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Pertussis; description and evaluation based on surveillance data of 1999 and 2000

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Abstract

To gain insight into the incidence and severity of pertussis in the Netherlands in 1999 and 2000, surveillance data based on notifications, laboratory data, hospitalisations and deaths were analysed for these two years and compared to the 1989-1998 period. Results of the paediatric surveillance are also presented here.
According to various sources the incidence of pertussis increased in 1999 compared to previous years and decreased again in 2000. The peak incidence according to notifications and positive serology was observed among 4- to 5-year-old children. In 1999 the incidence according to hospital admissions (3.2 per 100,000) was comparable to the incidence during the epidemic of 1996 (3.3 per 100,000) and decreased in 2000 (1.6 per 100,000). The paediatric surveillance showed that most hospitalised children were under one year of age and that complications (apnoea, cyanosis and administration of oxygen) were more frequently reported in the younger age groups. Vaccine efficacy, estimated by the screening method, was higher in 2000 compared to 1997-1999, particularly among 1- and 2-year olds. In conclusion, the incidence of pertussis in 1999 according to notifications increased to reach a higher level than in 1996. In 2000 the incidence decreased again. However, the number of hospital admissions was comparable to the figures for 1996 and 1999, and lower in 2000. Both unvaccinated and vaccinated persons can develop classical pertussis symptoms. Surveillance of pertussis based on various surveillance sources should be continued to monitor the incidence of pertussis and to study the effect of changes in vaccination strategies. Active paediatric surveillance and surveillance of hospital admissions are useful for verifying trends in routine surveillance and describing the severity of pertussis.

Contents

Samenvatting

Inleiding. In 1996/1997 werd met behulp van de routine-surveillance een uitbraak van kinkhoest waargenomen, met name onder gevaccineerde kinderen. Ook uit de pediatrische surveillance bleek dat onder gevaccineerden typische kinkhoest voorkwam. Er zijn aanwijzingen voor een mismatch tussen vaccin-geïnduceerde immuniteit en de circulerende *Bordetella pertussis* stammen. Dit rapport beschrijft de resultaten van de kinkhoest routine surveillance en de pediatrische surveillance, over 1999 en 2000.
Methoden. Surveillance gegevens op basis van verplichte meldingen bij de Inspectie van de Gezondheidszorg (IGZ), vrijwillige meldingen, serodiagnostiek verricht door het RIVM, *Bordetella* isolaties geregistreerd door streeklaboratoria en nationale registraties van ziekenhuisopnamen (SIG/Prismant) en sterfte (CBS) werden geanalyseerd voor 1999 en 2000 en vergeleken met de periode van 1989-1998. Bij de serodiagnostiekgegevens werd onderscheid gemaakt tussen positieve tweepuntsserologie (titerstijging) en positieve eenpuntsserologie (hoge titers in eerste serum). Daarnaast werden ziekenhuisopnamen ten gevolge van kinkhoest onder kinderen jonger dan 15 jaar gerapporteerd via het Nederlands Signaleringscentrum Kindergeneeskunde (NSCK). Met behulp van een vragenlijst werden hierbij gegevens verzameld over symptomatologie, vaccinatiestatus en laboratoriumdiagnostiek. Na informed consent werd de vaccinatiestatus geverifieerd bij de Provinciale Entadministratie.
Resultaten. Op grond van verschillende surveillance bronnen, steeg de incidentie van kinkhoest in 1999 na de relatief lage incidentie in 1998 en de epidemie in 1996/1997.
De gemiddelde incidentie op basis van meldingen was in de periode van 1989-1995 2,3, in 1996 27,3, in 1997 17,2, in 1998 16,0, in 1999 44,2 en in 2000 26,6 per 100.000. De incidentie op basis van eenpuntsserologie en tweepuntsserologie was in de periode van 1989-1995 8,2 vs. 2,1, in 1996 50,7 vs. 12,2, in 1997 26,4 vs. 5,9, in 1998 20,7 vs. 3,0, in 1999 34,1 vs. 5,4 en in 2000 18,8 vs. 2,9 per 100.000. De piekincidentie op basis van meldingen en positieve serologie werd in 1999 en 2000 net als in 1996-1998 waargenomen bij de 4- tot 5-jarigen. Het aantal ziekenhuisopnamen in 1999 was 509 (3,2 per 100.000) wat vergelijkbaar was met 1996 (3,3 per 100.000). In 2000 nam het aantal ziekenhuisopnamen weer af tot 247 (1,6 per 100.000). De incidentie voor de ziekenhuisopnamen in 1999 en 2000 was het hoogst voor de 0-jarigen en dan met name voor kinderen jonger dan 3 maanden. De pediatrische surveillance leverde in 1999 en 2000 248 (168 in 1999 en 80 in 2000) vragenlijsten op. De meeste kinderen waren jonger dan 1 jaar (73% in 1999 en 86% in 2000) en het percentage kinderen van 6-11 maanden oud (5%) was in 1999 en 2000 significant lager dan in 1997 en 1998 (11%). Het percentage kinderen jonger dan 2 maanden was daarentegen significant hoger (31% in 1997/1998 en 43% in 1999/2000). Ook het percentage ongevaccineerden nam toe in 1999/2000 (63%) vergeleken met 1997/1998 (51%). Apneu, cyanose en zuurstoftoediening werden vaker gerapporteerd in de lagere leeftijdsgroepen (≤ 5 maanden). De vaccin-effectiviteit zoals geschat op basis van de screeningsmethode was in 2000 hoger dan 1997-1999, met name voor één- en tweejarigen. Echter, veelal kon de vaccin-effectiviteit niet berekend worden vanwege een hoog percentage gevaccineerden onder de meldingen.

Conclusie. In 1999 steeg de incidentie van kinkhoest op basis van de meldingen naar een hoger niveau dan 1996. In 2000 nam de incidentie weer af. Het aantal ziekenhuisopnamen was echter vergelijkbaar in 1996 en 1999. Hoewel er sprake was van een toegenomen aangiftediscipline en vooral een toegenomen aangifte op basis van positieve eenpuntsserologie als gevolg van verandering van de case-definitie in april 1997, kon dit de verhoogde waargenomen incidentie niet geheel verklaren. Zowel ongevaccineerden als gevaccineerden kunnen klassieke kinkhoestklachten ontwikkelen. De kinkhoest surveillance moet gecontinueerd worden om trends in de kinkhoestincidentie en het effect van veranderingen van vaccinatiestrategieën te bestuderen. Vanwege veranderingen in case-definitie van aangifte en veranderingen in de diagnostiek moet deze gebaseerd zijn op gegevens uit diverse surveillancebronnen. Pediatrische surveillance en ziekenhuisopnames worden hierbij gebruikt om trends uit de routine surveillance te verifiëren en geeft inzicht in de ernst van kinkhoest.

Summary

Introduction. In 1996, based on routine surveillance an outbreak of pertussis was observed among mostly vaccinated children in the Netherlands. In addition, paediatric surveillance showed that also among vaccinated children typical pertussis occurred. There are indications for a mismatch between vaccine-induced immunity and the circulating *Bordetella pertussis* strains. This report describes the results of the routine surveillance and the paediatric surveillance of pertussis in 1999 and 2000 in the Netherlands.
Methods. Surveillance data based on obligatory notifications to the Health Care Inspectorate, voluntary notifications, laboratory data from the National Institute of Public Health and the Environment, isolations of *Bordetella* from regional public health laboratories and national registration of hospital admissions and deaths were analysed for 1999 and 2000, and compared to the period 1989-1998. For the serological results a distinction was made between positive one-point serology (high titre in the first serum sample) and positive two-point serology (increase in antibody titre). Besides, pertussis hospitalisations among children less than 15 years were reported monthly through the Dutch Paediatric Surveillance Centre (NSCK). For this surveillance questionnaire data on symptomatology, vaccination status and laboratory diagnosis was collected. After informed consent the vaccination status was verified at the Provincial Vaccination Administration.
Results. According to various surveillance sources the incidence of pertussis increased in 1999 after the relative low incidence in 1998 and the 1996/1997 epidemic. In 2000 a decrease could be seen. The annual incidence based on notifications was 2.3 in the period 1989-1995, 27.3 in 1996, 17.2 in 1997, 16.0 in 1998, 44.2 in 1999 and 26.6 per 100,000 in 2000. The annual incidence of cases with positive one-point and two-point serology was 8.2 vs. 2.1 per 100,000 in 1989-1995, compared to 50.7 vs. 12.2 in 1996, 26.4 vs. 5.9 in 1997, 20.7 vs. 3.0 in 1998, 34.1 vs. 5.4 in 1999 and 18.8 vs. 2.9 in 2000. As in 1996-1998, the peak incidence in 1999 and 2000 according to notifications and positive serology was observed among 4- to 5-year-old children. The number of hospital admissions was 509 in 1999 (3.2 per 100,000), which was comparable with 1996 (513, 3.3 per 100,000). In 2000 the number of hospital admissions decreased to 247 (1.6 per 100,000). In 1999-2000 the highest number of hospital admissions was reported for the 0-year-olds and than especially those less than three months of age. In 1999 and 2000 paediatric surveillance resulted in 248 questionnaires (168 in 1999 and 80 in 2000). Most children were less than 1 year old (73% in 1999 and 86% in 2000) and the percentage children aged 6-11 months was significantly lower in 1999/2000 (5%) than in 1997/1998 (11%). In contrast, the percentage children less than 2 months of age was significantly higher in 1999/2000 (43%) as compared to 1997/1998 (31%). Also the percentage unvaccinated children increased in 1999/2000 (63%) compared to 1997/1998 (51%). Apnoea, cyanosis and administration of oxygen were more frequently reported in younger age groups (≤ 5 months). Vaccine efficacy, estimated by the screening method, was higher in 2000 compared to 1997-1999, particularly for one- and two-year olds. However, the estimated vaccine efficacy often remained low or could not be calculated due to the high proportion of vaccinated individuals in the notifications.

Conclusions. In 1999, the incidence of pertussis according to notifications increased to a higher level than in 1996. In 2000 the incidence decreased again. However, the number of hospital admissions was comparable in 1996 and 1999, but lower in 2000. Although the notification rate increased and the proportion of notifications based on positive one-point serology increased due to the change of case definition, this could not totally explain the observed higher incidence of pertussis. Both unvaccinated and vaccinated children can develop classical pertussis symptoms. Surveillance of pertussis should be continued to monitor the incidence of pertussis and to study the effect of changes in vaccination strategies. Due to changes in the case definition of notifications and changes of laboratory diagnostics surveillance should be based on data from various surveillance sources. Active paediatric surveillance and surveillance of hospital admissions are useful to verify trends in routine surveillance and to describe severity of pertussis.

1. Introduction

1.1 Pathogenesis

Pertussis (whooping cough) is predominantly caused by the bacterium *Bordetella pertussis* and only rarely by *Bordetella parapertussis*. It is one of the most contagious diseases and causes an infection of the respiratory tract. Particularly among young unvaccinated infants pertussis can cause severe symptoms and complications. Classical pertussis follows an incubation period of 6-20 days. The disease is characterised by a catarrhal phase followed by a long-lasting paroxysmal cough. The paroxysmal cough can be accompanied by cyanosis, apnoea and fever. The principal complications of pertussis are secondary infections such as: otitis media, pneumonia, encephalopathy and seizures (1).
In vaccinated (older) children and adults the disease most often occurs with mild and often unrecognised symptoms (2). Although the occurrence of pertussis declined markedly after the introduction of whole cell vaccine, world-wide it remains an important cause of death among children. *B. pertussis* causes some 20-40 million cases of pertussis world-wide, 90% of which occur in developing countries, and an estimated 200-300,000 fatalities each year (3).

1.2 Surveillance and epidemiology of pertussis in the Netherlands

In the Netherlands, mass vaccination at the age of 3, 4, 5, and 11 months, with a whole cell pertussis vaccine was introduced in 1952 in the National Immunisation Programme. Since the introduction of routine vaccination, the incidence and mortality of pertussis decreased sharply. Insight into the incidence of pertussis is based on different surveillance sources; i.e. notifications, serology, hospital admissions and registrations of deaths. Since 1976 notification of pertussis is obligatory by law, but only in 1988 a strict case definition for notification of pertussis was introduced (Appendix 3). The serological tests for the confirmation of pertussis were from the eighties till 1998 almost exclusively performed by the Diagnostic Laboratory for infectious diseases and Perinatal Screening (Dutch acronym: LIS) at the National Institute of Public Health and the Environment (RIVM) in the Netherlands. In the period of 1989 to 1995, with a stable case definition for notification, increased numbers of cases were reported in 1989/1990 and in 1993/1994 despite a high vaccine coverage of 96% (4). In 1996, a sudden and sharp increase of notifications, positive cultures, positive serology and hospital admissions was observed. The epidemic in 1996 was compared with surveillance data of 1976 to 1995 and results have been described previously(4, 5). We concluded that the sudden increase reflected a true increase in pertussis incidence. Most cases occurred among vaccinated children aged 1-9 years, with a peak among 4-year olds, resulting in a lower estimation of vaccine efficacy as calculated retrospectively from notification data. Interestingly, a decline in estimated vaccine efficacy had already started in 1994 and 1995. However, the estimated vaccine-efficacy should be interpreted cautiously and explanations for the decrease are difficult to give. The increase in

notifications and as a result the decline in vaccine efficacy, suggests a mismatch between circulating strains and vaccine strains (4,6,7). A decline in vaccine quality could also be an explanation for the lower vaccine efficacy. Although pertussis was most severe among infants too young to be vaccinated, older children that were notified had developed typical pertussis as well. Thus, we could not conclude that the increase was due to increased notification of 'atypical mild disease' (8,9,10).
In the years 1997 and 1998 the vaccine efficacy as estimated by the screening method did not improve. However, the incidence of pertussis based on various surveillance sources started to decline in 1997 and further decreased in 1998. Still, the incidence was higher compared with the period 1989-1995 (8,9).

1.3 Pertussis in the Netherlands 1999-2000

The present report describes the results of pertussis surveillance in the Netherlands in the years 1999 and 2000 compared to the data of 1989-1998. For comparison with surveillance data before 1989, in which year the strict case definition for notification and positive serology was introduced, we refer to our previous report (5). Furthermore, results from the paediatric surveillance of pertussis hospitalisations are given for children admitted to hospital in 1999 and 2000. For 1997 and 1998 these data have been described in reports separate from the other surveillance sources (9,10).
When interpreting the surveillance data some changes over time must be taken into account. Firstly, since 1 January 1999 the vaccination schedule has changed. Nowadays children are vaccinated at the age of 2, 3, 4, and 11 months. Secondly, positive one-point serology has been re-introduced in 1997 as laboratory-confirmation in the case definition for notifications. Finally, since 1998 at least three of the 16 regional public health laboratories and also some other (hospital) laboratories have started to perform serology with population coverage of about 20% or more. Thus, the population coverage of serological surveillance based on serological data of LIS-RIVM has decreased from 100% to a maximum of 80%.

2. Methods

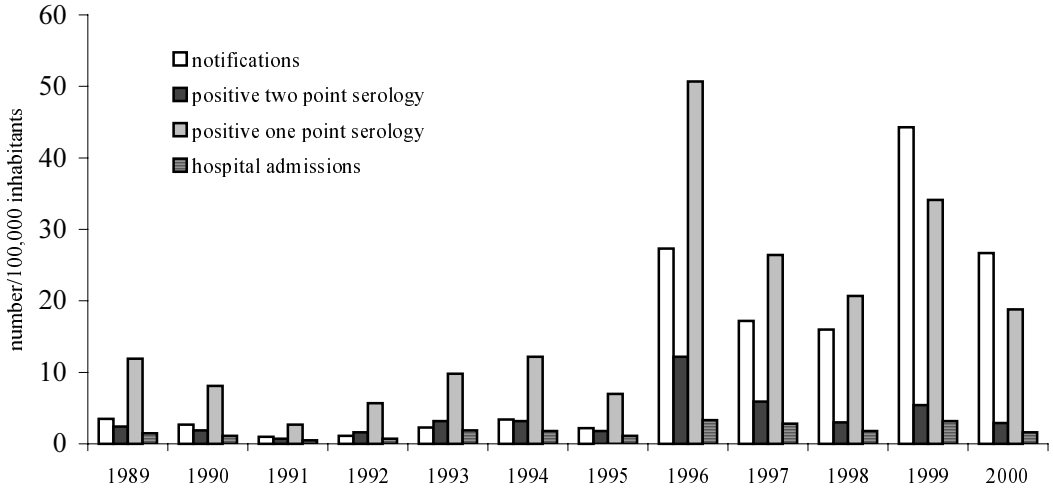
In Appendix 4 the methods and analysis of the data are described in detail. The same methodology is used as in previous years (1989-1998). In short, the incidences of pertussis per year, per month and / or per age group in the period 1989-2000 were estimated using notifications, positive one-point serology, positive two-point serology, isolations of *B. pertussis*, hospital admissions and deaths. Proportional age-distributions for notifications, positive one-point and/or two-point serology and hospital admissions were calculated. The annual vaccine efficacies for the age groups 1-9 years were estimated from data on notifications for 1999 and 2000 comparing vaccinated individuals with unvaccinated individuals. Here it should be considered that during 1999, the option 'incompletely vaccinated' was temporarily lapsed in the notification-questionnaire. Therefore, it is possible that people with one or two vaccinations were classified as 'vaccinated (for age)'.
For 1999 and 2000 the geographical distribution of reported cases of pertussis per quarter are given.
In 1999 a new Infectious Disease Law was introduced in the Netherlands. In this law surveillance was no aim anymore and therefore less data on reported cases was collected. As a result, data from notifications could not be linked with the serological database as we did in previous years. So, it has become impossible to estimate the coverage of the notification system for patients with positive two-point and positive one-point serology. Therefore, the RIVM started to collect additional data on notifications on a voluntary basis. Results from this 'voluntary notification' are given for the years 1999 (from the first of April) and 2000. Results of the surveillance are described in Chapter 3.

Since January 1997, hospitalisation due to pertussis is included in active paediatric surveillance through the Netherlands Paediatric Surveillance Centre (NSCK). In this surveillance paediatricians are asked to check monthly a number of disorders that they observed for the first time (new case) and to state the patient's initials and date of birth on a card. If paediatricians did not see any of the disorders listed, they had to mark 'no observation'. After a positive reaction paediatricians were asked to fill in a standardised questionnaire. For cases hospitalised due to pertussis information on about age, sex, clinical symptoms, length of hospital stay and laboratory results was collected. Additionally, in case the patient was 2 months or older, the parents were asked (by the treating physician) to fill in an informed consent form to collect information on the vaccination status from the concerning Provincial Immunisation Administration, Child Health Centre or Municipal Health Service. Information on vaccination status could only be obtained after such an informed consent. Differences in distribution of cases between 1997/1998 and 1999/2000 are tested with a χ^2-test. In Chapter 4 the results of the paediatric surveillance of 1999 and 2000 are described.

3. Surveillance data

3.1 Incidence of pertussis

Figure 1 shows the annual incidence of pertussis in the period 1989-2000 according to notifications, positive one- and positive two-point serology and hospital admissions. From this figure it can be seen that, for all surveillance sources, the incidence of pertussis in 1999 increased in comparison with the incidence in 1997 and 1998 but was, with exception of the notifications, lower than in 1996. The high incidences in 1999 declined for all sources in 2000 and resulted in incidences that were comparable with 1998, except for notifications. Compared to 1998 the annual incidence in 1999 estimated from notifications, positive one-point serology, positive two-point serology and hospital admissions increased with the factors 2.8, 1.7, 1.8 and 1.8, respectively. However, the incidence according to positive one- and two-point serology was lower than in 1996. The incidence estimated from notifications in 1999 increased with a factor 1.7 compared to 1996. For positive one–point serology the incidence decreased with a factor 1.5, for positive two-point serology it decreased with a factor 2.3 compared to 1996. In comparison with 1999 the incidence estimated from notifications, positive one-point serology, positive two-point serology and hospital admissions decreased in 2000 with a factor 1.7, 1.8, 1.9 and 2.1, respectively.



Number of cases												
Notifications	523	397	145	160	346	519	341	4231	2671	2508	6980	4229
Positive two-point serology	350	278	110	238	482	498	272	1885	924	468	855	458
Positive one-point serology	1760	1204	411	861	1489	1867	1070	7854	4107	3247	5377	2990
Hospital admissions	221	157	82	101	288	276	162	513	436	282	509	247

Figure 1. Incidence of pertussis per year in the period 1989-2000 estimated from notifications, positive two- and one-point serology and hospital admissions based on first day of illness.

In Figure 2 the absolute numbers of cases per month according to notifications, positive two-point serology, positive one-point serology and negative serology in the period 1989-2000 are presented. Monthly hospital admissions data were only available in the period of 1996 to 2000.
After the peak in 1996 the incidence declined in 1997 and 1998. A new peak in the incidence could be observed halfway 1999. Furthermore, a seasonal peak in the incidence can be observed every year in August-September except for the year 2000 where two peaks can be seen, one in August and one in October.
In the period of 1989 to 1995 the number of notified cases was comparable with the number of cases with two-point serology. However, since 1996 the number of cases according to notifications started to deviate from positive two-point serology to approach to the number of cases confirmed with one-point serology.
From 1989 to 2000, except for 1996, the peak incidence for negative serology was observed in October, about two months after the peak incidence for positive serology. In 1996, both the peaks for positive serology and negative serology were observed in October.
In 1999 the highest number of hospital admissions was observed in July, with a second peak in September. In 2000 the highest number of hospital admissions was observed in November.
The median length of stay in the hospital according to the hospital registration amounted 5 days in both 1999 and 2000, which was comparable with 1997 and 1998.

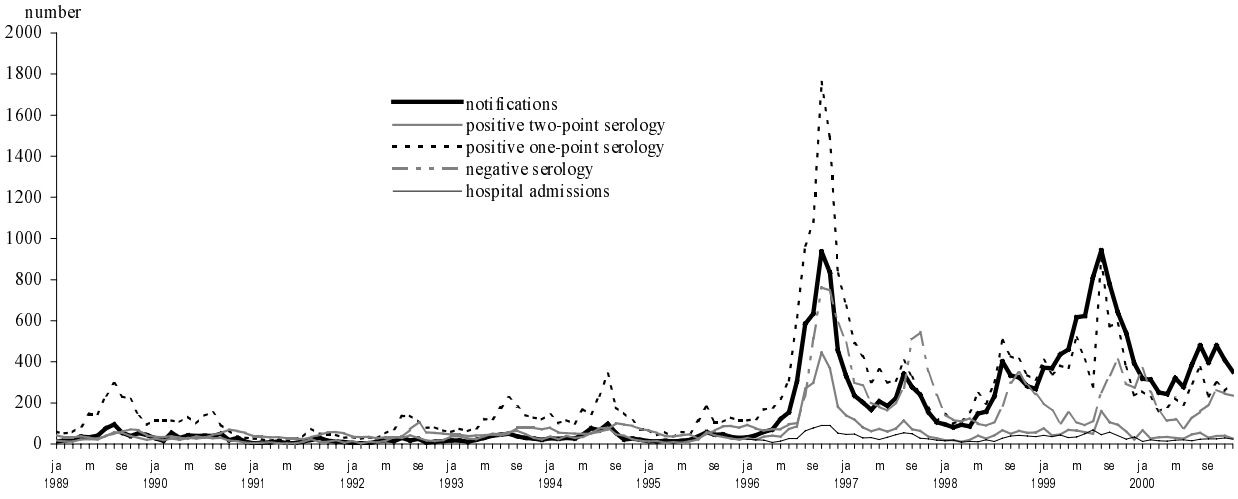


Figure 2. Pertussis in the period 1989-2000: Notifications, positive two-point serology, positive one-point serology and negative serology; hospital admissions in the period 1996-2000, based on first day of illness.

3.2 Serological results

Table 1 shows the proportional distribution (%) of serological results for pertussis in the period 1989-2000. Since the coverage of serology is declining, no numbers but proportions are given. As large differences between geographical areas in number of positive results are not expected, these proportions should stay similar over the last years. The years 1989-1995 are combined for convenience of comparison. The table shows that the proportion of total positive serology in the period 1997 to 2000 was lower than in 1996, although in 2000 a

slight increase is noticeable. Consequently, the proportions non-conclusive and negative serology were higher.

Table 1. Proportional distribution (%) of serological results for pertussis in the period 1989-2000

	1989-1995	1996	1997	1998	1999	2000
positive 2-point serology*	*9.2*	9.0	6.0	3.9	4.9	4.2
positive 1-point serology**	*35.8*	37.4	26.6	27.1	30.7	27.5
*total positive serology****	*45.0*	*46.4*	*32.6*	*31.0*	*35.6*	*31.7*
Negative serology	*19.1*	16.3	24.2	18.0	14.2	21.2
non-conclusive serology	*35.9*	37.4	43.3	51.1	50.2	47.1
Total	*100*	100	100	100	100	100

* significant titre rise in paired sera
** high titre in first serum sample, no second serum available or no significant increase in the second serum sample
*** positive two-point serology or positive one-point serology (see * and **)

3.3 Microbiological surveillance

In Table 2, the number of *Bordetella Pertussis* isolates by the 16 public health laboratories is given. Particularly the number of PCR's increased in 1999 and 2000 in comparison with previous years. In 1999 the number of PCR's increased 2.5-fold and in 2000 1.2-fold, compared with 1998. In 1999 the number of PCR's was higher than in the 1996 epidemic (1.9-fold).
The number of positive cultures increased in 1999 (2.9-fold) as compared with 1998, while in 2000 the number decreased 2.2-fold in comparison with 1998. In comparison with 1996, the number of positive cultures decreased in 1999 2.6-fold and in 2000 16.4-fold.

Table 2. Isolates of Bordetella pertussis in the period 1995-2000 as reported by the 16 regional public health laboratories

Method	1995	1996*	1997**	1998***	1999	2000
Culture	35	263	101	35	100	16
PCR	26	172	132	128	325	157
Unknown	--	81	42	17	20	23

* 1 both culture and PCR
** 5 double registered cultures excluded, 4 both culture and PCR
*** 8 double registered cultures excluded, 3 both culture and PCR

3.4 Pertussis deaths

According to the Central Statistics of the Netherlands 8 deaths due to pertussis were reported from 1996 to 1999: two in 1996, two in 1997, one in 1998 and three in 1999. For 2000 the number of deaths reported at the Central Statistics is yet unknown. In 1998 it concerned a 0-year-old boy, and in 1999 it concerned one boy and two girls, all 0 years old.

3.5 Notifications by gender in 1993-2000

Table 3 shows the sex distribution of notified cases in the period 1993-2000. In all years there was a lower proportion males than females.

Table 3. Gender distribution of reported cases in 1993-2000

Year	Gender	
	Males	females
1993	42.2%	57.8%
1994	48.9%	51.1%
1995	43.4%	56.6%
1996	44.8%	55.2%
1997	46.7%	53.3%
1998	47.2%	52.8%
1999	45.1%	54.9%
2000	45.2%	54.8%

3.6 Age specific incidence

In Table 4 to Table 8 the age-specific incidences of pertussis in the period 1989-2000 according to notifications, positive two-point serology, positive one-point serology, positive two and one-point serology and hospital admissions are given.

Overall, according to all surveillance sources the incidences for almost all age groups increased in 1999 as compared to 1998 but decreased again in 2000 to levels comparable with 1998. However, in both 1999 and 2000 the incidences estimated from notifications were higher than in 1997 and 1998, particularly for those of 15 years and older. For positive serology the incidences for children younger than 15 years, except for children aged 6-11 months, increased in 1999 but declined in 2000 to a lower level than in the period 1996-1998.

According to all sources in the period 1989-1995, the incidence was highest for infants less than one year, especially for those aged 0-5 months. Since 1996, a small shift towards older age groups could be observed. However, according to notifications and positive one-point serology the peak incidence was observed among 1-9 year olds with the exception for notifications in 1997 (highest incidence among infants less than one year). According to positive two-point serology and hospital admissions the incidence was still highest for infants less than one year in the period of 1996 to 2000.

Table 4. Age-specific incidence of pertussis per 100,000 as estimated from notifications in the period 1989-2000

Age	*1989-1995*	1996	1997	1998	1999	2000
0 yr	36.9	160.4	112.0	69.7	153.7	104.6
1-4 yr	12.0	152.4	90.1	91.9	186.4	124.8
5-9 yr	12.6	162.0	84.0	93.4	254.0	145.8
10-14 yr	3.8	57.1	33.0	28.7	94.5	45.1
15-19 yr	0.5	10.3	8.4	5.4	28.1	14.1
≥ 20 yr	0.3	4.4	4.6	3.5	12.8	8.4
Total	2.3	27.1	17.1	16.0	44.2	26.6

Table 5. Age-specific incidence of pertussis per 100,000 as estimated from positive two-point serology in the period 1989-2000

Age	*1989-1995*	1996	1997	1998	1999	2000
0-5 months	*67.6*	134.2	72.5	34.3	53.1	32.7
6-11 months	*18.8*	37.7	35.7	7.3	16.0	10.9
0 yr	*43.2*	85.6	54.1	20.8	34.6	21.8
1-4 yr	*12.2*	74.8	33.4	18.3	28.7	16.1
5-9 yr	*10.2*	76.7	32.8	19.2	34.5	16.8
10-14 yr	*3.2*	22.0	9.9	5.6	10.1	4.6
15-19 yr	*0.3*	3.6	1.9	0.9	1.4	1.0
≥ 20 yr	*0.1*	1.4	1.1	0.3	1.0	0.6
Total	*2.1*	12.2	5.9	3.0	5.4	2.9

Table 6. Age-specific incidence of pertussis per 100,000 as estimated from positive one-point serology in the period 1989-2000

Age	*1989-1995*	1996	1997	1998	1999	2000
0-5 months	*50.7*	159.4	102.0	79.0	112.2	39.7
6-11 months	*32.8*	138.4	113.6	48.9	71.1	40.6
0 yr	*41.8*	148.9	107.8	63.9	91.6	40.2
1-4 yr	*42.1*	281.2	149.8	144.8	185.1	109.1
5-9 yr	*47.9*	295.3	124.9	106.9	187.4	100.6
10-14 yr	*21.1*	110.9	52.4	36.7	67.9	32.8
15-19 yr	*3.4*	24.8	15.9	8.1	17.9	11.2
≥ 20 yr	*1.5*	10.8	7.5	4.5	9.1	5.2
Total	*8.2*	50.7	26.4	20.7	34.1	18.8

Table 7. Age-specific incidence of pertussis per 100,000 as estimated from positive one-point serology and positive two-point serology in the period 1989-2000

Age	*1989-1995*	1996	1997	1998	1999	2000
0-5 months	*118.3*	293.6	174.5	113.4	165.2	72.4
6-11 months	*51.7*	176.2	149.3	56.2	87.1	51.5
0 yr	*85.0*	234.9	161.9	84.8	126.2	62.0
1-4 yr	*54.2*	356.0	183.2	163.1	213.8	125.2
5-9 yr	*58.1*	372.0	157.8	126.1	221.9	117.4
10-14 yr	*24.3*	133.0	62.3	42.3	78.0	37.4
15-19 yr	*3.7*	28.4	17.8	9.0	19.3	12.2
≥ 20 yr	*1.7*	12.2	8.6	4.8	10.1	5.8
Total	*10.3*	62.9	32.3	23.7	39.5	21.7

Table 8. Age-specific incidence of pertussis per 100,000 as estimated from hospital admissions in the period 1989-2000

Age	1989-1995	1996	1997	1998	1999	2000
0 yr	66.2	184.0	150.9	99.8	189.3	91.7
1-4 yr	4.9	11.6	12.4	7.1	10.3	4.9
5-9 yr	1.3	4.9	3.4	2.2	2.5	1.4
10-14 yr	0.4	1.2	0.5	0.4	1.2	0.5
15-19 yr	<0.1	0.3	0	0.1	0.2	0
≥ 20 yr	<0.1	<0.1	0.1	0.1	0.1	0.05
total	1.2	3.3	2.8	1.8	3.2	1.6

In Figure 3 to Figure 5 the incidences per year of age are presented according to notifications, positive two-point serology and positive one-point serology for the years 1993 to 2000. In 1996, 1997, and 2000 the peak incidence occurred among 4-years-olds according to notifications, positive two-point serology, and positive one-point serology. For 1998 the peak incidence occurred among 5-year-olds according to notifications and positive two-point serology and among 4-year-olds for positive one-point serology. Also in 1999 the peak incidence occurred among 5-year-olds according notifications, but the peak incidence for and positive two- and positive one-point serology occurred among 4-year-olds.

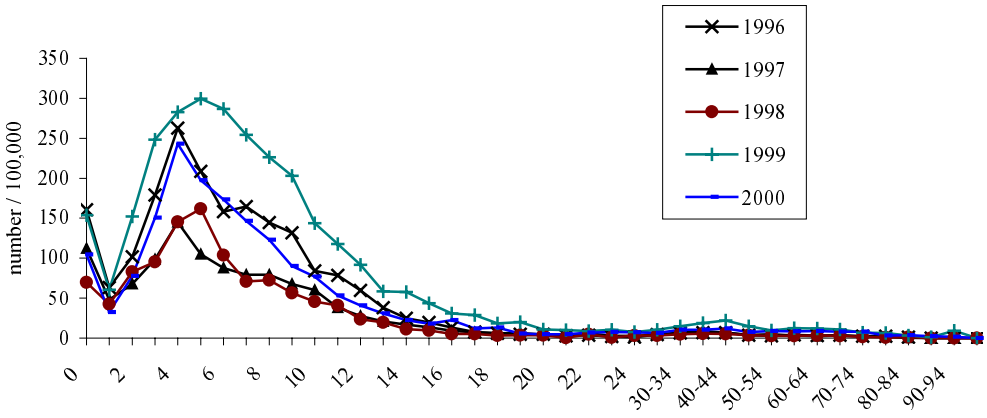


Figure 3. Age-specific incidence of pertussis in 1996-2000 according notifications, age in years

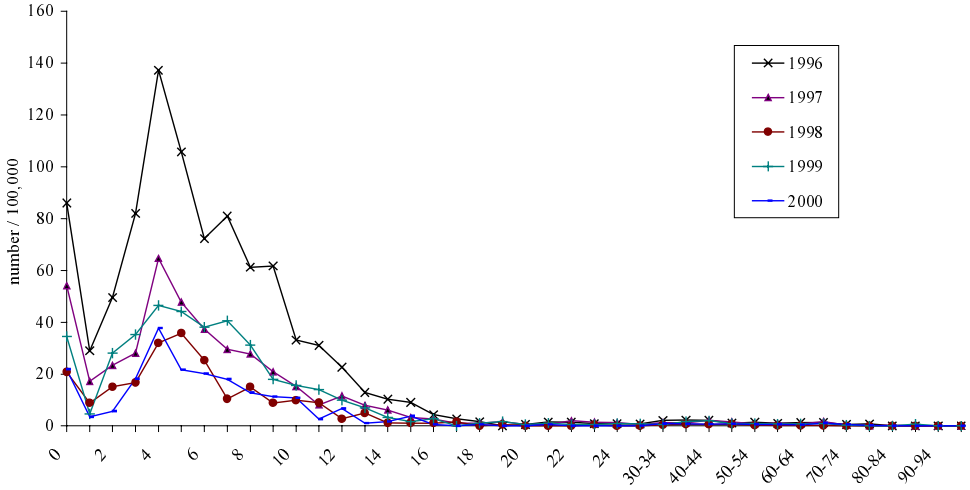


Figure 4. Age-specific incidence of pertussis in 1996-2000 according to positive two-point serology, age in years

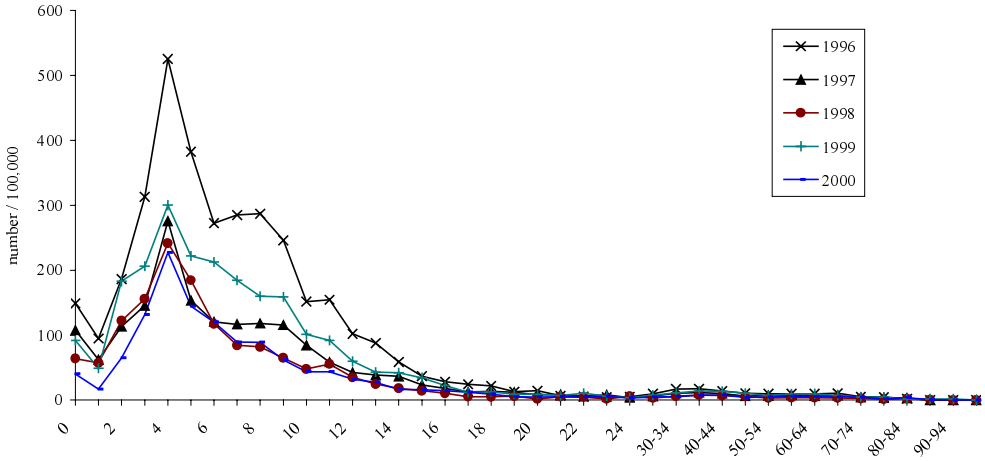


Figure 5. Age-specific incidence of pertussis in 1996-2000 according to positive one-point serology, age in years.

Since 1 January 1999, the vaccination schedule has changed. Nowadays children are vaccinated at 2, 3, 4 and 11 months of age. In Figure 6 the incidence according to notifications is given. Age is given partly in months and partly in years.
The incidences at three months of age declined in 1997, 1998, 1999 and 2000 with 28.6%, 56.3%, 37.5% and 36.8% regarded to the incidence at two months of age, respectively. The incidences at two months of age declined with 12.5%, 40.7%, 51.8% and 24.0% respectively, regarded to the incidence at one month of age.

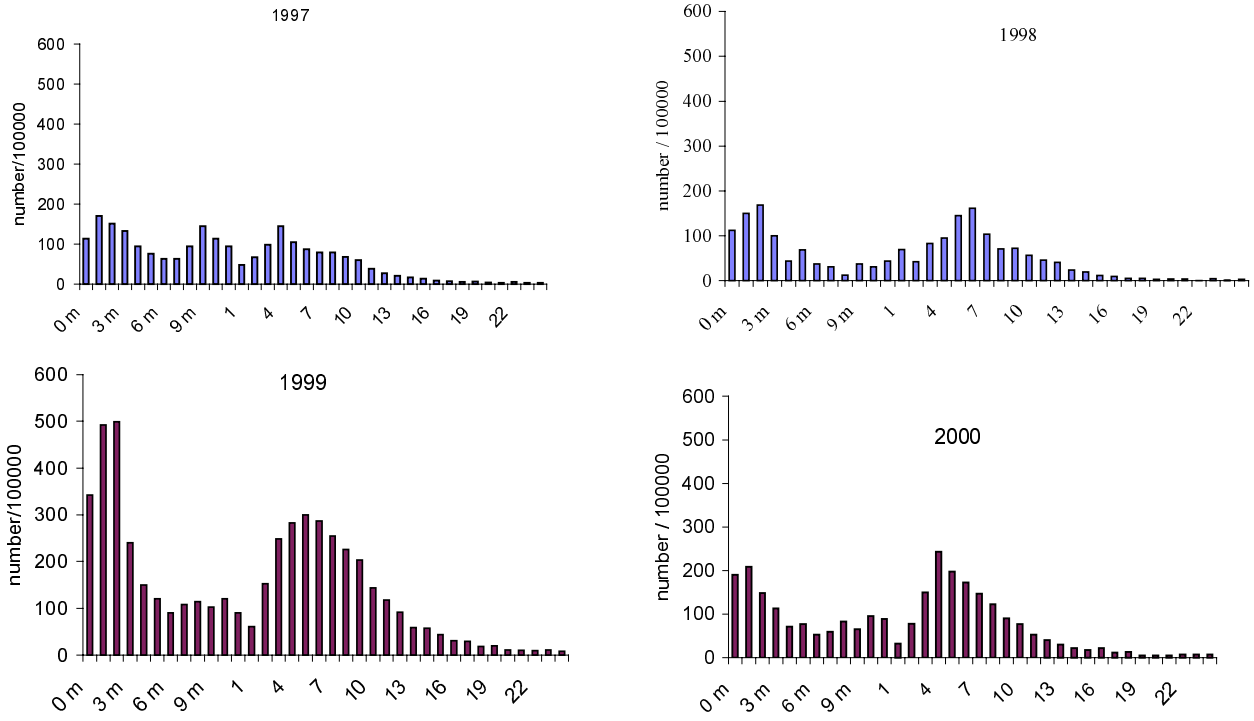


Figure 6. Age-specific incidence according to notifications for 1997, 1998, 1999 and 2000, age in months(m)/years.

3.7 Proportional age distributions

In Figure 7 to Figure 10 the proportional age distributions according to notifications, positive two-point serology, positive one-point serology, and hospital admissions in the period of 1989-2000 are shown. According to both notifications and positive serology the proportion less than 1 year has declined, while the proportion older than 19 years increased since 1996. For the years 1999 and 2000, according to both notifications and positive serology, the proportion of children aged 1-4 slightly increased in 2000, while the proportion children aged 5-9 years slightly decreased in 2000 as compared to 1999. Concerning hospital admissions it can be seen that the proportion 0-years-old slightly increased since 1996, while the percentage 5-9 year olds decreased (Figure 10).

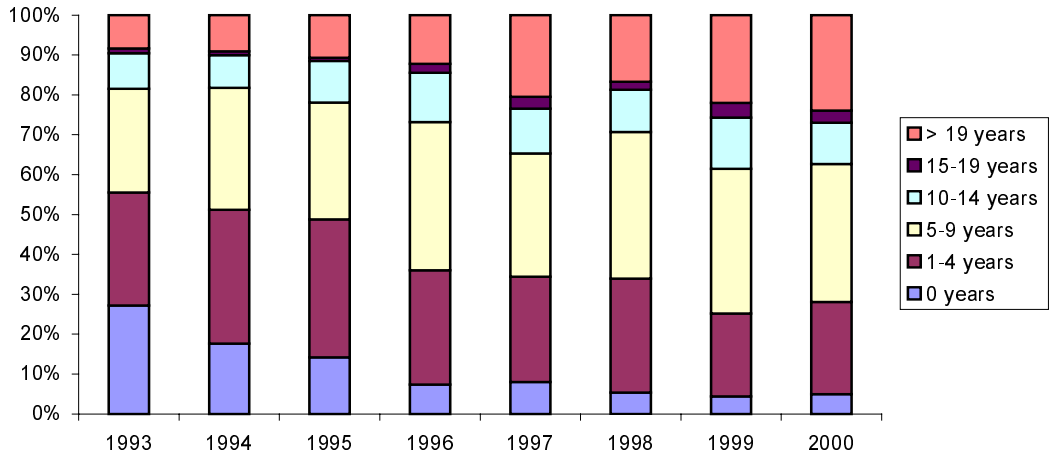


Figure 7. Proportional age distribution according to notifications due to pertussis in 1993-2000.

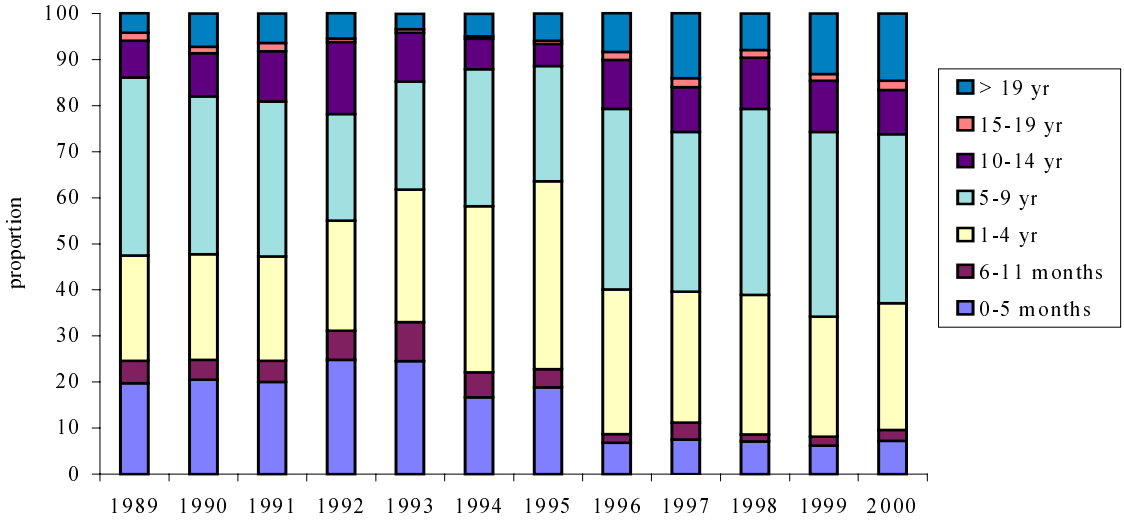


Figure 8. Proportional age distribution according to positive two-point serology for pertussis in 1989-2000

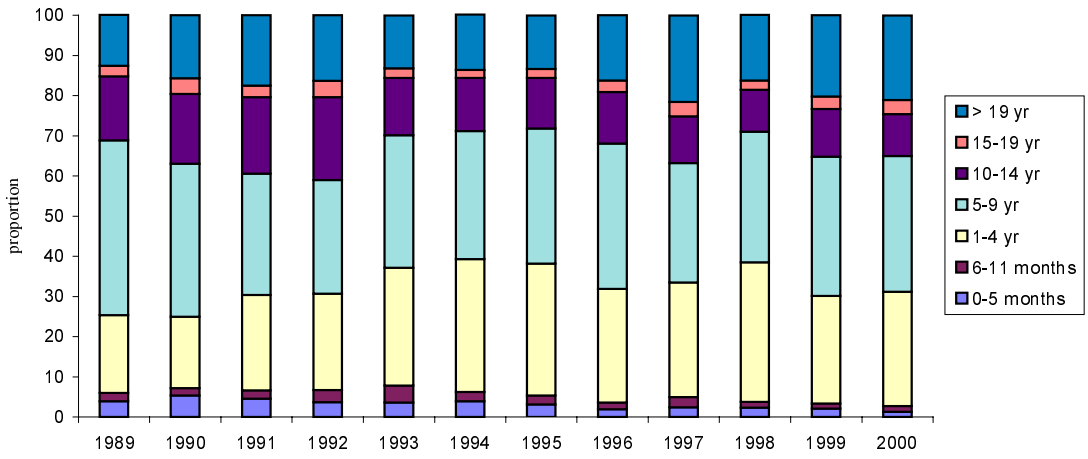


Figure 9. Proportional age distribution according to positive one-point serology for pertussis in 1989-2000

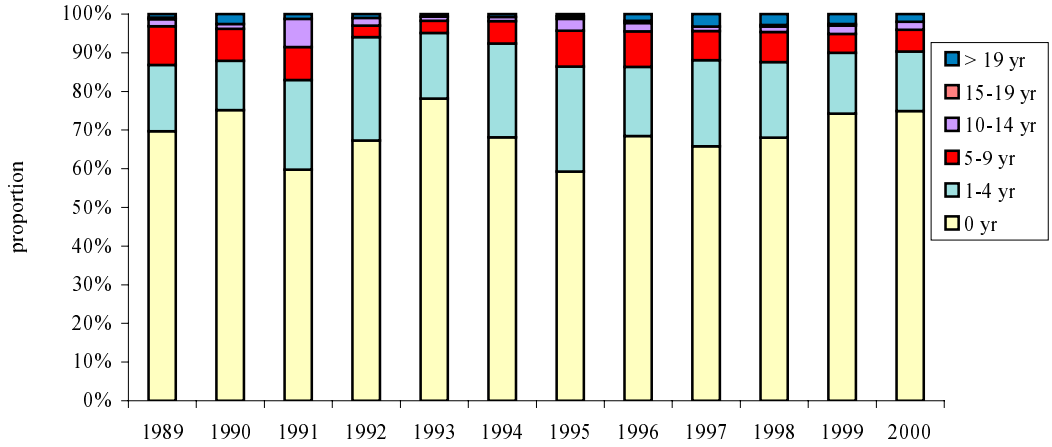


Figure 10. Proportional age distribution according to hospital admissions due to pertussis in 1993-2000

3.8 Notifications by vaccination status and vaccine efficacy

Figure 11 shows the total number of reported cases less than one year according to their age in months in 1998, 1999 and 2000. In 1998 51% of the cases in the age-category less than one year were less than three months of age and thus unvaccinated. In 1999 and 2000 these percentages were 46% and 44%, respectively. Since the vaccination schedule changed in 1999 and starts at two months of age, these children in 1999 and 2000 will have had at least one vaccination. In comparison, in 1999 and 2000 32% and 27% of the children less than one year was younger than two months and therefore unvaccinated. In 1998 31% of the cases in the age-category less than one year were less than two months of age.

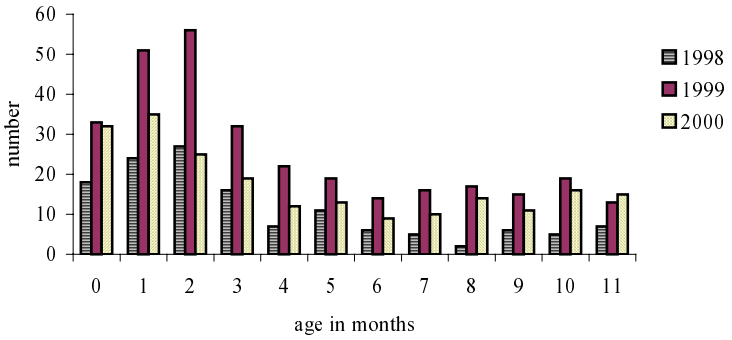


Figure 11. Absolute number of cases among infants less than one year of age reported in 1998, 1999 and 2000 according to their age in months.

Table 9 and Table 10 show the absolute number of reported cases (by first day of illness) according to their vaccination status (vaccinated, unvaccinated and unknown/missing) and their age in years, and the estimated vaccine efficacy in 1999 and 2000, respectively. Estimated vaccine-efficacy decreases with age and highest efficacies are observed for one year olds. Estimated vaccine-efficacies per age-group were higher in 2000 as compared to 1997, 1998 and 1999. Especially the vaccine-efficacy for the 1-year olds has increased over the last years: 29.8% in 1997, 38.0% in 1998, 62.9% in 1999 and 78.2% in 2000 (8). In addition, vaccine efficacy also increased for children of two years of age: negative in 1997, 32.3% in 1998, 22.3% in 1999 and 51.5% in 2000 (8). For some age-groups the proportion of vaccinated individuals exceeded the estimated vaccine coverage of the population (96%). Therefore, the vaccine efficacy could not be estimated (illustrated by '–') but the increased proportion of vaccinated individuals indicates a lower vaccine efficacy. However it has to be mentioned that estimating vaccine efficacy by the screening method, is problematic and results should be interpreted cautiously.

*Table 9. Absolute number of reported cases aged 1-9 years in 1999 according to vaccination status and year of age and estimation for vaccine efficacy**

	Vaccinated	Unvaccinated	Vaccination status unknown or missing	% vaccinated	estimated vaccine-efficacy
1 year	98	11	8	89.9	62.9%
2 years	261	14	17	94.9	22.3%
3 years	427	17	34	96.2	-
4 years	493	22	43	95.7	6.6%
5 years	534	15	37	97.3	-
6 years	506	21	44	96.0	-
7 years	465	11	35	97.7	-
8 years	415	4	38	99.0	-
9 years	359	9	26	97.6	-
1-4 years	1279	64	102	95.2	17.4%
5-9 years	2279	16	180	97.4	–

* a vaccine-coverage of 96% was used to estimate incidences and vaccine-efficacy

*Table 10. Absolute number of reported cases aged 1-9 years in 2000 according to vaccination status and year of age and estimation for vaccine-efficacy**

	Vaccinated	Unvaccinated	Vaccination status unknown or missing	% vaccinated	estimated vaccine-efficacy
1 year	47	9	8	83.9	78.2%
2 years	128	11	12	92.1	51.5%
3 years	264	5	16	98.1	-
4 years	424	15	28	96.6	-
5 years	350	18	23	95.1	19.1%
6 years	307	8	25	97.6	-
7 years	275	3	13	98.9	-
8 years	231	2	15	99.1	-
9 years	162	6	13	96.4	-
1-4 years	863	40	64	95.6	9.5%
5-9 years	1325	37	89	97.3	–

* a vaccine-coverage of 96% was used to estimate incidences and vaccine-efficacy

3.9 Geographical distribution notifications 1999 and 2000

In Figure 12 respectively Figure 13 the geographical distribution of pertussis according to notifications in 1999 and 2000 per quarter and per Municipal Health Centre (MHC) is given. The pertussis cases are widespread. From the dark colours in Figure 13 it can be concluded that the incidence according to notifications was high in 1999. In both 1999 and 2000 the highest incidence was observed in the third quarter.

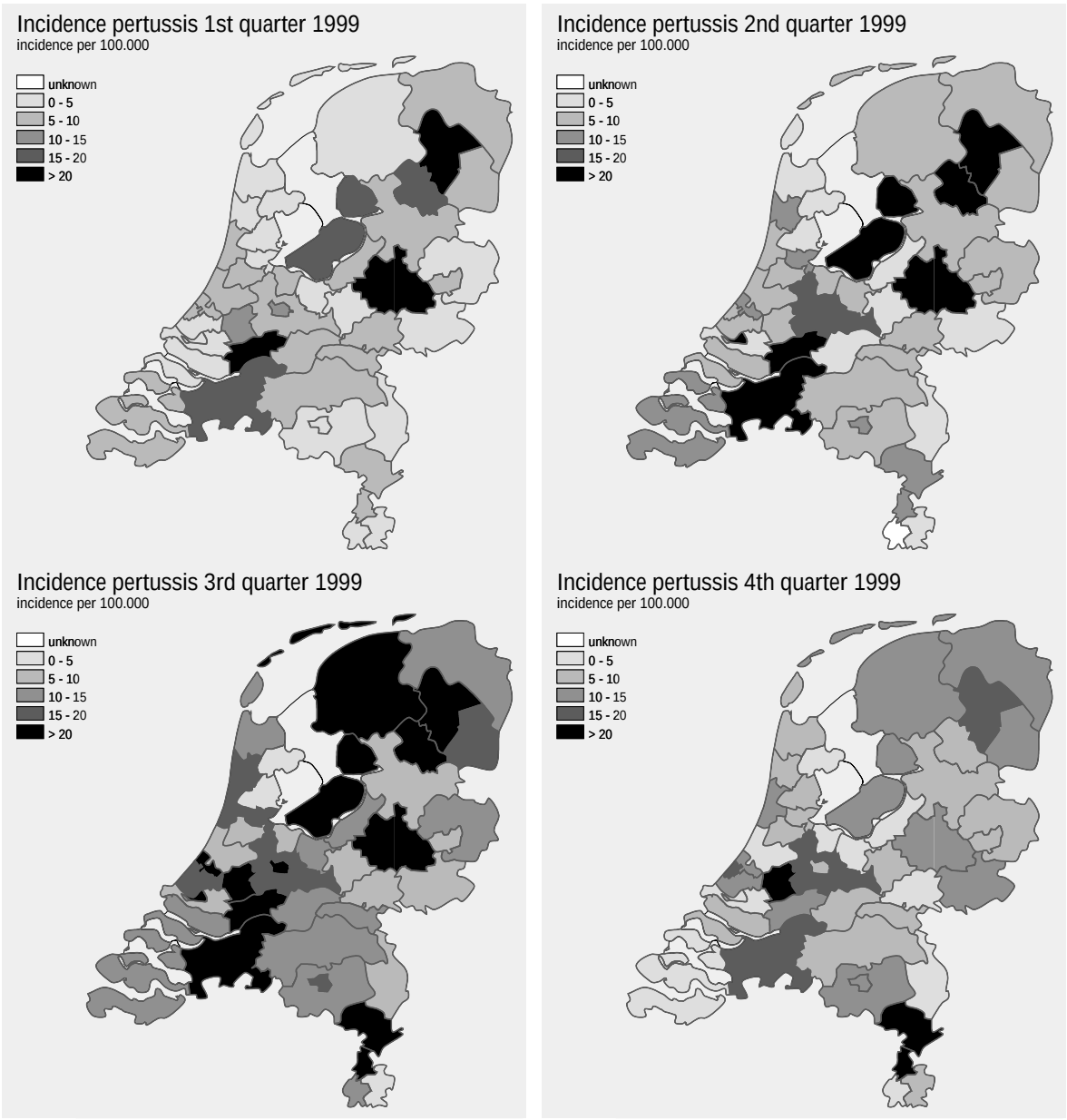


Figure 12. Geographical distribution according to notifications in 1999 per quarter per MHC.

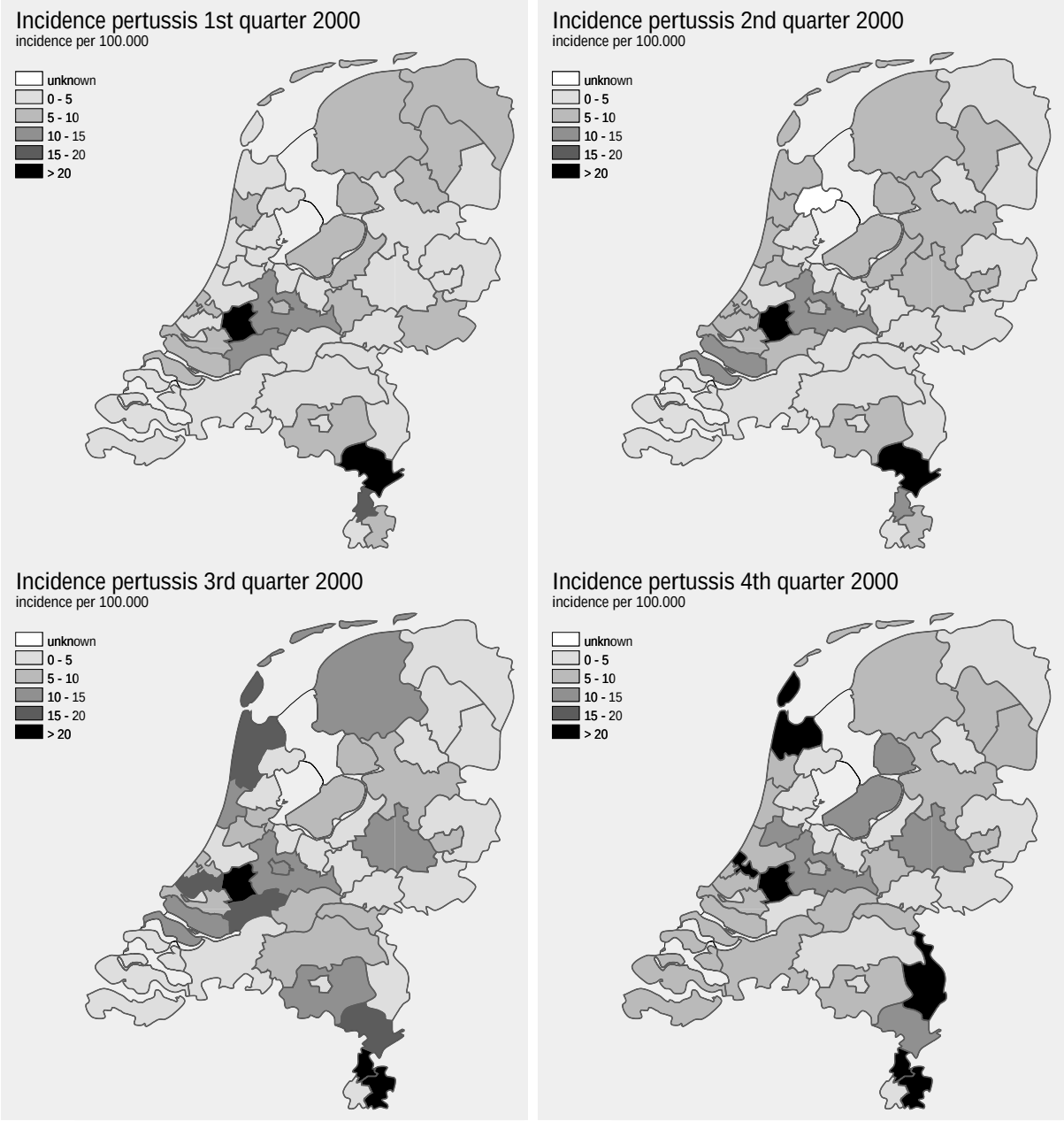


Figure 13. Geographical distribution according to notifications in 2000 per quarter per MHC.

3.10 Voluntary notifications

Besides notification data additional information on notifications, on voluntary basis, is collected by the RIVM since the first of April 1999. In 1999 and 2000 for 71% and 74% of the compulsory notifications additional information was available. In 1999 91% of the Municipal Health Services (MHS) participated in the voluntary notification and in 2000 87%. For these participating MHS additional information was available for 65% of their reported cases in 1999 and for 80% in 2000.

In 1999 according to the voluntary notification 3% of the cases was admitted to the hospital, in 2000 4%. This involves 31% and 45%, respectively, of the total number of hospitalisations for pertussis in that period according to the national registry of hospital admissions.
Vaccination status was also included in the voluntary notification, but in contrary to the compulsory notification data, before April 1999 the option 'incomplete vaccinated' lacked. The percentages vaccinated and unvaccinated cases were comparable among both notification systems. However, it was remarkable that for 7% and 3% of the unvaccinated cases according to the voluntary notification (in 1999 and 2000, respectively), the vaccination status in the compulsory notification was the opposite. In addition, the number of deaths did not correspond between both notifications. From the voluntary notification it appeared that 7 patients in 1999 and 2 patients in 2000 had died as a result of a pertussis infection, while in the compulsory notification system no deaths were registered. After verification with the municipal health centres it could be concluded that the reported deaths in the voluntary notification were inaccurate.
Furthermore, in 1999 and 2000 about 60% of the cases covered with the voluntary notification system were reported as solitary cases. For the remaining cases school and family were most frequently mentioned as source of infection, if source of infection was mentioned (30 % of the cases).

4. Paediatric surveillance

In Table 11 (1999 and 2000 together) and Appendix 5 (1999 and 2000 separately) the results of the paediatric surveillance are shown. Questionnaire data were available from 248 hospitalised cases aged 0-15 years (168 in 1999; 80 in 2000), which was 33% of the total number of hospitalisations for pertussis of children aged 0-15 years in that period according to the national registry of hospital admissions. Age and gender distribution and length of hospital stay were similar for both sources.

Most hospitalised cases were less than one year of age (73% in 1999 and 86% in 2000) with most of these cases occurring among infants less than three months of age, i.e. too young to be vaccinated.

In 1999 and 2000 a significant ($p=0.009$) lower percentage (11% in 1997/1998 vs. 5% in 1999/2000) of children aged 6-11 months could be observed, while the percentage of children younger than two months significantly ($p=0.003$) increased as compared to 1997 and 1998 (31% in 1997/1998 vs. 43% in 1999/2000). Concerning vaccination status the percentage of unvaccinated persons (according to reported vaccination status) increased significantly ($p=0.003$) in 1999 and 2000 (63%) compared to 1997 and 1998 (51%).

Cases 3 to 5 months old were mostly incompletely vaccinated or unvaccinated, while those aged at least 6 months of age were mostly vaccinated. As shown in Table 10 symptoms as coughing, paroxysmal cough and vomiting were reported for most hospitalised cases in all age groups. Whooping was less often observed among the youngest infants (0 months) compared to older age groups, while fever occurred frequently in all age groups.

Most complications were rare, but most complications that were reported, occurred less frequently with increasing age (apnoea, cyanosis, administration of oxygen). However, pneumonia was reported more frequently among the oldest age group (5-15 years).

The median time of hospitalisation decreased with age, while the median time between onset of disease and hospital admission increased with age.

The case (a boy) that died in 1999 was too young to be vaccinated and received oxygen and artificial respiration. The duration of hospital stay was 9 days and except for coughing (one week) there were no other symptoms or complications reported. In addition, no underlying respiratory disorder was reported.

The proportion of positive PCR or culture was highest for the youngest infants and decreased for older age groups, while the reverse was observed for positive serology.

Table 11. Characteristics of hospitalised cases reported in the paediatric study in 1999 and 2000

Hospitalised cases									
	0 mnth	1 mnth	2 mnths	3-5 mnths	6-11 mnths	1-2 yrs	3-4 yrs	5-15 yrs	Total
	N=42	N=70	N=38	N=31	N=13	N=24	N=8	N=22	N=248
	17%	28%	15%	13%	5%	10%	3%	9%	100%
Registered vaccination status*									
Vaccinated	0%	0%	0%	0%	31%	46%	75%	59%	14%
Incompletely vaccinated	0%	0%	21%	29%	0%	0%	0%	0%	7%
Unvaccinated	100%	100%	24%	32%	23%	0%	0%	5%	54%
Unknown	0%	0%	55%	39%	46%	54%	25%	36%	25%
Reported vaccination status**									
Vaccinated	0%	0%	39%	58%	54%	75%	88%	91%	34%
Unvaccinated	100%	70%	50%	42%	38%	21%	13%	5%	63%
Unknown	0%	0%	11%	0%	8%	4%	0%	5%	3%
Symptoms									
Coughing	100%	100%	100%	100%	100%	100%	100%	100%	100%
Paroxysmal coughing	69%	71%	87%	65%	54%	75%	25%	50%	69%
Whooping	10%	17%	11%	23%	23%	13%	50%	18%	17%
Vomiting	62%	63%	58%	58%	54%	58%	63%	64%	60%
Fever	38%	34%	37%	45%	62%	46%	38%	41%	40%
Complications									
Death	0%	1%	0%	0%	0%	0%	0%	0%	0%
Collaps	14%	6%	3%	13%	0%	13%	13%	5%	8%
Convulsion	0%	1%	0%	0%	0%	0%	0%	5%	1%

Table 11. Characteristics of hospitalised cases reported in the paediatric study in 1999 and 2000 (continued)

Encephalopathy	0%	0%	0%	0%	0%	0%	0%	0%	0%
Apnoea	21%	23%	13%	16%	0%	4%	0%	5%	15%
Pneumonia	0%	4%	5%	3%	0%	13%	13%	18%	6%
Cyanosis	81%	77%	74%	65%	77%	50%	25%	32%	67%
Artificial respiration	19%	4%	0%	0%	0%	0%	0%	0%	4%
Administration of oxygen	67%	49%	53%	26%	0%	21%	13%	14%	40%
Other									
Median days hospitalised	14.5 (1-63)	9 (2-61)	8 (2-35)	5 (1-24)	3 (2-9)	6 (1-206)	4 (1-7)	5 (1-25)	7 (1-206)
Median time (days) between onset disease and hospital admission	9 (2-108)	9 (2-38)	9 (2-59)	14 (0-48)	7 (4-38)	14 (1-31)	16 (4-58)	22.5 (1-58)	12 (2-108)
Laboratory diagnosis									
Positive PCR/culture	52%	50%	50%	58%	23%	13%	0%	9%	41%
Positive serology	26%	29%	24%	19%	54%	58%	100%	77%	37%
Other***	21%	21%	26%	23%	23%	29%	0%	14%	22%

* Vaccination status according to registration of health care administrations; unknown when no informed consent was obtained from patient/parent

** Vaccination status based on registration of health care administrations if available; if not available based on report of paediatrician. Vaccinated includes both incompletely and completely vaccinated patients.

*** Microbiological or serological tests not done, negative or missing or reported cases who are epidemiologically linked to laboratory confirmed case.

5. Discussion

5.1 Trends in incidence of surveillance sources

After a relative low endemic year (1998), following the 1996-1997 epidemic, the incidence of pertussis increased again in 1999. This increase is relatively soon as compared with normal epidemic cycles of every 3 to 5 years. Although the annual incidence of hospital admissions in 1999 was comparable with 1996, the incidence according to notifications had increased and the incidence estimated from positive one- and positive two-point serology had decreased compared to 1996. In 2000 the estimated incidences declined and approached the incidence of 1998, although the incidence estimated from notifications remained higher than in 1998. In comparison with 1999 the incidence estimated from notifications, positive one-point serology, positive two-point serology and hospital admissions decreased in 2000 with a factor 1.7, 1.8, 1.9 and 2.1, respectively. This indicates that surveillance can be considered as stable with respect to different surveillance sources. For the year 2001 the surveillance data collected until August indicate that the incidence according to notifications of pertussis increases again and might approach the 1996 peak.
As in 1996-1998, the highest incidence in 1999 and 2000 was observed among 4-5 year olds, while for hospital admissions the highest incidence was observed for infants less than one year, especially for those younger than three months.

The changes in incidence will partly demonstrate a true change in incidence of pertussis, but other factors could have been involved.
The increase in incidence according to notifications might be partly due to the enhanced application of positive one-point serology as laboratory confirmation for notification, particularly among the older age-groups. Since 1997 positive one-point serology has been formally accepted as laboratory confirmation for notifications. Thus in comparison to previous years a larger part of pertussis cases is recognised and reported. This could also explain the increase in incidence for children older than 15 years. Before 1996 the level of notifications was comparable with the level of positive two-point serology and much lower than the level of positive one-point serology. Since 1997 the level of notifications is about similar to the level of positive one-point serology. However, since a linkage between notification data and serology data is not possible anymore, it can not be demonstrated whether the proportion of notifications confirmed with positive one-point serology has increased. On the other hand, since 1998 several laboratories started to perform pertussis serology by themselves. As a result the coverage of the LIS-RIVM laboratory, from which serologic data for surveillance are obtained, has declined to ± 80%. Therefore, the true incidence based on positive serology is probably underestimated compared to previous years.

We assume that surveillance based on hospital admissions is less sensitive to changes over time. Thus, changes in case reporting or changes in data on positive serology are likely to reflect true changes if they are accompanied by similar trends in hospital admissions.

Although the estimated incidence for notifications in 1999 was much higher (44.3 vs. 27.4) than in 1996, the incidence estimated from hospital admissions was comparable within both years. This indicates that in both years the actual incidence of pertussis will have been similar and so that the high incidence in 1999 according to notification data is not only due to changes in surveillance sources.

From 1993 up to 2000, a decreasing trend in vaccine-efficacy was observed for the 1-4 years olds and the 5-9 years olds. However, since 1997 an increasing trend of the vaccine efficacy among 1-year olds and 2-years olds is observed. Still, interpretation of the estimated vaccine efficacy is difficult. For instance, since it is not possible anymore to distinguish vaccine efficacy according to method of diagnosis. Furthermore, vaccine efficacy might be affected by the increase in the number of notifications, probably caused by the enhanced application of positive one-point serology as mentioned before. Therefore, the percentage vaccinated persons might be artificial high since 1999, which results in a low vaccine efficacy. In addition, it was temporarily impossible to distinguish between complete and incomplete vaccinated in the notifications during 1999. Thus, it is possible that people with one or two vaccinations are classified as 'vaccinated (for age)'. As a result, the percentage completely vaccinated persons in 1999 might be overestimated and so the vaccine efficacy underestimated. When taking the above mentioned into account, a real increase in vaccine efficacy among the younger age-groups seems plausible.

As reported previously, the remarkable increase of reported vaccinated patients over a wide age range, starting two years before the outbreak of 1996, suggests a role of a mismatch between circulating and vaccine strains (5,7). The Dutch whole-cell vaccine induces low levels of antibodies against pertussis toxin and filamentous haemagluttinin and high levels of antibodies to agglutinogens and pertactin. Perhaps this immunogenicity profile has resulted in a greater vulnerability of the vaccinated Dutch population to antigenic changes in *B. pertussis*, possibly especially with respect to pertactin. In November 1997, a whole cell vaccine was introduced with a higher content of pertussis toxin. It was not yet possible to study the effect on the epidemiology of pertussis, but it could have affected vaccine efficacy. However, as mentioned before estimating vaccine-efficacy is problematic and should be interpreted cautiously.

5.2 Effects of changes in surveillance of pertussis in the Netherlands

As previously described, the interpretation of the surveillance data is complicated due to recent changes of the various surveillance sources. Below we will summarise the three main relevant changes in short.
Firstly, the levels of notifications in 1999 and 2000 should be interpreted cautiously, since some changes in registration have occurred. Since the outbreak in 1996 the alertness for pertussis might be increased which may have resulted in a higher case-reporting rate. In addition, positive one-point serology has been formally accepted as laboratory confirmation

for notification since 1997. This resulted in a less rigid case definition and thus a larger part of pertussis cases was recognised and/or reported.
In the second place concerning serology, one should consider that at least three large regional public health laboratories have started to perform pertussis-serology themselves since 1998. Before, only one laboratory (LIS-RIVM) performed serology for the whole country. Thus, the population coverage of serological surveillance of pertussis has decreased (till 80% or lower) and therefore the true incidence based on positive serology is underestimated compared with previous years. Furthermore, PCR as method of diagnosis is applied more general, especially among young children. As a result, a second serum sample is often not required anymore and the number of positive serology test decreases. Therefore, concentrating on serology alone is not valid anymore.
Thirdly, in previous years the notification-database could be matched with the serology-database. With this matching more insight was gained in whether observed changes in surveillance data represented true changes of incidence. However, in 1999 the law for disease-notification changed and from that time surveillance was no purpose of notification anymore. Although additional information about notifications (e.g. method of diagnosis) will be gathered by the RIVM from 2001 on voluntary base, a linkage between serologic data and notification-data is not possible anymore.

5.3 Voluntary notifications

In 1999 the Infectious Disease Law changed and from that time surveillance of infectious diseases was not a goal anymore, but was only for management purposes. Therefore the RIVM started to collect additional data on notifications on a voluntary basis. This voluntary notification system contained more information on vaccination status and source of infection. For about 70% of the notified cases in 1999 and 2000, additional information based on voluntary notification was available.
In case the source of infection was reported, most frequently school and family were mentioned as source. Hereby, it has to be said that for 70% of the notified cases for which a voluntary questionnaire was available, no information on source of infection was given. Remarkable was the difference between the number of deaths reported in the obligatory notification and the voluntary notification. In the voluntary notification 9 deaths were reported, while no deaths were reported in the obligatory notification, 3 deaths by the CBS and 1 in the paediatric surveillance. After verification with the Municipal Health Centres who notified the deaths, it appeared that those 9 cases were notified as death by mistake. Also concerning vaccination status some errors have occurred. For 7% and 3% of the unvaccinated cases according to the voluntary notification (in 1999 and 2000, respectively), the vaccination status in the compulsory notification was the opposite. From the beginning of 2001 the number of vaccination doses will also be collected in the voluntary notification. In order to be useful in surveillance of pertussis, the voluntary notification questionnaire should be completed carefully.

5.4 Paediatric surveillance

Although coverage of the paediatric surveillance was not complete and the response has decreased in comparison with 1997-1998 (from 38% to 33%) it was probably still representative for all hospital admissions in the study period (9,10). The age- and gender distribution and length of hospital stay were similar for the national registry of hospital admissions.
The paediatric study does not give insight into the total burden of disease due to pertussis in the Netherlands because it is limited to cases for which hospitalisation was necessary. However in 1999 the number of reports (168) was higher than in 1998 (115) and 2000 (80). Since the coverage of the system did not change very much between these years, this seems to reflect a real increase in incidence in 1999 as shown in the routine surveillance of notifications, serology and hospitalisations. Besides, the study gives important insight into characteristics of pertussis patients and severity of pertussis in the Netherlands. The study shows clearly that pertussis remains a potentially severe disease in the Netherlands especially among infants less than two months of age who are too young to be vaccinated. Although severe complications were unlikely and death rare, both vaccinated and unvaccinated children developed classical and long-lasting pertussis.

Complications (apnoea, cyanosis, and administration of oxygen) decreased with increasing age and the median duration of hospitalisation was longest for children younger than 3 months. A clear advantage of the shift in the vaccination schedule since 1999 (2,3,4 and 11 months instead of 3,4,5 and 11 months) cannot be seen, although the percentage hospitalised children younger than 2 months (i.e. before vaccination) has increased (31% in ‘97/’98, 40% in ’99 and 47% in 2000), while the proportion of children aged 6-11 months decreased. Those patterns suggest that already after the first vaccination at two months of age protection is present.
According to the Central Statistics of the Netherlands 3 deaths due to pertussis were reported in 1999, although by paediatric surveillance only one fatal case was registered. All deaths were 0 years old. Unfortunately, no linkage was possible between national registration and paediatric surveillance.

It is important that the paediatric surveillance will be continued in the coming years. Despite incomplete coverage, it provides insight into the occurrence of severe pertussis in the Netherlands. Important information on vaccination status, symptomatology and severity of pertussis can be collected. Because antigenic changes of *B. pertussis* may play a role in the increased incidence since 1996, it might be worthwhile to compare strains and severity of diseases of patients reported in the paediatric surveillance (7).

5.5 Pertussis in the Netherlands compared with other countries

Some 50 million cases of pertussis occur world-wide each year, 90% of which are found in developing countries. About 300,000 of these patients, mostly infants, die from the disease. The incidence of pertussis in older children and adults varies with the frequency of exposure to *B. pertussis* and vaccination coverage in the population. In Western countries about 10%-12% of all cases have been reported in persons aged >15 years (3). However, reliable incidence data are scarce, as atypical clinical courses and unrecognised infection are common in these age groups. In addition, laboratory confirmation of suspected cases is mostly unavailable. Asymptomatic carriers of *B. pertussis* seem to be rare among children, and although adolescents and adults are considered to be an important source of infection, the carrier rates in these age groups are largely unknown. Some recent articles describe an increase in the incidence of pertussis among adolescents and adults in Canada and the United States (11,12). In addition, the burden of disease appears to increase with age, smoking and asthma (13). In our data no real increase in incidence among older age categories is visible. Although according to both notifications and serology the proportion of cases older than 19 years slightly increased.
Because of great variation in case definitions and types of laboratory confirmation, comparing numbers of reported cases in different countries is meaningless. Hospitalisations, although limited to severe pertussis cases, might be more useful for international comparisons. Our results concerning hospital admissions regarding incidence and age-distribution, are in accordance with published data on hospitalisation for pertussis in Spain and England/Wales (14,15).

5.6 Further research

From September 2001 an acellular booster vaccination for 4-year old children will be introduced in the National Vaccination Programme. To evaluate the effect it is important to continue the surveillance. In addition, the change since 1999 of the vaccination programme from 3, 4, 5 and 11 months to 2, 3, 4 and 11 months, will also affect the incidence and thus the effect of this advancing vaccination should be followed carefully. A clear advantage of the shift in the vaccination schedule since 1999 (2,3,4 and 11 months instead of 3,4,5 and 11 months) cannot yet be seen in our routine surveillance data.
The active paediatric surveillance will more frequently be used to verify trends observed in routine sources, since the interpretation of our routine surveillance is hampered by various factors as mentioned before.
Because antigenic changes of *B. pertussis* possibly play a role in the increased incidence, strains of patients reported in the paediatric surveillance will be collected for molecular epidemiological research (5).

In addition to surveillance, epidemiological research should be focused on estimating the frequency of *B. pertussis* infection stratified by age. Our surveillance sources mainly provide data about the incidence of cases with (severe) clinical symptoms. However, *B. pertussis*

infection can run an asymptomatic or less severe symptomatic course as well, mainly in older vaccinated children and adults (11,12,13). In relation to this, another field of investigation is to study the source of infection for young unvaccinated infants, since protection of unvaccinated infants against severe pertussis is the main aim of vaccination. Adults and other family members are assumed to play an important role in the transmission of pertussis to (unvaccinated) infants (11,12).

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Appendix 1: Abbreviations

CBS	Centraal Bureau voor Statistiek / Central Statistics Netherlands
CIE	Centrum voor Infectieziekten Epidemiologie / Department for Infectious Diseases Epidemiology
ELISA	Enzyme-Linked Immunosorbent Assay
IGZ	Inspectie Gezondheidszorg / Health Care Inspectorate
LSI	Laboratorium Surveillance Infectieziekten / Laboratory Surveillance Infectious diseases
LIS	Laboratorium voor Infectieziekten diagnostiek en Screening / Laboratory for Infectious Diseases Diagnostics and Screening
LMR	Landelijk Medische Registratie / National Medical Registration
NSCK	Nederlands Signalerings-Centrum Kindergeneeskunde / Netherlands Paediatric Surveillance Centre
PCR	Polymerase Chain Reaction
RIVM	Rijksinstituut voor Volksgezondheid en Milieu / National Institute of Public Health and the Environment
SAS	Statistical Analysis Computer Program
SIG	Stichting Informatievoorziening Gezondheidszorg / Foundation Information Centre of Health Care
SOP	Standard Operating Procedure
VE	Vaccin effectiviteit / Vaccine-efficacy

Appendix 2: Mailing list

1	Waarnemend hoofdinspecteur voor de Gezondheidszorg, P.H. de Vree
2-3	Directeur-Generaal van de Volksgezondheid, drs. N.C. Oudendijk (wnd.)
4-5	Inspecteur Infectieziekten van de Inspectie Gezondheidszorg, drs. J.K. van Wijngaarden, arts
6	Hoofdinspectie voor de preventieve en curatieve gezondheidszorg, mr. H. Plokker
7	Voorzitter van de Gezondheidsraad, prof. Dr. J.A. Knottnerus
8	Secretaris Werkgroep RVP, Gezondheidsraad, J. Sekhuis, arts
9	WHO-GPV
10	WHO-EURO
11-12	GGD- Nederland
13-78	Artsen infectieziektenbestrijding van de GGD's
79	Bureau van de Landelijk Coördinatiestructuur Infectieziektenbestrijding
80-97	Streeklaboratoria
98-99	Nederlands Instituut voor onderzoek van de Gezondheidszorg
100-117	Leden IGZ-infectieziekten overleg RIVM
118	Nationale Vereniging Thuiszorg
119	Nederlandse Vereniging voor Kindergeneeskunde
120	Nederlandse Vereniging voor Infectieziekten, Prof.dr.J.van der Meer
121	Nederlandse Vereniging voor Medische Microbiologie, dr. M.F. Peeters
122	Dr. F. van Loock, Wetenschappelijk Instituut voor Volksgezondheid - Louis Pasteur, Brussel
123	Statens Seruminstitut, Copenhagen
124	Department of Infectious Disease Epidemiology, Helsinki
125	Réseau National de Santé Publique Hospital National Saint-Maurice, Saint-Maurice
126	Instituto Superiore di Sanita, Communicable Disease Unit, Lab. of Epidemiology & Biostatistics, Rome
127	Instituto Nacional de Saudé, Lisboa
128	Swedish Institute for Infectious Disease Control, Sweden
129	PHLS/Communicable Disease Surveillance Centre, London
130	Centro National de Epidemiologia
131	Prof. dr. J. Huisman
132	Prof. dr. J. van der Noordaa
133	Prof. dr. S.P. Verloove-Vanhorick, TNO-PG
134	Dr. H. Bijkerk
135	Dr. H. Cohen
136	Nederlands Signalerings Centrum Kindergeneeskunde, Dr. R. Rodrigues-Pereira
137	Depot Nederlandse Publicaties en Nederlandse bibliografie

138	Directie RIVM
139	Prof. dr. ir. D. Kromhout
140	Dr. A.D. Plantinga
141	Dr. J.G. Loeber
142	Dr. T.G. Kimman
143	Dr. ir. A.M. Henken
144	Dr. P.G.N. Kramers
145	Dr. ir. J. Seidell
146	Dr. J.D.A. van Embden
147	Dr. F.R. Mooi
148	Dr. H. van de Donk
149	Dr. W.A.M. Berbers
150	Dr. J.G. Kreeftenberg
151	Dr. W. Jiskoot
152	Ir. M. Thalen
153	Dr. E.C. Beuvery
154-174	Leden kinkhoestdwarsverbandoverleg
175-185	Medewerkers LIS
186-206	Medewerkers CIE
207-211	Auteurs
212	Hoofd Voorlichting en Public Relations RIVM
213	Bibliotheek RIVM
214	Bureau Rapportenregistratie
215-240	Bureau Rapportenbeheer
241-300	Reserve exemplaren

.

Appendix 3: Case-definition notification

Case-definition for notifications due to pertussis

1. **Pertussis**
   The diagnosis pertussis is made on the following criteria

1.1 Anamnestic one or more of the following symptoms:

a. A serious cough, with a duration of more than two weeks
b. Coughing attacks
c. Cough followed by vomiting

in combination with

1.2 One or more of the following signs, symptoms or findings

a. For young infants a period of apnoea and cyanosis after long-term coughing
b. For pertussis characteristic cough with whooping
c. Subconjunctival bleeding
d. Contact with a individual suspected for pertussis or with a confirmed case with pertussis in the previous three weeks
e. The occurrence of a pertussis outbreak locally
f. Leucocytosis from ≥ 15.000 lymphocytes per ml

and in combination with

1.3 Positive bacteriological and/or serological findings in the patient, or in the index patient (epidemiological criteria (included in the case-definition in 1992).

NB *Before April 1997: for serodiagnosis of pertussis the results are positive when a significant rise in titres in paired sera occurred (positive two-point serology)*
After April 1997: for serodiagnosis of pertussis the results are positive when a high titer in one serum (positive one-point serology) or a significant rise in paired sera occurred (positive two-point serology)

2. Atypical pertussis
   The diagnosis pertussis is made, when the patient coughs, and the criteria described in 1.1. and 1.2 were not met, but the criteria in 1.3 were met.

NB *An individual without symptoms has not to be reported independently on microbiological or serological findings which indicate that the individual has a pertussis infection.*

Appendix 4: Methods

1. Used data

1.1 Notification data

Since 1976 notification of pertussis to the Medical Inspectorate of Health is obligatory by law. In 1988 criteria for notification of pertussis were introduced (Appendix I). Before 1988 no case definition was used. Besides, the availability of laboratory diagnostics has influenced the surveillance. In 1981 and 1984, respectively, IgA an IgG immunoassays became available. Therefore in this report we limited pertussis surveillance from 1989 onwards. For this period of 1989-2000 data were available in a database (Registration InFectious diseases (RIF) database). The database includes age and date of notification. However, only since 1993 the first day of illness, vaccination status, date of birth and place of residence are also included in the database. However, since the change in the Infectious Disease Law in 1999, the date of birth is not exactly given anymore. For people older than two years of age only the year of birth is exactly given. The month of birth is equated with the month of notification and the day of birth is set at the first of that month. Age is estimated based on 30th June with the year of birth. For children ≤ 2years, the date of birth is based on the exact birth year and the first day of the exact month of birth. Age is estimated based on the 15th of the month.
In addition to the obligatory notification, people are asked to send a voluntary notification form, which contains additional information on e.g.vaccination status and source of infection.

For analysis, the distribution of cases over the years for notifications and serological results are based on the first day of illness. Therefore, for 1989-1992 the date of onset of symptoms was estimated by subtracting the median duration between first day of illness and date of notification in the period 1993/1994. The median duration amounted to 81 days. Also for reported cases in 1993-2000 for which the date of first illness was unknown this correction was made. In 1999 and 2000 the delay between onset of symptoms and the registration of reported cases was 66 days.
Data on vaccination status for the period 1989-1992 were only available on paper and per age groups (0-5 months, 6-11 months, 1-4 years, 5-9 and ≥ 10 years). Therefore, data on vaccination status are limited to the years 1993 to 2000 in the analyses. The analysis of vaccine-efficacy was restricted to those aged 1-4 years and 5-9 years because for these age groups the estimated vaccine-coverage is most reliable (vaccine coverage estimated at 96%). For the estimation of vaccine-efficacy incompletely vaccinated cases (one or two immunisations) were excluded thus completely vaccinated cases (at least three immunisations) were compared to unvaccinated cases (no immunisation).

1.2 Serological data 1989-2000

1.2.1 Immunoassays

Serology consisted of measurement of IgA antibodies against a crude cell-membrane preparation of *B. pertussis* and IgG antibodies against purified pertussis toxin in ELISA's, according to described methods (1,2). Sera were tested in 1:100 and 1:400 dilution's. Antibody-binding activity in patient sera was quantitatively expressed (units per millilitre) relative to the capability in a reference immunoglobulin preparation that had been obtained from convalescent sera of patients with culture-proven pertussis and preserved for long-term use. The reference preparation was arbitrarily defined to contain 100 U/ml each of IgA and IgG antibodies. The whole cell vaccine does not induce an IgA response, while the IgG response against pertussis toxin is either absent or very low and short lived (median IgG level: 1 U/ml before vaccination and 14 E/ml shortly thereafter).
Until April 1997, to prove a recent infection with *Bordetella pertussis* with serology a significant rise in titres in paired sera has to be shown to be in accordance with the criteria for notification. The first serum sample has to be taken as soon as possible after the first day of illness. For individuals less than one year, 1-4 years of age and > 4 years the time indication for the second blood sampling are minimal six, four and two weeks after the first day of illness. The minimal duration between the second and the first blood sampling has to amount at least two weeks. Since April 1997, a significant rise of titre in single sera has been accepted as the criteria for notifications. After measuring the concentration of IgG-antibodies against pertussis toxin in U/ml and the concentration of IgA-antibodies against whole cell sonicate in U/ml a height-category is calculated. The different height-categories are given in Table 1.

In the database patients with an identical last name en date of birth are matched. Based on the test result of two successive samples a conclusion is drawn for the patient. We studied whether, and at which level, high titres in a first serum sample are indicative for actual or recent pertussis. We concluded that IgA/IgG-titres above a defined age-specific cut-off value in the first serum sample of a patient with cough supports the diagnosis of recent infection with *Bordetella pertussis* strongly. The age-specific cut-off values of the height-category for positive one-point serology amounted ≥ 5 for individuals aged 0-4 years, ≥ 7 for individuals aged 5-14 years and ≥ 8 for individuals aged ≥ 15 years (3).

Table 1. Interpretation of serodiagnostic results: according to serodiagnostics in height category (1 to 12) based on IgA and IgG concentrations in ELISA.

IgA¯ ³ IgG® (U/ml)	0<15	15<30	30<60	60<120	120<240	>240
0<5	1	2	3	4	5	6
5<10	2	3	4	5	6	7
10<30	3	4	5	6	7	8
30<75	4	5	6	7	8	9
75<150	5	6	7	8	9	10
150<300	6	7	8	9	10	11
>300	7	8	9	10	11	12

In the following cases no second serum sample was asked:

a. When in the first serum sample the IgG and IgA concentrations are so high that no further increase is expected (height-category ≥8) (in the measurement area used). In those cases sending a second serum sample is not recommended and it is reported that is was not possible to prove a recent pertussis infection, but that it is very probable.

b. When for individuals ≥10 years of age the IgA and IgG concentrations in the first serum sample are very low (height-category <=3) and the first day of illness is more than four weeks before the first blood sampling. In those cases sending a second serum sample is not recommended and it is reported that a recent pertussis infection is very improbable.

When in the first serum sample a height category greater than or equal to the age specific cut off value but lower than 8 is found: in those cases it is reported that a recent pertussis infection is probable and although a second serum sample is asked for definitive proof, often no second serum sample is received.

In all other cases no conclusion is given but a second serum sample is asked. In those cases the following conclusions are possible:

A. Height-category of the second serum sample minus height-category of the first serum sample ≥2: conclusion "pertussis"
B. Height-category of the second serum sample minus height-category of the first serum sample <=1 and height-category of the first and second serum sample less than 4: conclusion ‘no pertussis’
C. Height-category of the second serum sample minus height-category of the first serum sample <=1 and height-category of the first serum sample ≥4 and < age specific cut off value: conclusion ‘no proof for recent infection, but proof of a pertussis infection in the past’; non-conclusive; either recent or past infection.

1.2.2 Serological results 1989-2000

Almost all serological tests for pertussis are performed at the National Institute of Public Health and the Environment. All data on pertussis serology for patients whose first day of illness was in the period 1989-2000 were included in the study. For each serum sample the following data were registered in a database: last name of the patient, date of birth, place of residence, date of blood sampling, first day of illness and the test result.

1.2.3 Case-definition serology

In the data analysis the following categories were used:

1. Proof of recent pertussis infection; positive two-point serology (conclusion A). Since 1996 in addition individuals for whom the height-category of the second serum sample minus height-category of the first serum sample <=2 (significant decrease in antibody-titres) also the conclusion "pertussis" is given. For 1996 the proportion of patients with a significant decrease in antibody-titres amounted to 0.7%.
2. Strong indications for pertussis infection: positive one-point serology (height-category in the *first* serum sample above the age-specific cut-off value; positive one-point serology). Since 1996 in addition individuals for whom the height category in the *second* serum sample was above the age-specific cut-off value were grouped in this category. For 1996 the proportion of patients for whom the height-category was above the age-specific cut-off value only in the second serum sample amounted to 0.6%.
3. No pertussis (see b and B)
5. 'Non-conclusive' (see C and all cases in which none of the above mentioned conclusions could be given).

1.2.4 Exclusion criteria

In Table 2 exclusion criteria that were used in the study are given. To draw a conclusion not only the height-category, but also the duration between the first day of illness and blood sampling and the age of the patient were taken into account. The databases used for analysis

of the data of 1989-1995 did not include sera of patients whose first day of illness or first date of birth were unknown. The proportion of serum samples for who the first day of illness was unknown amounted to less than 8% in 1989-1995. However, in 1996 the proportion of serum samples for which the first day of illness is unknown increased to 28%. This increase is probably caused by discontinuing the request to the physicians to supply information on the first day of illness when they have not given this information in first instance. Therefore it was decided not to exclude patients with unknown first day of illness from the database of 1996 onwards. For these patients the first day of illness was estimated by the subtracting the median duration between the first day of illness and the date of blood sampling (31 days in 1999 and 2000) from this last date.

Table 2. Exclusion criteria for laboratory surveillance

- Missing first day of illness (databases 1989-1995)
- Missing date of birth
- First day of illness more than 0.5 year before the first serum sample
- Sera collected for a specific study (for example in a local epidemic)

We assumed that serological tests performed more than 0.5 year after the first day of illness were not related to the identical period of illness. Serum samples of a particular study were excluded to prevent overestimation of the incidence of pertussis. When the duration between blood sampling in one individual was more than 100 days apart, we assumed that the second serum sample was related to a new period of illness; this sample was considered a new first serum sample.

1.3 Hospital admissions

Information on the number of hospital admissions due to pertussis (ICD-9-CM 033) in 1989-2000 by age group (1976-1980 0-4 years, 5-9 years etc., 1981-2000 0 year, 1-4 years, 5-9 years etc.) and sex were obtained from ‘SIG Zorginformatie’ / ‘Prismant’.

1.4 Laboratory Surveillance Infectious diseases (LSI)

Since 1989 all 16 Public Health Laboratories report the number of isolates of Bordetella on a weekly basis to the RIVM. In this study isolates of Bordetella registered in the period 1989-2000 were used. Since 1996, one Public Health Laboratory (Tilburg) has routinely performed PCR for pertussis covering the whole country.

1.5. Central Bureau of Statistics (CBS)

The age distribution of the Dutch population per year and deaths due to pertussis in the period 1989-1999 were obtained from the CBS.

1.6 Paediatric surveillance

Appendix 5 shows the NSCK reports of pertussis in 1999 and 2000. The total number of reports was 234 in 1999 and 112 in 2000. After exclusion of duplicate (6 in 1999 vs. 3 in 2000) or false cases (22 in 1999 vs. 12 in 2000), cases from which no questionnaire was received (26 in 1999 vs. 17 in 2000), and cases who had a first day of hospital admission not in 1999 or 2000 (12 in 1999 vs. 0 in 2000), 248 (168 in 1999 and 80 in 2000) cases were included in the analysis. In 1999 for 66 of 168 (with 67 children< 2 months) children vaccination status could be verified at the Provincial Immunisation Administrations. In 2000, for 42 children an informed consent was filled in, but twelve of these were not useful since those children were younger than 2 months during hospital admission. For three of the patients with an informed consent, no questionnaire was available and for one child it was explicitly mentioned in the case report that the child had not been vaccinated, which was confirmed by the data from the immunisation administration. Finally, for 24 of 80 children (with 45 children< 2 months) vaccination status could be verified at the Provincial Immunisation Administrations in 2000.
Vaccination status as registered at health care administrations was categorised as 'unvaccinated' (0 doses), 'incompletely vaccinated' (1 or 2 doses), 'vaccinated' (3 or 4 doses) or 'unknown' when no informed consent from the parents was obtained. Since the reporting paediatricians in many cases missed the opportunity to ask informed consent from the parents to verify the vaccination status, vaccination status was lacking for 49% of children at least 3 months of age. Therefore, a second classification of vaccination status was also used. For those with an unknown vaccination status, because of lacking of an informed consent, this classification was based on the vaccination status as reported by the paediatrician. Paediatricians did not distinguish between incompletely and completely vaccinated. Therefore these two classes were presented together in the second classification of vaccination status. The coverage of the paediatric study was calculated using hospitalisations with pertussis as main diagnosis (ICD-9-CM 033) in the national registry of hospital admissions.

2. Datamanagement and analysis

The Statistical Package SAS was used for analysis of the data. The χ^2-tests and vaccine-efficacies were calculated with EPI-INFO version 6.04.

2.1 Analyses of surveillance data 1989-2000

The annual incidence of pertussis per 100,000 inhabitants was estimated according to notifications, positive one-point serology, positive two-point serology, positive one-point serology and/or positive two-point serology and hospital admissions in the period 1989-2000. The number of reported cases per month, the number of patients with positive two-point

serology, positive one-point serology and negative serology were calculated per month. The proportional distribution of serological results per year were calculated for 1989 to 2000 The number of isolates of *Bordetella pertussis* in the period 1989-2000 as reported by the 16 regional public health laboratories are given.

The age-specific incidence in the years 1989-2000 was calculated for notifications (age-groups 0 years, 1-4, 5-9, 10-14, 15-19 and ≥ 20 years), positive one-point and two-point serology (age-groups 0-5 months, 6-11 months, 1-4 years, 5-9, 10-14, 15-19 and ≥ 20 years) and for hospital admissions (age-groups 0 year, 1-4, 5-9, 10-14, 15-19 and ≥ 20 years). For 1989-1995 the average age-specific incidence was calculated for notifications, positive two-point and/or positive one-point serology and hospital admissions (age groups 0 year, 1-4, 5-9, 10-14, 15-19 and ≥ 20 years). In addition, the age-specific incidence per age-year was calculated for positive two-point serology, positive one-point serology and notifications for the years 1993 to 2000 (information on year of age is not available for previous years for notifications).

The proportional age distributions according to positive one-point and positive two-point serology (age groups 0-5 months, 6-11 months, 1-4 years, 5-9, 10-14, 15-19 and ≥ 20 years) and notifications by first day of illness (age groups 0 year, 1-4, 5-9, 10-14, 15-19 and ≥ 20) in the period 1989-2000 and according to hospital admissions due to pertussis (age groups 0 year, 1-4, 5-9, ≥ 10) in the period 1989-2000 were calculated.

In many cases the vaccination-status of serodiagnosed patients is not given or when given, is considered to be unreliable. For hospital admissions no information on vaccination status was collected. Therefore, only the vaccination status as given at notification was used to differentiate vaccinated and unvaccinated individuals.
Because before 1993 the vaccination status of reported cases on an individual level was not available in the database but on paper only and per age group, data on vaccination status are limited to the years 1993 to 2000. Due to the high uncertainty of vaccine coverage of those aged less than one and ≥ 10 years, the analysis of vaccine-efficacy was restricted to those aged 1-4 years and 5-9 years (vaccine coverage estimated at 96%). For 1999 and 2000 the vaccine-efficacy was also estimated per year of age in the age group 1-9 years.

For the estimation of vaccine-efficacy incompletely vaccinated cases were excluded in contrast to chapter 4. Thus vaccinated cases were compared to unvaccinated cases.
The vaccine-efficacy (VE) was estimated with:

$$PCV = PPV-(PPVxVE) / 1- (PPVxVE)$$

Where PCV=proportion of cases vaccinated, PPV=proportion of population vaccinated, and VE=vaccine-efficacy.

3. References

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Appendix 5: Paediatric surveillance

Table 1 and Table 2 show the results of the paediatric surveillance for 1999 and 2000, respectively.

Table 1. Characteristics of hospitalised cases reported in the paediatric study in 1999

Hospitalised cases									
	0 mnth	**1 mnth**	**2 mnths**	**3-5 mnths**	**6-11 mnths**	**1-2 yrs**	**3-4 yrs**	**5-15 yrs**	**Total**
	N=27	N=40	N=26	N=24	N=8	N=21	N=4	N=18	N=168
	16%	24%	15%	14%	5%	13%	2%	12%	100%
Registered vaccination status*									
Vaccinated	0%	0%	0%	0%	0%	48%	50%	61%	14%
Incompletely vaccinated	0%	0%	12%	21%	0%	0%	0%	0%	5%
Unvaccinated	100%	100%	35%	42%	38%	0%	0%	6%	54%
Unknown	0%	0%	54%	38%	63%	53%	50%	33%	28%
Reported vaccination status**									
Vaccinated	0%	0%	15%	50%	38%	76%	75%	89%	32%
Unvaccinated	100%	100%	69%	50%	50%	19%	25%	6%	64%
Unknown	0%	0%	15%	0%	13%	5%	0%	6%	4%
Symptoms									
Coughing	100%	100%	100%	100%	100%	100%	100%	100%	100%
Paroxysmal coughing	74%	78%	85%	63%	50%	81%	25%	44%	70%
Whooping	7%	20%	12%	21%	25%	10%	0%	11%	14%
Vomiting	70%	58%	54%	63%	50%	62%	75%	61%	61%
Fever	52%	45%	46%	54%	63%	48%	75%	44%	49%
Complications									
Death	0%	3%	0%	0%	0%	0%	0%	0%	0.6%
Collaps	15%	3%	0%	13%	0%	10%	0%	0%	6%
Convulsion	0%	0%	0%	0%	0%	0%	0%	0%	0%

Encephalopathy	0%	0%	0%	0%	0%	0%	0%	0%	0%
Apnoea	30%	23%	15%	13%	0%	5%	0%	0%	15%
Pneumonia	0%	5%	0%	0%	0%	5%	25%	17%	4%
Cyanosis	78%	68%	73%	67%	88%	52%	0%	22%	63%
Artificial respiration	26%	3%	0%	0%	0%	0%	0%	0%	5%
Administration of oxygen	63%	40%	54%	21%	0%	19%	0%	11%	35%
Other									
Median days hospitalised	13 (1-63)	9 (2-61)	9 (2-32)	5 (2-24)	4 (2-9)	6 (1-206)	5 (1-7)	5 (1-18)	7 (1-206)
Median time (days) between onset disease and hospital admission	7 (2-108)	9 (0-38)	7 (2-54)	14 (0-48)	10 (4-38)	14 (4-30)	11 (13-58)	23 (1-58)	12 (0-108)
Laboratory diagnosis									
Positive PCR/culture	56%	40%	42%	58%	25%	14%	0%	11%	38%
Positive serology	26%	33%	27%	21%	50%	57%	100%	72%	39%
Other***	19%	28%	31%	21%	25%	29%	0%	17%	24%

* Vaccination status according to registration of health care administrations; unknown when no informed consent was obtained from patient/parent

** Vaccination status based on registration of health care administrations if available; if not available based on report of paediatrician. Vaccinated includes both incompletely and completely vaccinated patients.

*** Microbiological or serological tests not done, negative or missing or reported cases who are epidemiological linked to laboratory confirmed case

Table 2. Characteristics of hospitalised cases reported in the paediatric study in 2000

Hospitalised cases									
	0 mnth	**1 mnth**	**2 mnths**	**3-5 mnths**	**6-11 mnths**	**1-2 yrs**	**3-4 yrs**	**5-15 yrs**	**Total**
	N=15	N=30	N=12	N=7	N=5	N=3	N=4	N=4	N=80
	19%	38%	15%	9%	6%	4%	5%	5%	100%
Registered vaccination status*									
Vaccinated	0%	0%	0%	0%	80%	33%	100%	50%	14%
Incompletely vaccinated	0%	0%	42%	57%	0%	0%	0%	0%	14%
Unvaccinated	100%	100%	0%	0%	0%	0%	0%	0%	56%
Unknown	0%	0%	58%	43%	20%	67%	0%	50%	16%
Reported vaccination status**									
Vaccinated	0%	0%	92%	86%	80%	67%	100%	100%	39%
Unvaccinated	100%	100%	8%	14%	20%	33%	0%	0%	61%
Unknown	0%	0%	0%	0%	0%	0%	0%	0%	0%
Symptoms									
Coughing	100%	100%	100%	100%	100%	100%	100%	100%	100%
Paroxysmal coughing	60%	63%	92%	71%	60%	33%	25%	75%	65%
Whooping	13%	13%	8%	29%	20%	33%	0%	50%	16%
Vomiting	47%	70%	67%	43%	60%	33%	50%	75%	60%
Fever	13%	20%	17%	14%	60%	33%	0%	25%	20%
Complications									
Death	0%	0%	0%	0%	0%	0%	0%	0%	0%
Collaps	13%	10%	8%	14%	0%	33%	25%	25%	13%
Convulsion	0%	3%	0%	0%	0%	0%	0%	25%	3%

Encephalopathy	0%	0%	0%	0%	0%	0%	0%	0%	0%
Apnoea	7%	23%	8%	29%	0%	0%	0%	25%	15%
Pneumonia	0%	3%	17%	14%	0%	67%	0%	25%	9%
Cyanosis	87%	90%	75%	57%	60%	33%	50%	75%	78%
Artificial respiration	7%	7%	0%	0%	0%	0%	0%	0%	4%
Administration of oxygen	73%	60%	50%	43%	0%	33%	25%	25%	51%
Other									
Median days hospitalised	16 (4-24)	9 (3-30)	7.5 (2-35)	7 (1-22)	2 (2-9)	6 (3-7)	3 (1-6)	6.5 (2-25)	9 (1-35)
Median time (days) between onset disease and hospital admission	10 (3-16)	15 (0-31)	11 (4-59)	9 (0-14)	6 (5-27)	11 (1-31)	16.5 (4-44)	17.5 (8-38)	10 (0-59)
Laboratory diagnosis									
Positive PCR/culture	47%	63%	67%	57%	20%	0%	0%	0%	49%
Positive serology	27%	23%	17%	29%	60%	67%	100%	100%	35%
Other***	27%	13%	17%	14%	20%	33%	0%	0%	16%

* Vaccination status according to registration of health care administrations; unknown when no informed consent was obtained from patient/parent

** Vaccination status based on registration of health care administrations if available; if not available based on report of paediatrician. Vaccinated includes both incompletely and completely vaccinated patients.

*** Microbiological or serological tests not done, negative or missing or reported cases who are epidemiological linked to laboratory confirmed case

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