than two hours of inconsolable screaming was associated with the use of a cellular vaccine (odds ratio 4.72 (2.94-7.59)), but not with an acellular vaccine (odds ratio 1.43 (0.88-2.31)). When acellular vaccines were used, the frequencies of febrile convulsions, hypotonic hyporesponsive episodes, and more than two hours of inconsolable screaming were not significantly different from those associated with the use of a placebo.<sup>11</sup>

RIVM give the following estimates of adverse effects defined as highly unpleasant: febrile convulsions 1 child in 5000 to 1 child in 10000, hypotonic hyporesponsive episodes 1 in 1000, and more than three hours of intense screaming 1 in 100 to 1 in 1000.<sup>75</sup> These frequencies are based on extrapolations from RIVM's passive registration of adverse effects and on various specific studies in the Netherlands (PE Vermeer-de Bondt, written communication 2004). It is difficult to assess the validity of these estimates.

#### Other adverse effects

Clinical trials have shown that local reactions around the injection site, such as pain, redness or swelling, occur very frequently indeed. There was a clear difference in frequency between the use of cellular vaccines (local reactions in almost 30 percent of children) and acellular vaccines (less than 5 percent of children).<sup>11</sup> In addition, cellular vaccines more often lead to fever responses than do acellular vaccines. The corresponding rates were 1 and 0.2 percent of children suffering fevers in excess of 39°C in the first three days after vaccination.<sup>11,32</sup> Systemic symptoms are also very common, especially after vaccination with a cellular vaccine. Such symptoms include listlessness, reduced appetite, fever, grogginess, drowsiness, malaise and crying.

It was shown that, in comparison to cellular vaccines, acellular vaccines less often lead to local reactions (odds ratios for three-component and four-component acellular vaccines respectively are 0.12 (0.11-0.13) and 0.29 (0.19-0.44)) and to fevers in excess of 39°C (odds ratio 0.12 (0.07-0.20) and 0.25 (0.10-0.59) respectively). Unlike acellular vaccines, the frequencies of local symptoms and fever associated with the use of cellular vaccines were significantly higher than those associated with the use of a diphtheria-tetanus-vaccine or placebo.<sup>11</sup>

## Conclusion

Both cellular and acellular pertussis vaccines seldom or never produce serious adverse effects. Following vaccination with cellular vaccines, the frequencies of adverse effects in the categories ‘highly unpleasant’ and ‘other’ are generally higher than those associated with the use of acellular vaccines. In general, acellular vaccines undeniably have a more favourable adverse effect profile than cellular vaccines.

The data supporting the more favourable adverse-effect frequency of acellular vaccines all came from trials involving the basic vaccination for infants. Theoretically, it is conceivable that sensitisation would produce a higher frequency of adverse effects when such vaccines are used at a later stage, as a booster. However, published data obtained from several years of experience with the use of acellular pertussis vaccines also confirms that their adverse effect profile is more favourable than that of cellular vaccines.<sup>76</sup>

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### 4.2.4 *Estimating the number of avoidable adverse effects*

Making a few assumptions, it is possible to estimate the number of adverse effects that could be avoided if an acellular vaccine were to be used instead of a cellular vaccine.

On the basis of the meta-analysis carried out by Jefferson *et al*, the total frequency of adverse effects defined as highly unpleasant which are associated with the use of a cellular vaccine would be set at 1.4 percent. The corresponding rate for an acellular vaccine would be about 0.3 percent. Taking 750 000 injections of the vaccine as a basis, the use of an acellular vaccine would enable 8250 cases of highly unpleasant adverse effects to be avoided each year, in addition to numerous ‘other adverse effects’.

On the basis of RIVM’s estimates, the total frequency of adverse effects defined as highly unpleasant (convulsions, hypotonic hyporesponsive episodes, persistent, inconsolable screaming), which are associated with the use of the current vaccine, can be set at 0.3-1.2 percent. Accordingly, if we take 750 000 injections as a basis, this would result in 2250 to 9000 cases of such vaccine-induced adverse effects each year. As previously stated, however, it is difficult to assess the validity of these estimates. Furthermore, this source does not include an estimate of the number of adverse effects associated with the use of an acellular vaccine.

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## 4.3 **New data on the immunology of pertussis**

Since the year 2000 advisory report was written, important new insights have been published on the immunology of pertussis and, more generally, on the functioning of the innate immune system. The Committee will investigate the extent to which these insights are currently influencing vaccine selection.

## The immunology of pertussis

The immunology of pertussis is complex and certainly still not fully understood. With regard to pertussis vaccines, until a few years ago the emphasis was very much on the extent to which they generate antibody production. Antibodies against pertussis toxin, pertactin and fimbriae are considered to be particularly important in terms of protection.<sup>77,78</sup> While the immunity generated by natural infection provides a good model for protective immunity against pertussis, research in this area is still at a very early stage. However, it has since become clear that cellular immunity, mediated by T-helper cells and the innate immune system, is also an extremely important aspect of protection against pertussis.<sup>79,80</sup>

## The function of the innate immune system

Broadly speaking, the immune system can be divided into two compartments. On the one hand there is the innate immune system. This is present at birth and has several general antimicrobial functions, which vary little from one individual to another. On the other hand, there is the much more complex acquired immune system. On the basis of previous exposure, this can initiate an immune response that is specific to the antigen in question. The innate immune system is designed to stop pathogens with an immediate immune response, while it may take several days or weeks for the acquired immune system to develop an immune response.

What may well be the most exciting recent discoveries in the field of immunology are now emerging from research into the innate immune system and its interaction with the acquired immune system. The quality of the acquired response is partly determined by the innate immune system. It appears that stimulation of the innate immune system by bacterial material (such as lipopolysaccharide (LPS), CpG DNA and heat shock proteins) leads to a more effective and better regulated immune response.

The cells which present antigens to the B and T lymphocytes of the acquired immune system appear to possess receptors for various products secreted by bacteria. Various types of these Toll-like receptors are activated, dependent on the nature of the bacterial product in question. This in turn triggers the production of a wide range of interleukins and other messenger proteins. This system of Toll-like receptors and interleukins permits fine regulation of the immune response mediated by B cells (antibody production) and T cells (cellular immune response). It produces an initial inflammation reaction followed by suppression of an undesirable allergic or autoimmune response. By means of the same system, bacterial products can have a reinforcing (adjuvant) action on certain antigens. In some cases it would not even be possible to generate an immune response without this system. This supports the empirical observation that extracts of

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mycobacteria, for example, can act as powerful stimulants in the responses of T-cells and B-cells to antigens.

The innate immune system seems to be a vital part of the immune system as a whole. It helps maintain a good balance between immunity, allergy and autoimmunity.<sup>81,82</sup> The innate and acquired immune systems are finely attuned to one another, in an interaction that has evolved over millions of years.

### Implications for vaccine development

Our growing understanding of the workings of the innate immune system may have implications for vaccine development. The mechanism which is probably involved here is the mutual harmonisation of various groups of T lymphocytes, known as T helper cells (Th). These cells have a regulatory function in the immune system and are important in maintaining a balance between immunity, allergy and autoimmunity.

‘Immunity’ involves an adequate and measured response to intruders. ‘Allergy’ involves a response directed at antigens from outside the body which are normally well tolerated. Autoimmunity is a response directed against self-antigens, which are also normally well tolerated, of course. Immunity, allergy and autoimmunity are the various possible manifestations of a single, complex, regulated system. In an ideal situation, the immune system provides adequate immunity, without lapsing into allergy or autoimmunity.

When an individual is born, the acquired immune system is still not fully developed. The predominant type of T-helper lymphocyte is the Th2 type. At this stage, protection against infectious diseases is still largely based on antibodies obtained from the mother. However, there is soon a shift to a new equilibrium involving T helper 1 lymphocytes (Th1 cells). Not only are Th1 cells important to the development of cellular immunity, they also kill bacteria by phagocytosis. It may be that the immune system is unable to make the switch to Th1 entirely on its own.

Infections may have a part to play in this, via the innate immune system and the system of Toll-like receptors. If the Th2 cells continue to dominate, then the individual in question may become more susceptible to the development of allergies. On the other hand, excessive activity by the Th1 system appears to predispose individuals to autoimmunity. Given that extensive exposure to worm infections throughout large areas of the non-Western world generally does not result in allergy (despite a predominance of Th2 cells) Yazdanbakhsh has hypothesised that there is yet another central regulatory system, involving interleukin 10 and T regulatory cells.<sup>83</sup> However, the exact function and regulation of the innate immune system is still unknown.

The current generation of vaccines was developed on the basis of trial and error. Often there is no detailed understanding of their mode of action, nor of the reason for

their efficacy. Adjuvants, processed substances which enhance the immune response, are often selected on the basis of their ability to stimulate the production of antibodies (humoral immunity). Yet an increasing body of evidence underlines the importance of cell-mediated immunity. Many current vaccines and adjuvants (usually aluminium) exert little or no control over the receptors of the innate immune system. Our new understanding of the workings of the innate immune system can be put to use in the development of future vaccines.

Recent insights into the workings of the innate immune system have also stimulated research into the immunology of pertussis and the development of pertussis vaccines. That research could improve our understanding of various favourable side effects which, under certain conditions, may result from vaccination against pertussis. For example, it appears that cellular pertussis vaccine can have a reinforcing (adjuvant) action on other vaccinations.<sup>84,85</sup> Whether this also applies to the cellular vaccine used in the Netherlands, however, is by no means certain. There is also evidence that some pertussis vaccines, particularly cellular vaccines, contain immune-modulating substances which assist the immune system with the above-mentioned switch to Th1.

Cellular vaccines contain many hundreds of different antigens. While only a few of these are important in the generation of an effective immune response, they may also give rise to adverse effects. The acellular vaccines mentioned earlier were developed to boost efficacy, while reducing the frequency of adverse effects. They contain only a limited number of purified proteins. The challenge now is to develop a vaccine which is free of useless components, which do nothing but give rise to adverse effects. Such vaccines must, however, contain all of the components that are important for immunity against pertussis, as well as for adjuvant action and Th1 stimulation. Other important factors, aside from the components themselves, are the additives and the preparation method.

As previously stated, probably the most important ingredients for the generation of an effective immune response are pertussis toxin, pertactin and fimbriae. Lipopolysaccharide (LPS) is mainly responsible for the adverse effects caused by cellular vaccines. In addition, there is evidence that pertussis toxin also contributes to adjuvant action and Th1 stimulation.<sup>86</sup> Further research is required to identify other proteins or cellular components which should ideally be present in sufficient amounts in the vaccine.

#### Implications for the selection of a cellular or an acellular vaccine

Some of the current vaccines mainly stimulate a Th1 response. This is generally true of live attenuated vaccines, such as the Mumps, Measles and Rubella vaccine (MMR) and the BCG vaccine against tuberculosis. The same applies to vaccines prepared on the basis of killed, whole bacterial cells, such as the cellular pertussis vaccine. The Commit-

tee therefore wondered whether, in the light of our rapidly improving understanding of the immune system, it would be better to select a cellular pertussis vaccine rather than an acellular one.

Cellular vaccines, which after all are based on killed, whole bacterial cells, might be assumed to generate immune responses that are more comparable to those which are triggered by natural infections. In this connection, it is relevant to ask the following questions:

- Are cellular vaccines better able to manipulate the complex control mechanisms of the Toll-like receptors of the innate immune system? Vaccination against diphtheria and tetanus has indeed been reported to lead to the production of IgE antibodies, unless a cellular pertussis vaccine was added.<sup>87</sup> However, the clinical relevance of this finding is still unclear.
- Aside from reducing adverse effects, might a switch to acellular vaccines also weaken the beneficial effects, such as adjuvant action or immune modulation? Some researchers have indeed found that acellular vaccines, unlike cellular vaccines, initiate selective stimulation of the Th2 response (Mascart, written communication 2004).<sup>88,89</sup> Conversely, other workers see this simply as a transient effect.<sup>90</sup>

However, acellular vaccines may also have certain immunological advantages. Their higher concentration of purified antigens often enables them to generate a more powerful antibody response than cellular vaccines.<sup>91</sup> Some researchers have reported that acellular vaccines also generate more powerful and longer lasting cellular immunity than either natural infections or cellular vaccines.<sup>92,93</sup>

Clearly, the debate surrounding the immunological comparison of cellular and acellular vaccines is far from over. In the Committee's view, it is extremely important that research into this matter be continued. In particular, further research is required into the adjuvant action and Th1 stimulatory effects of pertussis vaccines, as well as the part that the innate immune system plays in this. The Committee feels that cellular vaccines may well have immunological advantages. However, in the current scientific situation, there is no sound basis for preferring cellular vaccines to acellular vaccines.

## Conclusion

Many questions still remain to be answered concerning the immunology of pertussis. In addition to antibodies, it is likely that cellular immunity, which involves T-helper cells and the innate immune system, is also an extremely important aspect of protection against pertussis. While it was shown that the pertussis vaccine can have a reinforcing (adjuvant) action on other vaccinations, it is not known exactly which components are responsible for this effect. There is also evidence that some pertussis vaccines contain

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substances which assist with the maturation of the immune system. Further research is required to identify other substances which should ideally be present in sufficient amounts in the vaccine, for this purpose.

Clearly, the debate surrounding the immunological comparison of cellular and acellular vaccines is far from over. In the Committee's view, it is extremely important that targeted research be conducted into this matter. However, the latest insights in the field of immunology are still unable to play a decisive part in recommendations regarding vaccination. Nevertheless, the Committee does take them into account when evaluating vaccination scenarios.

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#### **4.4 The importance of national vaccine production**

In many countries, vaccines for national vaccination programmes were initially manufactured in public health institutes. In most western countries, however, national vaccine manufacturers have bowed out following a world-wide wave of mergers. This resulted from the exorbitant costs incurred by the mandatory safety policy, together with the escalating cost of developing new vaccines. In the Western world, only a handful of major manufacturers are currently producing basic vaccines for the vaccination of infants. There are very few countries in which national vaccine manufacturers are still active.

This has led to a world-wide shortage of production capacity. There is no quick fix for this shortage, since it takes a long time to get new production facilities up and running. Furthermore, the profit margins are narrower than for medicinal products, and there is increasing demand from developing countries. In several countries, including the United States, this situation has led to the repeated rationing of vaccines.<sup>94,95</sup>

For many people, the importance of expertise in the field of infectious diseases and vaccine preparation, and of production capacity, was re-emphasised in the debates on bioterrorism that took place in the wake of the 9/11 attacks in New York and Washington. This development contributed to the Dutch government's decision to establish the Netherlands Vaccine Institute (NVI), in the Cabinet decision of 1 February 2002. The NVI consists of the vaccine development and production units that were hived off from RIVM and the Foundation for the Advancement of Public Health and Environmental Protection (SVM). One of the NVI's tasks is to supply vaccines for the NVP. The NVI has the option of developing its own vaccines, or of purchasing vaccine from elsewhere.

The Committee feels that the NVI is extremely important for public health, both as a knowledge-based institute and as a production facility. Accordingly, the continuity of the NVI is a major consideration. However, the importance of a safe, effective pertussis vaccine should also be considered on its own merits. In this context, the Committee has assessed the advantages of purchasing a combined vaccine for use against pertussis. In a



more general context, the Committee urges that recommendations concerning vaccine selection be kept separate from vaccine production and purchasing to avoid any conflict of interests.

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#### **4.5 The availability of specific combined vaccines**

Several of the vaccines cited in the tables in annex C are no longer available. This includes all of the cited cellular vaccines from manufacturers other than the NVI. The Committee takes the view that acellular vaccines containing only pertussis toxin (PT) and filamentous haemagglutinin (FHA) are not eligible. Our current understanding of the immunology of pertussis suggests that, in addition to pertussis toxin, acellular vaccines should also contain pertactin (PRN). This narrows the field to the DaPTP/Hib combined vaccines manufactured by GlaxoSmithKline (Infanrix with PT, FHA and PRN) and Aventis (Pediaceel with PT, FHA, PRN and fimbriae (FIM)). GlaxoSmithKline's DaPTP/Hib combined vaccine has been registered in the Netherlands. The DaPTP/Hib combined vaccine manufactured by Aventis has been registered in the United Kingdom. The manufacturer can request assessment for registration in the Netherlands on the basis of so-called mutual recognition. The Committee has no preference with regard to these combination vaccines.



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## **Assessment of scenarios for the vaccination of infants**

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The Committee has considered various scenarios for the improvement of pertussis vaccination. Three scenarios have been selected, based on the availability of combined vaccines. In this chapter, these scenarios are assessed against the criteria of effectiveness, adverse effects, immunological effects, and the importance of national vaccine production. The Committee considered these criteria in the above order, assigning equal importance to effectiveness and adverse effects. It then considered the time at which a booster can best be administered, and the cost effectiveness of the selected scenario for pertussis vaccination.

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### **5.1 Reference scenario**

This scenario involves the implementation of ministry decisions that are based on the Health Council advisory reports published in 1997 and the year 2000. The goal is the earliest possible introduction of an acellular DaPTP/Hib vaccine developed by the NVI, in collaboration with Aventis (four components) or GSK (three components).<sup>\*</sup> Meanwhile, the current cellular DcwPTP/Hib vaccine will continue to be used. The previous recommendation was based on information which indicated that it would be possible to introduce the new combined vaccine in 2004.<sup>3</sup> As it now appears that the new vaccine will not be available until 2007, at the earliest, a new situation has arisen.

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\* In this chapter, 'aP' is used to indicate an acellular pertussis vaccine, while cellular pertussis vaccines are designated as 'wP'.

### **Effectiveness**

The efficacy of the current NVI vaccine was never assessed in formal trials. However, the vaccine's effectiveness (VE) was determined in children aged 1 to 4, using the screening method. During 1993 this was still 96%, but from 1994 onwards it underwent a dramatic decline. From 2001, the VE appeared to increase again. The assessment for 2002 was 39% (95% confidence interval 16-55). The effectiveness of the vaccine which is to be developed partly depends on which basic product is selected. Trials carried out in Stockholm from 1993 to 1996 produced data on the relative risks of pertussis infection associated with various vaccines. Compared to the Evans-Wellcome DcPT vaccine, use of the D5aPT vaccine manufactured by Aventis (Pediace) had a relative risk of 0.85 (0.41-1.79). Compared to the D3aPT vaccine from Chiron (Acelluvax), the relative risk was 0.62 (0.31-1.2).<sup>61</sup> In Italy, during 1992, the acellular vaccine Acelluvax had a VE of 84% (95% confidence interval 76-89), which equalled that of GSK's DaPT vaccine (Infanrix).<sup>60</sup> Accordingly, when Pediace and Infanrix are compared indirectly, the former appears to have the advantage. In the 1993-1996 Stockholm trial, Pediace provided better protection than the DcPT vaccine from Evans-Wellcome. However, the follow-up study showed considerably less long-term protection (the incidence after five years was 56/100 000 and 32/100 000 respectively).<sup>31</sup>

### **Adverse effects**

There is no detailed information concerning the frequency of adverse effects associated with use of the NVI vaccine. Cohen reported a hypotonic hyporesponsive episode (HHE) frequency of 0.4/1000 and a frequency for seizures lasting < 48 hours of 0.06/1000.<sup>97</sup> However, it is not clear whether these figures are generally valid. Accordingly, in terms of adverse effects, the Committee has assessed the NVI vaccine as the average cellular vaccine in the analysis carried out by Jefferson *et al.* For details of the vaccine which is to be developed see Aventis D5aPT and Infanrix in section 4.2 and in table 4 annex C.

### **Immunology**

Cellular vaccines may have a more powerful adjuvant action and Th1 stimulatory effect than acellular vaccines. It is not known to what extent this also applies to the current NVI vaccine. The current mismatch between vaccine and circulating bacterial strains could increase still further before the vaccine which is to be developed can be introduced. One advantage of this scenario is that it allows a period of several years in which immunological research can clarify the requirements to be imposed on a good pertussis vaccine.

### *National vaccine production*

No suspension of vaccine production by the NVI.

### *Considerations*

The current vaccine is characterised by poor effectiveness and relatively many adverse effects. Until the switch-over, there will be unnecessary morbidity, and possibly also mortality, as a result of the use of a sub-optimal vaccine. This might also serve to undermine people's confidence in the NVP. The vaccine which is to be developed may have fewer adverse effects. It may also be comparable to a good cellular vaccine in terms of its effectiveness. However, this vaccine does not yet exist. Nor is it certain when, or even if, it will become available. One benefit is that no further changes to the NVP are required. This is because of recent changes associated with group C meningococci and hepatitis B, as well as the anticipated introduction of vaccination against pneumococci. The Committee feels that this scenario involves relatively large drawbacks and uncertainties. This scenario does not meet with the Committee's approval.

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## **5.2 Temporary purchase of quantities of pertussis vaccine**

In this scenario, the basic vaccinations given at 2, 3, 4 and 11 months of age would involve the use of an acellular pertussis vaccine from a different manufacturer, supplemented with DTP and Hib (licence) from the NVI. Only GSK provides a separate pertussis vaccine for infants (3aP, Tricomponent Acellular Pertussis Vaccine).

### *Effectiveness*

Like Infanrix (see reference scenario).

### *Adverse effects*

For details of the adverse effects produced by the 3aP vaccine from GSK, see section 4.2 and table 4 in annex C.

### *Immunology*

While acellular vaccines generate good immunity against pertussis, they may have a weaker adjuvant action and Th1 stimulatory effect than some cellular vaccines.

### *National vaccine production*

Minimum encroachment upon vaccine production by the NVI.

### *Considerations*

This involves a complex amendment to the NVP, requiring three injections at a single consultation for the basic vaccinations. The need to administer three separate injections on a single occasion could be avoided by delaying the

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administration of DTP (and possibly also Hib) until the second half of the first year of life. However, the DTP vaccine produced by the NVI is actually intended for use in revaccination (booster). Because its use as a basic vaccination has never been studied, it has not been registered for this purpose. The active doses of diphtheria and tetanus toxin are much lower than those in the DPTP vaccine. It therefore seems that splitting up the DPTP/Hib vaccine gives rise to insuperable fundamental and practical problems. Accordingly, the Committee feels that this scenario is neither desirable nor feasible.

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### **5.3 Temporary purchase of existing DPTP/Hib vaccines**

This scenario involves choosing from a currently available range of combined vaccines. In practice, this involves two combined vaccines with an acellular pertussis component. One is D3aPTP/Hib (Infanrix-IPV+Hib) from GSK and the other is D5apt<sub>vero</sub>Hib (Pediace) from Aventis. The Committee has no preference with regard to these vaccines.

#### *Effectiveness*

The effectiveness of the 5aP vaccine from Aventis (Pediace) and that of the 3aP vaccine from GSK (Infanrix) are discussed in the reference scenario.

#### *Adverse effects*

For details of the adverse effects produced by the 5aP vaccine from Aventis and the 3aP vaccine from GSK, see section 4.2 and table 4 in annex C.

#### *Immunology*

While acellular vaccines generate good immunity against pertussis, they may have a weaker adjuvant action and Th1 stimulatory effect than some cellular vaccines.

#### *National vaccine production*

Temporary suspension of DPTP vaccine production by the NVI.

#### *Considerations*

The cellular vaccines from Evans-Wellcome (DcPT) and Aventis (DcPTP/Hib, Pent-Act-Hib) are expected to provide the best protection against pertussis. However, these vaccines are no longer available. With regard to the possible advantages of cellular vaccines in terms of adjuvant action or immune modulation, the jury is still out. The above-mentioned acellular combined vaccines blend a high degree of effectiveness with a low frequency of adverse effects. The combination vaccines in question can easily be incorporated into the NVP. The Committee emphasises that opting for this scenario and for the temporary suspension of vaccine production by the NVI

has certain implications. Steps will need to be taken to retain expertise and to avoid jeopardising the long-term prospects for independent vaccine production in the Netherlands. This scenario meets with the Committee's approval.

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#### **5.4 Time at which a booster can be administered**

On the basis of the advisory report published by the Health Council in the year 2000, an acellular vaccine booster has been introduced for children aged four. This booster was necessitated by the short period of protection provided by the Dutch vaccine. In contrast to most other countries, the peak of pertussis cases in the Netherlands was seen in children aged from four to six. The booster was therefore introduced in advance of improvements to the basic vaccination. Good vaccines provide protection against pertussis that lasts for an average of six to eight years. Thus, when such vaccines become available, administration of the booster could be switched to a later date. The Committee recommends that this be done on the basis of model studies, and in association with the vaccination of older children and certain groups of adults. As stated, the purpose of the latter vaccination is to protect children who have either not yet been vaccinated or have not completed their course of vaccination, by curtailing the circulation of the pertussis bacterium within the population.

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#### **5.5 Efficiency of the preferred scenario**

The Committee is cognisant of the fact that any temporary purchase of DaPTP/Hib vaccine would involve considerable additional expense.

While the Committee was unable to find an independent cost-effectiveness study, it was able to examine an analysis carried out by the NVI. That analysis involved the investigation of a limited number of relevant factors. Only a brief summary and the conclusions drawn from the study by the NVI were ever published.<sup>98</sup>

The NVI study was limited by the simplicity of the statistical model used. While that model permits the use of rough assumptions about the indirect beneficial effects of vaccination by group immunity, it lacks the support of a dynamic population model. Group immunity is mainly important in terms of the protection of very young children who have either not yet been vaccinated or have not completed their course of vaccination. As stated, the most serious cases of pertussis occur in this particular group of children.

Another major limitation of the NVI study was the yardstick that it used. This was costs per year of life gained. As mentioned, the number of deaths was probably under-reported. Nevertheless, the number of deaths as a result of pertussis is probably relatively small. Accordingly, the costs per year of life gained are high. However, the pri-

mary aim of vaccination against pertussis is to prevent *disease*. The Committee therefore feels that it would be better to give the cost of vaccination per prevented case of disease, adverse effect, or per QALY (Quality Adjusted Life Year). One obstacle to calculating costs per QALY, however, is the lack of data regarding the effects that disease and adverse effects have on an individual's quality of life.

The NVI model did include the monetary cost of adverse effects. However, there were no details on convulsions, hypotonic hyporesponsive episodes, and persistent, inconsolable screaming, which the Committee sees as significant adverse effects.

The analysis therefore underestimates the beneficial effects of vaccination. On the other hand, the Committee takes the view that the cost of a temporary vaccine purchasing programme has been overestimated. In this context, the entire cost of retaining expertise and maintaining the NVI's production facilities was charged to the purchasing scenario. However, the current situation also involves costs related to the maintenance of the NVI (primarily covered by government subsidies). In making the comparison, therefore, these costs should also be charged to the current situation.\* The cost of purchasing the vaccine therefore makes up the extra cost of the purchasing scenario. Conversely, the variable costs of vaccine production by the NVI are temporarily suspended, and can therefore be deducted.

In the analysis submitted to the Committee, the annual cost associated with the temporary purchase of vaccine was roughly equivalent to that of retaining expertise and maintaining the NVI's production facilities. Other functions of the NVI may also be included in the latter cost item. The Committee urges that these other functions, and their associated costs, be rendered more transparent by conducting a thorough, independent cost-effectiveness analysis. An analysis set up in this way would enable the cost and the effects of the current situation to be compared with various other options. For example, these factors could be compared to the cost of temporarily purchasing a DPTP/Hib vaccine while retaining all expertise relating to research and development, in addition to the production facilities. Or they could be compared to the option in which the NVI produces another manufacturer's combination vaccine under licence. Lastly, they could be compared to the option in which a combination vaccine of this type would always be purchased from another manufacturer. The choice between the current situation and the three alternatives would then be political in nature. When assessing the efficiency of vaccination, however, it is vitally important that there be a clear understanding of the costs of the various options.

The cost and effects of pertussis vaccination have been investigated in various studies carried out in other countries. Some of these studies focused on the cost effectiveness of pertussis vaccination as such, as compared to a situation in which there was no vacci-

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\* The researchers have since modified the analysis to take account of this issue (JM Bos, written communication 2004).

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nation against pertussis whatsoever. Others investigated the transition from a cellular to an acellular vaccine. Major differences in epidemiology and in the organisation of healthcare mean that none of these analyses can directly be translated into the Dutch situation.

In terms of cost effectiveness, however, even allowing for all the differences between these studies and the situations investigated, there is broad agreement between the analyses. Vaccination against pertussis as such produces cost savings for the health service.

In addition, three countries have investigated the transition from a cellular to an acellular combined vaccine. These were Canada, the United States and Germany. In Canada and the United States, while the savings achieved using an acellular vaccine were slightly less than those associated with a cellular vaccine, they were still considerable.<sup>99,100</sup> However, the researchers emphasised that major benefits (not expressed in financial terms in these studies) were associated with the use of an acellular vaccine. They stated that these were linked to the lower frequency of adverse effects. In Germany, it was shown that a cellular vaccine was the most financially attractive option at a vaccination level of less than 50 percent. However, once the vaccination level rises above 50 percent, acellular vaccines produce greater healthcare savings, as a result of their more favourable adverse effect profile.<sup>101</sup>

While the Canadian and German studies were sponsored by vaccine manufacturers, the American analysis was entirely independent. The three studies all indicate the same thing, namely a favourable cost-effectiveness ratio. The Canadian, American and German results are in sharp contrast to the findings of the NVI study. The NVI's report concluded that, in any realistic scenario, the transition to an acellular vaccine could never be cost effective.<sup>98</sup> Given our current understanding, it is impossible to accurately identify the reasons for these major differences. Various factors are involved, such as the type of model (or cost model) used, the chosen yardstick, the burden of disease in the population, the organisation of the health service, and vaccination coverage. In addition, one important difference between these foreign studies and that carried out by the NVI is that the former did not include the cost of a national institute for the development and production of vaccines.

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## **5.6 Conclusion**

The Committee has assessed vaccination against pertussis using the criteria to be met before vaccinations can be incorporated into the NVP. On the basis of this assessment, the Committee recommends that a combined vaccine with an acellular pertussis component be made available for the NVP as soon as possible. The Committee is cognisant of the fact that the temporary purchase of an acellular combined vaccine will be associated

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with relatively high costs. This involves a considerable improvement to an intervention which has been designated as an important part of the NVP, one of the most important programmes for primary prevention. As yet, no thorough, independent cost-effectiveness analysis has been carried out. The Committee emphasises that the suspension of vaccine production by the NVI has certain implications. Steps will need to be taken to retain expertise and to avoid jeopardising the long-term prospects for independent vaccine production in the Netherlands.

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## **Assessment of additional measures**

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The vaccination of infants is a basic requirement when combating pertussis. The previous chapter dealt with scenarios for reinforcing this foundation. However, even when a highly effective vaccine is used, the vaccination of infants (and administering boosters to toddlers) is not enough. Waning immunity among older children and adults has led to an increase in symptomatic infections in these age groups. As a result, infants who are too young to have experienced a full vaccination cycle under the current vaccination policy run a greater risk of becoming infected. However, these are precisely the individuals who need protection.

In theory, there are two types of additional measures for achieving the effective protection of very young infants. In section 6.1, the Committee addresses the options for protecting infants at an earlier stage, either by vaccinating expectant mothers or by reducing the vaccination age. In section 6.2, the Committee addresses the options for reducing the exposure of very young infants to the pertussis bacterium, by vaccinating older children and certain groups of adults, such as parents and carers.

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### **6.1 Vaccinating mothers and reducing the vaccination age**

#### Protection via the mother

A mother transfers antibodies to her child throughout pregnancy or via breastfeeding. While this usually provides transient and passive protection, until recently it was generally thought that this did not apply to pertussis. Antibodies to pertussis bacteria can cross

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the placenta. Furthermore, immunoglobulin G1 antibodies are actively transported. This produces levels of these antibodies in the child that are almost twice as high as in the mother.<sup>102</sup> However, people believed that these antibodies had no protective effect, since pertussis also occurs in children with antibodies.

Nevertheless, many have gradually come to accept the view that the transfer of antibodies from mother to child can indeed provide newborns with a certain degree of protection.<sup>103,104</sup> It is even conceivable that maternal antibodies are involved in the development of the immune system.<sup>105</sup> Research is needed into the potential and limitations of vaccinating mothers.

The loss of maternal antibodies could partly account for the world-wide upsurge of pertussis among children who are too young to have experienced a full vaccination cycle. In the past, pertussis was widespread. Even older children and adults regularly became reinfected, which boosted their immunity. At that time, mothers generally had high and protective levels of antibodies against this disease. They also transferred these high antibody levels to their newborn children.

The switch to vaccination has meant that the protective antibody levels acquired by older children and adults, in response to natural infection, have gradually been 'flushed' out of the population. They have been replaced by vaccine-induced immunity in infants and young children. One result was an increase in susceptibility to pertussis among older children and adults, which exposed very young infants to a risk of infection. Another was a decline in the levels of protective antibodies in expectant mothers.

If maternal antibodies are indeed important for the protection of newborn children, then this would seem to offer a new option for intervention. The vaccination, or re-vaccination, of expectant mothers before or during pregnancy would then be an option worthy of consideration. This would enable them to transfer the resultant high antibody levels to their children, thereby contributing to protection throughout the important first few months of life. However, there can be no vaccination of expectant mothers until the above-mentioned scientific research into the importance of maternal antibodies has been carried out. In addition, this approach suffers from the potential limitation that vaccine manufacturers continue to advise against the use of vaccines during pregnancy, and reject any liability for such use.<sup>106-108</sup>

### Early inoculation

Another way of protecting the youngest infants is to reduce the vaccination age. Research has shown that the immune system of newborns is able to develop effective immunity to pertussis following vaccination.<sup>89,109</sup> Consideration could be given to administering the first vaccination in the NVP at birth, followed by subsequent doses at one and two months of age. The Committee feels that this option merits further investi-

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gation. Such a switch cannot be recommended, however, until the effectiveness and safety of this approach has been confirmed in repeated studies. Any such studies must also incorporate the other diseases targeted by the DTP/Hib vaccine. Research should also be carried out to survey parents' views on the acceptability of vaccinating children at such an early age.

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## 6.2 Vaccinating older children and adults

It is possible to devise strategies aimed at eradicating the pertussis bacterium from the entire population. Post-vaccination protection against pertussis is of only limited duration, lasting around six to eight years on average. Any eradication programme would therefore involve vaccinating the entire population at regular intervals. The Committee takes the view that a programme of this type would not only be difficult to implement, it would probably also be quite unnecessary.

Conversely, it has opted for an approach that is attuned to the vaccine's original purpose, the prevention of disease and death in children from birth to about five years of age. It has now become clear that the present infant vaccination is inadequate for this purpose. Accordingly, the Committee wondered which groups of older children, adolescents and adults would need to be vaccinated to achieve an adequate level of protection for infants who are too young to have experienced a full vaccination cycle.

Many studies have shown that group vaccination also provides indirect protection, particularly to unvaccinated individuals. This phenomenon is referred to as group immunity. In the current situation, group immunity provides the basis for the protection of very young infants. It has repeatedly been shown that effective infant vaccination can also lead to a reduction in the number of cases of pertussis among infants who are too young to have experienced a full vaccination cycle.<sup>8,27,28</sup>

However, there is yet another means of protecting very young infants. It appears that infections in this group are largely caused by contacts with older children in the family, as well as parents, grandparents and carers.<sup>110-112</sup> As yet, only limited research has been carried out into the sources of infection for very young infants. Any such studies must be in keeping with the local situation pertaining in the Netherlands. They could form the basis for recommendations regarding the targeted vaccination of specific groups of older children and adults.

The Committee strongly recommends that research be carried out into the sources of infection for very young infants, in the situation pertaining in the Netherlands. Dependent on the results of that study, vaccinations could, for example, be administered to groups of adults who have a greater chance of coming into contact with very young infants. These could include the children's parents and grandparents, as well as health workers and crèche personnel.

Model studies can be helpful in efforts to find a balance between the effort invested in, and benefits accrued from, vaccination strategies directed at older children and adults.<sup>37,58,113</sup> Such model studies should also investigate the most efficient means of boosting immunity against pertussis. On the basis of these studies, it might be possible to switch administration of the first booster (which occurs at the age of four in the current situation) to a later date.

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### **6.3 Conclusion**

Besides effective infant vaccination, additional measures are needed to ensure that very young infants receive sufficient protection. However, the context of this advisory report precludes exhaustive discussions of such measures. The Committee recommends that research be carried out into the sources of infections in very young infants in the Netherlands. This could provide evidence to support the effectiveness of targeted vaccination for specific groups of older children and adults. Model studies can be helpful in efforts to find a balance between the effort invested in, and benefits accrued from, vaccination strategies directed at older children and adults.

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## **Dilemmas and recommendations**

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In this chapter, the Committee responds to the request for recommendations concerning the measures needed to improve vaccination against pertussis. The chapter opens, however, with a summary of the dilemmas encountered by the Committee in the course of its deliberations.

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### **7.1 Five dilemmas**

The advisory report published by the Health Council in the year 2000 was quite clear. Research efforts to uncover the causes of the 1996 epidemic had to be redoubled, surveillance had to be improved, and considerable energy had to be devoted to the development of a combined vaccine with an acellular pertussis component.<sup>2</sup> At the time, it appeared that an acellular combination vaccine for the NVP might be available in 2004. By the time that the present advisory report on vaccination against pertussis was drawn up, the situation had become much more complicated. Accordingly, the Committee found itself confronted with several unexpected dilemmas.

The first dilemma arose from a conviction which had been held as far back as the year 2000. It was felt that, by itself, the development of a more effective and safer vaccine for the vaccination of infants was not enough to combat pertussis in very young children, where protection is the most important factor. In chapter six, therefore, the Committee briefly considers which additional measures are both feasible and necessary for the protection of very young infants. However, the context of this advisory report precluded

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exhaustive discussions, since the Committee felt obliged to discuss, once again, the vaccination of infants.

The second dilemma concerned the occurrence of genetic variants of *Bordetella pertussis*. In the Netherlands, there is a widely held view that genetic variants are an important element in the explanation for the vaccine's reduced effectiveness in the 1996-1997 epidemic. In general, researchers outside the Netherlands have found no evidence to suggest that genetic variants played an important part in the changing epidemiology of pertussis in their own countries. For this reason, the Committee discussed this problem at length in chapter three.

Since the alternative vaccines were developed on the basis of identical or virtually identical bacterial strains, it is proposed that they are just as inadequate as the NVI vaccine in terms of providing protection against genetic variants.

In an attempt to break through the impasse, the Committee has carried out a thorough analysis of the results obtained by international research into the genetic variants of *Bordetella pertussis*. The Committee concludes that the Dutch vaccine, more so than other vaccines, is susceptible to the appearance of virulent genetic variants.

Since the year 2000 advisory report was published, important new insights have been published on the functioning of the immune system. These insights are of relevance to the decision about whether to select a cellular or an acellular pertussis vaccine. The third dilemma involved the weight to be assigned to these new insights.

The Committee concluded that currently available scientific data cannot be used to decide the selection of a vaccine, one way or the other. It nevertheless takes the view that new insights in fundamental immunology are quite likely to influence the development of new vaccines. In the year 2000, the Health Council still took the position that no priority whatsoever should be assigned to the development of an improved cellular vaccine. Today, the Committee recommends that targeted research be carried out into the immunology of pertussis and the possible immunological significance of the adjuvant action and Th1 stimulatory effects of cellular vaccine components which have yet to be identified.

The fourth dilemma arose from the NVI's inability to meet its own target. In 2003, it became clear that the new combination vaccine with an acellular pertussis component would not be available in 2004. The Committee took account of this in its deliberations by addressing the issue of the importance of the national vaccine manufacturer. It also dealt with the related matter of the weighting to be assigned to this issue.

The political decision to establish the NVI had already been taken. The Committee was fully aware of this importance of this issue in terms of public health. When it



became clear that the target would not be achieved, the Committee was compelled to take account of the importance of this issue. This affected its recommendation concerning the possible purchase, from another manufacturer, of a combined vaccine for use against pertussis.

The fifth dilemma became apparent when the Committee realised that the temporary purchase of an acellular combined vaccine will be associated with relatively high costs. While decisions concerning cost are outside the Committee's area of competence, it nevertheless feels that it is duty-bound to provide the minister, where possible, with clear details concerning the efficiency of interventions. In the international scientific literature, the Committee has found evidence of a favourable cost-effectiveness ratio. However, there has been no thorough, independent cost-effectiveness analysis of the Dutch situation.

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## **7.2 Recommendations**

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### **7.2.1 *The vaccination of infants***

The Committee has assessed vaccination against pertussis using the criteria to be met before vaccinations can be incorporated into the NVP. On the basis of this assessment, using the criteria in question, the Committee recommends that a combined vaccine with an acellular pertussis component be made available for the NVP as soon as possible. This involves a considerable improvement to an existing intervention which has been designated as an important part of the NVP, one of the most important programmes for primary prevention. The Committee feels that Dutch citizens must be able to feel confident that the vaccines used in the NVP meet strict requirements with regard to effectiveness and safety.

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### **7.2.2 *Vaccinating older children and adults***

In this advisory report, the Committee makes no recommendations concerning the vaccination of older children and adults. It will deal with this issue in a subsequent advisory report. This will be partly based on the results of the study described in section 7.2.4, into the sources of infection for very young infants. The report will also make use of the model study into the effectiveness of vaccination strategies directed at older children and adults, described in section 7.2.5.

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### 7.2.3 *Immunological research and vaccine development*

In the Committee's view, it is extremely important that targeted research be conducted into the immunology of pertussis and the possible immunological significance of the adjuvant reinforcing action and Th1 stimulatory effects of cellular vaccine components which have yet to be identified. These findings may have repercussions for the development of future vaccines.

The surveillance of bacterial strains must be continued. The Committee recommends that research be carried out, by researchers who are not dependent on vaccine manufacturers, into the effect of genetic variation in *Bordetella pertussis* on the effectiveness of pertussis vaccines. Research of this kind is important to the understanding of protective immunity against pertussis and to the monitoring of vaccine effectiveness.

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### 7.2.4 *Research into the sources of infection for very young infants*

The Committee recommends that research be carried out into the sources of infections in very young infants in the Netherlands. The results obtained from such research may provide a basis for recommendations concerning targeted vaccination for specific groups of older children and adults.

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### 7.2.5 *Modelling of vaccination strategies for older children and adults*

The Committee recommends that model studies be carried out to identify an efficient strategy for the vaccination of older children and adults, specifically for the protection of very young infants (who have either not yet been vaccinated or have not completed their course of vaccination). On the basis of the results from such model studies, consideration could also be given to switching administration of the current booster from four-year-olds to older children.

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### 7.2.6 *International collaboration*

The Committee recommends that international research be carried out into the epidemiology and immunology of pertussis. Aside from leading to the fragmentation of data, the present national organisation of surveillance and research makes it difficult to compare results. This hampers the effectiveness of efforts to combat pertussis. The mutual exchange of knowledge and experience with developing countries, together with the maintenance of support for cellular pertussis vaccines, is vital to efforts to combat pertussis in large areas of the world. This is because, while many countries cannot afford to

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purchase acellular pertussis vaccines from commercial manufacturers, they are capable of producing cellular vaccines.



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A Request for advice

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B The Committee and the experts consulted

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C Composition, antibody response, effectiveness and adverse of combined vaccines against pertussis

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## Annexes



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## Request for advice

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On 7 May 1997, the former State Secretary for Health, Welfare and Sport asked the Health Council to assess the upsurge of pertussis in the Netherlands. In response, the Health Council published an advisory report entitled ‘Pertussis: a critical appraisal’ on 30 June 1997.<sup>1</sup> On 12 November 1999, the former Minister of Health, Welfare and Sport approached the Health Council to request that it re-assess the situation in the light of currently available information. In particular, the Council was asked to make a recommendation concerning the possible introduction of a booster vaccination for four-year-olds. The advisory report entitled ‘Pertussis: a critical appraisal (2)’ was published on 28 June 2000.<sup>1</sup>

September 2000 saw the publication of an RIVM report entitled ‘Naar een vaccinatieprogramma voor Nederland in de 21<sup>e</sup> eeuw’ (Towards a Dutch national vaccination programme for the 21st century), which analysed relevant developments in the field of vaccines and vaccination from 2000 to 2020. All available and anticipated vaccines are assessed in terms of preventable burden of illness, efficiency and suitability for inclusion in the National Vaccination Programme (NVP). On 29 September 2000, with reference to that report, the Minister of Health, Welfare and Sport asked the Health Council for its recommendations with regard to (letter no. GZB/GZ 2.108.780):

- the desirability of introducing new vaccines into the NVP;
- the selection of specific vaccines and combinations of vaccines, with particular reference to any anticipated adverse effects;
- the age at which the vaccines are administered;

- the basic assumptions made by the RIVM when calculating the cost effectiveness of the vaccines in question;
- the number of injections that can be given at one time, in terms of public acceptance;
- the total number of injections that can be given, in view of the workings of the immune system;
- the possibility/desirability of terminating certain parts of the current NVP.

The present advisory report was conceived in the context of the above-mentioned broad-based request for advice concerning the NVP.



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## The Committe and the experts consulted

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### The National Vaccination Programme Review Committee

- Prof. EJ Ruitenberg, *chairman*  
Professor of Immunology; University of Utrecht; Professor of International Public Health; Vrije Universiteit, Amsterdam
  - A Ambler-Huiskes, *consultant*  
community medicine physician; Dutch Health Care Inspectorate, The Hague
  - DJA Bolscher  
youth health care physician, Gelderland Provincial Vaccination Administration Foundation, Arnhem; Overijssel-Flevoland Provincial Vaccination Administration Foundation, Ommen
  - G van 't Bosch, *consultant* (since 1 October 2003)  
Ministry of Health, Welfare and Sport, The Hague
  - W Dol, *consultant* (until 1 October 2003)  
Ministry of Health, Welfare and Sport, The Hague
  - Prof. W van Eden  
clinical microbiologist / Professor of Veterinary Immunology; University of Utrecht
  - Prof. R de Groot  
Professor of Paediatrics; Erasmus University Rotterdam
  - Prof. J Huisman  
Emeritus Professor of Infectious Disease Control, Rotterdam
  - Dr HE de Melker, *consultant* (since 1 July 2003)  
epidemiologist; National Institute of Public Health and the Environment, Bilthoven
-

- Prof. JT van Oirschot  
Professor of Veterinary Vaccinology; University of Utrecht, ID Lelystad
- Dr TGWM Paulussen  
Senior Research Officer in Health Promotion; TNO Prevention and Health, Leiden
- Dr MJ Postma  
health economist; University of Groningen
- Prof. JJ Roord  
Professor of Paediatrics; Vrije Universiteit, Amsterdam
- J Sekhuis, *consultant* (until 31 December 2003)  
physician; Health Council, The Hague
- Prof. SP Verloove-Vanhorick  
Professor of Preventive and Curative Healthcare for Children; University of Leiden,  
TNO Prevention and Health, Leiden
- Dr HP Verbrugge  
youth health care physician; Santpoort
- Dr M Verweij  
ethicist; Ethics Institute, University of Utrecht
- ACG Voordouw, *consultant*  
physician, MPH; Medicines Evaluation Board, The Hague
- Dr HL Zaaijer  
clinical microbiologist; Academic Medical Centre, Amsterdam
- Dr H Houweling, *secretary*  
clinical epidemiologist; Health Council, The Hague

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**The Committee consulted the following experts:**

- B Bissumbhar, Consultancy Technology Transfer, Utrecht
  - Dr TW de Graaf, NVI
  - S de Greeff, RIVM
  - Prof. N Guiso, Institut Pasteur, Paris
  - Prof. JDF Habbema, University Medical Centre Rotterdam
  - L Hessel MD, Aventis Pasteur MSD, Lyon
  - Dr E Miller, Health Protection Agency, London
  - Prof. FR Mooi, RIVM
  - Dr Th van Oers, Bio Science Application International BV, Amsterdam
  - Dr JT Poolman, GlaxoSmithKline, Rixensart
  - Dr AJ Reynolds, Department of Health, London
  - Dr DM Salisbury, Department of Health, London
  - Dr JFP Schellekens, RIVM
-

- H Villard MD, Aventis Pasteur MSD, Brussels
- Prof. BAM van der Zeijst, NVI

The Committee would like to thank Ms S de Greeff (RIVM) for the provision and processing of epidemiological data.



## Composition, antibody response, effectiveness and adverse effects of combined vaccines against pertussis

*Table 1* Composition of various single and combined vaccines with an acellular pertussis component (source: Edwards<sup>32</sup>).

Manufacturer	Name and composition of vaccine	Pertussis antigenen ( $\mu\text{g}/\text{dosis}$ )				Difterie-toxoid (Lf/dosis)	Tetanus-toxoid (Lf/dosis)
		PT	FHA	PRN	FIM		
Aventis	Tetravac D2aPTP	25	25	-	-	15	5
GSK*	SKB-2 2aP	25	25	-	-	25	10
GSK	Tricomponent 3aP	25	25	8	-	-	-
Chiron*	Triacelluvax D3aPT	5	2,5	2,5	-	25	10
GSK	Infanrix D3aPT	25	25	8	-	25	10
Aventis	Pediacel D5aPT	10	5	3	5	15	5

\* = withdrawn from production, - = not present; GSK = GlaxoSmithKline; D = diphtheria, P = pertussis, aP = acellular pertussis, T = tetanus, P = polio; PT = pertussis toxin, FHA = filamentous haemagglutinin, PRN = pertactin, FIM = fimbriae

Table 2 Antibody levels against selected pertussis antigens one month after the third dose of the combined vaccine (Multicenter Acellular Pertussis Trial and follow-up) (source: Edwards<sup>32</sup>).

Manufacturer	Name and composition of vaccine	GMT (95%BI) one month after vaccination at the ages of 2, 4 and 6 months			
		PT	FHA	PRN	FIM
Wyeth-Lederle*	DPT	67 (54-83)	3,0 (2,7-3,4)	63 (54-74)	191 (161-227)
Aventis	Tetrvac D2aPTP	68 (60-76)	143 (126-161)	3,3 (3,1-3,6)	1,9 (1,6-2,1)
GSK*	SKB-2	104 (94-116)	110 (99-122)	3,3 (3,1-3,5)	1,9 (1,7-2,1)
Chiron*	Triacelluvax D3aPT	99 (87-113)	21 (18-25)	65 (53-79)	1,9 (1,7-2,1)
GSK	Infanrix D3aPT	54 (46-64)	103 (88-120)	185 (148-231)	1,9 (1,7-2,2)
Aventis	Pediacel D5aPT	36 (32-41)	37 (32-42)	114 (93-139)	240 (204-282)

\* = withdrawn from production, GSK = GlaxoSmithKline, D = diphtheria, P = pertussis, aP = acellular pertussis, T = tetanus, P = polio  
PT = pertussis toxin, FHA = filamentous haemagglutinin, PRN = pertactin, FIM = fimbriae

Table 3 The vaccine effectiveness of selected combined vaccines against pertussis (WHO definition of pertussis), absolute percentage or relative risk of pertussis (95% confidence interval), determined in formal trials (source: Edwards<sup>32</sup>).

Vaccine	VE-absolute % (95%BI)	relative risk (95%BI)	remarks
Wyeth-Lederle*	93 (83-97)		
Aventis DPT*	92 (81-97)		also available as DPTPHib (PentActHib)
Tetrvac D2aPTP	74 (51-86)	2,42 (1,4-4,3)	compared with PentActHib (DTP)
SKB-2*	59 (51-66)	2,3 (1,5-3,5)	compared with Evans-Wellcome DTP
Acelluvax*	84 (76-90)	1,38 (0,71-2,69)	compared with Evans-Wellcome DTP
Infanrix D3aPT	84 (76-89)		also available as D3aPTPHib
Aventis D5aPT		0,85 (0,41-1,79)	with regard to Evans-Wellcome DKT. also available as D5aPTPHib (Pediacel)

\* = withdrawn from production GSK = GlaxoSmithKline D = diphtheria, P = pertussis, aP = acellular pertussis, T = tetanus, P = polio, Hib = Haemophilus influenzae type b

Table 4 Frequency (per 1000 doses) of selected adverse effects after primary vaccination with combined vaccines with a pertussis component, trials 1992-1997(after Edwards<sup>32</sup>).

Name of vaccine	no of doses	fever > 40°	HHE	persistent screaming (> 3 hrs)	convulsions
Evans-Wellcome DPT*	60.792	0.61	0.55	-	0.21
Aventis DPT*	6.595	-	0	1.2	0.39
Wyeth-Lederle DPT*	16.424	0.19	0.06	8.8	0.18
Acelluvax*	13.713	0.29	0.07	0.66	0
Infanrix D3aPT	13.761	0.36	0	0.44	0.07
Pediacel D5aPT	61.220	0.11	0.47	-	0.06

\* = withdrawn from production, - = not measured GSK = GlaxoSmithKline D = diphtheria, P = pertussis, aP = acellular pertussis, T = tetanus HHE = hypotonic hyporesponsive episodes

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# **Addendum Estimate of adverse effects by Dutch Cochrane Centre**

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To the Minister of Health, Welfare and Sport

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Subject : Adverse effects pertussis vaccination  
Your reference : -  
Our reference : U-1133/JAK/HH  
Appendices : 1  
Date : 24 August 2004

Minister,

This spring, in the advisory report entitled *Vaccination against pertussis*, the Health Council of the Netherlands (in line with previous advisory reports in 1997 and 2000) recommended a switch to a different, acellular vaccine. The most recent advisory report recommended that stocks of this vaccine should be purchased abroad, on a temporary basis, since the Netherlands Vaccine Institute will not be able to produce the vaccine until 2007. The National Vaccination Programme Review Committee, which is charged with making recommendations concerning the NVP, made this recommendation because the recommended acellular vaccines can primarily be expected to be more effective and to have fewer adverse effects. In response to the Netherlands Vaccine Institute's criticism of the estimated number of highly unpleasant adverse effects that could be avoided by switching to an acellular vaccine (persistent, inconsolable crying, hypotonic hyporesponsive episodes, convulsions), I have asked the Dutch Cochrane Centre (DCC) to assess the meta-analysis carried out by Jefferson et al (2003), on which the estimate in the advisory report was based. This included an examination of the quality of the meta-analysis, and the way in which the Committee interpreted it. The DCC also included a previous meta-analysis (Tinnion and Hanlon (2002)) in its assessment. The DCC then made its own estimate of the number of highly unpleasant adverse effects that could be avoided by switching vaccines. I have enclosed a copy of the DCC's report with this letter.

On the basis of this assessment, my conclusions are as follows:

- Given the lack of data from direct comparisons involving the Dutch pertussis vaccine, any estimate of the difference in adverse effects relative to an acellular vaccine can only be based on a meta-analysis of available randomised controlled trials on other vaccines. This



Subject : Bijwerkingen kinkhoestvaccin  
Our reference : U-1133/JAK/HH  
Page : 2  
Date : 24 August 2004

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is a question of using the 'best available evidence'. In this regard, the DCC's analysis makes better use of the available study data than did Jefferson's analysis. Quite rightly, the DCC's analysis uses a child's vaccination series as the unit of analysis, unlike Jefferson's analysis, which used the observations of adverse effects for this purpose. Accordingly, preference should be given to the DCC's analysis for the purposes of estimating the number of avoidable adverse effects.

- As the National Vaccination Programme Review Committee has already found, the available scientific data reveals that, on average, acellular vaccines clearly cause fewer adverse effects than do cellular vaccines. The extrapolated figure for the Netherlands, produced by the DCC, is a total of 5472 avoidable highly unpleasant adverse effects per annum (95% confidence interval 3961-6177). More specifically, this would involve 128 cases of convulsion \*, 162 cases of hypotonic hypo-responsive episodes, and 5182 cases of persistent, inconsolable crying for more than three hours. The estimated number of 5472 avoidable highly unpleasant adverse effects per annum is lower than the estimate of approx. 8000 made by the National Vaccination Programme Review Committee.
- When interpreting the above-mentioned numbers, it is important that the Committee uses a criterion of 'more than two hours' in the definition of persistent, inconsolable crying, rather than 'more than three hours'. Furthermore, the DCC (as is usual in international studies) worked on the assumption that the primary series would consist of three vaccination sessions. In the Netherlands, vaccine is administered in the course of four such sessions, which means that the number of avoidable adverse effects involved may be slightly larger.
- Any estimate of the numbers of avoidable highly unpleasant adverse effects that is based on the extrapolation of data from abroad implies a degree of uncertainty. The results indicate a given order of magnitude.

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\* The estimated number of convulsions might be adjusted downwards on the basis of information that is not presently available (see report for details).



Subject : Bijwerkingen kinkhoestvaccin  
Our reference : U-1133/JAK/HH  
Page : 3  
Date : 24 August 2004

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- It is very important to collect active and prospective data on the frequency of adverse effects in the Dutch situation. Various initiatives now under way may well contribute towards filling this gap in our knowledge.

For the record, I would also point out that these matters have no repercussions in terms of the advisory report itself which, from the viewpoints of effectiveness and of the pattern of adverse effects, recommends a switch to an acellular vaccine. At the same time, there should be no misunderstanding concerning the vital importance of continuing to vaccinate with the current vaccine, in accordance with the usual schedule, until the new vaccine becomes available.

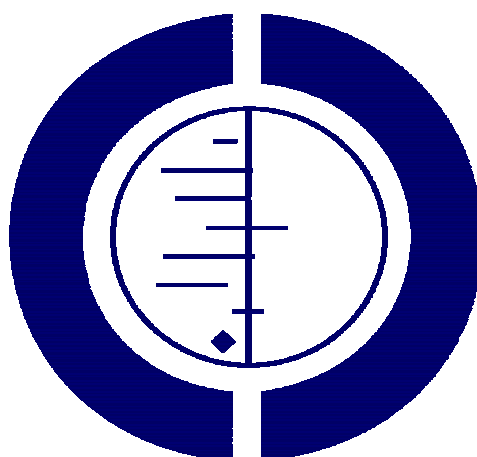
This letter, together with the DCC's report, will be appended to the advisory report entitled *Vaccination against pertussis*.

Yours faithfully,

(Signed)  
Prof. JA Knottnerus



**ESTIMATE OF THE NUMBER OF  
AVOIDABLE HIGHLY UNPLEASANT ADVERSE EFFECTS  
ASSOCIATED WITH THE USE OF AN  
ACELLULAR PERTUSSIS VACCINE  
RELATIVE TO A CELLULAR VACCINE**



**THE COCHRANE  
COLLABORATION®**

L. Hooft, epidemiologist  
Dr L.C.M. Kremer, paediatrician  
Dr S. Middeldorp, internist  
Prof. M. Offringa, paediatrician/epidemiologist  
Dr R.J.P.M. Scholten, physician/epidemiologist

DUTCH COCHRANE CENTRE  
PO Box 22660  
1100 DD AMSTERDAM  
The Netherlands  
Telephone: +31 – (0)20 – 5665602  
Fax: +31 – (0)20 – 6912683  
E-mail: [cochrane@amc.uva.nl](mailto:cochrane@amc.uva.nl)

**18 August 2004**

## **Introduction**

In June 2004, the President of the Health Council of the Netherlands asked the Dutch Cochrane Centre (DCC) for a second opinion with regard to the calculation of the number of avoidable highly unpleasant adverse effects produced by acellular versus cellular pertussis vaccines, using the meta-analysis designed by Jefferson et al (Jefferson, 2003).

One aspect of this was whether the meta-analysis in question was of acceptable quality, the other was whether the Health Council's NVP Committee's interpretation of this meta-analysis was justifiable.

In 2003, Jefferson et al published a systematic review on the efficacy and safety of cellular and acellular pertussis vaccines (Jefferson, 2003). Jefferson is involved with The Cochrane Collaboration, however this case does not involve a Cochrane Review. The review is not included in the material published in the context of the Cochrane Library collection. However, a comparable review has been published in the Cochrane Library series (Tinnion & Hanlon, 2002), as part of the Cochrane Acute Respiratory Infections Group. While it is more dated, the latter Cochrane Review was also included in the analysis.

First the methodological quality of both systematic reviews was critically evaluated. Next, meta-analyses were again performed on the occurrence of highly unpleasant adverse effects produced by acellular vaccines versus cellular ones. On the basis of the results of these renewed meta-analyses, estimates were made of the number of avoidable highly unpleasant adverse effects produced by the use of an acellular pertussis vaccine relative to a cellular one.

## **I. Methodological quality of the systematic reviews by Jefferson et al. and Tinnion & Hanlon**

### **Method**

The methodological quality of both reviews was assessed, using eight criteria. This assessment confined itself to the quality of the direct comparison, in terms of the safety results obtained from acellular pertussis vaccines versus cellular ones (head-to-head comparisons). Meta-analyses involving indirect comparisons (in which the results of comparative studies of vaccines are indirectly compared with one another) are vulnerable to bias, which generally causes the effect in question to be overestimated (Bucher, 1997; Deeks, 2001; Song, 2003).

### **Results**

The results of the methodological assessment are summarised in Table 1.

The search carried out by Jefferson et al. was both extensive and recent. The selection of studies, the determination of their methodological quality, and the data extraction were carried out independently by two different reviewers. In the case of the meta-analysis, however, they used 'observations' as the denominator instead of 'participants'. Denominators of this kind produce so-called dependent observations, which can lead to biased results.

Results relating to the different types of acellular pertussis vaccines were presented separately.

Tinnion & Hanlon carried out a limited search, which is now somewhat dated (last search, January 1998). The selection of studies, the determination of their methodological quality, and the data extraction were carried out by one of the two reviewers, using clear criteria. The meta-analysis involved the correct unit of analysis ('participants').

The various acellular pertussis vaccines were presented in clusters. The various adverse effects were analysed separately and, in most cases, presented per vaccination session.

### **Conclusion**

While the quality of both systematic reviews is generally good, the quality of their various components is inconsistent. Such is the transparency of both reviews, however, that it is possible to compensate for their inadequacies in the course of a re-analysis.

Following this, Tinnion & Hanlon's Cochrane review can be updated using recent studies found by Jefferson et al. In addition, the analyses of the adverse effects (as defined by the Health Council) are repeated, at which time the analysis error made by Jefferson et al ('observations' instead of 'children') can be corrected.

**Table 1. Methodological quality of the systematic reviews by Jefferson et al. and Tinnion & Hanlon on the 'adverse effect' result from a comparison of acellular pertussis vaccines versus cellular ones**

Quality criteria	Jefferson	Tinnion & Hanlon
1. Is the research question adequately formulated?	Yes (general and implicit)	Clearly defined
2. Was the search of the literature adequate?	Very extensive Search was done in December 2001	No EMBASE No additional searches, such as checks of references and letters to authors and producers Search was done in January 1998
3. Was the selection procedure of articles adequate?	Yes	Clear criteria for inclusion and exclusion; 1 reviewer
4. Was the assessment of quality adequate?	"Following Cochrane handbook", so probably yes. Independent by 2 reviewers	Only concealment of allocation (double blindedness was a criterium for inclusion); 1 reviewer
5. Is the description of data extraction adequate?	Independent by 2 reviewers	Clear, transparent criteria; 1 reviewer
6. Is a description of the most important characteristics of the original studies given?	No	Yes
7. Is clinical and statistical heterogeneity dealt with adequately?	Yes	Yes, assessment of clinical heterogeneity was part of the decision whether or not to pool data; power of Q-test was increased by choosing a higher threshold for statistical significance (<0,1)
8. Was statistical pooling done in a correct manner?	No: unit of analysis was observations rather than children	Yes



## **//. Calculation of the potentially avoidable highly unpleasant adverse effects produced by the use of an acellular pertussis vaccine versus a cellular one**

### **Method**

#### *Update review*

Tinnion & Hanlon's systematic review was used as a basis. The review was updated using the more recent studies found by Jefferson et al.

#### *Adverse effects examined*

Prolonged crying is calculated per vaccination session (excluding boosters) per child. This ensures that the observations are independent. The following categories are used:

1. crying for > 3 hours
2. crying for > 1 hour

For the first (and most clear-cut) definition, an analysis of prolonged crying was also carried out during at least one of the three vaccination sessions. Fresh calculations were made, per child.

With regard to the adverse effects of convulsions and hypotonic hyporesponsive episodes, it was not possible to carry out an analysis per vaccination session. It is assumed that children who experience such a drastic event only do so once during the first series. As a result, such events would have been counted only once in the meta-analysis carried out by Tinnion & Hanlon. Accordingly, this analysis addresses instances of convulsions and hypotonic hyporesponsive episodes that occurred during at least one of the three vaccination sessions. Here too, the calculations are carried out per child.

[NB In the Netherlands, the primary series of four vaccinations is given at 2, 3, 4, and 11 months, as opposed to most trials, in which three vaccinations are administered at varying intervals. This means that the number of adverse effects will be larger than the figures derived from subsequent calculations.]

#### *Contrasts*

Only those studies in which acellular vaccines (of any type) were directly compared to cellular vaccines (of any type) were included in the meta-analysis.

#### *Meta-analysis*

In the event of unusual results (convulsions and hypotonic hyporesponsive episodes), the Peto odds ratio (OR) was used as the effect parameter (Deeks 1998). In all other cases, a relative risk (RR) was calculated. Where there was statistical heterogeneity (highly varied results), the random effects model was used. In the event of homogeneity, the fixed effect model was used.

On the basis of the pooled results, a 'number needed to prevent' (NNP = the number of children that must be vaccinated with an acellular vaccine in order to prevent one adverse effect, compared to a cellular vaccine) was calculated for each adverse effect. The NNP was calculated for the following risks of an adverse effect when using a cellular vaccine (background risk):

1. The pooled risk of an adverse effect in the cellular vaccination group, calculated for all of the studies included in the meta-analysis in question (based on the updated systematic review by Tinnion & Hanlon).
2. The pooled risk of an adverse effect in the cellular vaccination group, as previously calculated by the Health Council on the basis of the studies included in Jefferson's meta-analysis.

The following formulae were used to derive the NNPs:

In the event of a pooled RR:

$$\text{NNP} = 1 / (\text{background risk} - \text{RR} * \text{background risk})$$

In the event of a pooled OR:

$$\text{NNP} = (1 / (\text{background risk} - (1 / (1 + (1 - \text{background risk}) / (\text{OR} * \text{background risk}))))))$$

Next, the potentially avoidable number of cases of the adverse effects in question was calculated per 200,000 vaccinated children per annum, by dividing 200,000 by the derived NNP.

An elaborated example of these calculations is presented in the appendix.

## Results

It was found that all of the studies included in Jefferson et al had already been included in Tinnion & Hanlon's Cochrane Review (Table 2). The latter workers combined all of the publications on the same type of study, and gave these groups a single label. Accordingly, no more recent studies have been published, and Tinnion & Hanlon's Cochrane Review can be considered to be up-to-date with regard to the direct comparison of cellular and acellular pertussis vaccines.

The results of the various meta-analyses are shown in Figures 1a to 1d.

We have based these results on the numbers of adverse effects cited in Tinnion & Hanlon's Cochrane Review. The various studies were checked individually when it came to the result category of 'crying for more than 3 hours'.

A discrepancy was found between two original studies and Tinnion & Hanlon's systematic review with regard to the number of convulsions following use of the cellular vaccine (Figure 1A): Tinnion & Hanlon reported eleven convulsions in Greco's study (instead of the three reported in the source document) and eight convulsions in Gustafsson's study (instead of the three reported in the source document). No explanation for this discrepancy could be found in the description of the methods and results. The discrepancy could be due either to an error made when copying the respective figures or to a correction of the published data on the basis of supplementary information which the reviewers may have had at their disposal. We have requested clarification from the reviewers with regard to this discrepancy. As yet, however, they have not been able to reply. From here on the numbers reported by Tinnion & Hanlon are used as a basis, and the results (based on the numbers reported in the source documents) are given in a footnote.

**Table 2. Comparison of the included studies on direct comparisons of cellular and acellular pertussis vaccines in the systematic reviews by Jefferson et al. and Tinnion & Hanlon**

<u>Adverse effect: Convulsion</u>		<u>Adverse effect: Collapse</u>			
Study	Jefferson 2003	Tinnion 2002	Study	Jefferson 2003	Tinnion 2002
Decker, 1995	X	X	Feldman, 1993	X	X
Feldman, 1993	X	X	Gustafsson, 1996	X	X
Gustafsson, 1996	X	X	Decker, 1995	X	X
Simondon, 1997	X	X	Greco, 1996	X	X
Greco, 1996	X	X	Podda, 1994	X	X
Podda, 1994	X	X	Pichichero, 1994	X	X
AHGSPV97:			Halperin, 1995	X	X
- Heijbel, 1997 <sup>a</sup>	---	X	Pichichero, 1997	X	Halperin, 1996
- Heijbel, 1997 <sup>b</sup>	---		AHGSPV97:		
- Olin, 1997 <sup>c</sup>	---		- Heijbel, 1997 <sup>a</sup>	---	X
- Olin, 1997 <sup>d</sup>	X		- Heijbel, 1997 <sup>b</sup>	---	
Afari, 1996	---	X	- Olin, 1997 <sup>c</sup>	---	
Anderson, 1988	---	X	- Olin, 1997 <sup>d</sup>	X	
Black, 1997	---	X	Blennow, 1988	---	X
Blennow, 1988	---	X	Blumberg, 1991	---	X
Blumberg, 1991	---	X	Simondon, 1997	X	X
Edwards, 1989	---	X	PVSG97:		
Halperin, 1996	---	X	- Heijbel, 1997 <sup>a</sup>	---	X
PVSG97:		X	- Schmitt-Grohe, 1997 <sup>e</sup>	---	
- Heijbel, 1997 <sup>a</sup>	---		- Stehr, 1997 <sup>f</sup>	Stehr, 1998	
- Schmitt-Grohe, 1997 <sup>e</sup>	---		- Uberall, 1997 <sup>g</sup>	---	
- Stehr, 1997 <sup>f</sup>	---				
- Uberall, 1997 <sup>g</sup>	---				

<sup>a</sup> Heijbel H *et al.*, Dev Biol Stand 1997; 89: 101-3

<sup>c</sup> Olin P *et al.*, Dev Biol Stand 1997; 89: 52-4

<sup>e</sup> Schmitt-Grohe *et al.*, Dev Biol Stand 1997; 89: 113-8

<sup>g</sup> Uberall *et al.*, Dev Biol Stand 1997; 89: 83-9

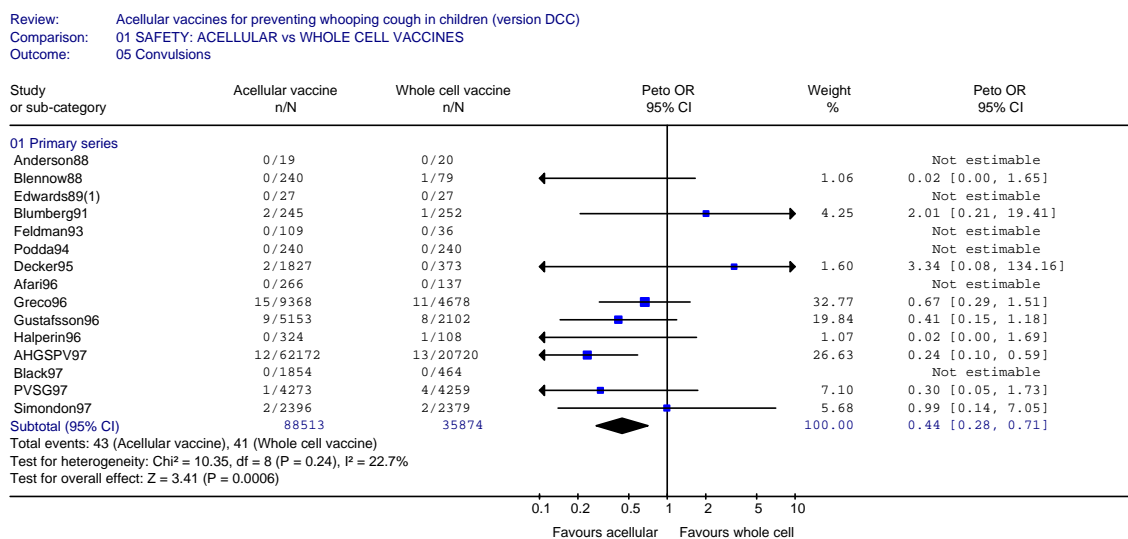
<sup>b</sup> Heijbel H *et al.*, Dev Biol Stand 1997; 89: 99-100

<sup>d</sup> Olin P *et al.*, Lancet 1997; 350: 1569-77

<sup>f</sup> Stehr *et al.*, Dev Biol Stand 1997; 89: 58-62

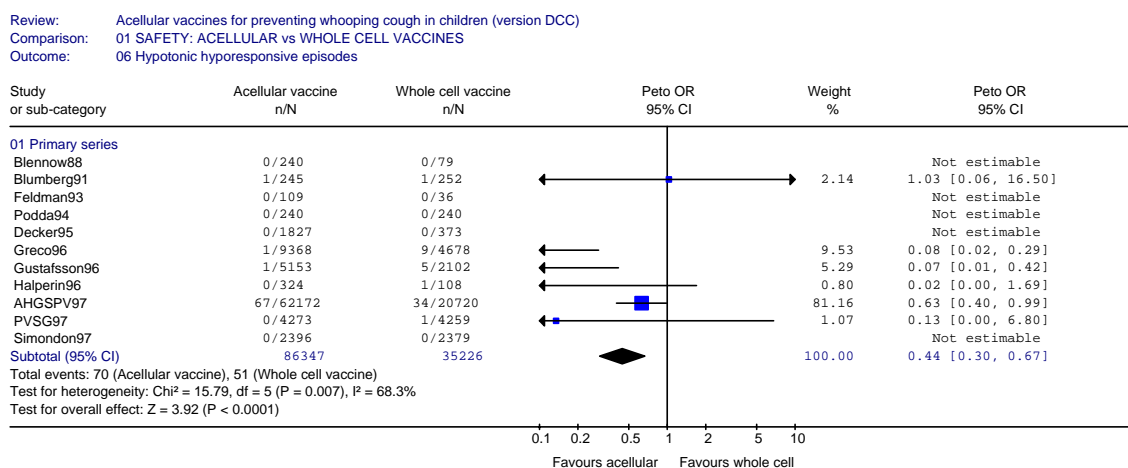
The odds ratio for the occurrence of convulsions associated with acellular vaccines relative to those associated with cellular vaccines is 0.44 (95% confidence interval (CI) from 0.28 to 0.71) (Figure 1A).<sup>1</sup>

**Figure 1A. Meta-analysis of direct comparisons of acellular versus cellular pertussis vaccines. Result: convulsions in the first series of vaccinations (at any point in time) per child**



The odds ratio for the occurrence of 'hypotonic hyporesponsive episodes' associated with acellular vaccines relative to those associated with cellular vaccines is 0.44 (95% CI from 0.30 to 0.67) (Figure 1B).

**Figure 1B. Meta-analysis of direct comparisons of acellular versus cellular pertussis vaccines. Result: 'hypotonic hyporesponsive episodes' in the first series of vaccinations (at any point in time) per child**

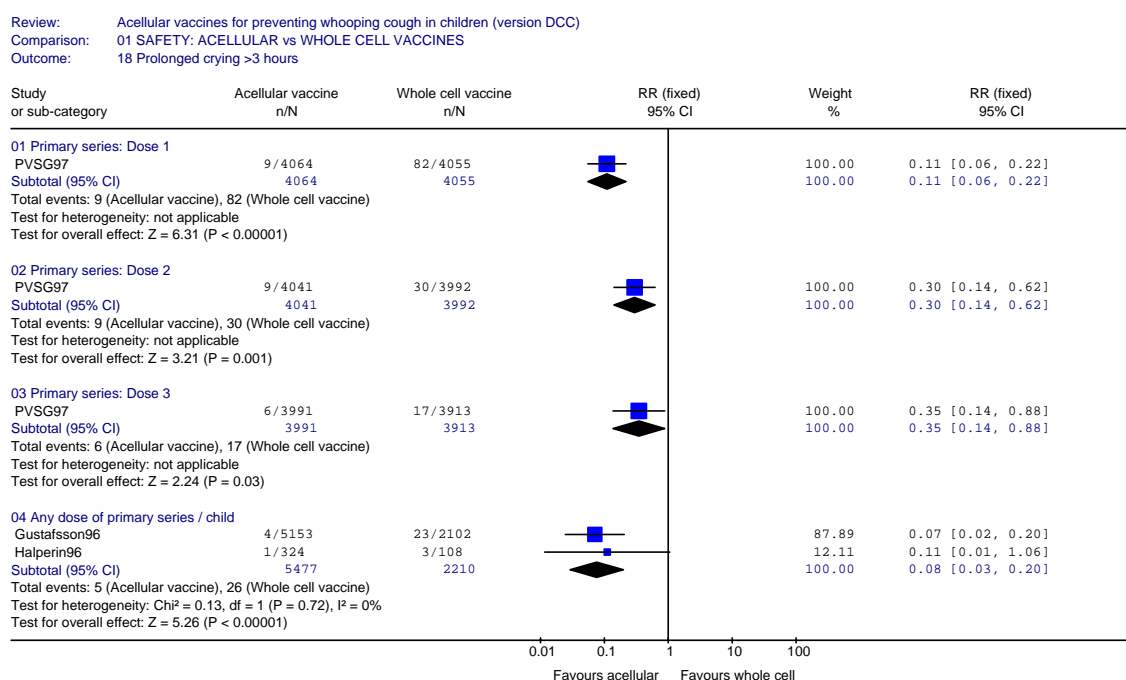


<sup>1</sup> If the numbers of convulsions reported by Greco and Gustafsson are taken as a basis, then this odds ratio is 0.69 (95% CI of 0.42 to 1.15).

The relative risk of the occurrence of ‘prolonged crying for more than three hours’ that is associated with acellular vaccines relative to cellular vaccines is 0.11 (95% CI of 0.06 to 0.22) for the first vaccination (one study), 0.30 (95% CI of 0.14 to 0.62) for the second vaccination (one study), and 0.35 (95% CI of 0.14 to 0.88) for the third vaccination (one study) (Figure 1C).

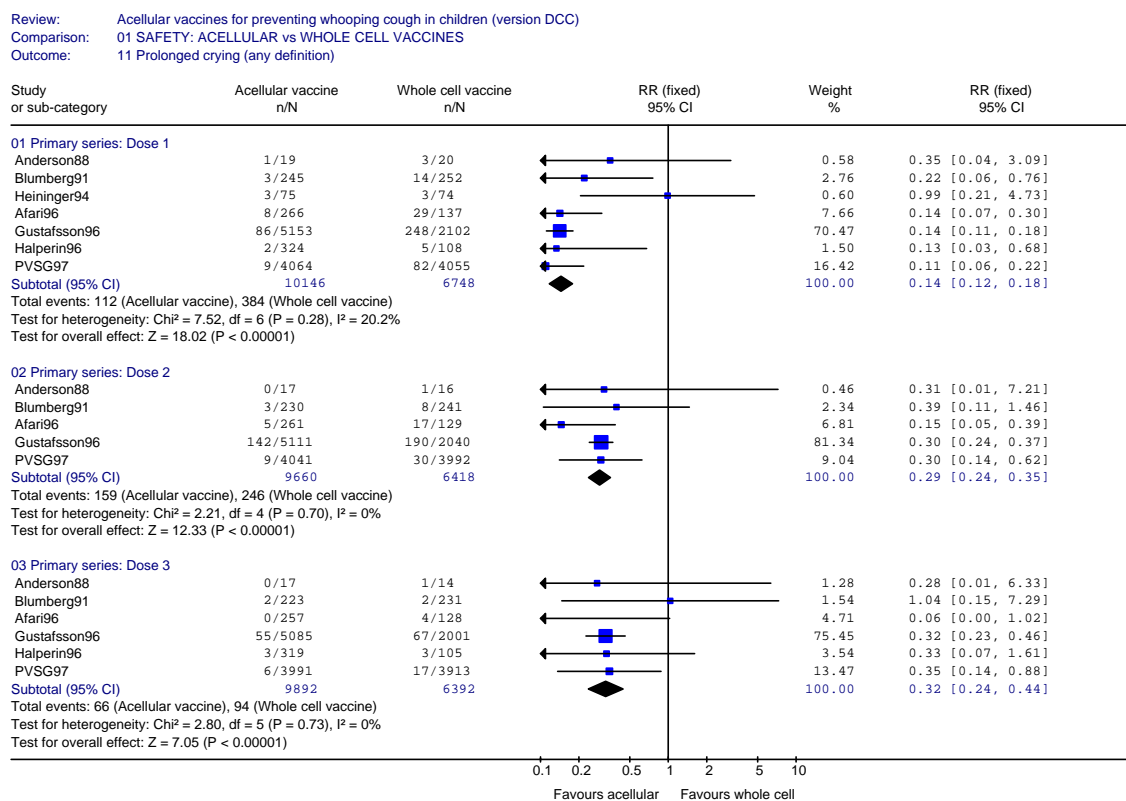
The relative risk of the occurrence of ‘prolonged crying for more than three hours during at least one of the first three vaccinations’ that is associated with acellular vaccines relative to cellular vaccines is 0.08 (95% CI of 0.03 to 0.20) (two studies) (Figure 1C).

**Figure 1C. Meta-analysis of direct comparisons of acellular versus cellular pertussis vaccines. Result: ‘prolonged crying > 3 hours’ per child per vaccination session**



The relative risk of the occurrence of ‘prolonged crying for more than one hour’ that is associated with acellular vaccines relative to cellular vaccines is 0.14 (95% CI of 0.12 to 0.18) for the first vaccination (seven studies), 0.29 (95% CI of 0.24 to 0.35) for the second vaccination (five studies), and 0.32 (95% CI of 0.24 to 0.44) for the third vaccination (six studies) (Figure 1D).

**Figure 1D. Meta-analysis of direct comparisons of acellular versus cellular pertussis vaccines. Result: 'prolonged crying of at least 1 hour' per child per vaccination session**



The method used to calculate the background risks (risk of an adverse effect when using a cellular pertussis vaccine) is shown in Table 3.

Jefferson et al do not present data separately for each individual vaccination session. Accordingly, the background risks for the second and third vaccination session were estimated, using the same relationship as the one derived from the DCC calculation.

**Table 3. Calculation of background risks**

	Dutch Cochrane Centre	Health Council
Convulsions	41/35874 = 0,00114 (Figure 1A)	4/6780 (Jefferson, 2003)
Collapse	51/35226 = 0,00145 (Figure 1B)	14/6780 (Jefferson, 2003)
Prolonged crying >3 hours: vaccination 1	82/4055 = 0,02022 (Figure 1C)	81/6851=0,01182 (Jefferson, 2003)
Prolonged crying >3 hours: vaccination 2	30/3992 = 0,00752 (Figure 1C)	0,00752/0,02022 * 0,01182 = 0,00439
Prolonged crying >3 hours: vaccination 3	17/3913 = 0,00434 (Figure 1C)	0,00434/0,00752 * 0,00439 = 0,00254
Prolonged crying >3 hours: vaccination 1-3	26/2210 = 0,01176 (Figure 1C)	81/6851=0,01182 (Jefferson, 2003)

The estimated numbers of avoidable highly unpleasant adverse effects per annum in 200,000 children who commenced the series of vaccinations is given in Table 4A.

**Table 4A. Number of potentially avoidable highly unpleasant adverse effects produced by the use of an acellular pertussis vaccine relative to a cellular one in 200,000 children scheduled for vaccination per annum**

<b>CONVULSIONS</b>	<b>OR (95% CI) =</b>	<b>0,44</b>	<b>(0,28</b>	<b>0,71)</b>			
	<b>Estimated risk with a cellular vaccine</b>	<b>NNP</b>	<b>(95% BI)</b>		<b># avoidable adverse effects/year (95% CI)</b>		
Dutch Cochrane Centre	0,00114	1564	1216	3020	<b>128</b>	66	164
Health Council	0,00059	3028	2355	5848	<b>66</b>	34	85
<b>COLLAPSE</b>	<b>OR (95% CI) =</b>	<b>0,44</b>	<b>(0,30</b>	<b>0,67)</b>			
	<b>Estimated risk with a cellular vaccine</b>	<b>NNP</b>	<b>(95% BI)</b>		<b># avoidable adverse effects/year (95% CI)</b>		
Dutch Cochrane Centre	0,00145	1235	988	2096	<b>162</b>	95	202
Health Council	0,00206	866	693	1470	<b>231</b>	136	289
<b>CRYING &gt; 3 UUR</b>							
<b>Vaccination 1</b>	<b>RR (95% CI) =</b>	<b>0,11</b>	<b>(0,06</b>	<b>0,22)</b>			
	<b>Estimated risk with a cellular vaccine</b>	<b>NNP</b>	<b>(95% BI)</b>		<b># avoidable adverse effects/year (95% CI)</b>		
Dutch Cochrane Centre	0,02022	56	53	64	<b>3571</b>	3125	3774
Health Council	0,01182	96	90	109	<b>2083</b>	1835	2222
<b>Vaccination 2</b>	<b>RR (95% CI) =</b>	<b>0,30</b>	<b>(0,14</b>	<b>0,62)</b>			
	<b>Estimated risk with a cellular vaccine</b>	<b>NNP</b>	<b>(95% CI)</b>		<b># avoidable adverse effects/year (95% CI)</b>		
Dutch Cochrane Centre	0,00752	191	155	351	<b>1047</b>	570	1290
Health Council	0,00439	326	265	599	<b>613</b>	334	755
<b>Vaccination 3</b>	<b>RR (95% CI) =</b>	<b>0,35</b>	<b>(0,14</b>	<b>0,88)</b>			
	<b>Estimated risk with a cellular vaccine</b>	<b>NNP</b>	<b>(95% CI)</b>		<b># avoidable adverse effects/year (95% CI)</b>		
Dutch Cochrane Centre	0,00434	355	268	1919	<b>563</b>	104	746
Health Council	0,00254	606	458	3281	<b>330</b>	61	437
<b>Total crying &gt; 3 uur</b>					<b># avoidable adverse effects/year (95% CI)</b>		
Dutch Cochrane Centre					<b>5182</b>	3799	5810
Health Council					<b>3027</b>	2230	3414
<b>Estimated total of avoidable adverse effects/year</b>					<b># avoidable adverse effects/year (95% CI)</b>		
Dutch Cochrane Centre					<b>5472</b>	3961	6177
Health Council					<b>3324</b>	2400	3787

**Table 4B. Number of potentially avoidable cases of 'prolonged crying > 3 hours', in at least one of the vaccinations in the primary series, produced by the use of an acellular pertussis vaccine relative to a cellular one in 200,000 children scheduled for vaccination per annum**

**CRYING >3 UUR**

>= 1 vaccination	<i>RR (95% CI) = 0,08 (0,03 0,20)</i>			# avoidable adverse effects/year (95% CI)		
	Estimated risk with a cellular vaccine	NNP	(95% CI)			
Dutch Cochrane Centre	0,01176	93	88 107	2151	1869	2273
Health Council	0,01182	92	88 106	2174	1887	2273

**Table 4C. Number of potentially avoidable cases of 'prolonged crying > 1 hour' produced by the use of an acellular pertussis vaccine relative to a cellular one in 200,000 children scheduled for vaccination per annum**

**CRYING >1 UUR**

Vaccination 1	<i>RR (95% CI) = 0,14 (0,12 0,18)</i>			# avoidable adverse effects/year (95% CI)		
	Estimated risk with a cellular vaccine	NNP	(95% CI)			
Dutch Cochrane Centre	0,05691	21	20 22	9524	9091	10000
Vaccination 2	<i>RR (95% CI) = 0,29 (0,24 0,35)</i>			# avoidable adverse effects/year (95% CI)		
	Estimated risk with a cellular vaccine	NNP	(95% CI)			
Dutch Cochrane Centre	0,03833	37	35 41	5405	4878	5714
Vaccination 3	<i>RR (95% CI) = 0,32 (0,24 0,44)</i>			# avoidable adverse effects/year (95% CI)		
	Estimated risk with a cellular vaccine	NNP	(95% CI)			
Dutch Cochrane Centre	0,01471	100	90 122	2000	1639	2222
Total crying > 1 uur				# avoidable adverse effects/year (95% CI)		
Dutch Cochrane Centre				16929	15608	17937

On the basis of the background risk calculated in all of the studies included in the meta-analysis in question then, on an annual basis, 5472 (95% CI of 3961 to 6177) cases of highly unpleasant adverse effects could potentially be avoided by the use of an acellular pertussis vaccine relative to a cellular one. This involves 128 cases of convulsions, 162 cases of hypotonic hyporesponsive episodes, and 5182 cases of 'prolonged crying' for more than three hours.<sup>2</sup>

<sup>2</sup> If one uses the number of convulsions reported by Greco and Gustafsson in the source documents, then the background risk of convulsions is  $28/35874 = 0.00078$ . When the odds ratio for the occurrence of convulsions associated with acellular vaccines relative to those associated with cellular vaccines is 0.69 then the number of potentially avoidable convulsions declines from 128 to 48 and the total number of potentially avoidable highly unpleasant adverse effects declines from 5472 to 5392.



If 'prolonged crying' is defined as crying for at least one hour (Table 4C), then the total number involved is 17,219 children (95% CI of 15,770 to 18,303) with a highly unpleasant adverse effect. This higher figure is a direct consequence of the other definition.<sup>3</sup>

If the calculations are made on the basis of background risks, as calculated by the Health Council (and with the same odds ratio at vaccination sessions 2 and 3 as in the DCC calculations), then the number of avoidable adverse effects (involving 'crying for more than three hours') is 3324 (Table 4A).

## Discussion

We estimate the number of avoidable highly unpleasant adverse effects (convulsions, hypotonic hyporesponsive episodes, and 'prolonged crying for more than three hours') produced by the use of an acellular pertussis vaccine relative to a cellular one to be 5472 (95% CI of 3961 to 6177). We arrived at our estimates by calculating NNPs (on the basis of a meta-analysis) for a number of highly unpleasant adverse effects produced by acellular pertussis vaccines relative to cellular vaccines.

Controversy concerning the use of a meta-analysis in this context stems from the possible existence of clinical heterogeneity (Simondon, 2004). However, we take the view that the use of a meta-analysis is indeed justifiable in such situations, as long as it is interpreted in the right way. Accordingly, we have quantified the average number of avoidable highly unpleasant adverse effects. Our calculation should be interpreted as follows.

The present comparison involves the entire group (heterogeneous or otherwise) of acellular vaccines relative to the entire group (heterogeneous or otherwise) of cellular vaccines. Any verdicts therefore relate to 'the highest common denominators' that can be used to refute the null hypothesis that 'The two groups of vaccines do not differ in terms of their adverse effects'. On average, the acellular-vaccine group had fewer adverse effects than the cellular-vaccine group. Accordingly, switching to an acellular vaccine (as a group) would, on average, avoid approx. 5000 adverse effects in 200,000 children.

The calculations presented here are based on the results of a meta-analysis of randomised controlled trials (RCTs) involving direct comparisons of acellular pertussis vaccines versus cellular pertussis vaccines. These RCTs were of good methodological quality (Tinnion & Hanlon). This is currently the best possible available evidence on which to estimate the difference between acellular pertussis vaccines and cellular vaccines in terms of a difference in adverse effects.

However, it is not possible to deliver verdicts about specific vaccines on the basis of analyses of this kind.

It is difficult to extrapolate this to the Dutch situation. This is because the cellular vaccine currently used in the Netherlands has never been investigated in direct comparison to an acellular vaccine, in the context of a scientifically valid study. This does not detract from the fact that the very lack of proof does not, of itself, constitute proof that no effect (difference) exists.

Consideration could be given to making assumptions about what constitutes reasonable lower limits and upper limits for the background risks of the vaccine currently used in the Netherlands. This would make it possible to obtain an impression of the numbers of

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<sup>3</sup> See notes 1 and 2: the total number of potentially avoidable highly unpleasant adverse effects then becomes  $17,219 - 80 = 17,139$

avoidable highly unpleasant adverse effects. The transparency of the present meta-analysis makes this exercise possible.

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## APPENDIX

### Sample calculation the number of avoidable adverse effects: convulsions

Background risk (DCC) =  $41 / 35874 = 0.00114$  (Figure 1A)

Odds ratio (OR) = 0.44 (95% CI of 0.28 to 0.71) (Figure 1A)

$(1 / (0.00114 - (1 / (1 + (1 - 0.00114) / (0.44 * 0.00114)))) = 1563.24$  (rounded off to 1564)

Number of avoidable adverse effects in 200,000 children scheduled for vaccination per annum

=  $200,000 / 1564 = 128$