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Pertussis; description and evaluation based on surveillance data of 1997 and 1998

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Abbrevations

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

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Contents

Samenvatting

Inleiding. In 1996 werd een uitbraak van kinkhoest waargenomen onder met name gevaccineerde kinderen in Nederland. Toegenomen aandacht, veranderde diagnostiek en daling van de vaccinatiegraad konden de epidemie niet verklaren. Wel waren er aanwijzingen dat een mogelijke mismatch was ontstaan tussen vaccin-geïnduceerde immuniteit en de circulerende *Bordetella pertussis* stammen.
Methoden. Surveillance gegevens op basis van aangiften bij de Inspectie van de Gezondheidszorg (IGZ), serodiagnostiek verricht door het RIVM, *Bordetella* isolaties geregistreerd door streeklaboratoria en nationale registraties van ziekenhuisopnamen (SIG) en sterfte (CBS) werden geanalyseerd voor 1997 en 1998 en vergeleken met de periode van 1989-1995 en 1996. Bij de serodiagnostiek gegevens werd onderscheid gemaakt tussen positieve tweepuntsserologie (titerstijging) en positieve eenpuntsserologie (hoge titers in eerste serum). Door koppeling van aangiften met serodiagnostiekgegevens op individueel niveau, kon geverifieerd worden op basis van welk criterium (positieve een- of tweepuntsserologie) aangifte werd gedaan.
Resultaten. Op grond van verschillende surveillance bronnen, daalde de incidentie van kinkhoest in 1997 en 1998 na de epidemie in 1996. Echter, de incidentie in 1997 en 1998 was nog steeds verhoogd ten opzichte van de gemiddelde incidentie in de periode van 1989-1995. De gemiddelde incidentie op basis van aangiften was in de periode van 1989-1995 2,3, in 1996 27,3, in 1997 17,2 en in 1998 16,0 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 and in 1998 20.7 vs. 3.0 per 100.000. De piekincidentie op basis van aangiften en positieve serologie werd in 1997 en 1998 waargenomen onder de 4- tot 5- jarigen en was vergelijkbaar met 1996. Het aantal ziekenhuisopnamen in 1997 was 436 (2.8 per 100.000) en hoger ten opzichte van 1998 (282, 1.8 per 100.000) maar lager ten opzichte van 1996 (513, 3.3 per 100.000). In de periode van 1989-1995 werd het hoogst aantal ziekenhuisopnamen geregistreerd in het laatste epidemische jaar 1993 (288, 1.9 per 100.000). In 1997 zijn 2 ongevaccineerde zuigelingen jonger dan 3 maanden overleden en in 1998 1 zuigeling in vergelijking met 2 zuigelingen in zowel 1996 als 1993. In de periode van 1993-1996 daalde de vaccin-effectiviteit zoals geschat op basis van de screeningsmethode. De vaccin-effectiviteit voor 1997 en 1998 kon veelal niet berekend worden vanwege een hoog percentage gevaccineerden onder de aangiften.
Conclusie. In 1997 en 1998 daalde de incidentie van kinkhoest ten opzichte van 1996. Echter, de incidentie was hoogst waarschijnlijk nog wel verhoogd in vergelijking met de periode 1989-1995. 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. De kinkhoest surveillance moet gecontinueerd worden om trends in de kinkhoestincidentie en het effect van veranderingen van vaccinatiestrategieën te bestuderen. Vanwege veranderingen in casus-definitie van aangifte en veranderingen in de diagnostiek moet deze gebaseerd zijn op gegevens uit diverse surveillancebronnen.

Summary

Introduction. In 1996, an outbreak of pertussis was observed among mostly vaccinated children in the Netherlands. A greater awareness, changes in diagnostic practice or a lower vaccine coverage could not explain the epidemic. The epidemic was postulated as possibly being related to a mismatch between the vaccine-induced immunity and the circulating *Bordetella pertussis* strains.
Methods. Surveillance data based on notifications to the Health Care Inspectorate, 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 1997 and 1998, and compared to the period 1989-1995 and 1996. 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). Notification data were linked on individual level with serological data to verify the underlying serodiagnosis (positive one-point or two-point serology) on which the notification was based.
Results. After the outbreak of pertussis in 1996, the incidence declined according to various surveillance sources in 1997 and further in 1998. Still, levels in 1997 and 1998 remained higher compared to 1989-1995, in particularly for notifications. The annual incidence based on notifications was 2.3 in the period 1989-1995, 27.3 in 1996, 17.2 in 1997 and 16.0 per 100,000 in 1998. In the period of 1989-1995 the annual incidence of cases with positive one-point and two-point serology was 8.2 vs. 2.1 per 100,000, compared to 50.7 vs. 12.2 in 1996, 26.4 vs. 5.9 in 1997 and 20.7 vs. 3.0 in 1998. According to notifications and positive serology,the peak incidence in 1997 and 1998 was comparable with 1996 and observed among 4- to 5-year-old children. The number of hospital admissions was 436 in 1997 (2.8 per 100,000). This was higher compared to 1998 (282, 1.8 per 100,000) but lower compared to 1996 (513, 3.3 per 100,000). In the period 1989-1995 the highest number of hospital admissions were reported in the previous epidemic year of 1993 (288, 1.9 per 100,000). Two fatal unvaccinated babies less than 3 months of age were reported for 1997, 1 in 1998 compared to 2 in 1996 and 2 in 1993. From 1993 to 1996 the vaccine efficacy, estimated by the screening method, showed a decreasing trend. For 1997 and 1998 the estimated vaccine efficacy remained low or could not be calculated due to the high proportion of vaccinated individuals in the notifications.
Conclusions. In 1997 and 1998, the incidence of pertussis declined when compared to 1996 but was probably still higher compared to 1989-1995. Although the notification rate increased and the proportion of notifications based on positive one-point serology increased due to the change of case definition, it could not totally explain the observed higher incidence of pertussis. 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 notification and changes of laboratory diagnostics surveillance should be based on data from various surveillance sources.

1. Introduction

Pertussis (whooping cough) is caused by the bacterium *Bordetella pertussis* or less frequently by *Bordetella parapertussis* (1). 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. In vaccinated older children and adults the disease most often occurs with mild and often unrecognised symptoms (2, 3, 4). Although the occurrence of pertussis declined markedly after the introduction of whole cell vaccine, worldwide it remains an important cause of death among children. In 1994, the estimated number of pertussis cases was 40 million resulting in 360.000 deaths (3).

Pertussis in the Netherlands 1952-1996

In the Netherlands, mass vaccination with a whole cell pertussis vaccine was introduced in 1952. Already before 1952, the incidence of pertussis declined but it further decreased after 1952 while death due to pertussis became very rare. Until 1980, only incidentally cases of pertussis were reported. During the 1980s, the number of pertussis notifications increased yearly from 50 in 1981 to 2156 in 1986 and 2709 in 1987. It was considered that notifications were affected by the introduction of serology for laboratory diagnosis of pertussis at the beginning of the eighties and its too liberal interpretation at that time (detection of moderate levels of IgA/IgG antibodies in a single serum were considered indicative of pertussis). However, in contrast to opinions at that time (5, 6), we previously reported that the 1986-1987 epidemic wave might have reflected a true increase. It might have been associated with the temporary reduction of the potency of the Dutch vaccine from 16 to 10 opacity units per dose in the period of 1976 to 1984 (7). In 1988, a restrictive case definition that included criteria for laboratory diagnosis (e.g. serology) was introduced (Appendix I). The case-definition included defined clinical symptoms and laboratory confirmation by positive culture of *B. pertussis* or *B. parapertussis* or positive serology. Serology as laboratory confirmation was only accepted when in paired sera a significant titre-rise of IgG antibodies against pertussis toxin and /or IgA antibodies against *B. pertussis* had been documented. The number of reported cases fell drastically from 2709 in 1987 to 112 in 1988. Certainly, this massive decline was directly related to the introduction of the very strict case definition for notification. However, the decline was also reflected in lower numbers of hospital admission and therefore may have been real since it occurred four years after resuming "full dose" pertussis vaccinations.
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% (8). This pattern seemed to be consistent with other countries with epidemic cycles every 3 to 5 year (9). However, in 1996, a sudden 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 (7,10). We concluded that the sudden increase reflected a true increase in pertussis incidence. Most cases occurred among vaccinated children aged 1-9 years resulting in a lower estimation of vaccine efficacy as calculated retrospectively from notification data. Interestingly, a decline of estimated vaccine efficacy had already begun in 1994 and 1995. The constant ratio of hospital admissions and notifications and of hospital admissions and cases with two-point serology among infants less than one year of age, indicated that the virulence of the circulating strains did not change. However, in older age groups the increase in hospital admissions was relatively low compared to the increase observed in notification data and positive serology data. Additional studies among hospital admissions and reported cases showed that hospital admission and severe symptoms were most frequently reported among unvaccinated young infants less than 3 months of age (11). Still, despite vaccination, older children that were notified, had developed typical pertussis as well (11). Thus, we could not conclude that the increase was due to increased notification of "atypical mild disease". On the other hand the number of hospital admissions for pertussis among 1-9 years proportionally had increased much less than the number of notifications and positive serology in that age-category (suggesting that the surplus of cases was less severe). Furthermore, the outbreak could not be explained by a decrease in vaccination coverage, a change in vaccine quality or interference with the introduction of vaccination *Haemophilus influenzae* type b in 1993 (10, 12). Interestingly, the re-emergence of pertussis was found to be associated with the expansion of strains, which are antigenically distinct from the vaccine strains (13). Studies to explain the unexpected course of pertussis in the Netherlands, e.g. further molecular biological research, are still in progress. Thus, although solid scientific proof is lacking, we believe it to be possible that the decline of vaccine efficacy since 1994 and the strongly increased incidence of pertussis since 1996 are related to antigenic changes of *B. pertussis* over time leading to a relative mismatch between vaccine-induced immunity and presently circulating strains. We speculated that the Dutch population might be more vulnerable to such antigenic changes because the Dutch whole cell vaccine has been shown to contain a relatively small spectrum of protective antigens (13).

Pertussis in the Netherlands 1997 - 1998

The present report describes the results of pertussis surveillance in the Netherlands in the years 1997 and 1998, which data are shown in relation to the data of 1989 - 1996. For comparison with surveillance data before 1988, in which year the strict case definition for notification and positive serology was introduced, we refer to our previous report (7). The importance of continues surveillance is underscored by the necessity to monitor possible effects of the change in vaccination-strategy, which occurred in November 1997 when a whole cell vaccine with slightly higher pertussis toxin content was introduced. Careful

analysis of various surveillance sources (notifications, hospital admissions, deaths, laboratory reports of positive one-point and positive two-point serology, laboratory reports of positive cultures and of positive PCR) remains necessary for other reasons too. Firstly, alertness and notification-discipline may have changed over time and influenced the number of notifications. However, we assume that hospital admissions are less affected. Secondly, because the criteria for notification include laboratory confirmation, changes in availability of methods or changes in interpretation of results may have a large influence on numbers of notifications and indeed such changes have occurred. In 1996, a *B. pertussis / parapertussis*- PCR became routinely available in one laboratory (Tilburg) for the whole country. The sensitivity of PCR has been shown to be 2.4 fold the sensitivity of culture (14). In the third place, since April 1997 positive one-point serology has been re-introduced in the case definition to be accepted as laboratory-confirmation for notification. With respect to the latter it should be emphasised that age-specific cut-off values of IgG/IgA antibody concentrations indicative for recent of actual infection with *B. pertussis* (values $\geq$ cut-off value = positive one-point serology) have been defined by studying 1) a large number of sera of the population of all ages, 2) the effect on IgG/IgA titres of 3 and 4 vaccinations with DTP-IPV and 3) the duration of high IgG/IgA values after natural infections (15). Consequently, the criteria for positive one-point serology are very specific (97.5-99%) and considerably more strict than the criteria for positive one-point serology that were applied in the eighties. Finally, we mention that serological data used to be a valuable and easy available tool in surveillance because only one laboratory (LIS-RIVM) performed serology for the whole country. However, in 1998 at least three large regional public health laboratories started to perform pertussis serology themselves with commercially available assays. Since then, probably more laboratories have followed that example. Therefore, since 1998 the population coverage of the serodiagnostic database of LIS-RIVM is declining at an unknown rate. These above-mentioned changes over time have to be taken into account when interpreting the surveillance data.

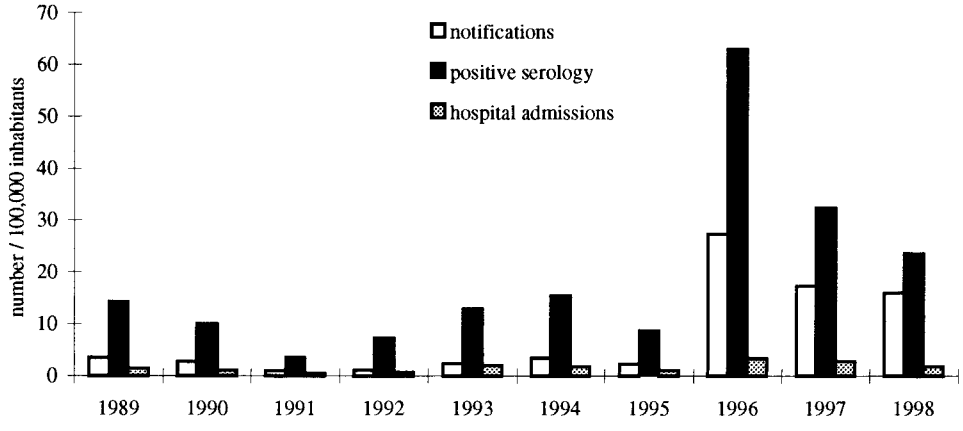
2. Methods

In appendix II the methods and analysis of the data are described in detail. The same methodology is used as in previous years (1989-1996). In short, the incidences of pertussis per year, per month and / or per age group in the period 1989-1998 were estimated using notifications, positive one-point serology, positive two-point serology, isolations of *B. pertussis*, hospital admissions and deaths. Proportional age-distributions according to positive one-point and/or two-point serology, notifications and hospital admissions were calculated. The annual vaccine-efficacies for the age groups 1-4 years and 5-9 years were estimated from data on notifications for 1993 to 1998 comparing vaccinated individuals with unvaccinated individuals. For 1997 and 1998 the geographical distribution of reported cases of pertussis per quarter are given. For 1993 to 1998, the database with the records of notification and the database with records of serodiagnosis were linked on the level of individual patients. In this way, the type of serodiagnosis (one-point serology or two-point serology) on which notification was based on could be verified. The linkage was restricted to the years 1993 to 1998 because before 1993 no data on date of birth on the individual level was available.

3. Surveillance data 1989-1998

3.1 Incidence of pertussis 1989-1998

Figure 1 shows the annual incidence in the period 1989-1998 of pertussis according to notifications, positive serology and hospital admissions. According to all surveillance sources the incidence of pertussis declined in 1997 and 1998 in comparison with 1996. Compared to 1996 the annual incidence estimated from notifications decreased by a factor 1.6 in 1997 and by a factor 1.7 in 1998. The estimated incidence based on positive serology decreased by a factor 1.9 in 1997 and 2.7 in 1998 and estimated from hospital admissions by a factor 1.2 respectively 1.8 compared with 1996.



total number of cases										
notifications	523	397	145	160	346	519	341	4231	2671	2508
positive serology	2110	1482	521	1099	1971	2365	1342	9739	5031	3715
hospital admissions	221	157	82	101	288	276	162	513	436	282

Figure 1. Incidence of pertussis per year in the period 1989-1998 estimated from notifications, positive (two-point serology and/or one-point) serology and hospital admissions

In Figure 2 the absolute number of cases per month according to positive two-point serology, positive one-point serology and notifications in the period 1989-1998 are presented. Monthly hospital admissions data were only available in the period of 1996 to 1998. Overall, the trend for the incidence according to the various surveillance systems was comparable in the period 1989-1998. After the peak in 1996 the incidence declined in the beginning of 1997. The incidence increased again in June/July with a peak in August 1997. The same seasonal trend was observed in 1998. In the period of 1989 to 1995 the number of notified cases were 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 and to approach one-point serology, particularly

in 1997 and 1998. Besides, while the incidence according to positive one-point serology in the years of 1997 and 1998 was still considerable higher compared to 1989-1995, the incidence according to positive two-point serology was only slightly higher compared to 1989-1995. The incidence in 1997 that was estimated from positive two-point serology decreased by a factor 2.1 compared with 1996, while the incidence in 1997 estimated by positive one-point serology decreased by a factor 1.9. For 1998 compared with 1996 these factors amounted 4.1 and 2.4 for positive two-point and one-point serology, respectively. In the period of 1989 to 1995 and in the years 1997 and 1998, the peak incidence for negative serology was observed in October. In this period the highest number of individuals with negative serological results was observed about two months after the peak incidence according to positive serology. In 1996, both the peaks for positive serology and negative serology were observed in October. For 1996 and 1998 the highest number of hospital admissions occurred in October. In 1997, the highest number of hospital admissions was observed around August.

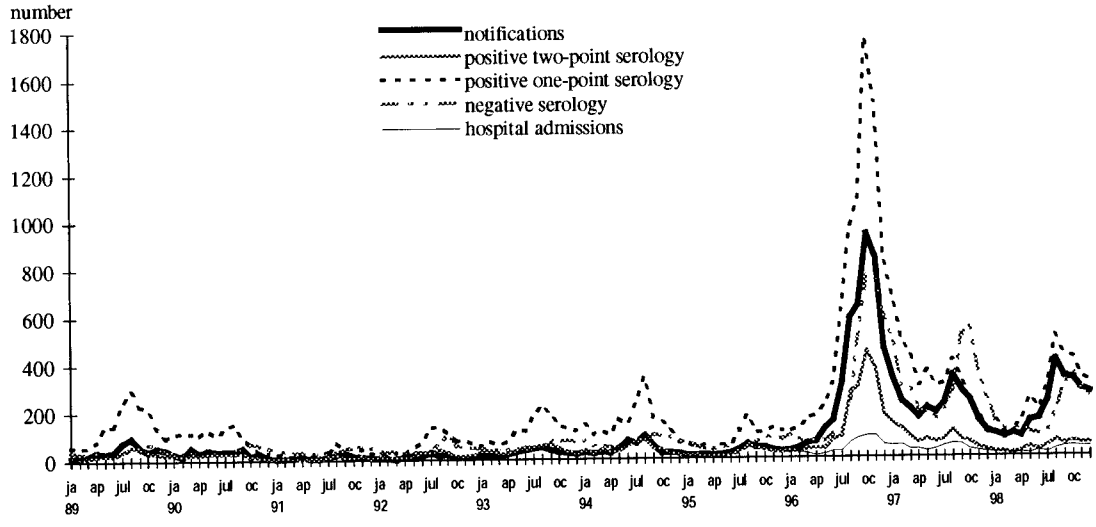


Figure 2. Pertussis in the period 1989-1998: Notifications, positive two-point serology, positive one-point serology and negative serology for pertussis; hospital admissions in the period 1996-1998.

- Compared with 1996, the decrease in 1997 and 1998 was the largest for positive two point (2.1- fold resp. 4.1-fold) and the lowest for hospital admissions (1.2-fold resp. 1.8-fold).
- Similar with 1989-1995, in 1997 and 1998 the seasonal peaks were observed in August.

3.2 Serological results 1989-1998

Table 1 shows that the proportional distribution of serological results for 1997 and 1998 are different from the average distribution in the period 1989-1995 and 1996. The total proportion of positive serology was much lower in 1997 (32.6%) and 1998 (31.0%) compared with 1996 (46.4%) and 1989-1995 (45.0%). Consequently, the proportion of negative (1997) and in particularly non-conclusive serology was higher. In 1998, the proportion of two-point serology was the lowest and of non-conclusive serology the highest in comparison with previous years.

Table 1. Proportional distribution (%) of serological results for pertussis in the period 1989-1998

	1989	1990	1991	1992	1993	1994	1995	*89-95*	1996	1997	1998
positive 2-point serology*	8.6	9.3	6.5	9.0	12.4	10.2	8.6	*9.2*	9.0	6.0	3.9
positive 1-point serology**	43.0	40.3	24.4	32.4	38.4	38.3	33.9	*35.8*	37.4	26.6	27.1
*total positive serology****	*51.5*	*49.6*	*30.9*	*41.3*	*50.8*	*48.5*	*42.5*	*45.0*	*46.4*	*32.6*	*31.0*
negative serology	12.7	17.0	27.6	21.2	16.9	16.8	21.4	*19.1*	16.3	24.2	18.0
non-conclusive serology	35.8	33.4	41.6	37.4	32.4	34.7	36.1	*35.9*	37.4	43.3	51.1
total	100	100	100	100	100	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 and/or positive one-point serology (see * and **)

- The proportion positive serological results decreased in 1997 and 1998 compared with 1996.
- In 1998, the lowest proportion of positive two-point and the highest proportion of non-conclusive serology were observed compared with previous years.

3.3 Microbiological surveillance

The number of *Bordetella pertussis* isolates in 1989-1998 by the 16 public health laboratories is given in Table 2. In 1997 the number of positive cultures decreased 1.8-fold in comparison with 1996. The number of PCR's in 1997 decreased 1.3-fold in comparison with 1996. In 1998 the number of positive cultures decreased strongly compared with 1996 (5.3) while the number of PCR's decreased 1.3-fold.

Table 2. Isolates of Bordetella pertussis in the period 1989-1998 as reported by the 16 regional public health laboratories

method	1989	1990	1991	1992	1993	1994	1995	1996*	1997**	1998** *
culture	31	57	7	20	37	51	35	185	101	35
PCR	--	--	--	--	--	5	26	172	132	128
unknown	--	--	--	--	--	--	--	81	42	17

* 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 Netherlands 6 deaths due to pertussis in the period of 1989 to 1997 were reported: two in 1993, two in 1996, two in 1997 and one in 1998. These children were less than one year of age except one in 1993 in the age group of 5-9 years.

3.5 Age-specific incidence 1989-1998

In Table 3 to Table 7 the age-specific incidences of pertussis in the period 1989-1998 according to positive two-point serology, positive one-point serology, positive two and one-point serology, notifications and hospital admissions are given. In Figure 3 the average age-specific incidences for notifications, positive serological results and hospital admissions are given for 1989-1995, 1996, 1997 and 1998, respectively.

Overall, according to all surveillance sources, the incidences in every age group were higher in 1996 compared with the average annual incidences in the period of 1989 to 1995. The incidences in almost all age groups decreased in 1997 and declined further in 1998 compared to 1996 but were still higher compared with the period of 1989-1995. Only for infants less than one year the positive two-point serology in 1998 showed a lower incidence compared with average annual incidence in 1989-1995.

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 shift towards older age groups has occurred. According to positive one-point serology and notifications 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). However, according to positive two-point serology and hospital admissions in the period of 1996 to 1998 the incidence was still highest for infants less than one year.

For infants less than one year of age, according to all surveillance sources, the incidence in 1996 increased 2- to 4- fold compared with the annual incidence in 1989-1995. In contrast, for older age groups the increase of incidence in 1996 was much higher compared with 1989-1995 according to the surveillance sources except for hospital admissions. Among 1-9 year olds, an increased incidence in 1996 compared with 1989-1995 was approximately 7- fold according to positive serology and 13-fold according to notifications. The incidence among infants less than one year was about 1.5 to 2.5-fold lower in 1997/1998 compared with 1996 and 1 to 3 fold higher compared with the annual incidence in 1989-1995 according to both positive one- en two-point serology and notifications. Among 1-9 year olds, the incidence in 1997 and 1998 was about 2 to 3-fold higher according to positive one- and two-point serology and 7-fold higher according to notifications.

Table 3. Age-specific incidence of pertussis per 100,000 as estimated from positive two-point serology in the period 1989-1998

Age	1989	1990	1991	1992	1993	1994	1995	*1989-1995*	1996	1997	1998
0-5 months	73.9	59.2	22.3	59.9	120.4	85.1	52.3	*67.6*	134.2	72.5	34.3
6-11 months	18.2	12.5	5.1	15.2	41.8	27.7	11.3	*18.8*	37.7	35.7	7.3
1-4 yr	10.9	8.6	3.3	7.4	17.9	22.9	14.1	*12.2*	74.8	33.4	18.3
5-9 yr	15.2	10.7	4.1	6.1	12.4	15.9	7.3	*10.2*	76.7	32.8	19.2
10-14 yr	3.1	2.9	1.3	4.1	5.6	3.7	1.4	*3.2*	22.0	9.9	5.6
15-19 yr	0.5	0.4	0.2	0.2	0.4	0.3	0.2	*0.3*	3.6	1.9	0.9
≥ 20 yr	0.1	0.2	0.1	0.1	0.1	0.2	0.1	*0.1*	1.4	1.1	0.3
total	2.4	1.9	0.7	1.6	3.2	3.2	1.8	*2.1*	12.2	5.9	3.0

Table 4. Age-specific incidence of pertussis per 100,000 as estimated from positive one-point serology in the period 1989-1998

Age	1989	1990	1991	1992	1993	1994	1995	*1989-1995*	1996	1997	1998
0-5 months	72.9	67.6	19.2	32.5	55.1	73.9	33.9	*50.7*	159.4	102.0	79.0
6-11 months	38.6	22.8	8.1	26.4	64.3	44.1	25.6	*32.8*	138.4	113.6	48.9
1-4 yr	46.6	28.7	12.9	26.9	56.3	78.4	44.6	*42.1*	281.2	149.8	144.8
5-9 yr	86.2	51.5	13.9	27.0	53.9	63.9	38.7	*47.9*	295.3	124.9	106.9
10-14 yr	31.1	23.3	8.6	19.5	23.4	27.2	14.9	*21.1*	110.9	52.4	36.7
15-19 yr	4.0	4.4	1.2	3.6	3.8	4.0	2.6	*3.4*	24.8	15.9	8.1
≥ 20 yr	2.0	1.7	0.6	1.2	1.7	2.2	1.2	*1.5*	10.8	7.5	4.5
total	11.9	8.1	2.7	5.7	9.8	12.2	7.0	*8.2*	50.7	26.4	20.7

Table 5. Age-specific incidence of pertussis per 100,000 as estimated from positive one-point serology and positive two-point serology in the period 1989-1998

Age	1989	1990	1991	1992	1993	1994	1995	*1989-1995*	1996	1997	1998
0-5 months	146.8	126.8	41.5	92.4	175.5	159.0	86.2	*118.3*	293.6	174.5	113.4
6-11 months	56.8	35.3	13.2	41.7	106.1	71.9	36.9	*51.7*	176.2	149.3	56.2
1-4 yr	57.5	37.3	16.2	34.3	74.2	101.3	58.7	*54.2*	356.0	183.2	163.1
5-9 yr	101.4	62.2	18.1	33.1	66.3	79.8	46.0	*58.1*	372.0	157.8	126.1
10-14 yr	34.2	26.2	9.9	23.6	29.0	30.9	16.4	*24.3*	133.0	62.3	42.3
15-19 yr	4.5	4.7	1.4	3.8	4.2	4.3	2.8	*3.7*	28.4	17.8	9.0
≥ 20 yr	2.2	1.9	0.7	1.3	1.8	2.4	1.4	*1.7*	12.2	8.6	4.8
total	14.3	10.0	3.5	7.3	12.9	15.4	8.7	*10.3*	62.9	32.3	23.7

Table 6. Age-specific incidence of pertussis per 100,000 as estimated from notifications in the period 1989-1998

Age	1989	1990	1991	1992	1993	1994	1995	*1989-1995*	1996	1997	1998
0 yr	61.1	46.8	14.7	16.3	42.3	40.5	25.1	*35.3*	138.9	93.1	62.4
1-4 yr	14.7	11.3	4.5	4.4	13.0	21.2	14.9	*12.0*	143.0	85.6	85.1
5-9 yr	23.0	16.8	5.8	5.3	10.0	18.9	10.9	*13.0*	170.8	88.3	98.2
10-14 yr	6.1	3.9	2.0	2.8	4.2	5.0	3.9	*4.0*	61.0	35.2	30.4
15-19 yr	0.8	0.6	0.1	0.4	0.4	0.5	0.3	*0.4*	11.4	9.1	5.8
≥ 20 yr	0.3	0.3	0.1	0.1	0.2	0.4	0.3	*0.2*	4.4	4.7	3.5
total	3.5	2.7	1.0	1.1	2.3	3.4	2.2	*2.3*	27.3	17.2	16.0

Table 7. Age-specific incidence of pertussis per 100,000 as estimated from hospital admissions in the period 1989-1998

Age	1989	1990	1991	1992	1993	1994	1995	*1989-1995*	1996	1997	1998
0 yr	82.5	61.3	24.8	34.5	114.8	96.4	49.2	*66.2*	184.0	150.9	99.8
1-4 yr	5.2	2.7	2.5	3.5	6.3	8.5	5.6	*4.9*	11.6	12.4	7.1
5-9 yr	2.5	1.5	0.8	0.3	1.0	1.7	1.6	*1.3*	4.9	3.4	2.2
10-14 yr	0.4	0.2	0.7	0.2	0.3	0.3	0.6	*0.4*	1.2	0.5	0.4
15-19 yr	<0.1	0.0	0.0	0.0	0.0	0.0	0.0	*<0.1*	0.3	0	0.1
≥ 20 yr	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	*<0.1*	<0.1	0.1	0.1
total	1.5	1.1	0.5	0.7	1.9	1.8	1.1	*1.2*	3.3	2.8	1.8

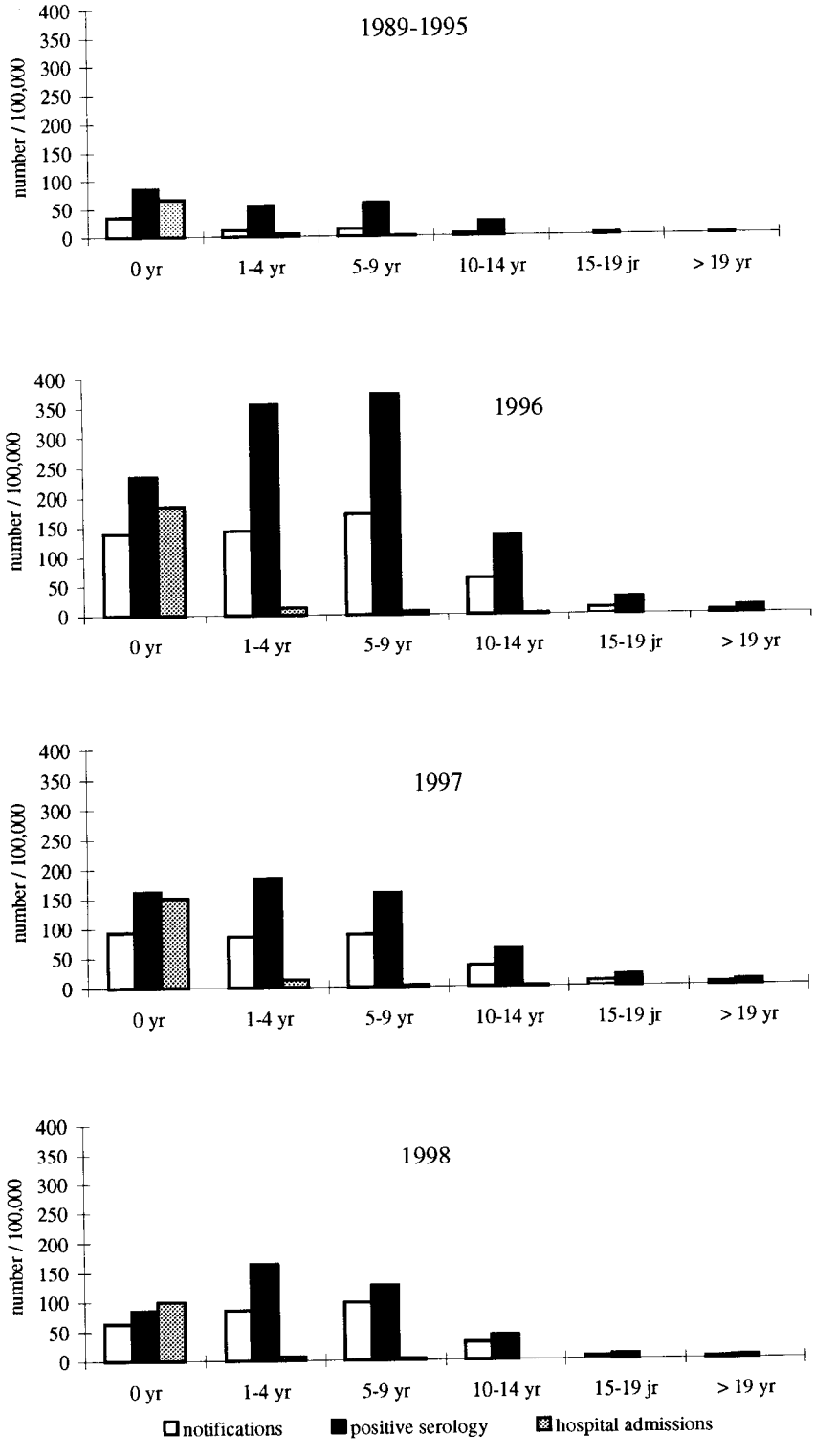


Figure 3. Age-specific incidence of pertussis in 1989 to 1998 according to notifications, positive serology and hospital admissions.

In Figure 4 to Figure 6 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 1998. For positive two-point serology and notifications the peak incidence in the period 1993-1995 was seen among children less than 1 year of age while for positive one-point serology the peak incidence was seen among 4-year-olds. In 1996 and 1997 the peak incidence occurred among 4-years-olds according to positive one-point serology, positive two-point serology and notifications. For 1998 the peak incidence occurred among 5-year-olds according to positive two-point serology and notifications and among 4-year-olds for positive one-point serology.

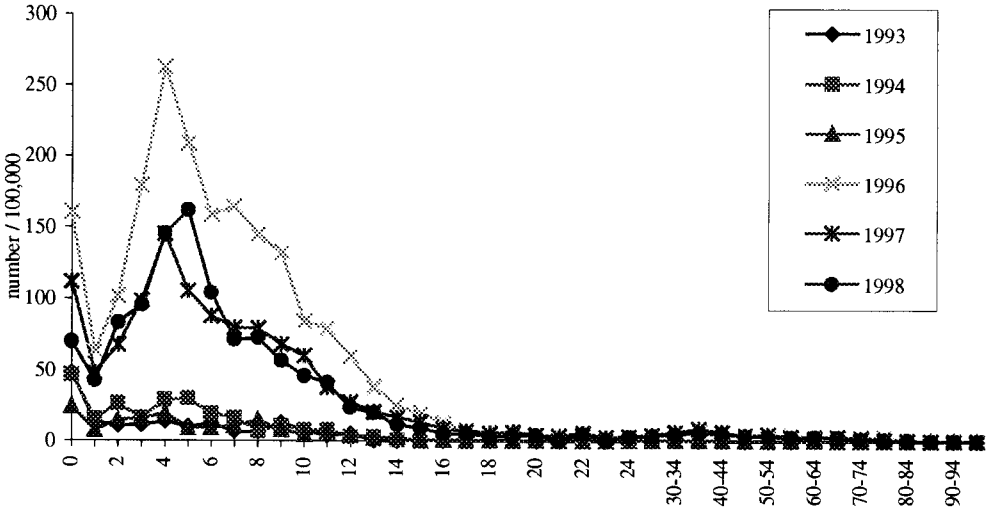


Figure 4. Age-specific incidence of pertussis in 1993-1998 according notifications

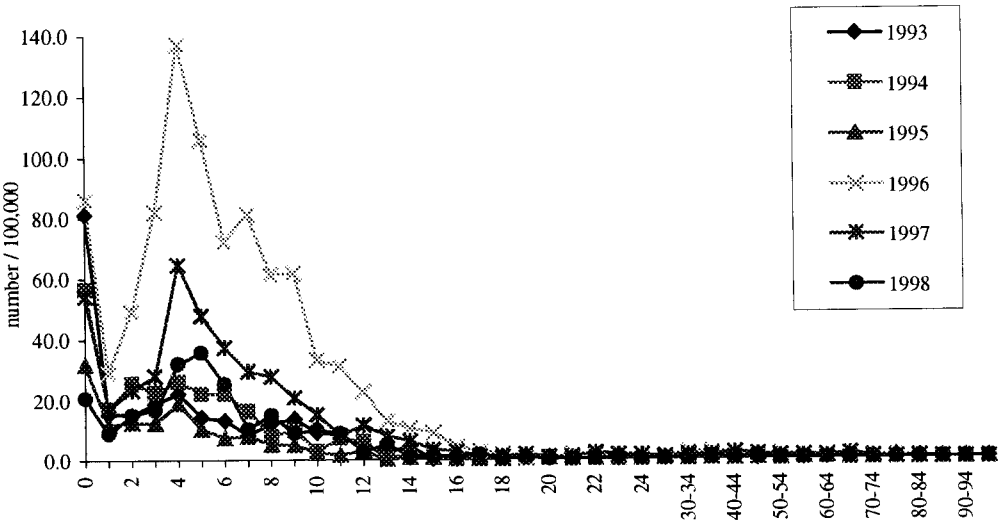


Figure 5. Age-specific incidence of pertussis in 1993-1998 according to positive two-point serology

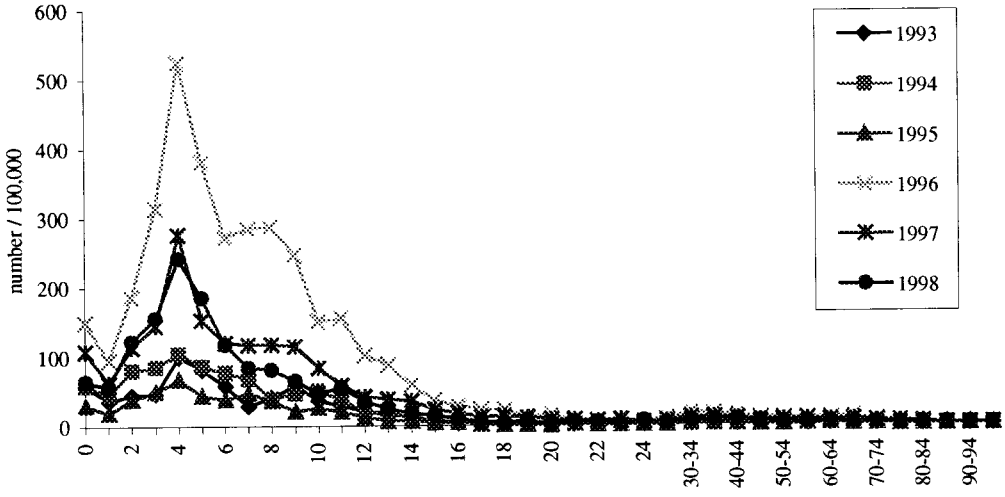


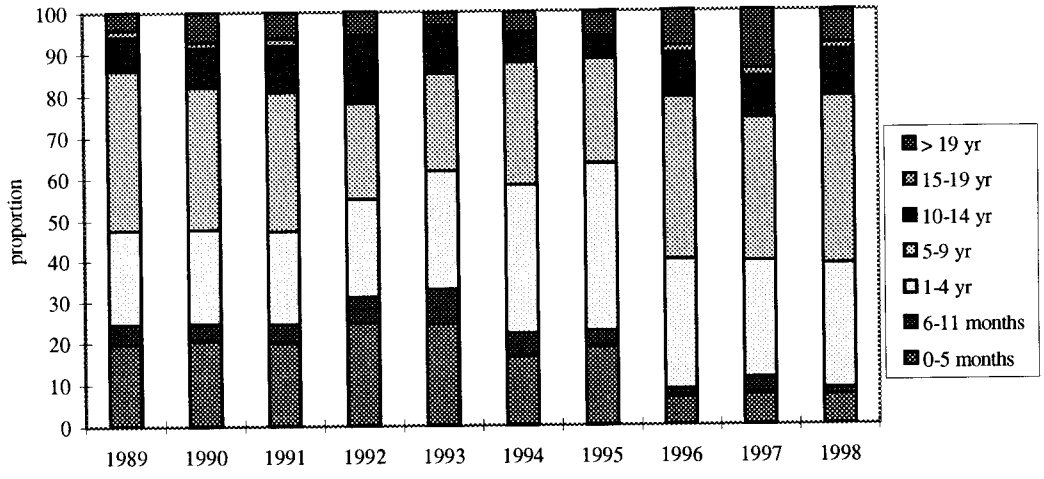
Figure 6. Age-specific incidence of pertussis in 1993-1998 according to positive one-point serology

- Overall, in 1997 and 1998 the incidence for almost all age groups was higher compared with 1989-1995 but lower compared with 1996 according to all surveillance sources.
- Similar with previous years, in 1997 and 1998 the highest incidence for hospital admissions occurred among infants less than one year of age.
- According to notifications and positive one- and two-point serology, the peak incidence in 1996 and 1997 occurred among children of 4 years of age. In 1998 the peak incidence was observed among 5-year-olds according to notifications and positive two-point serology but among 4-year-olds for positive one-point serology.

3.6 Proportional age distribution 1989-1998

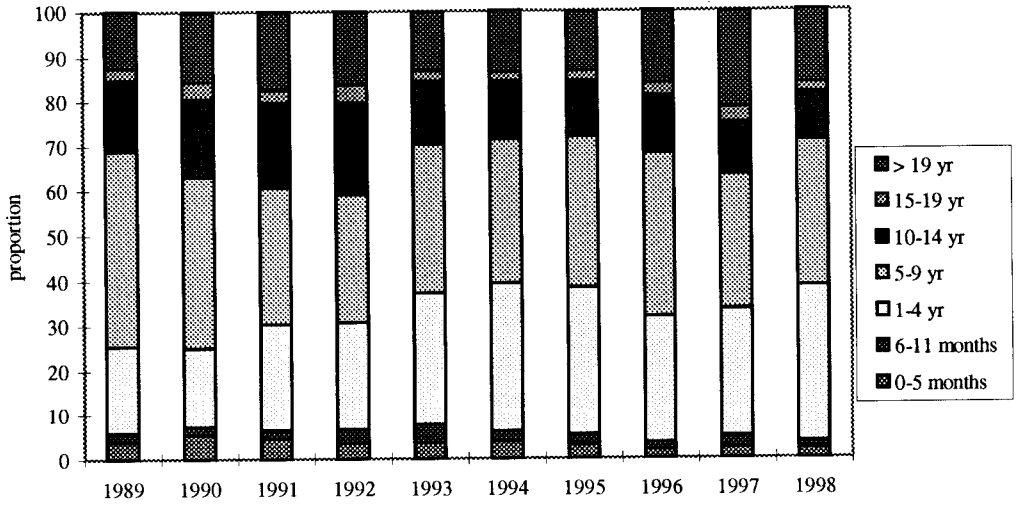
In Figure 7 to Figure 10 the proportional age distribution according to positive two-point serology, positive one-point serology, notifications and hospital admissions in the period of 1989-1998 are shown. Overall, according to the surveillance sources the age distribution in 1997 and 1998 were rather similar with the age distribution in 1996. The proportion of infants less than one year of age was lower in the period of 1996-1998 compared with 1989-1995. The proportion of children aged 1-4 year was almost similar in the period of 1989-1995 compared with 1996-1998 except for positive one-point serology with a slightly higher proportion in the period of 1996 to 1998 and particularly in 1998. In 1996 the proportion of children aged 5-9 year increased compared with 1989-1995. In 1997 the proportion of 5-9 year olds was slightly lower compared with 1996 according to positive serology and notifications. However, in 1998 the 5-9 year old proportion was comparable again with the 5-9 year old proportion in 1996. According to positive two-point serology and notifications the proportion of patients aged 10 years and older increased in the period of 1996 to 1998 in comparison to 1989-1995, especially in 1997. The age distribution for hospital admission in 1997 and 1998 were similar with the age distribution in 1996.

In paragraph 3.11 the results are presented of the linkage of the notification database with the database of serodiagnosis. By this linkage, the diagnostic method could be verified which was used to confirm the clinical diagnosis of the reported cases. These results were used to compare the age distributions between reported cases confirmed by microbiological method, cases confirmed with positive two-point serology and cases with positive one-point serology. Age was calculated at the day of onset of disease and therefore comparison was only possible since 1993. The age distributions of reported cases for period of 1993 to 1998 showed comparable changes if stratification to diagnostic method was performed. The age distribution for cases confirmed with culture/PCR, cases confirmed with positive two-point serology and one-point serology shifted towards higher proportions among older age groups. In addition, microbiologically confirmed cases are mostly young infants while cases confirmed with positive one-point serology included mostly older cases.



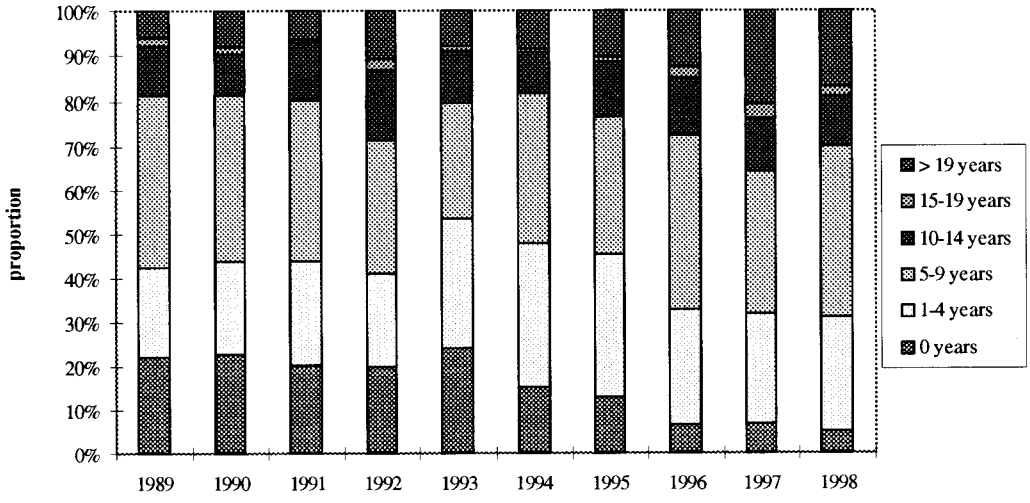
	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
total number of cases	**350**	**278**	**110**	**238**	**482**	**498**	**272**	**1885**	**924**	**468**

Figure 7. Proportional age distribution according to positive two-point serology for pertussis in 1989-1998



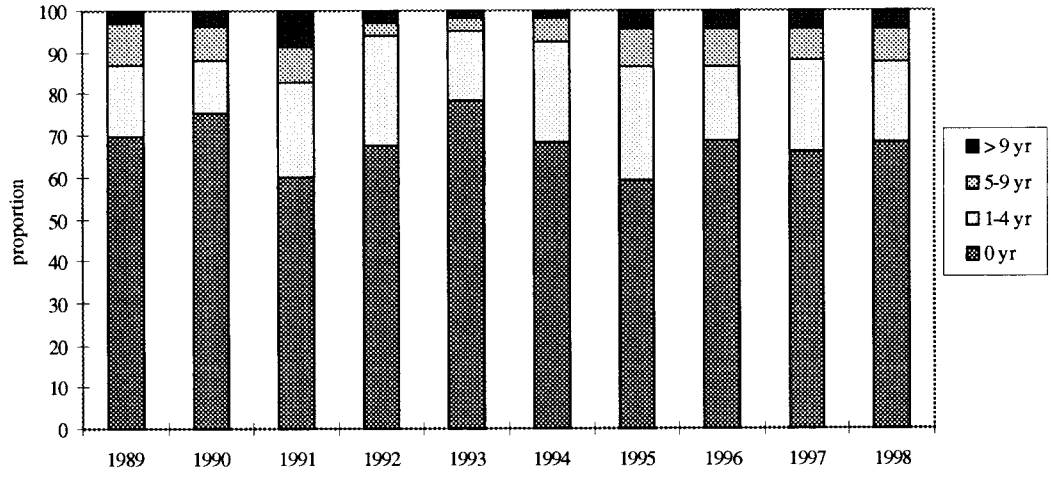
	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
total number of cases	**1760**	**1204**	**411**	**861**	**1489**	**1867**	**1070**	**7854**	**4107**	**3247**

Figure 8. Proportional age distribution according to positive one-point serology for pertussis in 1989-1998.



	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
total number of cases	**523**	**397**	**145**	**160**	**346**	**519**	**341**	**4231**	**2671**	**2508**

Figure 9. Proportional age distribution according to notifications due to pertussis in 1989-1998.



	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998
total number of cases	**221**	**157**	**82**	**101**	**288**	**276**	**162**	**513**	**436**	**282**

Figure 10. Proportional age distribution according to hospital admissions due to pertussis in 1989-1998.

- Overall, the proportional age distribution in 1997 and 1998 was similar with 1996 for notifications, positive one- and two point serology and hospital admissions.
- The proportion of infants less than one year of age in the period of 1996 to 1998 was lower compared with the period of 1989-1995.
- The proportion of cases ≥10 years was rather higher in the period of 1996 to 1998 in comparison with 1989-1995.

3.7 Notifications by vaccination status in 1993-1998

Figure 11 shows the total number of reported cases less than one year according to their age (in months) in 1997 and 1998. Besides, the same reported cases less than one year of age are presented according to their age and vaccination status as well. In 1996 and 1997, a third of the cases in the age category less than one year were less than 3 months of age and unvaccinated while in 1998 half of the cases were less than 3 months of age. In Figure 12 and Figure 13 the absolute numbers of reported cases according to their vaccination status and age (in years) are given for 1997 and 1998.

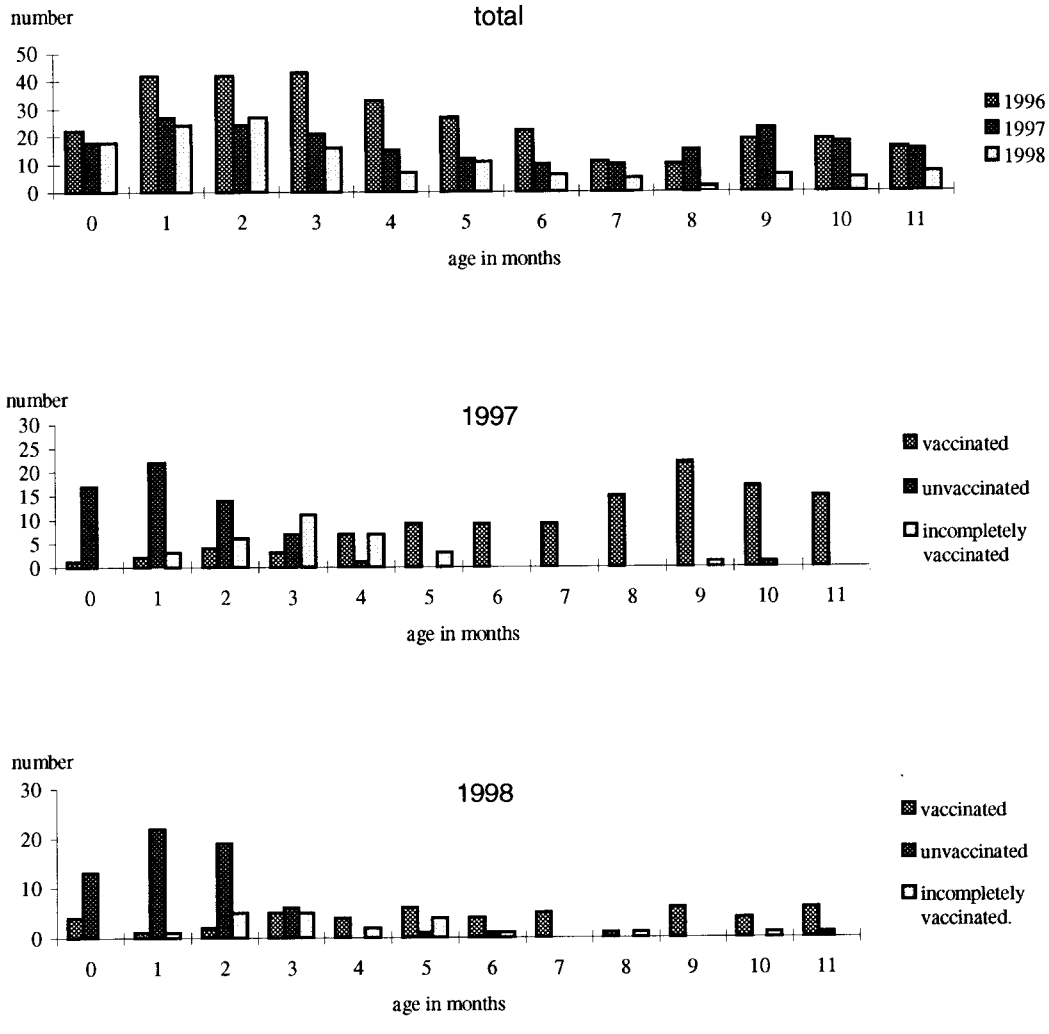


Figure 11. Absolute total number of cases reported in 1996, 1997 and 1998 according to their age and for 1997 and 1998 according to their vaccination status and age (in months) for infants less than one year

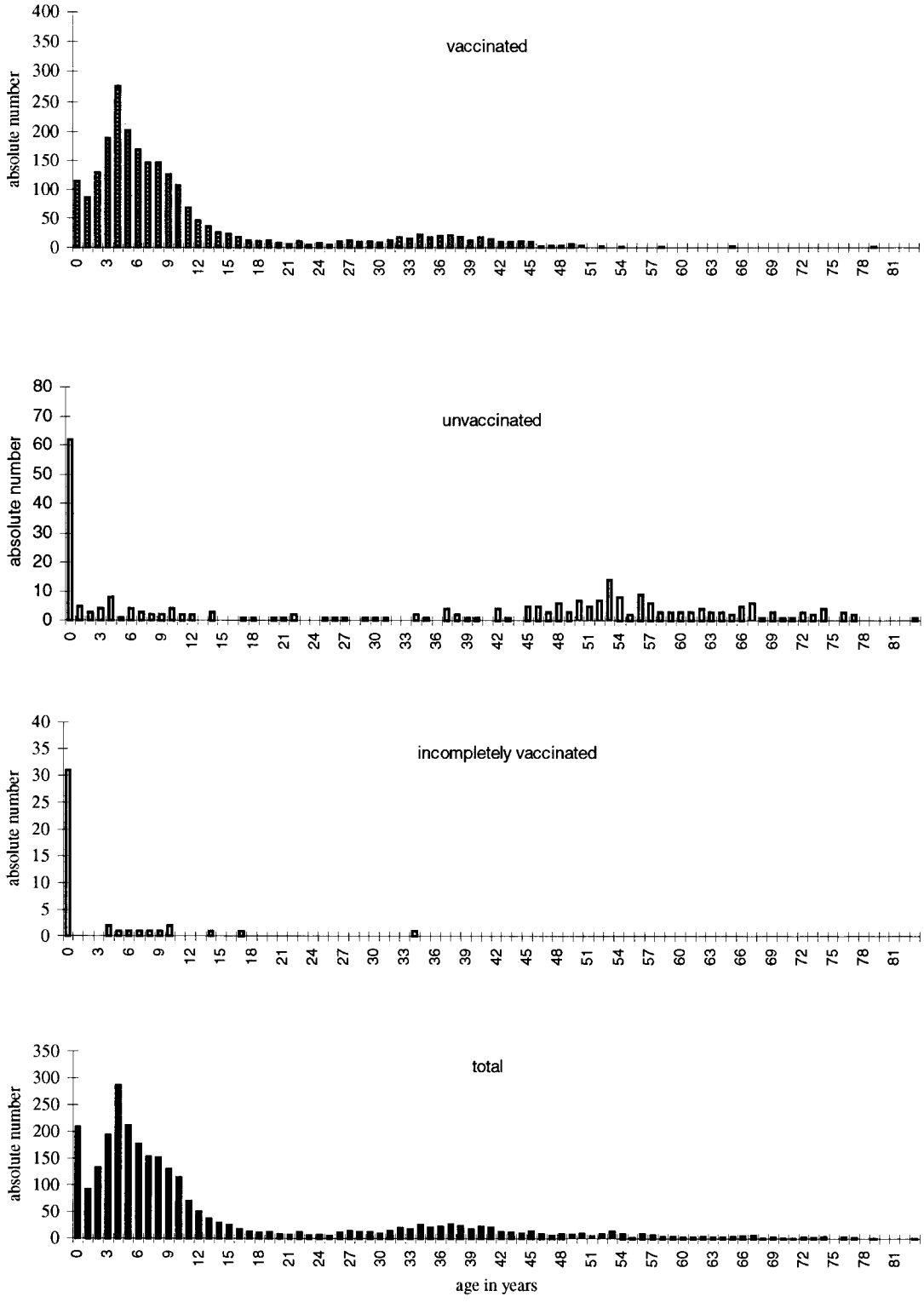


Figure 12. Absolute number of cases reported in 1997 according to vaccination status and age (years).

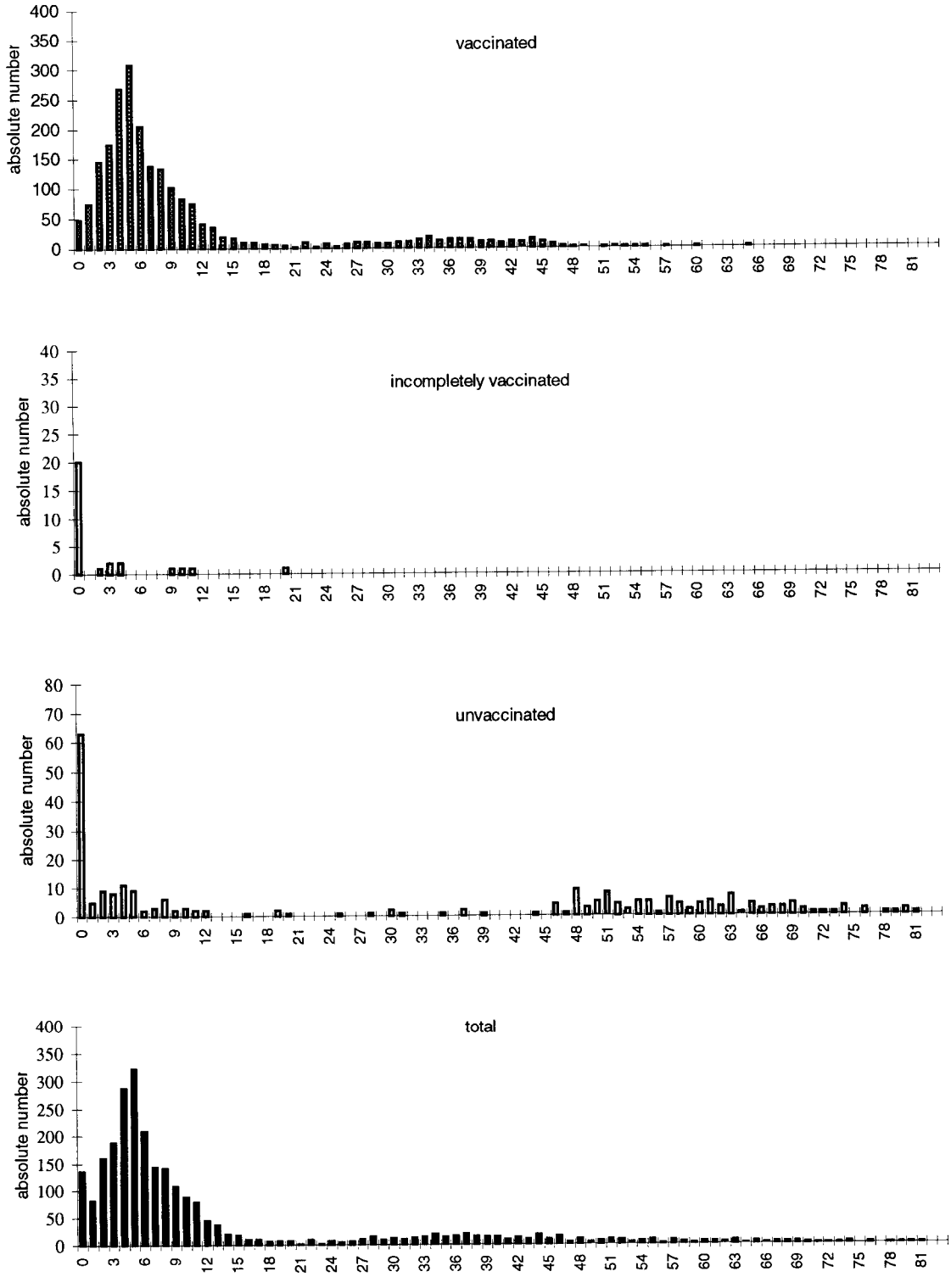


Figure 13. Absolute number of cases reported in 1998 according to vaccination status and age (years).

Table 8 and Table 9 present the absolute number of reported cases (by first day of illness) according to the vaccination status (vaccinated vs. unvaccinated) and the estimated vaccine-efficacy by year and method of diagnosis for 1-4 year olds and 5-9 year olds, respectively. In 1993, for both 1-4 as 5-9 year olds, the highest vaccine-efficacies were estimated (due to the lowest proportion of vaccinated individuals) for all strata of diagnosis. From 1994 up to 1997, a decreasing trend in vaccine-efficacy was observed in both age groups. In the period of 1996 to 1998 (and in a lesser extent in 1995) the proportion of vaccinated individuals exceeded the estimated vaccine coverage of the

*Table 8. Absolute number of reported cases (1-4 years) according to vaccination status and estimation for vaccine-efficacy according to method of diagnosis**

year	method of diagnosis	unvaccinated	vaccinated	vaccination status unknown	% vaccinated	estimated vaccine-efficacy
1993	microbiological	4	9	0	69.2%	90.6%
	two-point serology	8	17	0	68.0%	91.2%
	one-point serology	3	20	0	87.0%	72.1%
	other**	18	17	0	48.6%	96.1%
	total	**33**	**63**	**0**	**65.6%**	**92.1%**
1994	microbiological	1	21	1	95.5%	11.6%
	two-point serology	3	32	0	91.4%	55.7%
	one-point serology	6	55	2	90.1%	61.7%
	other**	9	27	11	75.0%	87.5%
	total	**19**	**135**	**14**	**87.7%**	**70.3%**
1995	microbiological	3	11	0	78.6%	84.7%
	two-point serology	5	22	0	81.5%	81.6%
	one-point serology	4	35	0	84.7%	63.7%
	other**	3	34	0	91.9%	52.7%
	total	**15**	**102**	**0**	**87.2%**	**71.6%**
1996	microbiological	12	103	1	89.6%	64.1%
	two-point serology	7	236	0	97.1%	0%?
	one-point serology	17	528	4	97.4%	0%?
	other**	28	258	3	90.2%	61.7%
	total	**64**	**1125**	**8**	**94.6%**	**27.0%**
1997	microbiological	5	58	0	92.1%	51.4%
	two-point serology	3	107	1	97.3%	0%?
	one-point serology	5	278	2	98.2%	0%?
	other**	9	235	2	96.3%	0%?
	total	**22**	**678**	**5**	**96.9%**	**0%?**
1998	microbiological	2	29	0	93.5%	40.1%
	two-point serology	3	70	1	95.9%	2.5%
	one-point serology	17	351	5	95.4%	13.6%
	other**	15	208	7	93.3%	42.0%
	total	**37**	**658**	**13**	**94.7%**	**25.6%**

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

** epidemiological, serological (differentiation between positive two-point serology and positive one-point serology not possible, clinical, method of diagnosis unknown)

*Table 9. Absolute number of reported cases (5-9 years) according to vaccination status and estimation for vaccine-efficacy according to method of diagnosis**

year	method of diagnosis	unvaccinated	vaccinated	vaccination status unknown	% vaccinated	estimated vaccine-efficacy
1993	microbiological	6	8	0	57.1%	94.5%
	two-point serology	4	24	1	85.7%	75.0%
	one-point serology	1	24	1	96.0%	0%?
	other**	6	14	0	70.0%	90.3%
	total	**17**	**70**	**2**	**80.5%**	**82.8%**
1994	microbiological	1	14	0	93.3%	42.0%
	two-point serology	6	29	0	82.9%	82.7%
	one-point serology	1	63	1	98.4%	0%?
	other**	9	20	12	64.0%	90.7%
	total	**18**	**126**	**13**	**87.5%**	**70.8%**
1995	microbiological	1	8	0	88.9%	66.6%
	two-point serology	0	17	0	100%	0%?
	one-point serology	1	44	1	97.8%	0%?
	other**	3	24	0	88.9%	66.6%
	total	**5**	**93**	**0**	**94.9%**	**22.5%**
1996	microbiological	5	118	0	96.0%	2.5%
	two-point serology	19	266	5	93.3%	42%
	one-point serology	21	760	4	97.3%	0%?
	other**	22	332	4	93.8%	37.0%
	total	**58**	**1476**	**13**	**96.2%**	**7.3%**
1997	microbiological	6	62	0	91.0%	57.9%
	two-point serology	4	127	3	95.5%	11.6%
	one-point serology	6	339	7	98.3%	0%?
	other**	1	259	4	99.6%	0%?
	total	**17**	**787**	**14**	**97.8%**	**0%?**
1998	microbiological	0	30	0	100%	0%?
	two-point serology	4	88	1	95.7%	7.3%
	one-point serology	7	388	5	98.2%	0%?
	other**	12	379	4	97.2%	0%?
	total	**23**	**885**	**10**	**97.5%**	**0%?**

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

** epidemiological, serological (differentiation between positive two-point serology and positive one-point serology not possible, clinical, method of diagnosis unknown)

population (96%). Therefore, the vaccine-efficacy could not be estimated (illustrated by 0%?) but the increased proportion of vaccinated indicated a lower vaccine-efficacy. Only for 1-4 year olds (with the exception of microbiological) a slightly higher vaccine-efficacy was observed in 1998 compared with 1997.

For 1997 and 1998 the vaccine-efficacy was also estimated for 1-9 year olds per year of age (Table 10 and Table 11). For 1998 the proportion of vaccinated cases showed an increasing trend with age although not consistent but no such trend could be observed for 1997.

*Table 10. Absolute number of reported cases aged 1-9 years in 1997 according to vaccination status and year of age and estimation for vaccine-efficacy**

	unvaccinated	vaccinated	vaccination status unknown	% vaccinated	estimated vaccine-efficacy
1 year	5	85	2	94.4%	29.8%
2 year	3	129	1	97.7%	0%?
3 year	4	188	1	97.9%	0%?
4 year	8	276	1	97.2%	0%?
5 year	1	201	8	99.5%	0%?
6 year	4	169	2	97.7%	0%?
7 year	3	146	3	98.0%	0%?
8 year	2	146	2	98.6%	0%?
9 year	2	125	2	98.4%	0%?

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

*Table 11. Absolute number of reported cases aged 1-9 years in 1998 according to vaccination status and year of age and estimation for vaccine-efficacy**

	unvaccinated	vaccinated	vaccination status unknown	% vaccinated	estimated vaccine-efficacy
1 year	5	74	2	93.7%	38.0%
2 year	9	145	4	94.2%	32.3%
3 year	8	174	3	95.6%	9.5%
4 year	11	268	4	96.0%	0%?
5 year	9	308	3	97.2%	0%?
6 year	2	204	3	99.0%	0%?
7 year	3	138	1	97.9%	0%?
8 year	6	133	1	95.7%	7.3%
9 year	2	102	2	98.0%	0%?

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

- The lowest vaccine-efficacies stratified by method of diagnosis were estimated for 1997 and the highest were estimated for 1993.

3.8 Notifications due to typical and atypical pertussis in 1989-1998

The proportion of patients reported with atypical pertussis ranged from 17.4% in 1990 to 1.1% in 1998 (Table 12). In the period of 1995 to 1998 the proportion atypical pertussis decreased compared with previous years.

Table 12. Absolute number and proportion of notifications due to typical and atypical pertussis in the period 1989-1998

year	atypical pertussis		typical pertussis	
	number	(%)	number	(%)
1989	77	(14.7%)	446	(85.3%)
1990	69	(17.4%)	328	(82.6%)
1991	17	(11.7%)	128	(88.3%)
1992	16	(10.0%)	144	(90.0%)
1993	35	(10.1%)	311	(89.9%)
1994	79	(15.2%)	440	(84.8%)
1995	18	(5.3%)	323	(94.7%)
1996*	166	(3.9%)	4228	(96.1%)
1997**	44	(1.7%)	2619	(98.3%)
1998***	28	(1.1%)	2468	(98.9%)

* In 1996 for 3 cases unknown
** In 1997 for 8 cases unknown
*** In 1998 for 12 cases unknown

- In the period of 1995 to 1998 the proportion of atypical pertussis decreased compared with previous years.

3.9 Notifications by gender in 1993-1998

Table 13 shows that during 1993 to 1998 the proportion of males was lower than the proportion of females.

Table 13. Gender distribution of reported cases in 1993 to 1998

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%

- The proportion males to females amounted 1:1.2

3.10 Geographical distribution notifications 1997 and 1998

In Figure 14 respectively Figure 15 the geographical distribution of pertussis according to notifications in 1997 and 1998 given per quarter. The pertussis cases were widespread. The figures show that the incidence of pertussis after the epidemic, which started in 1996 decreased during the first two quarters of 1997 followed by an increase in August. In 1998 the highest incidence was observed in the third quarter.

- No geographical clustering was observed in 1997 and 1998

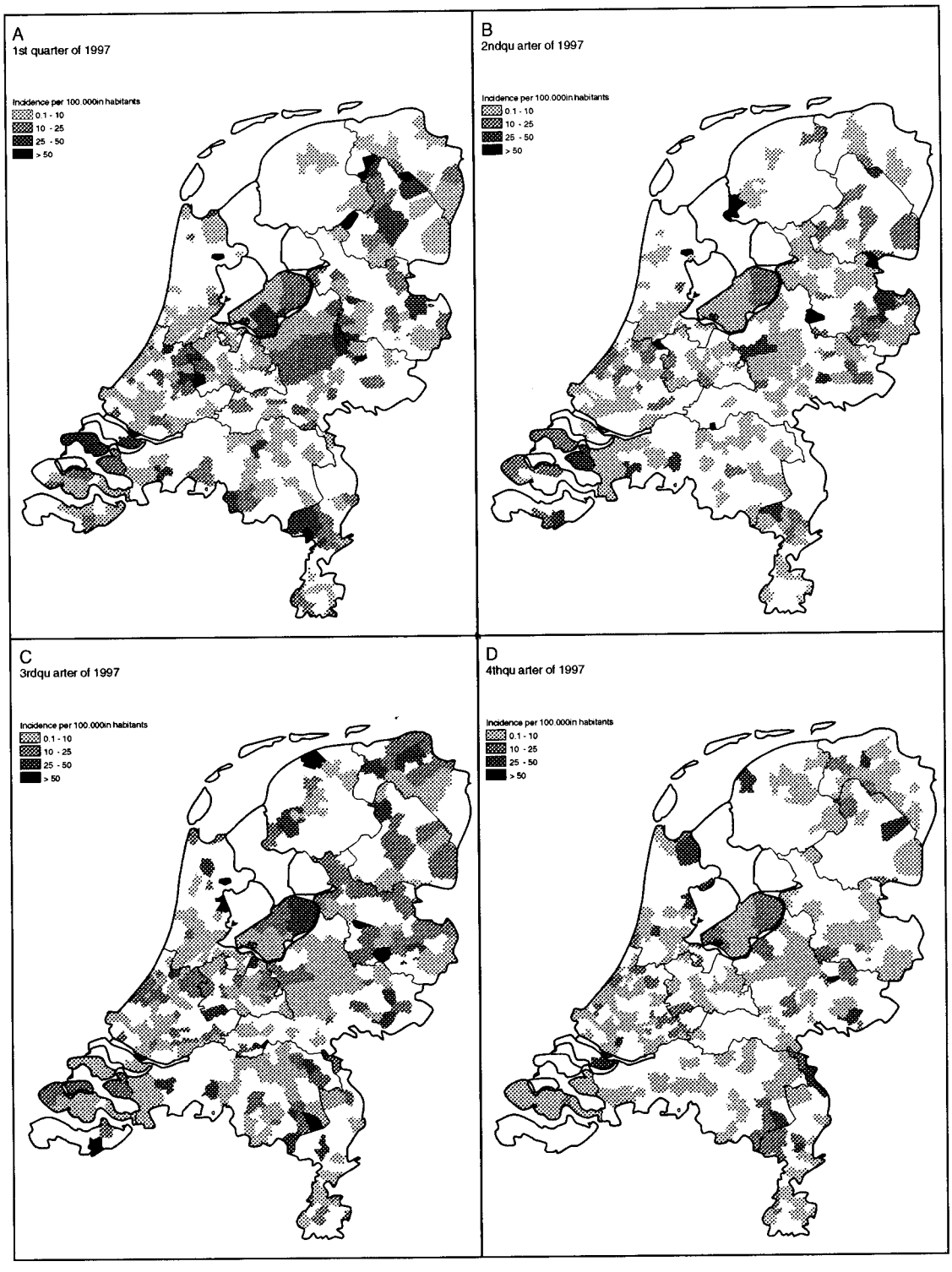


Figure 14. Geographical distribution according to notifications in 1997 per quarter

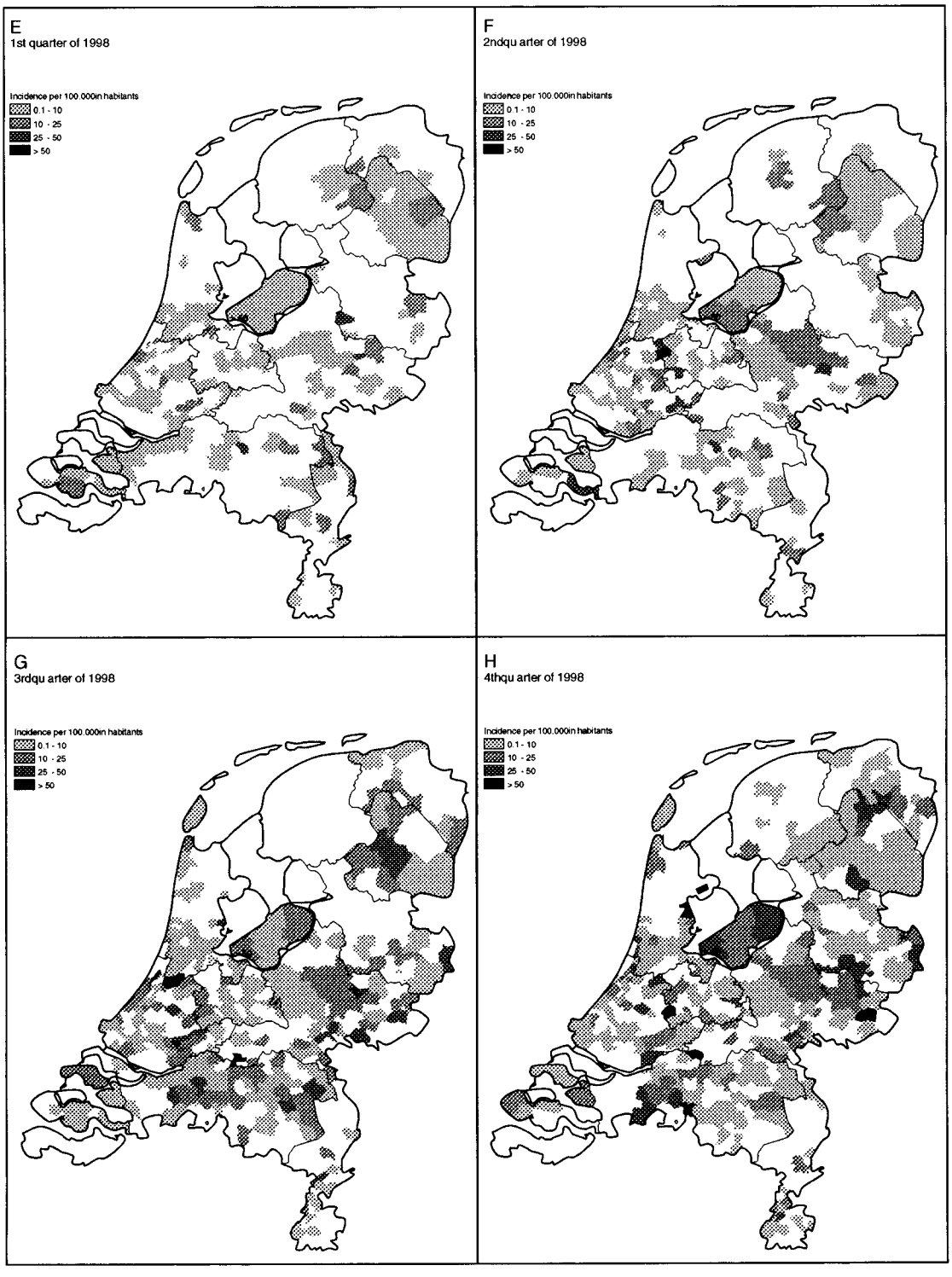


Figure 15. Geographical distribution according to notifications in 1998 per quarter

3.11 Linkage of notifications with serodiagnostic data 1993-1998

In Table 14 the results are given for the individual matching between the notifications and the data of serodiagnosis. In some cases records from the database of serodiagnostics were matched with records of the notification database for which serology was not registered as method of diagnosis. Therefore, the sum of the fourth and fifth column is higher than the numbers given in the third column of the table. The proportion not-matched records for which according to the notification data serology was performed increased from 6.1% in 1993 to 29.7% in 1998. This increase of not-matched cases is related with the increasing number of serodiagnostics performed by other public health laboratories. Since 1993, the proportion of notifications based on positive serology has increased with the highest proportion in 1998 (90.9%).

Table 14. Total notifications, notifications for which serology was used as method of diagnosis, cases matched to database of serological results and not-matched cases for which serology was used as method of diagnosis.

	notifications	notifications with serology as diagnosis method	notifications matched with serology	notifications not-matched with serology and with serology as diagnosis method
1993	346	212 (61.3%)	241 (69.7%)	21 (6.1%)
1994	519	370 (71.3%)	373 (71.9%)	41 (7.9%)
1995	341	259 (76.0%)	226 (66.3%)	59 (17.3%)
1996	4231	3506 (82.9%)	3151 (74.5%)	555 (13.1%)
1997	2671	2004 (75.0%)	1749 (65.5%)	541 (20.3%)
1998	2508	2281 (90.9%)	1536 (61.2%)	745 (29.7%)

Table 15 the method of diagnosis as registered in the notification database for matched reported cases according to serodiagnostic result and for not-matched reported cases. The proportion of cases with positive two-point serology among the notifications decreased from 33.2% in 1993 to 9.1% in 1998. However, the proportion cases with positive one-point serology among the notifications increased from 27.2% in 1993 to 49.4% in 1996 and amounted to 46.7% in 1998. This increase is among others related with the changed criteria for notification in April 1997. Since then, positive one-point serology has been accepted as laboratory confirmation for pertussis as well.

Table 15. Method of diagnosis as registered in the notification database for matched reported cases according to serodiagnostic result and for not-matched reported cases.

	1993		1994		1995		1996		1997		1998	
MATCHED PATIENTS												
two-point serology[1]	**115**	**33.2%**	**129**	**24.9%**	**75**	**22.0%**	**788**	**18.6%**	**394**	**14.8 %**	**227**	**9.1%**
serological method	88	25.4%	114	22.0%	59	17.3%	747	17.7%	382	14.3%	224	8.9%
serological and microbiological method	5	1.4%	5	1.0%	3	0.9%	7	0.2%	3	0.1%	1	0.04%
serological and epidemiological method	1	0.3%	1	0.2%	2	0.6%	8	0.2%	--	--	--	--
microbiological method	10	2.8%	8	1.5%	10	2.9%	20	0.5%	8	0.3%	--	--
epidemiological method	--	--	--	--	--	--	1	0.02%	1	0.03%	1	0.04%
microbiological and epidemiological method	--	--	--	--	--	--	1	0.02%	--	--	--	--
clinical diagnosis	2	0.6%	--	--	--	--	3	0.07%	--	--	--	--
method of diagnosis unknown	9	2.6%	1	0.2%	1	0.3%	1	0.02%	--	--	1	0.04%
one-point serology	**94**	**27.2%**	**193**	**37.2%**	**126**	**37.0%**	**2089**	**49.4%**	**1198**	**44.9 %**	**1170**	**46.7%**
serological method[2]	82	23.7%	169	32.6%	113	33.1%	1984	46.9%	1153	43.2%	1138	45.4%
serological and microbiological method[1]	3	0.9%	10	1.9%	1	0.3%	16	0.4%	16	0.6%	2	0.08%
serological and epidemiological method[1]	1	0.3%	5	1.0%	5	1.5%	24	0.6%	10	0.4%	--	--
microbiological method[1]	4	1.2%	3	0.6%	6	1.8%	29	0.7%	10	0.4%	18	0.7%
epidemiological method[1]	1	0.3%	1	0.2%	1	0.3%	15	0.4%	2	0.07%	3	0.2%
microbiological and epidemiological method[1]	--	--	--	--	--	--	3	0.07%	--	--	--	--
clinical diagnosis[2]	1	0.3%	4	0.8%	--	--	10	0.2%	4	0.15%	--	--
method of diagnosis unknown[2]	2	0.6%	1	0.2%	--	--	8	0.2%	3	0.11%	9	0.4%
negative serology	**3**	**0.9%**	**1**	**0.2%**	**--**	**--**	**17**	**0.4%**	**10**	**0.4%**	**10**	**0.4%**
serological method[3]	--	--	--	--	--	--	11	0.3%	6	0.2%	6	0.2%
serological and microbiological method[1]	--	--	--	--	--	--	1	0.02%	--	--	--	--
microbiological method[1]	1	0.3%	--	--%	--	--	3	0.07%	2	0.07%	2	0.08%
epidemiological method[1]	--	--	1	0.2%	--	--	1	0.02%	--	--	1	0.04%
clinical diagnosis[3]	1	0.3%	--	--	--	--	1	0.02%	2	0.07%	1	0.04%
method of diagnosis unknown[3]	1	0.3%	--	--	--	--	--	--	--	--		
'non-conclusive' serology	**29**	**8.4%**	**50**	**9.6%**	**25**	**7.3%**	**257**	**6.1%**	**147**	**5.5%**	**187**	**7.5%**
Serological method[3]	10	2.9%	19	3.7%	11	3.2%	140	3.3%	88	3.3%	155	6.2%
serological and microbiological method[1]	1	0.3%	5	1.0%	3	0.9%	7	0.2%	7	0.3%	3	0.2%
serological and epidemiological method[1]	--	--	1	0.2%	--	--	5	0.1%	1	0.04%	3	0.2%
microbiological method[1]	16	4.6%	22	4.2%	8	2.3%	80	1.9%	40	1.5%	20	0.8%
epidemiological method[1]	1	0.3%	--	--	1	0.3%	12	0.3%	5	0.2%	4	0.2%
microbiological and epidemiological method[1]	--	--	--	--	1	0.3%	2	0.05%	2	0.07%	--	--
clinical diagnosis[3]	--	--	2	0.4%	--	--	8	0.2%	3	0.1%	1	0.04%
method of diagnosis unknown[3]	1	0.3%	1	0.2%	1	0.3%	3	0.07%	1	0.04%	1	0.04%
NOT-MATCHED PATIENTS	**105**	**30.2%**	**146**	**28.1%**	**115**	**33.7%**	**1080**	**25.5%**	**922**	**34.5 %**	**914**	**36.4%**
- serological method[4]	20	5.8%	39	7.5%	56	16.4%	526	12.4%	601	22.5%	734	29.3%
serological and microbiological method[1]	1	0.3%	2	0.4%	3	0.9%	11	0.3%	6	0.2%	3	0.2%
serological and epidemiological method[1]	--	--	--	--	3	0.9%	18	0.4%	8	0.3%	8	0.4%
microbiological method[1]	31	9.0%	34	6.6%	16	4.7%	231	5.5%	138	5.2%	55	2.2%
epidemiological method[1]	37	10.7%	38	7.3%	26	7.6%	160	3.8%	90	3.4%	59	2.3%
microbiological and epidemiological method[1]	1	0.3%	--	--	--	--	7	0.2%	3	0.1%	3	0.2%
clinical diagnosis[5]	14	4.1%	31	6.0%	2	0.6%	114	2.7%	68	2.5%	34	1.4%
method of diagnosis unknown[6]	1	0.3%	2	0.2%	9	2.6%	13	0.3%	8	0.3%	18	0.7%
TOTAL	**346**	**100%**	**519**	**100%**	**341**	**100%**	**423 1**	**100%**	**2671**	**100%**	**2508**	**100%**

[1] Diagnosis confirmation in accordance with former case-definition for notification
[2] Positive one-point serology. Diagnosis method not in accordance with former case-definition for notification
[3] Serological results or other method of diagnosis did not meet the former case-definition for notification
[4] Unknown whether the serological method used to confirm the diagnosis met the former case-definition for notification
[5] Diagnosis was only made clinically or the method of diagnosis was unknown; diagnosis did not meet the former case-definition for notification
[6] Diagnosis was only made clinically or the method of diagnosis was unknown; diagnosis did not meet the former case-definition for notification

The number of cases reported in accordance with the former formal case-definition for notification (positive two-point serology, microbiological or epidemiological criteria) decreased from 61.6% in 1993 (n=213), 48.4% in 1994 (n=251), 43.7% in 1995 (n=149) 33.3% in 1996 (n=1411), 27.5% in 1997 (n=734) to 16.4% in 1998 (n=411) (Table 15[1]). For an increasing proportion the reported cases were confirmed with one-point serology (24.6% in 1993, 33.5% in 1994, 33.5% in 1995, 47.3% in 1996, 43.7% in 1997 to 46.0% in 1998) (Table 15[2]). For another 3.8% of the reported cases in 1993, 4.3% in 1994, 3.5% in 1995, 3.9% in 1996, 3.7% in 1997 to 6.6% in 1998 the serological results were negative or 'non-conclusive' (Table 15[3]). These cases did not meet any other criterion for notification. The proportion of reported cases for which according to the notification database serology was used to confirm the diagnosis has increased through the years: 5.8% in 1993, 7.5% in 1994, 16.4% in 1995, 12.4% in 1996, 22.5% in 1997 and 29.3% in 1998 (Table 15[4]). In addition for 4.4% in 1993, 6.2% in 1994, 3.2% in 1995, 3.0% in 1996, 2.8% in 1997 and 2.1% of the reported cases in 1998 which were also not-matched to the database of serodiagnosis only a clinical diagnosis was performed or the diagnosis method was unknown according the notification database (Table 15[5,6]). As mentioned before this increasing proportion of not-matched cases is related with the decentralisation of performed serodiagnostics.

In Table 16 and Table 17 estimations of the proportion of cases with positive two-point and one-point serology that were reported in 1993 to 1998 are presented. The estimated proportions of cases with positive two-point serology that were reported increased from 25.8% in 1993 to 70.8% in 1998. Thus, the estimated proportion of underreporting for cases with positive two-point serology decreased from 74.2% in 1993 to 29.2% in 1998. In addition, because of a higher proportion of not matched serology in 1998, the estimated proportions are more depended on the assumption as described in the footnote of the table. Since April 1997 positive one-point serology has been formally accepted as laboratory-confirmation of pertussis. An increasing proportion of such cases is reported through the years (6.2% in 1993 and 49.1% in 1998). Proportionally the increase of notification of cases with positive one-point serology was much higher from 1993 to 1998 than the increase of notification of cases confirmed with two-point serology (49.1/6.2=7.9-fold versus 70.8/25.8=2.7-fold).

Table 16. Estimated absolute number and proportion of cases with positive two-point serology which were reported.

	1993 number (%)	1994 number (%)	1995 number (%)	1996 number (%)	1997 number (%)	1998 number (%)
number of positive two-point serology	482 (100%)	498 (100%)	272 (100%)	1885 (100%)	924 (100%)	468 (100%)
- number of reported matched cases with positive two-point serology	*115 (23.9%)*	*129 (25.9%)*	*75 (27.6%)*	*788(41.8%)*	*394 (42.6%)*	*227(48.5%)*
*- estimated number of reported not-matched cases with positive two-point serology**	*9.5 (2.0%)*	*13.5 (2.7%)*	*18.6 (6.8%)*	*131.5 (7.0%)*	*135.2 (14.6%)*	*104.2(22.3%)*
estimated total number of reported cases among positive two-point serology	**124.5 (25.8%)**	**142.5 (28.6%)**	**93.6 (34.4%)**	**919.5(48.8%)**	**529.2(57.3%)**	**331.2(70.8%)**

* The proportion of positive two-point serological results for not-matched cases for which serology was used to confirm the diagnosis, was assumed to be similar to the proportion of positive two-point serological results for matched cases (1993 47.7%; 1994 34.6%; 1995 33.0%; 1996 25.0%; 1997 22.5% ; 1998 14.2%).

Table 17. Estimated absolute number and proportion of cases with positive one-point serology which were reported.

	1993 number (%)	1994 number (%)	1995 number (%)	1996 number (%)	1997 number (%)	1998 number (%)
number of positive one-point serology	1489 (100%)	1867 (100%)	1070 (100%)	7854 (100%)	4107 (100%)	3247 (100%)
- number of reported matched cases with positive one-point serology	*85 (5.7%)*	*175 (9.4%)*	*113(10.6%)*	*2089 (26.6%)*	*1198 (29.2%)*	*1054 (32.5%)*
*- estimated number of reported not-matched cases with positive one-point serology**	*7.1 (0.5%)*	*18.3 (1.0%)*	*28(2.6%)*	*348.7 (4.4%)*	*411.7 (10.0%)*	*538.8 (16.6%)*
estimated total number of reported cases among positive one-point serology	**92.1 (6.2%)**	**193.3 (10.4%)**	**141(13.2%)**	**2437.7(31.0%)**	**1609.7(39.2%)**	**1592.8(49.1%)**

* The proportion of positive one-point serological results for not-matched cases for which serology was used to confirm the diagnosis, was assumed to be similar to the proportion of positive one-point serological results for matched cases (1993 35.3%; 1994 46.9%; 1995 50.0%; 1996 66,3%; 1997 68.5%, 1998 73.4%)

Possible changes in laboratory-confirmation of reported pertussis were investigated by attributing a hierarchical order to method of laboratory (Table 18). First, from the notification data-base microbiologically-confirmed cases (culture or PCR) were selected (part of those were also diagnosed with serology), secondly, from the remaining cases the ones confirmed with positive two-point serology were selected (as determined by matching with the serodiagnostic data-base), thirdly, the remaining cases with positive one-point serology, fourth, the remaining cases confirmed with serology (but not-matched with the serodiagnostic data-base: differentiation between positive one-point serology and two-point serology not possible), and lastly, the remaining cases in which no laboratory diagnosis was registered. The proportion of microbiologically confirmed reported cases decreased from 21.1% in 1993 to 4.3% in 1998.

The proportion of reported cases confirmed with positive serology (matched plus not matched) increased from 59.8% in 1993 to 84.5% in 1998. However, the proportion confirmed with positive two-point serology decreased from 28.9% in 1993 to 9.0% in 1998 while the proportion confirmed with positive one-point serology increased from 25.1% in 1993 to 45.9% in 1998. In addition, interpretation of these shifts is hampered by the changes of serologically confirmed reported cases which could not be matched with the serodiagnostic database and therefore could not be differentiated in positive one-point and positive two-point serology.

Table 18. Method of diagnosis in hierarchical order from the results of matching the notification database with the database of serodiagnostics in the years 1993-1998*

Method of diagnosis	1993		1994		1995		1996		1997		1998	
microbiological	73	21.1%	89	17.1%	51	15.0%	418	9.9%	235	8.8%	107	4.3%
two-point serology	100	28.9%	116	22.4%	62	18.2%	760	18.0%	383	14.3%	226	9.0%
one-point serology	87	25.1%	180	34.7%	119	34.9%	2041	48.2%	1172	43.9%	1150	45.9%
serological (not matched)	20	5.8%	39	7.5%	59	17.3%	544	12.9%	609	22.8%	742	29.6%
epidemiological	38	11.0%	40	7.7%	27	7.9%	178	4.2%	96	3.6%	64	2.6%
other	28	8.1%	55	10.6%	23	6.7%	290	6.9%	176	6.6%	216	8.4%
total	*346*	*100%*	*519*	*100%*	*341*	*100%*	*4231*	*100%*	*2671*	*100%*	*2508*	*100%*

* The method of diagnosis was scored according to the following hierarchy: microbiological, positive two-point serology, positive one-point serology, serological (not matched), epidemiological and other (clinical, method of diagnosis unknown, negative or non-conclusive serology)

- The proportion of reported cases confirmed with positive one-point serology increased in the 1996 and remained high in 1997 and 1998. The proportion of positive two-point serology decreased further in 1997 and 1998.
- The notification rate increased for both positive one- and two-point serology.

4. Discussion

4.1 Surveillance data in 1997 and 1998

4.1.1 Trends in incidence

After the outbreak in 1996, according to various surveillance sources, the incidence of pertussis declined in 1997 and further in 1998. Like other years a seasonal peak occurred in both years around August. The estimated incidences for 1997 and 1998 remained higher compared with the annual incidences over the period of 1989-1995, in particularly according to notifications and positive one-point serology. According to positive two-point serology and hospital admissions the estimated incidence of 1998 approached the incidence of 1993-1994. In these years as well as in 1989-1990 somewhat higher incidences were observed.

The level of notifications in 1997 and 1998 compared tot previous years should be interpreted with caution mainly because of two factors. Firstly, the notification rate (as calculated for cases with positive one- and two-point serology by linking the serological database with the notification data) has increased probably as a result of increased awareness after the outbreak in 1996. Secondly, the linkage of the notification data with the serological data showed that the proportion of notifications confirmed with positive one-point serology sharply increased in recent years. Since April 1997, positive one-point serology has been formally accepted as laboratory confirmation for notification. While before 1996 the level of notifications was similar to the level of positive two-point serology and much lower than the number of cases with positive one-point serology, it started to approach the level of positive one-point serology in 1996. In 1997 and 1998, the level of notifications was about similar to the level of positive one-point serology. Thus, in comparison to previous years, a larger part of pertussis cases is recognised and/or reported. On the other hand, in 1998 at least tree large regional public health laboratories have started to perform pertussis-serology themselves with a population coverage of 15-20% (see chapter 1). Before, only one laboratory (LIS-RIVM) performed serology for the whole country. Thus, the population coverage of serological surveillance of pertussis has decreased and therefore the true incidence based on positive serology might be underestimated compared with previous years.

In contrast with surveillance based on notification and serology, we assume that surveillance based on hospital admission data is less sensitive for changes over time and reflects the incidence of severe pertussis. The number of hospital admissions in 1997 and 1998 compared with 1996 decreased as well. This confirms the decline in incidence, which was shown by the surveillance, based on notifications and positive serology.

Recent surveillance data indicated that the incidence levels over the first half year period of 1999 were higher again compared with the same period of 1998.

With respect to mortality of pertussis, two fatal unvaccinated cases less than three months of age were reported for both 1996 and 1997. In 1998 one fatal case was registered according to the national registration although by paediatric surveillance 3 fatal cases were registered in 1998. Unfortunately linkage between the national registration and the paediatric surveillance was impossible.

4.1.2 Age distribution

According to notification data and serological data, in 1996 the peak incidence shifted from infants less than one year towards children of four years of age. The proportion of children less than one year decreased in 1996 compared to previous years (1989-1995). The age distribution in 1997 and 1998 for positive serology and notifications was similar to 1996. Peak incidence was observed among four-year-olds in 1997 and five-year-olds in 1998. For hospital admissions the highest incidence in 1997 and 1998 was observed among infants less than one year of age and similar with previous years (1989-1996). The increase among infants less than one year for hospital admissions and notifications was similar in 1996. Also for 1997 and 1998 this ratio hospital admissions to notifications was similar. This indicates the virulence of pertussis among the youngest (unvaccinated) children did not change.

4.1.3 Vaccine efficacy

The vaccine efficacy that had already declined in 1994 and 1995 declined further in 1996 and 1997. For 5-9-year-olds the estimated vaccine efficacy remained low in 1998, while for 1-4-year-olds the estimates were comparable with 1996. Unlikely great changes in selective reporting of vaccinated patients and in misclassifications of cases with respect to vaccination status or vaccination coverage must be assumed to nullify the decrease in vaccine efficacy estimated by the screening method (16). Although estimates predicted less vaccine efficacy for cases with positive one-point serology, the greater proportion of these cases among the reported cases could not fully explain the decrease either. For reported cases that were microbiologically confirmed and reported cases with two-point serology, the estimates for 1 to 4-year-olds and 5 to 9-year-olds declined as well. Furthermore, additional information of notifications obtained for reported cases in 1997 showed that typical and long-term pertussis symptoms occurred among vaccinated reported cases (11). This indicates that the increased pertussis incidence was not only due to an increase in mild pertussis cases as we assumed before. However, data from the Netherlands Paediatric Surveillance Centre (NSCK) confirmed that pertussis is most severe among unvaccinated young infants less than 3 months of age (11).

As we 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 (7, 13, 17, 18). 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.

4.2 Changes in surveillance of pertussis

As previously described, the interpretation of the surveillance data is complicated due to recent changes of the various surveillance sources. Below we summarise the most relevant changes:

1. Change of case-definition for notification since April 1997; formal acceptance of positive one-point serology besides two-point serology to confirm clinical pertussis.
2. Increased notification rate since the epidemic in 1996.
3. Decreasing coverage of serosurveillance performed by the LIS-RIVM.
4. Increasing performance of PCR and as a consequence a decreasing use of culture to confirm clinical pertussis.
5. Introduction of new notification law since April 1999. Since then, it is not possible to link the notification data and the serological data to collect information about the type of diagnostics on which the notification is based on. Furthermore, the type of collected data on vaccination status has been changed.

With respect to these recent changes we need to continue and perhaps adapt our surveillance based on the various sources (as we did before) to distinguish surveillance artefacts from real epidemiological effects. Surveillance of pertussis is needed for mainly two reasons. Firstly, to monitor the trends in the incidence of pertussis in Netherlands. Secondly, to study the effect of changes in vaccination strategies such as the possible effect of the introduction of the whole cell vaccine with a higher content of pertussis toxin. We expect that we can only observe a change in our notification data in case of a relatively strong effect of the new vaccine. Further on, since January 1999 the vaccination schedule has been changed. Since then, children are vaccinated at the age of 2, 3, 4 and 11 months instead of 3, 4, 5 and 11 months. As result infants might be protected at an earlier age.

4.3 Further research

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 clinical symptoms. However, *B. pertussis* infection can run an asymptomatic course as well mainly in older vaccinated children and adults (19,20,21). Possibly since the introduction of whole cell vaccine, the number of symptomatic pertussis has decreased much more than the number of infections. Seroprevalence data of IgG against pertussis toxin measured in a population based cross-sectional study and longitudinal data of the declining IgG after pertussis infection will be used to estimate the frequency of *B. pertussis* infection (symptomatic and asymptomatic) in various age groups. Preliminary analysis of this data suggested that in the Dutch population frequent infections occurred among older children and adults.

Another field of research is to study the source of infection for young unvaccinated infants. 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 but so far no data are available for the Netherlands (19,21). Results of such studies might play an important role in the decision-making concerning the introduction of booster vaccination.

5. Conclusions

- The incidence of pertussis based on various surveillance sources in 1997 and 1998 was lower compared with 1996 but higher compared with the period of 1989-1995.
- Most cases occurred among vaccinated children of 1-9 years of age with a peak incidence among 4-5 years olds. Consequently estimated vaccine efficacies based on the screening method showed a further decline in 1997 and 1998.
- Interpretation of surveillance data becomes more difficult over time because of recent changes of the case-definition for notification, the increased notification rate and the decreased coverage of the serosurveillance. Therefore, surveillance of pertussis should be based on various surveillance sources to distinguish surveillance artefacts and real epidemiological effects. Hospital admission data are assumed to be less sensitive by such changes over time and therefore considered to be the most stable surveillance source.
- Surveillance of pertussis is important to monitor the incidence of pertussis in the Netherlands and study the effect of changes in vaccination strategies.

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Appendix I: 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 II: Methods

1. Used data

1.1 Notification data 1989-1998

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 (1, 2). Therefore in this report we limited pertussis surveillance from 1989 onwards. For this period of 1989-1998 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, place of residence and method used for diagnosis are also included in the database.

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 1993-1996 for which the date of first illness was unknown this correction was made. In 1997 and 1998 the delay between onset of symptoms and the registration of reported cases was 62 respectively 67 days.

The classification used to register the method of diagnosis for a reported case is: microbiological, epidemiological, serological and clinical. 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 1998 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 1989-1998

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 convascelent 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 19.

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 19. 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 1989-1998

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 1989-1998 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)
4. '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 20 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. In 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 (25 days in 1996, 26 days in 1997 and 27 days in 1998) from this last date.

Table 20. 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 1989-1998 by age group (1976-1980 0-4 years, 5-9 years etc., 1981-1998 0 year, 1-4 years, 5-9 years etc.) and sex were obtained from SIG Zorginformatie.

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 1989-1998 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 1989-1998 were obtained from the CBS.

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 1989-1998

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 1989-1998. 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 1998. The number of isolates of *Bordetella pertussis* in the period 1989-1998 as reported by the 16 regional public health laboratories are given.

The age-specific incidence in the years 1989-1998 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 1998 (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 1989-1998 and according to hospital admissions due to pertussis (age groups 0 year, 1-4, 5-9, ≥ 10) in the period 1989-1998 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 1998. 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 1997 and 1998 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.

Notifications in 1993-1998 were individually matched with the data of serodiagnosis. For notifications in 1989-1992 no information on the date of birth (only age at notification) was available in the database. For 1989 to 1995 the matching was performed in the following steps:

1. matching by first four characters of the last name, date of birth and gender
2. selection of not-matched patients for whom the day and month of notification was similar to the day and month of birth. For those patients the date of birth was not known and it was estimated from the date of notification. These records were not included in step 3 to 5.
3. matching of not-matched records by the first four characters of the last name and the date of birth.
4. matching of not-matched records by the first three characters of the last name, date of birth and gender.
5. matching of not-matched records by the first four characters of the last name, gender, month of birth, year of birth and/or matching by the first four characters of the last name, first four characters of the place of residence and gender and/or matching by the first four characters of the last name, first initial, gender and year of birth.
6. matching of those records selected in step two by the first four characters of the last name, the first four characters of the place of residence and gender and/or first four characters of the last name, first initial, gender and year of birth.

7. matching of the not-matched records by the first day of illness and the first four characters of the last name
8. matching of the not-matched records by the first day of illness and the first four characters of the place of residence
9. matching of the not-matched records by the first day of illness and the date of birth.
10. selection of records that were matched twice.

For 1996 the matching was performed in the following steps:
1. matching by first four characters of the last name, date of birth, gender and postal code
2. matching of not-matched records by the first four characters of the last name, the date of birth and gender.
3. matching of not-matched records by the postal code, date of birth and gender.
4. matching of not-matched records by the first four characters of the last name, date of birth and postal code.
5. matching of the not-matched records by the first day of illness, date of birth, numbers of postal code and gender.
6. matching of the not-matched records by the first day of illness, date of birth and gender
7. matching of the not-matched records by gender, postal code and year of birth
8. matching of the not-matched records by first four characters of the last name, gender and first day of illness.
9. matching of the not-matched records by first four characters of the last name, gender and place of residence.
10. matching of the not-matched records by first four characters of the last name, first day of illness and place of residence.

For 1997 and 1998 the matching was performed in the following steps:
1. matching first four characters of the last name, date of birth, gender en postal code.
2. matching of not-matched records by first four characters of the last name, date of birth and gender.
3. matching of not-matched records by the postal code, date of birth, and gender.
4. matching of not-matched records date of birth and postal code.
5. matching of the not-matched records by the first day of illness, date of birth, numbers of postal code and gender.
6. matching of the not-matched records by the first day of illness, date of birth and gender.
7. matching of the not-matched records by gender, postal code and year of birth.

8. matching of the not-matched records by first four characters of the last name, gender and first day of illness.
9. matching of the not-matched records date of birth, gender and postal code (numbers).
10. matching of the not-matched records by date of birth, postal code (numbers).
11. matching of the not-matched records by postal code, first character last name, first letter last name (women).
12. matching of the not-matched records by postal code (numbers), first character first name.
13. matching of the not-matched records by first four characters last name (women), place of residence.
14. matching of the not-matched records by first four characters last name (women), date of birth.
15. matching of the not-matched records by first four characters address, place of residence.

The absolute number and proportional distribution of serological results and the method of diagnosis according to the notification data were calculated. The absolute number and proportion of underreporting for cases with positive two-point serology were estimated. The number of reported not-matched cases for which serology was used to confirm the diagnosis (as registered in the notification file) was assumed to be similar to the proportion of positive two-point serological results for matched cases.

The number of reported cases that met the case-definition (positive two-point serology, microbiological criteria and epidemiological criteria: before April 1997) was calculated from the matching results. The proportional age-distribution and the vaccine-efficacy for those cases was estimated for the period 1993-1998.

Possible changes in laboratory-confirmation of reported pertussis by attributing a hierarchical order to method of laboratory diagnosis. First, from the notification data-base microbiologically confirmed cases were selected (part of those were also diagnosed with serology), secondly, from the remaining cases the ones confirmed with positive two-point serology were selected (as determined by matching with the serodiagnostic data-base), thirdly, the remaining cases with positive one-point serology, fourth, the remaining cases confirmed with serology (but not-matched with the serodiagnostic data-base: differentiation between positive one-point serology and two-point serology not possible), and lastly, the remaining cases in which no laboratory diagnosis was registered.

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