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Pertussis in the Netherlands, 2001-2002

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Abstract

To gain insight into the incidence and severity of pertussis in the Netherlands in 2001 and 2002, surveillance data based on notifications, laboratory data, hospitalisations and deaths were analysed for these two years and compared to the years before. The decreasing coverage of serologic data from the LIS-RIVM compared with 1996 was taken into account.
According to various surveillance sources pertussis is still endemic with epidemic peaks every two to three years (in 1996, 1999 and 2001). The reported incidence of notified cases was highest in 2001 (50.2/100,000) and decreased in 2002 (28.0). The incidence/100,000 in 2001 calculated from positive two-point serology amounted to 4.4 (corrected for decreasing coverage 8.0) and positive one-point serology 30.7 (corrected 55.8) and hospital admissions 2.5. The incidence calculated from these surveillance sources was again lower in 2002: incidence/100,000 positive two-point serology 2.1 (corrected 4.1), positive one-point serology 15.4 (corrected 29.9) and hospitalisations 1.6. Highest incidence of hospitalisations was reported among infants less than 1 year (especially those aged < 3 months).
In 2002 – the first year an effect of the booster vaccination for four-year-olds might be visible- all surveillance sources showed a decrease in the incidence of the 3 and 4 year-olds compared with previous years. Besides, small increases in the number of patients older than 5 years were seen. Estimations of vaccine efficacy based on surveillance data showed a slight improvement in vaccine-efficacy for the 1-year-olds in the period 1998-2002 compared with 1996-1997.
Still, pertussis is endemic with peaks every 2 to 3 years and with a higher incidence compared to the period prior to the epidemic in 1996-1997. The introduction of the acellular booster-vaccination for 4-year-olds in 2001 has caused a decrease in the incidence of pertussis among the target-population. Long-term surveillance will be necessary to provide insight into the possible effect among the population at large. Estimations of vaccine-efficacy have improved in 1998-2002 compared to 1996-1997, probably as a result of the introduction of a ‘stronger’ pertussis vaccine in 1997. Pertussis is still most severe among young unvaccinated infants. The latter should be taken into account with the development of future vaccination-strategies (e.g. boostering of adults/care givers).

Contents

Samenvatting

Inleiding. In 1996-1997 werd met behulp van verschillende surveillancebronnen een epidemie van kinkhoest waargenomen, met name onder gevaccineerde kinderen. In de daarop volgende jaren werd een hogere kinkhoest-incidentie waargenomen, vergeleken met de periode vóór 1996, met een verheffing in 1999. Dit rapport beschrijft de resultaten van de kinkhoest routinesurveillance over 2001 en 2002.
Methoden. Surveillancegegevens op basis van verplichte meldingen bij de Inspectie voor de Gezondheidszorg (IGZ), serodiagnostiek (positieve twee- en eenpuntsserologie) verricht door het LIS-RIVM, *B. pertussis* isolaten geregistreerd door streeklaboratoria en landelijke registraties van ziekenhuisopnamen (SIG/Prismant) en sterfte (CBS) werden geanalyseerd voor 2001 en 2002 en vergeleken met de periode 1989-2000. Hierbij is rekening gehouden met de afnemende dekking van de kinkhoestserologie uitgevoerd door het RIVM. Verder werden via het Nederlands Signaleringscentrum Kindergeneeskunde (NSCK) ziekenhuisopnamen ten gevolge van kinkhoest bij kinderen jonger dan 15 jaar gerapporteerd.
Resultaten. De surveillance data laten zien dat de afgelopen 7 jaar elke twee à drie jaar een verheffing in de incidentie van kinkhoest in Nederland optrad. Hierbij waren de jaren 1996, 1999 en 2001 epidemische jaren. De incidentie op basis van de aangiften was het hoogste in 2001 (50,2/100000) en nam weer af in 2002 (28,0/100000). De incidentie/100000 in 2001 op basis van positieve tweepuntsserologie bedroeg 4,4 (gecorrigeerd voor afnemende dekking 8,0), positieve eenpuntsserologie 30,7 (gecorrigeerd 55,8) en de ziekenhuisopnamen 2,5. Ook op basis van deze surveillance bronnen was de incidentie/100000 in 2002 gedaald: incidentie positieve tweepuntsserologie 2,1 (gecorrigeerd 4,1); positieve eenpuntsserologie 15,4 (gecorrigeerd 29,9) en ziekenhuisopnamen 1,6. De piekincidentie voor ziekenhuisopname lag bij zuigelingen jonger dan 1 jaar (voornamelijk < 3 maanden). In 2002 –het eerste jaar dat een mogelijk effect van de boostervaccinatie op 4-jarige leeftijd zichtbaar kan zijn– werd op basis van alle surveillancebronnen een daling in de incidentie ten opzichte van voorgaande jaren waargenomen voor de 3 en 4 jarigen. Onafhankelijk hiervan werd een lichte toename gezien in de incidentie van >5 jarigen. Schattingen van vaccin-effectiviteit op basis van surveillancedata laten voor de periode 1998-2002 een lichte verbetering zien voor 1 jarigen, ten opzichte van 1996-1997.
Conclusie. Kinkhoest is nog steeds endemisch met een hogere incidentie ten opzichte van vóór de epidemie in 1996-1997 en met elke 2 à 3 jaar een verheffing van de incidentie. De introductie van de acellulaire boostervaccinatie voor vierjarigen in 2001, heeft geleid tot een daling van het aantal patiënten in de leeftijdsgroep zelf. Op langere termijn zal het mogelijk effect van de boostervaccinatie op populatieniveau zichtbaar worden. Schattingen van vaccin-effectiviteit zijn in de periode 1998-2002 verbeterd ten opzichte van 1996-1997, mogelijk als gevolg van de invoering van het ‘versterkte’ kinkhoestvaccin in november 1997. Kinkhoest verloopt nog steeds het meest ernstig bij jonge ongevaccineerde zuigelingen. De toekomstige vaccinatiestrategie (bijvoorbeeld revaccinatie van ouders/verzorgers) moet hierop worden afgestemd.

Summary

Introduction. In 1996-1997 different surveillance sources revealed an outbreak of pertussis among mostly vaccinated children in the Netherlands. In the following years the incidence of pertussis remained higher than in the period before 1996 and in 1999 another peak was observed. This report describes the results of the surveillance of pertussis in 2001 and 2002 in the Netherlands.
Methods. Surveillance data based on obligatory notifications to the Health Care Inspectorate, laboratory data (positive one- and two-point serology) from the National Institute for Public Health and the Environment, isolations of *B. pertussis* from regional public health laboratories and the national registrations of hospital admissions and deaths were analysed for 2001 and 2002, and compared to the period 1989-2000. Herewith, the decreasing coverage of the serologic data from LIS-RIVM was taken into account. Furthermore, pertussis hospitalisations among children under 15 years were reported monthly through the Dutch Paediatric Surveillance Centre (NSCK).
Results. The surveillance data showed an increase in the incidence of pertussis every two to three years in the Netherlands in the past seven years, with epidemic peaks in 1996, 1999 and 2001. The reported incidence of notified cases was highest in 2001 (50.2/100,000) decreased in 2002 (28.0). The incidence/100,000 in 2001 calculated from positive two-point serology amounted 4.4 (corrected for decreasing coverage 8.0) and positive one-point serology 30.7 (corrected 55.8) and hospital admissions 2.5. The incidence calculated from these surveillance sources was again lower in 2002: incidence/100,000 positive two-point serology 2.1 (corrected 4.1), positive one-point serology 15.4 (corrected 29.9) and hospitalisations 1.6. Highest incidence of hospitalisations was reported among infants less than 1 year (especially those aged < 3 months). In 2002 – the first year an effect of the booster vaccination for four-year-olds might be visible- all surveillance sources showed a decrease in the incidence of the 3 and 4 year-olds compared with previous years. Besides, small increases in the number of patients older than 5 years were seen. Estimations of vaccine efficacy based on surveillance data, showed a slight improvement in vaccine-efficacy for the 1-year-olds in the period 1998-2002 compared to 1996-1997.
Conclusions. Pertussis is still endemic with a higher incidence compared to the period prior to the epidemic in 1996-1997 and with a peak in the incidence every two to three years. The introduction of an acellular booster-vaccination for 4-year-olds in 2001 has caused a decrease in the incidence of pertussis among the target-population itself. Long-term surveillance will be necessary to provide insight into the possible effect among the population at large. Estimations of vaccine-efficacy based on surveillance data have improved in 1998-2002 when compared to 1996-1997, probably as a result of the introduction of the ‘stronger’ pertussis vaccine in 1997. Pertussis is still most severe among young unvaccinated infants. With future vaccination-strategies (e.g. boostering of adults/care givers) the latter must be taken into account.

1 Introduction

1.1 Background

Pertussis, or whooping cough, is a respiratory infection mainly caused by *Bordetella pertussis* and more rarely by *Bordetella parapertussis*. Classical pertussis follows an incubation period of 6-20 days. The disease is characterised by a catarrhal phase followed by a long-lasting paroxysmal cough. The latter can be accompanied by cyanosis, apnoea and fever. The most prevalent complications of pertussis are otitis media, pneumonia, encephalopathy and seizures. (1) Particularly among young unvaccinated infants pertussis can cause severe symptoms and complications. In vaccinated (older) children and adults the disease most often occurs with milder and/or unrecognised symptoms. (2) In the 1940s effective whole-cell vaccines against *B. pertussis* were developed and more recently (1970s) acellular vaccines were developed which are less frequently associated with negative side effects. (3) Since the introduction of routine vaccination, the incidence and mortality of pertussis decreased sharply. However, pertussis remains an important cause of death among (young) children world-wide. The WHO reports yearly some 20-40 million cases of pertussis world-wide (90% of which occur in developing countries) and the number of deaths from pertussis is estimated at 200-300,000 each year. (4) Since the last decade many developed countries experience a re-emergence of pertussis, even countries that have had high vaccination coverage for many years. (5, 6, 7) Because of waning natural-derived and vaccine induced immunity older children and adults are susceptible to infection again. Therefore it is assumed that infection-frequency is probably highest in adolescents and adults and consequently those age groups are the main source of infection for infants. (5, 7, 8)

This report describes the results obtained from the surveillance of pertussis in the Netherlands in the years 2001 and 2002. Data from 1989 to 2000 have been analysed and reported in detail previously. (9, 10, 17, 18, 19, 21)

1.2 Surveillance and epidemiology of pertussis in the Netherlands until 2001

In the Netherlands, mass vaccination, with a whole cell pertussis vaccine was introduced in 1952 in the National Immunisation Programme. After the introduction of routine vaccination, the incidence and mortality of pertussis decreased sharply. However, despite a high vaccination coverage pertussis is still endemic in the Netherlands, with epidemic peaks every 2 to 3 years during the last decade.
Insight into the incidence of pertussis is based on different surveillance sources; i.e. notifications, serology data, hospital admissions and registrations of deaths. In the period of 1989 to 1995, with a stable case definition for notification, increased numbers of pertussis

cases were reported in 1989/1990 and in 1993/1994 despite a high vaccine coverage of 96% (9). Then in 1996, a sudden and sharp increase of notifications, positive cultures, positive serology and hospital admissions was observed. In addition, estimations of vaccine effectiveness using the screening method (Appendix 4), which had already declined in 1994 and 1995, declined further in 1996. Different suggestions as to the cause of the sudden increase have been given. (9,10) As mentioned above waning immunity plays a role in international pertussis epidemiology . However, it is very unlikely to be the sole factor explaining the sudden, sharp rise of pertussis over a wide age-range in the Netherlands. While changes in vaccination coverage, serological practice, notification rate and interference with the introduction of *Haemophilus influenzae* type b vaccination could not explain the epidemic, a mismatch between circulating strains and vaccine strains was emerged. Studies showed antigenic divergence between vaccine strains and clinical isolates for both pertactin and pertussis toxin. (11,12) More recently it was shown that the Dutch WCV was less effective against non-vaccine type strains in a mouse model. (13, 14, 15, 16)
In 1997-1998 the incidence of pertussis started to decline. Still, the incidence was higher compared with the period 1989-1995. (17, 18, 19) In 1999, again an increase of the incidence of pertussis was observed. However, in 2000 the incidence decreased again and approached the incidence of 1998.
Besides a description of the trends in the epidemiology of pertussis in the Netherlands in 2001 and 2002 in this report attention is given to the first effects of the booster-vaccination with acellular pertussis vaccine, which was introduced in November 2001 for children aged 4 years old.

1.3 Recent changes in surveillance

Determining the epidemiology of pertussis by case-reporting data is hampered by changes in surveillance sources, diagnostic practices and the vaccination schedule. Therefore, with the interpretation of the surveillance data some changes over time must be taken into account (see also Table 1).

Notification data
The formal acceptation of positive one-point serology as laboratory confirmation for notification in 1997 has resulted in a less rigid case definition and thus a larger part of pertussis cases was recognised and/or reported from that time. Furthermore, since the outbreak in 1996 the alertness for pertussis might be increased which may have resulted in a higher case-reporting rate. In previous years more insight was gained in whether observed changes in surveillance data represented true changes in incidence by matching the notification-database with the serology-database. However, in 1999 the law for disease-notification changed and from that time notification data had become less suitable for surveillance, for instance since date of birth was less accurate registered. Although additional information on notifications (e.g. method of diagnosis) was gathered by the RIVM since 2001

on a voluntary base, a linkage between serologic data and notification-data was not possible anymore.

Serology
Before 1996 all serological tests for pertussis were performed at the LIS-RIVM. However, since 1998 at least three of the 16 regional Public Health Laboratories and also some other (hospital) laboratories have started to perform serology with commercial available assays. Consequently, the population coverage of serological surveillance based on serological data of LIS-RIVM is now estimated to have decreased from 100% in 1996 to less than 50% in 2002. Furthermore, PCR as method of diagnosis is applied more general, especially among young children. This could partly have 'replaced' serology as diagnostic method but could also have resulted in an increased diagnosis of pertussis.

Paediatric surveillance
Although the paediatric study has not given insight into the total burden of disease due to pertussis in the Netherlands, the study has given important insight into characteristics of pertussis patients and severity of pertussis in the Netherlands in the period 1997-2002. The study demonstrated clearly that pertussis remains a potentially severe disease in the Netherlands especially among young infants (often too young to be vaccinated). However, in 2003 this paediatric surveillance is stopped, partly due to the low response compared to the national register of hospitalisations. Continuing the paediatric surveillance does not offer much more information, especially considering the already available information collected the last five years.

Vaccine and vaccination
The Dutch whole cell vaccine has been used in the National Immunisation Programme since 1953. However, since November 1997 small changes in the production process of the vaccine (increased scale of culturing of the bacteria and accelerated inactivation), and increased release criteria for the bulk and final product, have resulted in a higher protection as measured in the release test in mice, and an increased consistency of the production process. (20, personal communication)
Furthermore, since 1 January 1999 the primary vaccination for pertussis has been advanced. From that time children are vaccinated at the age of 2, 3, 4, and 11 months, instead of 3, 4, 5 and 11 months. Finally, in November 2001 a booster vaccination with an acellular vaccine, comprised of Ptx, Prn and FHA, was introduced in the National Immunisation Programme at the age of 4 years.

Table 1. Recent changes in pertussis surveillance and vaccination

Date	Event
1988 (January)	Introduction of case-definition for notification, including clinical symptoms and laboratory confirmation (either positive culture and/or positive two-point serology)
1994 -	Increased use of positive one-point serology for laboratory confirmation; high titres indicated 'possible pertussis'
1996 - continuing	Decreasing coverage of serology data LIS-RIVM
1997 (April)	Positive polymerase chain reaction and positive one-point serology formally accepted as laboratory confirmation for notified patients
1997 (November)	Introduction of a 'stronger' whole cell vaccine into the National Immunisation Programme, i.e. with a higher content of pertussis toxin.
1999 (January)	Acceleration of vaccine schedule at the age of 2, 3, 4, 11 months instead of 3, 4, 5, 11 months.
1999 (April)	Change in Infectious Disease Law: verification of notification rate through linkage with serological diagnoses-database impossible.
2001 (October)	Introduction of acellular booster vaccination for four year olds into the National Immunisation Programme
2003	End of pediatric surveillance

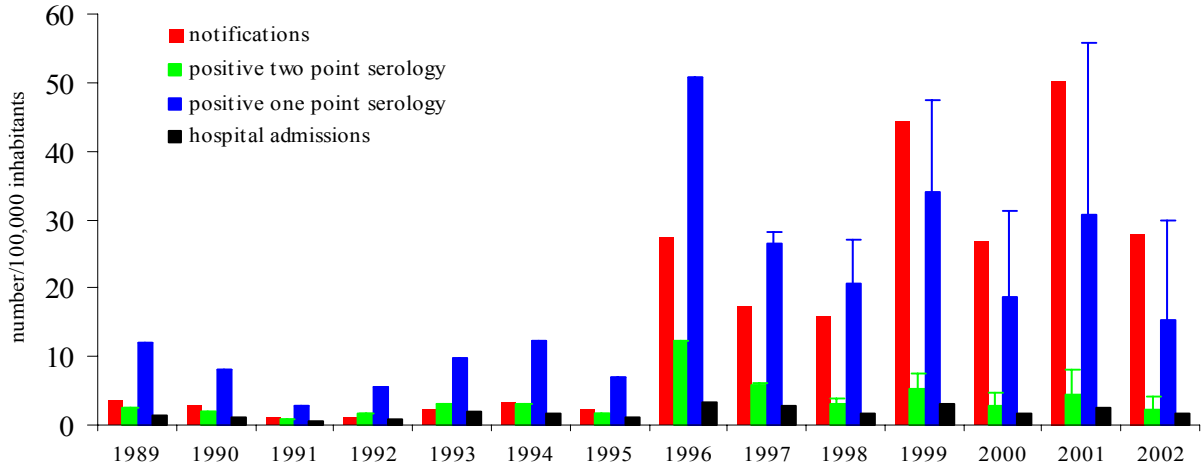
2 Methods

In Appendix 4 the methods and analysis of the data are described in detail. The same methodology is used as in previous years (1989-2000).
In short, the incidences of pertussis per year, per month and / or per age group in the period 1989-2002 were estimated using notifications, positive one-point serology, positive two-point serology, isolations of *B. pertussis*, hospital admissions and deaths collected in different registrations during this time period. As denominator the number of people on the first of January in the concerning year was used. The decreasing coverage of the serologic data from the LIS-RIVM, was calculated as follows:
Beforehand the coverage in 1996 was assumed to be 100%, since up to and including 1996 the LIS-RIVM was the only laboratory in the Netherlands performing serology, while from 1997 onwards commercial assays have increasingly been used, resulting in a lower coverage from LIS-RIVM. Then, for every year the labs that stopped sending their samples to the LIS-RIVM from that year on, were marked. Subsequently, the contribution of these marked labs in 1996 to the total number of samples in 1996 was calculated. This percentage revealed the decrease in coverage for that year in comparison with 1996 and hence the coverage in the concerned year was calculated as 100% minus this decrease. The number of samples from laboratories that started to send samples after 1996 was very low and therefore not taken into account.
Proportional age-distributions for notifications, positive one-point and/or two-point serology and hospital admissions were calculated. The annual vaccine efficacy for the 1-9 year-olds, per age-year and age group, was estimated with the screening method (see Appendix 4) according to data on notifications, comparing vaccinated individuals with unvaccinated individuals. For 2001 and 2002 the geographical distribution of reported cases of pertussis per quarter and per Municipal Health Service (MHS) are given.
From January 1997 to January 2003, hospitalisation due to pertussis was included in an active paediatric surveillance conducted by the Netherlands Paediatric Surveillance Centre (NSCK). In this surveillance paediatricians were asked to check monthly a number of disorders that they observed for the first time (new case) and to state the patient's initials and date of birth on a card. If paediatricians did not see any of the disorders listed, they were asked to mark 'no observation'. After a positive reaction, paediatricians were asked to fill in a standardised questionnaire. For patients hospitalised due to pertussis information on age, sex, clinical symptoms, length of hospital stay and laboratory results was collected. Additionally, in case the patient was 2 months or older, the parents were asked (by the treating physician) to fill in an informed consent form to collect information on the vaccination status from the concerning Provincial Immunisation Administration, Child Health Centre or Municipal Health Service. Information on vaccination status could only be obtained after such an informed consent. Differences in distribution of cases between 1999/2000 and 2001/2002 were tested with a χ^2-test. In Chapter 4 the results of the paediatric surveillance in 2001 and 2002 are described.

3 Surveillance data

3.1 Incidence of pertussis

Figure 1 shows the annual incidence of pertussis in the period 2001-2002 calculated from notifications, positive two- and positive one-point serology and hospital admissions. According to all surveillance sources the incidence of pertussis in 2001 was higher than in the year 2000. In comparison with 2000 the annual incidence in 2001 had increased with the factors 1.8 for notifications, 1.5 for the positive two-point serology, 1.6 for positive one-point serology and 1.6 for the hospital admissions. Compared to the epidemic year 1999 the annual incidence in 2001 calculated from notifications had increased with a factor 1.1, while the annual incidence calculated from positive two- and positive one-point serology and hospital admissions had decreased with the factors 0.8, 0.9 and 0.8, respectively. Thin lines in the figure indicate the estimated number based on positive serology, when corrected for the decreasing coverage. The years 1996, 1999 and 2001 are then more comparable concerning serology. In 2002 the incidence calculated from serology (both corrected and not-corrected for decreasing coverage) had decreased again to a level somewhat lower than in 2000, while the number of notifications and hospitalisations was slightly higher.



	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Notifications	523	397	145	160	346	519	341	4231	2671	2508	6980	4229	8030	4504
Positive two point serology	350	278	110	238	482	498	272	1885	924	468	855	458	701	344
Positive one point serology	1760	1204	411	861	1489	1867	1070	7854	4107	3247	5377	2990	4914	2473
Estimated coverage of serologic data	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*100%*	*94%*	*77%*	*72%*	*60%*	*55%*	*51%*
Hospital admissions	221	157	82	101	288	276	162	513	436	282	509	247	397	261

Figure 1. Incidence and absolute number of pertussis (in table) per year and per source, in the period 1989-2002. The thin lines indicate the estimated incidence of positive serology when corrected for the decreasing coverage of serology compared to 1996 (see table).

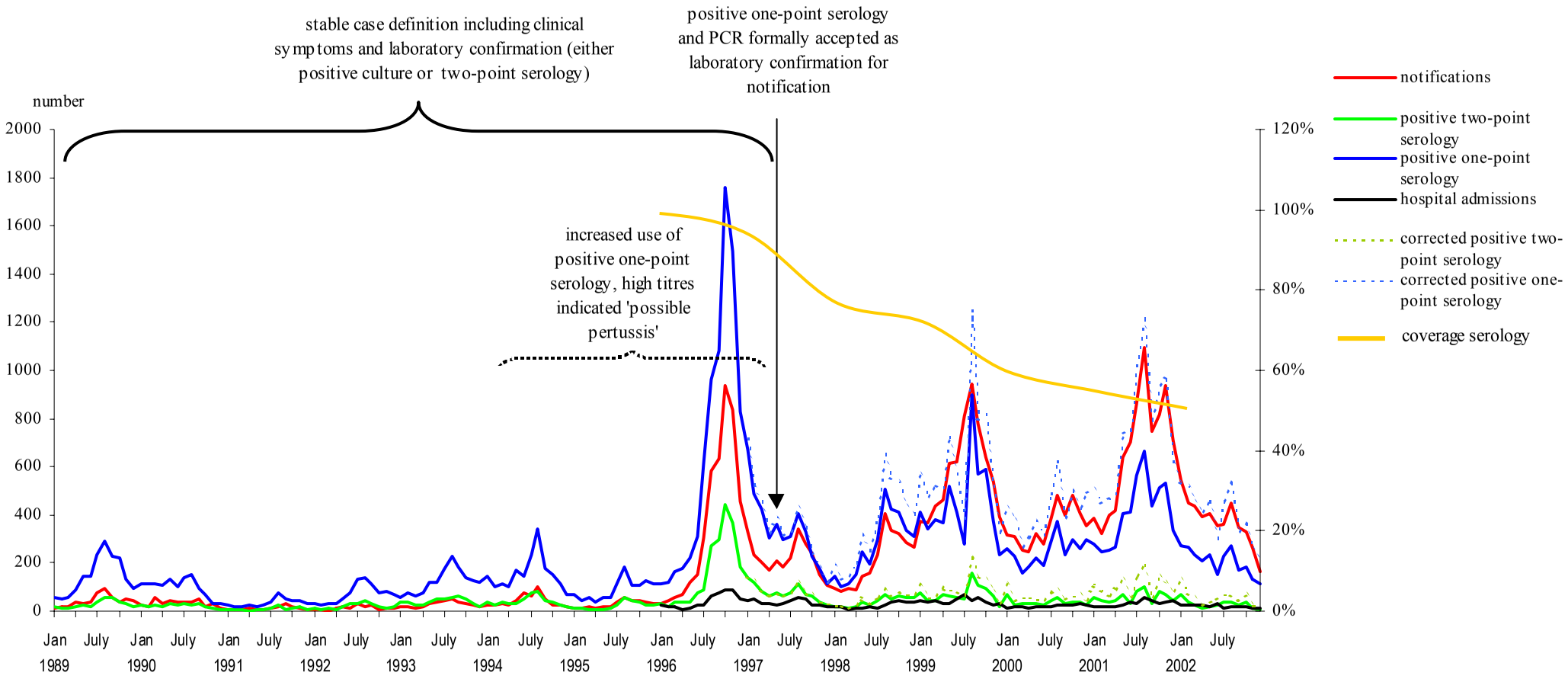


Figure 2. Pertussis in the period 1989-2002: notifications, positive two-point serology, positive one-point serology and negative serology; hospital admissions in the period 1996-2002, based on first day of illness. In yellow the decreasing coverage of the LIS-RIVM serology as compared to 1996.

In Figure 2 the absolute number of cases per month according to notifications, positive two-point serology, positive one-point serology and negative serology in the period 1995-2002 are presented. For information on numbers in the years before 1995 we refer to previous reports. (10, 21) Monthly hospital admissions data were only available in the period of 1996 to 2002. In yellow the decreasing coverage in comparison with 1996 of serology data from the LIS-RIVM is shown. The dotted lines give an estimation of the number of patients with positive serology, when corrected for the declining coverage. After the peak in 1996 the number of pertussis cases declined in 1997 and 1998 and new peaks were observed in late summer of 1999 and 2001 (peaks in August). In the period prior to 1995 the number of notified cases was comparable to the number of cases with positive two-point serology. However, since 1996 the number of cases with positive one-point serology has started to approach the number of notified cases as a result of the including of positive one-point serology in the formal case definition for notification. Since 2000 the number of notified cases even has exceeded the number of laboratory confirmed cases. However, when adjusting for the decreasing coverage of serologic data compared to 1996, the number of notified cases remained lower than the number of patients diagnosed with positive serology. As can be seen from Figure 2 the incidence of pertussis has shown an increase every 2-3 years in the period 1995-2002, while in the period 1989-1995 peaks were observed in 1989 and 1993/1994, suggesting epidemic peaks every 4 years. Furthermore, a seasonal peak of the number of pertussis cases can be seen for every year at the end of summer.

3.2 Serological results

Table 2 shows the proportional distribution (%) of serological results for pertussis in the period 1989-2002. The table shows that the percentage of total positive serology in the 2001 was comparable with the percentage in 1999. In 2002 the percentage positive serology was slightly lower than the percentages in 1998 and 2000.

Table 2. Proportional distribution (%) of serological results for pertussis in the period 1989-2002 (not corrected for decreasing coverage)

	1989-1995	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**
Estimated coverage of serologic data in comparison with 1996	*100%*	*100%*	*94%*	*77%*	*72%*	*60%*	*55%*	*51%*
Positive 2-point serology*	*9.2*	9.0	6.0	3.9	4.9	4.2	4.4	3.3
Positive 1-point serology**	*35.8*	37.4	26.6	27.1	30.7	27.5	31.1	23.5
Total positive serology***	*45.0*	*46.4*	*32.6*	*31.0*	*35.6*	*31.7*	*35.5*	*26.8*
Negative serology	*19.1*	16.3	24.2	18.0	14.2	21.2	18.0	21.5
Non-conclusive serology	*35.9*	37.4	43.3	51.1	50.2	47.1	46.5	52.0
Total (absolute number)	*100*	100	100	100	100	100	100	100
	(23346)	(21020)	(15461)	(11985)	(17505)	(10892)	(15798)	(10526)

* significant titre rise in paired sera

** high titre in first serum sample, no second serum available or no significant increase in the second serum sample

*** positive two-point serology or positive one-point serology (see * and **)

3.3 Microbiological surveillance

In Table 3, the number of *B. pertussis* strains detected by culture or PCR by the 16 public health laboratories is given. Particularly the number of PCR's increased in 2001 and 2002 in comparison with previous years. In 2001 the number of PCR's increased 1.2-fold compared to 1999 and 2.6-fold compared with 2000. Although, the number of PCR's in 2002 was lower than in 2001 (a year with a higher overall incidence of pertussis) the number was higher than in 2000 (1.2-fold). The number of positive cultures decreased in both 2001 and 2002 compared to previous years.

Table 3. Number of B. pertussis strains, detected by culture or PCR in the period 1995-2002 as reported by the 16 regional public health laboratories

Method	1995	1996*	1997**	1998***	1999	2000	2001α	2002
Culture	35	263	101	35	100	16	20	7
PCR	26	172	132	128	325	157	403	187
Unknown	--	81	42	17	20	23	28	21

* 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
α 3 double registered PCR excluded (all 3 both culture and PCR)

3.4 Pertussis deaths

According to the Central Statistics of the Netherlands in 1989-1995 2 deaths due to pertussis were reported. In the period 1996-2002 8 deaths due to pertussis were reported: two in 1996, two in 1997, one in 1998 and three in 1999. For the years 2000, 2001 and 2002 no deaths due to pertussis were reported.

3.5 Notifications by gender in 1993-2000

Table 4 shows the sex distribution of notified cases in the period 1993-2002. In all years there was a lower proportion males than females.

Table 4. Gender distribution of reported cases in 1993-2002

Year	Gender	
	Males	**Females**
1993	42.2%	57.8%
1994	48.9%	51.1%
1995	43.4%	56.6%
1996	44.8%	55.2%
1997	46.7%	53.3%
1998	47.2%	52.8%
1999	45.1%	54.9%
2000	45.2%	54.8%
2001	45.0%	55.0%
2002	44.6%	55.4%

3.6 Age specific incidence

In Table 5 to Table 9 the age-specific incidences of pertussis in the period 1989-2002 according to notifications, positive two-point serology, positive one-point serology, positive two and one-point serology and hospital admissions are given. The 0-year olds are divided in the age categories 0-5 months and 6-11 months, respectively. In 2001 the incidence of notified cases was for all age groups higher than in 2000 with highest increase among ≥5 year olds. In addition the incidence of notified cases in 2001 was higher than in the epidemic year 1999, which was due to the higher incidence among the 6-11 month olds and the 1-4, 5-9 year olds and to a lesser extent the ≥20 year olds. In 2002 the incidence of notified cases for all age-groups was lower than in 2001. Interestingly, although the total incidence in 2002 was similar to 2000 the incidence in the age category 1- years was lower in 2002 compared to 2000 (respectively, 82.2 and 124.8). This effect is probably due to the introduction of a booster vaccination in 2002 at the age of 3-4 years. In 2002 the incidence calculated from notified cases among 1-4 year olds, is a factor 2.6 lower than in the previous year. This is mainly due to the decreasing incidence among 3-4 year olds (see also Figure 3)

Table 5. Age-specific incidence of pertussis per 100,000 as estimated from notifications in the period 1989-2002

Age	*1989-1995*	1996	1997	1998	1999	2000	2001	2002
0-5 months	-	219.2	123.0	107.1	213.3	134.8	205.7	118.6
6-11 months	-	101.7	95.7	32.2	94.1	74.3	125.5	75.5
0 yr	36.9	160.4	112.0	69.7	153.7	104.6	165.6	97.0
1-4 yr	12.0	152.4	90.1	91.9	186.4	124.8	211.1	82.2
5-9 yr	12.6	162.0	84.0	93.4	254.0	145.8	302.4	155.7
10-14 yr	3.8	57.1	33.0	28.7	94.5	45.1	93.3	62.1
15-19 yr	0.5	10.3	8.4	5.4	28.1	14.1	27.3	25.4
≥ 20 yr	0.3	4.4	4.6	3.5	12.8	8.4	14.9	10.1
Total	2.3	27.1	17.1	16.0	44.2	26.6	50.2	28.0

In Table 6-8 the age-specific incidences of positive serology are given. In addition, coverage as compared to 1996 of serologic data from LIS-RIVM is given.
For all age-groups the incidence of positive serology in general was higher in 2001 than in 2000 but lower than in 1999, although the latter does not hold for the incidence of positive two-point serology among 15-19 year olds and positive one-point serology among ≥ 20 year olds. With the interpretation of differences the decreasing coverage of serology has to be taken into account.
In 2002, the age-specific incidence of both positive two- and one-point serology was lower than in 2001, with the highest decrease among the 1-4 year olds (factor 3.1). In comparison with 2000 the total incidence of positive serology was lower in 2002, but among the ≥10-year-olds the incidence for one-point serology in 2002 was higher. In general, as written before, for the notifications a shift towards the older age groups can be observed.

Table 6. Age-specific incidence of pertussis per 100,000 as estimated from positive two-point serology in the period 1989-2002 (not corrected for decreasing coverage)

Age	***1989-1995***	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**
Estimated coverage of data compared to 1996	*100%*	*100%*	*94%*	*77%*	*72%*	*60%*	*55%*	*51%*
0-5 months	*67.6*	134.2	72.5	34.3	53.1	32.7	35.7	13.7
6-11 months	*18.8*	37.7	35.7	7.3	16.0	10.9	13.5	5.9
0 yr	*43.2*	85.6	54.1	20.8	34.6	21.8	24.6	9.8
1-4 yr	*12.2*	74.8	33.4	18.3	28.7	16.1	21.4	6.8
5-9 yr	*10.2*	76.7	32.8	19.2	34.5	16.8	30.4	16.6
10-14 yr	*3.2*	22.0	9.9	5.6	10.1	4.6	8.1	3.2
15-19 yr	*0.3*	3.6	1.9	0.9	1.4	1.0	1.5	1.2
≥ 20 yr	*0.1*	1.4	1.1	0.3	1.0	0.6	0.7	0.5
Total	*2.1*	12.2	5.9	3.0	5.4	2.9	4.4	2.1

Table 7. Age-specific incidence of pertussis per 100,000 as estimated from positive one-point serology in the period 1989-2002 (not corrected for decreasing coverage)

Age	*1989-1995*	1996	1997	1998	1999	2000	2001	2002
Estimated coverage of data compared to 1996	*100%*	*100%*	*94%*	*77%*	*72%*	*60%*	*55%*	*51%*
0-5 months	*50.7*	159.4	102.0	79.0	112.2	39.7	55.0	25.5
6-11 months	*32.8*	138.4	113.6	48.9	71.1	40.6	59.9	22.5
0 yr	*41.8*	148.9	107.8	63.9	91.6	40.2	57.5	24.0
1-4 yr	*42.1*	281.2	149.8	144.8	185.1	109.1	148.1	50.0
5-9 yr	*47.9*	295.3	124.9	106.9	187.4	100.6	173.2	76.5
10-14 yr	*21.1*	110.9	52.4	36.7	67.9	32.8	62.1	37.3
15-19 yr	*3.4*	24.8	15.9	8.1	17.9	11.2	15.9	16.8
≥ 20 yr	*1.5*	10.8	7.5	4.5	9.1	5.2	9.4	6.0
Total	*8.2*	50.7	26.4	20.7	34.1	18.8	30.7	15.4

Table 8. Age-specific incidence of pertussis per 100,000 as estimated from positive one-point serology and positive two-point serology in the period 1989-2002 (not corrected for decreasing coverage)

Age	*1989-1995*	1996	1997	1998	1999	2000	2001	2002
Estimated coverage of data compared to 1996	*100%*	*100%*	*94%*	*77%*	*72%*	*60%*	*55%*	*51%*
0-5 months	*118.3*	293.6	174.5	113.4	165.2	72.4	90.8	39.2
6-11 months	*51.7*	176.2	149.3	56.2	87.1	51.5	73.4	28.4
0 yr	*85.0*	234.9	161.9	84.8	126.2	62.0	82.1	33.8
1-4 yr	*54.2*	356.0	183.2	163.1	213.8	125.2	169.5	56.7
5-9 yr	*58.1*	372.0	157.8	126.1	221.9	117.4	203.7	93.1
10-14 yr	*24.3*	133.0	62.3	42.3	78.0	37.4	70.2	40.5
15-19 yr	*3.7*	28.4	17.8	9.0	19.3	12.2	17.4	17.9
≥ 20 yr	*1.7*	12.2	8.6	4.8	10.1	5.8	10.1	6.5
Total	*10.3*	62.9	32.3	23.7	39.5	21.7	35.1	17.5

In Table 9 it can be seen that the incidence of hospitalised cases in 2001 is higher than in 2000 for all age groups except for the ≥10 year-olds for whom a slightly lower incidence was observed and for the 1-4 year olds who had a similar incidence. In comparison with 1999 the total incidence of hospitalised cases in 2001 is lower. However, the incidence for the 6-11 month olds and the 5-9 year olds was higher. In 2002 the total incidence of hospitalised cases had decreased again compared to 2001 and was similar to the incidence in 2000.

However, compared to 2000 the incidence for the 6-11 month olds and the 5-9 year olds had almost doubled, while the incidence for the 1-4 year-olds decreased.

Table 9. Age-specific incidence of pertussis per 100,000 as estimated from hospital admissions in the period 1989-2002

Age	***1989-1995***	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**
0-5 months	-	-	247.1	176.8	354.5	164.6	267.5	164.7
6-11 months	-	-	54.7	22.9	24.0	18.8	39.6	30.4
0 yr	*66.2*	184.0	150.9	99.8	189.3	91.7	153.6	97.5
1-4 yr	*4.9*	11.6	12.4	7.1	10.3	4.9	5.0	3.1
5-9 yr	*1.3*	4.9	3.4	2.2	2.5	1.4	3.3	2.7
10-14 yr	*0.4*	1.2	0.5	0.4	1.2	0.5	0.1	0.4
15-19 yr	*<0.1*	0.3	0	0.1	0.2	0	0.0	0.0
≥ 20 yr	*<0.1*	<0.1	0.1	0.1	0.1	0.05	0.0	0.0
Total	*1.2*	3.3	2.8	1.8	3.2	1.6	2.5	1.6

In Figure 3 to Figure 5 the incidences per year of age calculated from notifications, positive two-point serology and positive one-point serology are presented for the years 1999 to 2002. In 1999 and 2000 the peak incidence according to notifications, positive two-point serology, and positive one-point serology occurred among 4-years-olds. In 2001 the peak incidences for positive two- and one-point serology was also observed among 4 year olds, while the peak incidence for notified cases was seen among 5 year olds. In contrast, in 2002 – the first year the effect of the introduction of a booster-vaccination at 4 years of age can possibly be seen- the peak incidences according to notifications, positive two- and positive one-point serology were observed for the 6, 7 and 5 year olds, respectively. In general, it can be said that the 'peak age' has increased in the last two years with a dip among the 3-4 year olds as a result of the introduction of a booster-vaccination in 2002. For all sources this dip can be observed which emphasises the positive effect of the introduction of a booster-vaccination for at least the targeted age group.

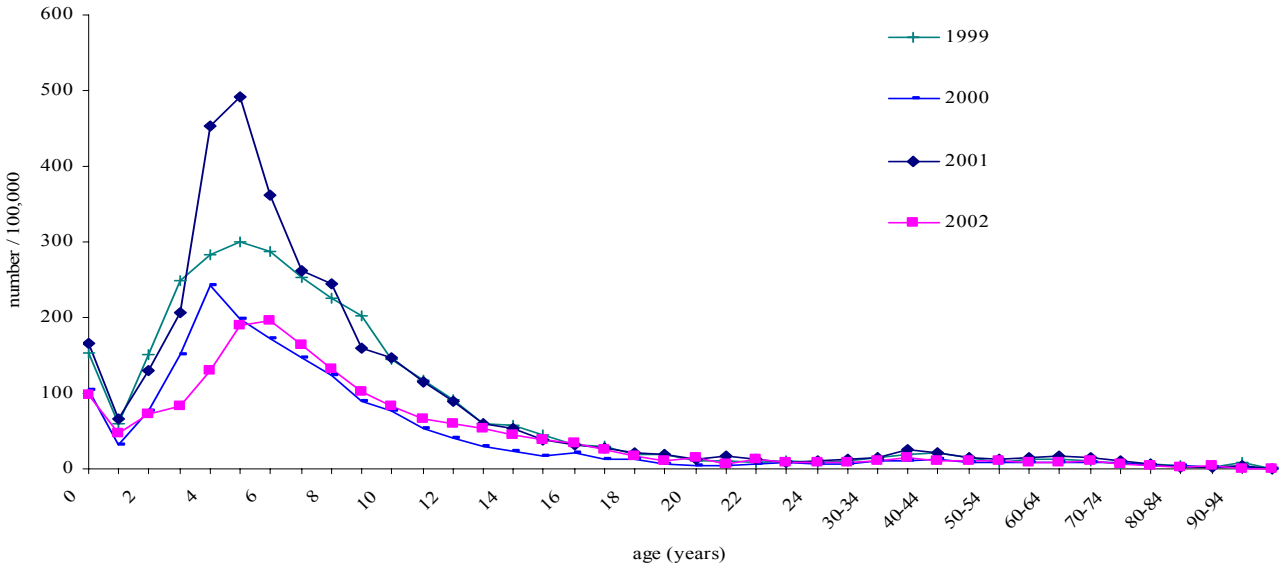


Figure 3 Age-specific incidence of pertussis in 1999-2002 according to notifications, age in years

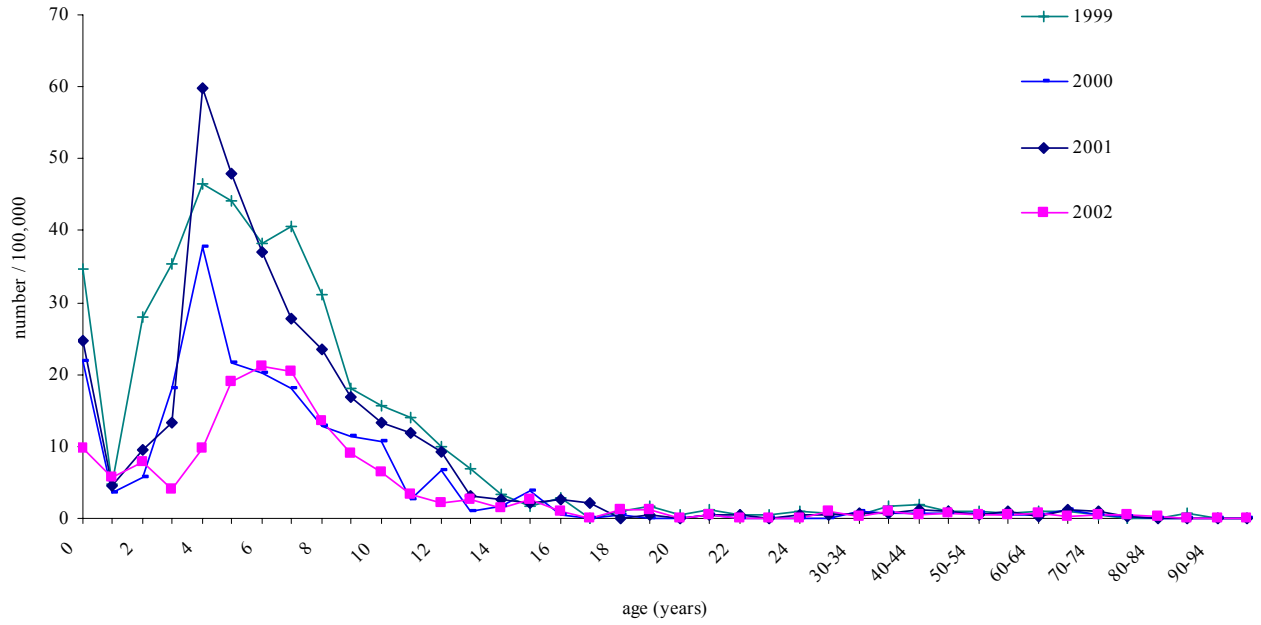


Figure 4. Age-specific incidence of pertussis in 1999-2002 according to positive two-point serology, age in years

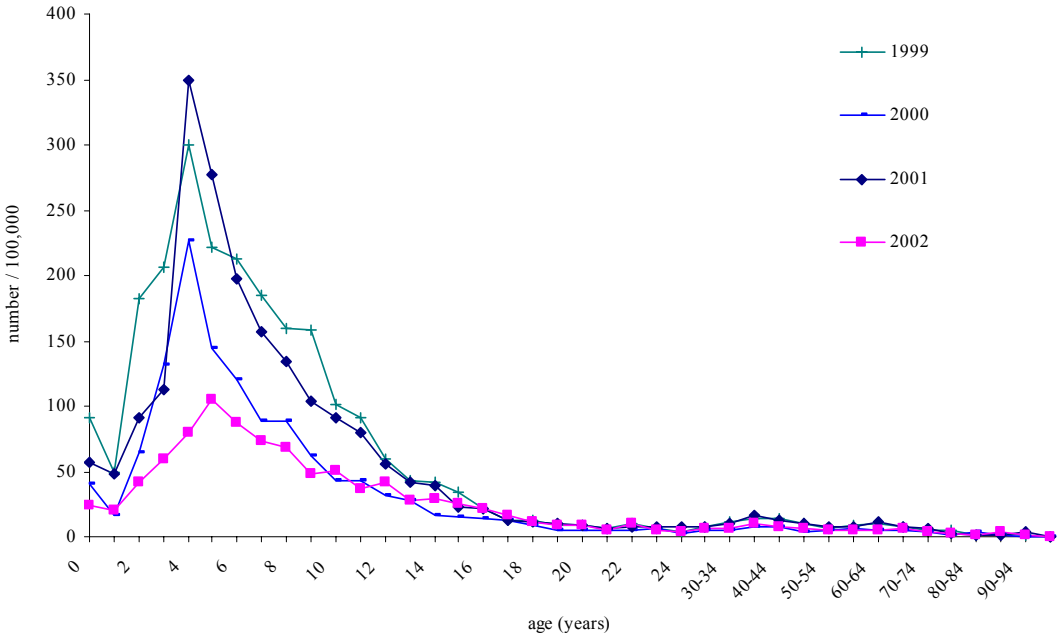


Figure 5. Age-specific incidence of pertussis in 1999-2002 according to positive one-point serology, age in years.

Figure 6 shows the age-specific incidence of patients hospitalised due to pertussis in 2001 (dark bars) and 2002 (white bars). In the right corner the number of patients younger than 1 year old is given by age in months. As in previous years, the highest incidence was observed for the less than 1-year-olds. In comparison with 2000 the incidence of hospitalised cases in 2001 was higher for all age categories, except for the 3-year-olds where the incidence had decreased with a factor 2.0. In 2002 the overall incidence of hospitalised cases was equal to the incidence of hospitalised cases in 2000. However, the incidence among both 3- and 4-year- olds had decreased with a factor 2.6, while the incidence among the 5 year olds had increased with a factor 2.6 compared to 2000. In comparison with 2001, the overall incidence of hospitalised cases in 2002 was lower. Again, the highest decrease was observed among the 4 year-olds: the incidence among this age group decreased with a factor 2.8.

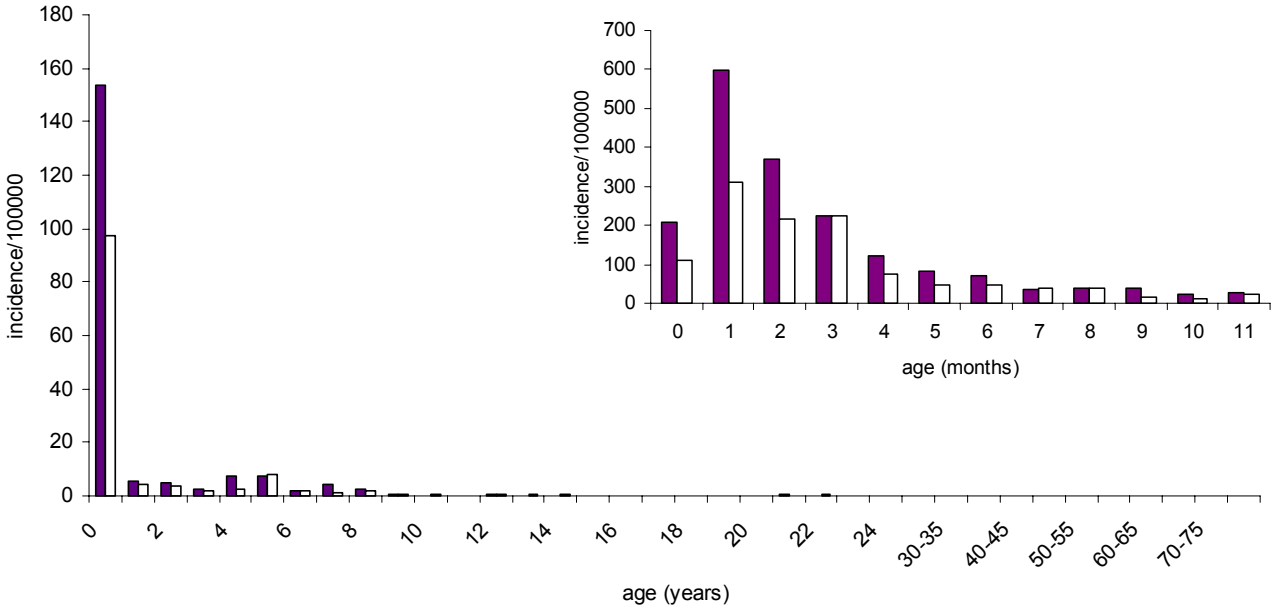


Figure 6. Age-specific incidence according to hospital admissions 2001(dark bars) and 2002 (white bars), age in years and months (children less than 1 year, see right corner).

3.7 Proportional age distributions

In Figure 7 to Figure 10 the proportional age distributions for notifications, positive two-point serology, positive one-point serology, and hospital admissions in the period 1993-2002 are shown. For both notifications and serology a trend towards the older age groups can be seen. Although the percentages notified cases aged 0-year remained stable the last 5 years, the percentage 5-9 year olds and >19 year olds increased. The same trend can be observed for the age distribution of positive-two and positive one-point serology: here also the contribution of the 5-9, 10-14 and >19 age groups has increased. For both the notifications and positive-serology the percentage 1-4 year olds decreased.
Regarding hospitalisations (Figure 10) the percentage hospitalised patients aged 1-4 years old also decreased in recent years, while the percentage 5-9 year olds increased.
In 2002 76% of patients admitted to the hospital were younger than 1 year. Comparatively, this percentage was 68% in 1998, 74 % in 1999, 75% in 2000 and 80% in 2001. Since January 1st 1999, the vaccination schedule has been advanced and nowadays children are vaccinated at 2, 3, 4 and 11 months of age. The percentage of hospitalisations affecting children below the age of 2 months -i.e. too young to be vaccinated- increased slightly in the period 1999-2002 compared to the years before and amounted 21% in 1997, 25% in 1998, 29% in 1999, 30% in 2000, 35% in 2001 and 28% in 2002.

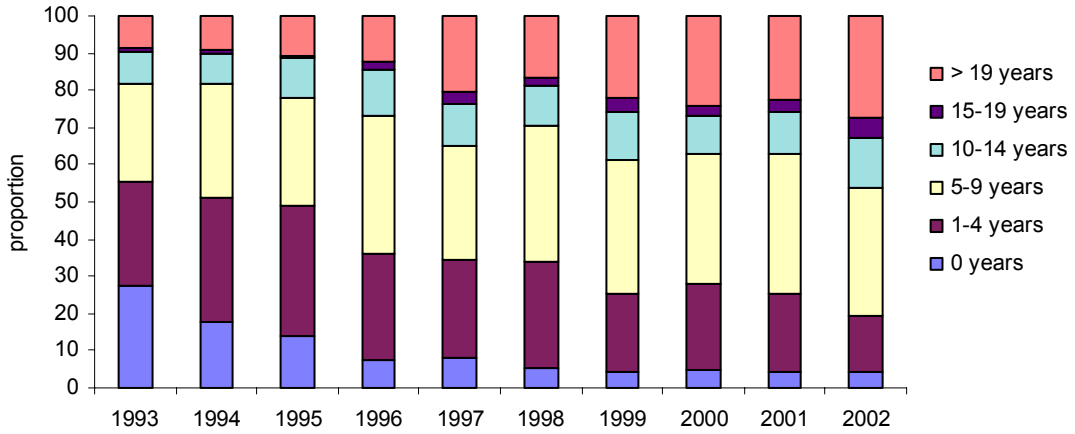


Figure 7. Proportional age distribution according to notifications due to pertussis in 1993-2000.

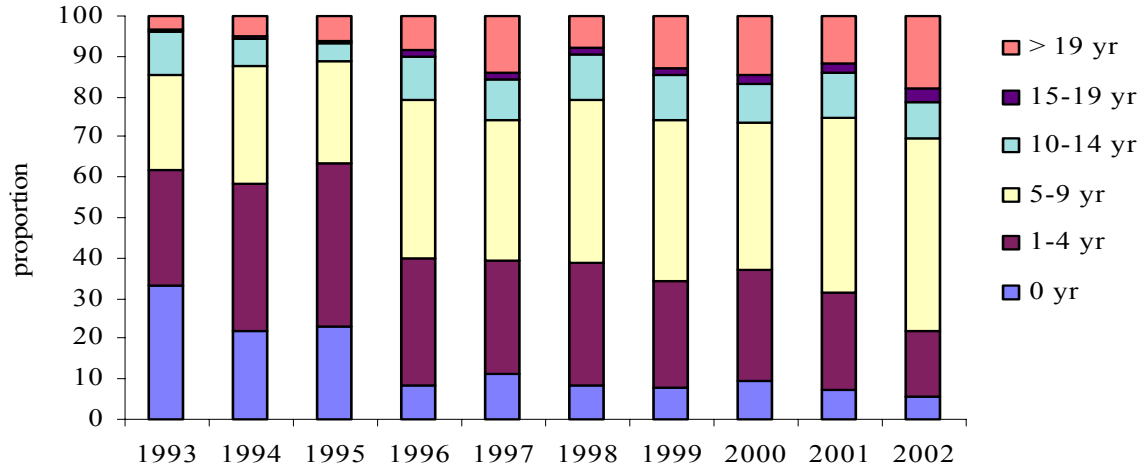


Figure 8. Proportional age distribution according to positive two-point serology for pertussis in 1993-2002

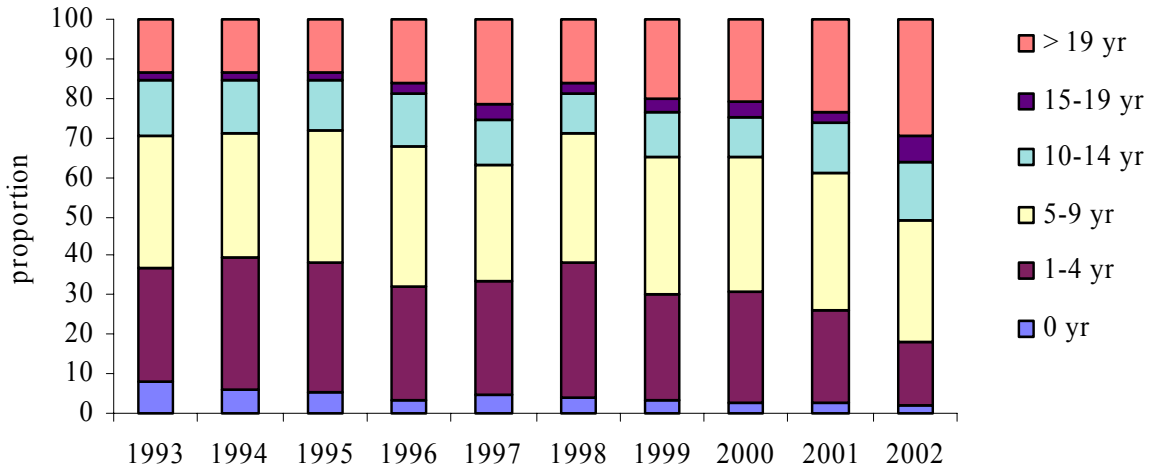


Figure 9. Proportional age distribution according to positive one-point serology for pertussis in 1993-2002

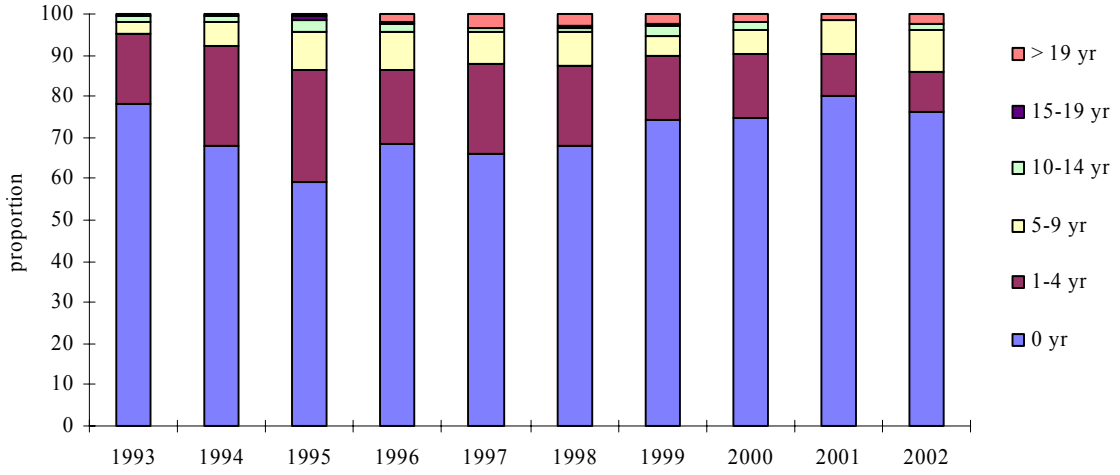


Figure 10. Proportional age distribution according to hospital admissions due to pertussis in 1993-2002

3.8 Notifications by vaccination status and vaccine efficacy

Table 10 and Table 11, respectively, show the absolute number of reported cases in 2001 and 2002 (by first day of illness) according to their vaccination status (vaccinated, unvaccinated and unknown/missing) and their age in years. In the final column estimated vaccine efficacy is given. Table 12 shows the estimated vaccine efficacy by age-year (1-9 years) and Table 13 shows the estimated vaccine efficacy by age-group (1-4 year olds and 5-9 year olds) with the 95 confidence-interval in the period 1993-2002.

Vaccine efficacy is calculated with the screening method (see appendix 4). For some ages and age groups the proportion of vaccinated individuals exceeded the estimated vaccine coverage of the population (96%). Therefore, the vaccine efficacy could not be estimated (illustrated by '–'). However, an increased proportion of vaccinated individuals indicates a lower vaccine efficacy.
As in the last five years vaccine efficacy in 2001 and 2002 was highest for the 1-year-olds and decreased with age. Among the 1-year-olds the efficacy was higher than in the epidemic years 1996-1997 (Table 12). Although the vaccine efficacy for the 1-4 year olds in 2001 and 2002, as well as in 1999-2000, was still lower than before the epidemic years 1996-1997, the estimated vaccine-efficacy for this age-group has been increasing in recent years. However, for 2002 an effect of the booster vaccination to 4-year-olds (given in the year that the child turns 4) could not be excluded. Excluding in 2002 3.5–4-year-olds (who could have received a booster) resulted in estimated vaccine-efficacies of 11% for 3-3.5-year-olds and 29% for 1-3.5-year-olds. These estimates are still slightly higher compared to previous years.

However, it has to be mentioned that estimating vaccine efficacy by the screening method is problematic and results must be interpreted cautiously. Furthermore, as a result of small numbers the confident intervals are wide (Table 13).

*Table 10. Absolute number of reported cases aged 1-9 years in 2001 according to vaccination status and year of age, and estimation for vaccine efficacy**

	vaccinated	**unvaccinated**	**Vaccination status unknown or missing**	**% vaccinated**	**estimated vaccine-efficacy**
1 year	105	16	10	86.8	72.6%
2 years	220	17	18	92.8	46.3%
3 years	365	15	18	96.1	-
4 years	789	27	57	96.7	-
5 years	867	18	66	98.0	-
6 years	654	13	51	98.1	-
7 years	461	9	47	98.1	-
8 years	435	8	45	98.2	-
9 years	286	3	36	99.0	-

* 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 2002 according to vaccination status and year of age, and estimation for vaccine-efficacy **

	vaccinated	unvaccinated	Vaccination status unknown or missing	% vaccinated	estimated vaccine-efficacy
1 year	81	9	2	90.0	62.5%
2 years	127	9	9	93.4	41.0%
3 years	143	13	5	91.7	54.0%
4 years	233	9	12	96.3	-
5 years	330	11	24	96.8	-
6 years	358	7	11	98.1	-
7 years	306	4	15	98.7	-
8 years	248	3	11	98.8	-
9 years	192	3	9	98.5	-

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

*Table 12. Estimated vaccine efficacy by age year (1-9 years) and age group (1-4 years and 5-9 years) in the years 1993-2002**

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
1 year	94%	77%	91%	31%	29%	38%	63%	78%	73%	63%
2 years	92%	58%	42%	63%	-	32%	22%	52%	46%	41%
3 years	94%	79%	59%	38%	-	9%	-	-	-	54%
4 years	85%	76%	70%	-	-	-	7%	-	-	-
5 years	65%	84%	29%	12%	-	-	-	19%	-	-
6 years	84%	61%	33%	21%	-	-	-	-	-	-
7 years	94%	50%	20%	40%	-	-	-	-	-	-
8 years	93%	81%	-	-	-	8%	-	-	-	-
9 years	17%	75%	72%	-	-	-	-	-	-	-

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

*Table 13. Estimated vaccine efficacy (95% CI) by age-group (1-4 years and 5-9 years) in the years 1993-2002**

	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
1-4 years (CI)	96% (93↔97)	79% (69↔86)	71% (47↔84)	51% (36↔62)	-	17% (-18↔41)	17% (-7↔35)	10% (-23↔35)	18% (-4↔35)	39% (16↔56)
5-9 years (CI)	86% (78↔92)	72% (56↔83)	61% (22↔80)	31% (11↔47)	-	-	-	-	-	-

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

3.9 Geographical distribution notifications 2001 and 2002

In Figure 11 respectively Figure 12 the geographical distribution of pertussis according to notifications in 2001 and 2002 per quarter and per Municipal Health Centre (MHC) is given. The maps in both figures show that the pertussis cases are widespread. From the dark colours it can be concluded that the incidence according to notifications is much higher in 2001 than in 2002. The highest incidences were reported in the second half of 2001 and after the second quarter of 2002 the incidence had decreased again in most areas.

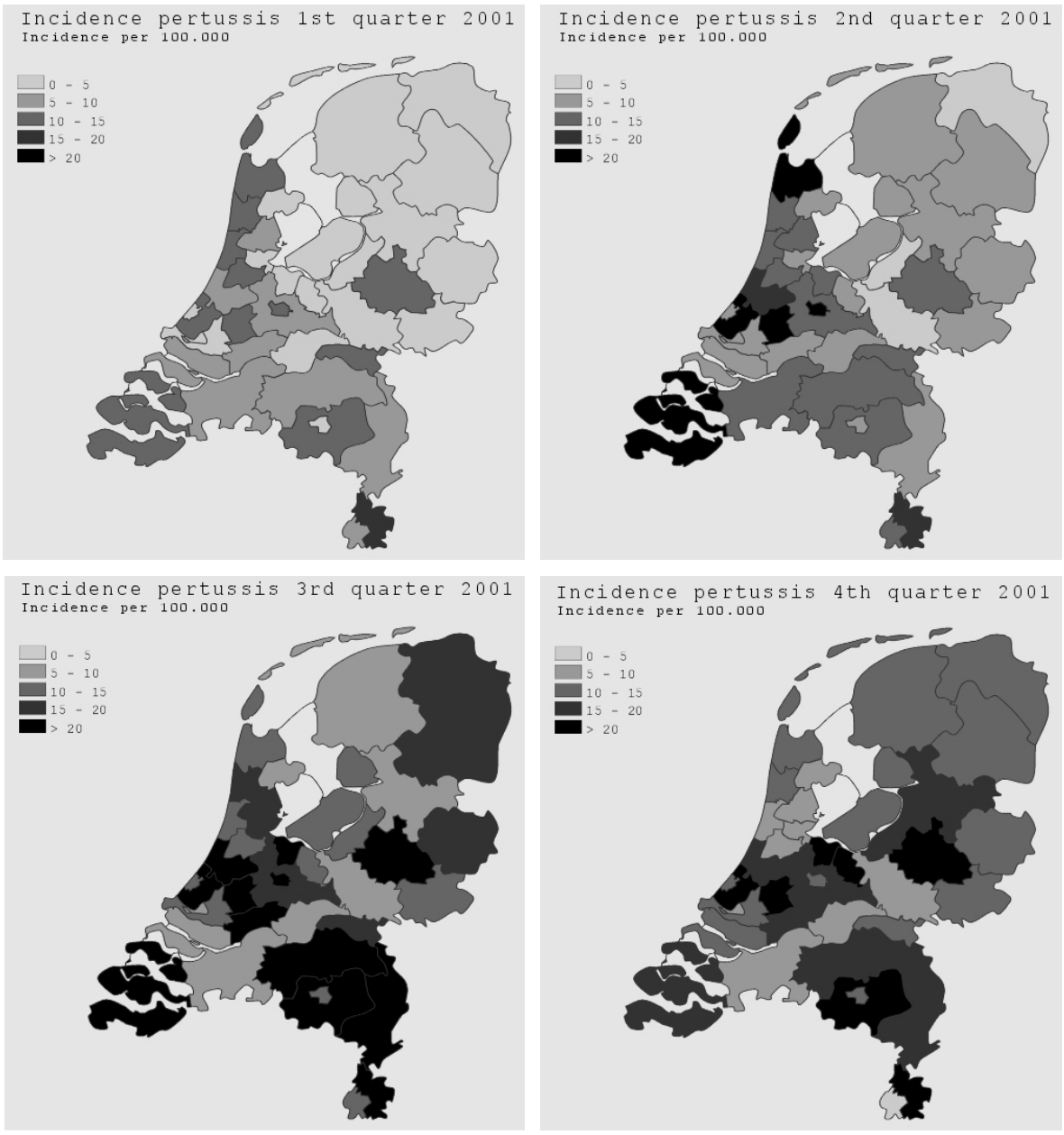


Figure 11. Geographical distribution according to notifications in 2001 per quarter per MHC.

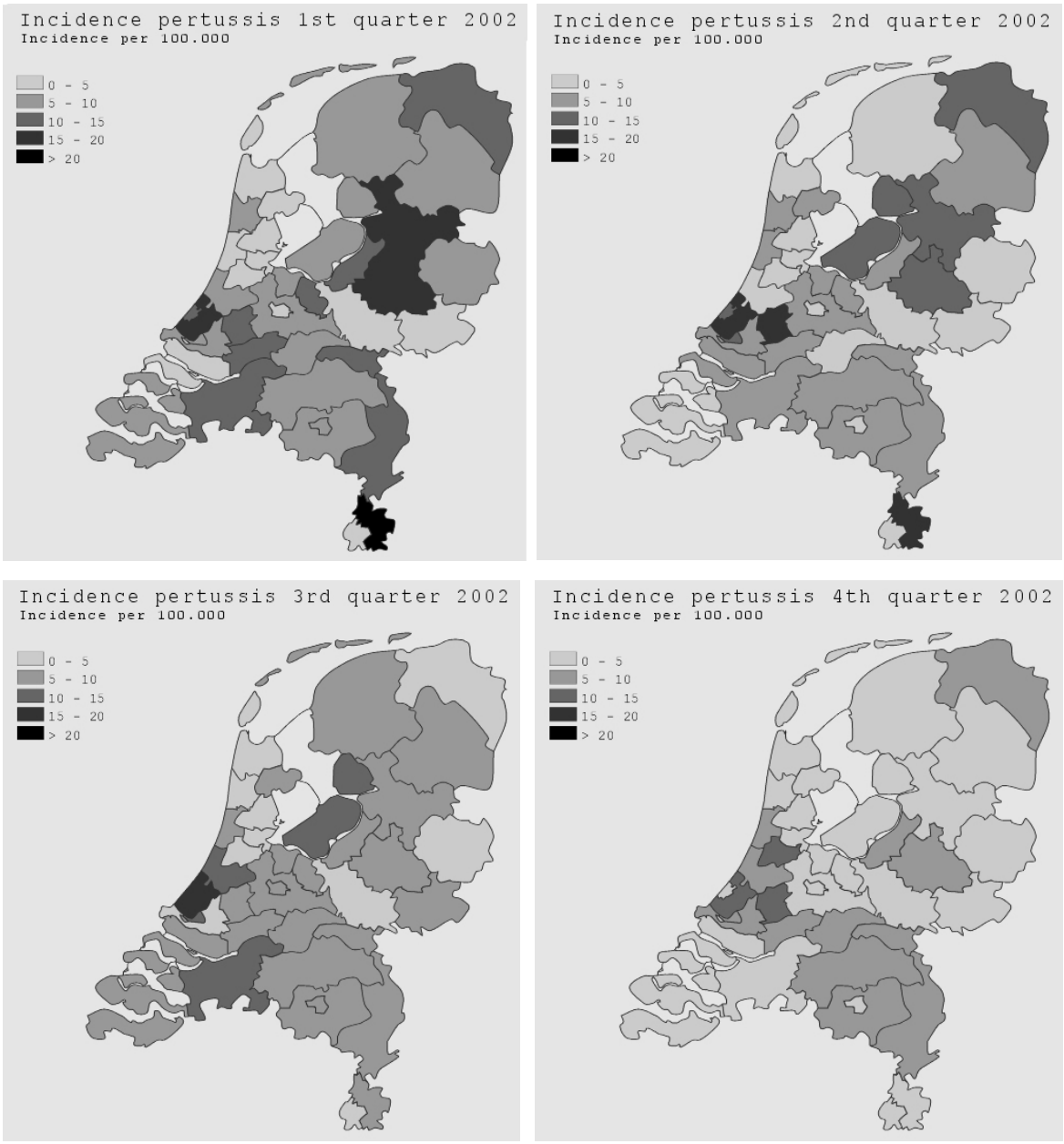


Figure 12. Geographical distribution according to notifications in 2002 per quarter per MHC.

4 Paediatric surveillance

In Table 14 (2001 and 2002 combined) and Appendix 5 (2001 and 2002 separately) the results of the paediatric surveillance are shown. Questionnaire data by age-group were available for 247 hospitalised cases aged 0-15 years (154 in 2001; 93 in 2002), which was 38% of the total number of hospitalisations for pertussis of children aged 0-15 years in that period according to the national registry of hospital admissions. Gender distribution was similar for both sources. Median length of hospital stay was longer according to the paediatric surveillance than according to the hospital registration for 0-15 year olds (8 vs. 6 days in 2001 and 7 vs. 4 days in 2002, respectively). In 2001, according to both paediatric surveillance and hospital registration the median age was 2 months. In 2002, median age of hospitalised cases was 2 months according to the paediatric surveillance and 3 months according to the hospital registration.

Most hospitalised cases in the paediatric surveillance were younger than one year of age (86% in 2001 and 74% in 2002) with most of these cases occurring among infants less than three months of age, i.e. too young to be vaccinated. In 2001/2002 the percentage of children younger than 3 months was almost equal to the percentage younger than 3 months in 1999/2000 (62% in 2001/2002 vs. 60% in 1999/2000).

Concerning vaccination status the percentage of vaccinated persons (according to reported vaccination status) has increased significantly ($p=0.002$) in 2001/2002 (48%) compared to 1999/2000 (34%). However, in 2001/2002 the vaccination status is more often based on the reporting of the paediatrician and therefore less reliable since this is not confirmed by the health care administration.

Cases older than 3-5 months were mostly incompletely vaccinated while those aged at least 6 months of age were almost all vaccinated. As shown in Table 10 symptoms as coughing, paroxysmal cough and vomiting were reported for most hospitalised cases in all age groups. This was also seen in previous years. Whooping was less often observed among the younger children compared to older age groups. Fever was more frequently reported in ‘older’ age groups, however it was in general less frequently reported than in 1999/2000.

Most complications were rare, but the complications that were reported, occurred less frequently with increasing age (cyanosis, administration of oxygen). Apnoea occurred among the less than 1-year-olds, but not among the older children. However, pneumonia was reported more frequently among the oldest age group (5-15 years). No deaths were reported in 2001/2002.

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

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

Table 14. Characteristics of hospitalised cases reported in the paediatric study in 2001 and 2002

Hospitalised cases									
	0 mnth N=52 21%	1 mnth N=57 23%	2 mnths N=45 18%	3-5 mnths N=28 11%	6-11 mnths N=20 8%	1-2 yrs N=11 4%	3-4 yrs N=5 2%	5-15 yrs N=29 12%	Total N=247 100%
Registered vaccination status*									
Vaccinated	0%	0%	0%	11%	20%	64%	100%	62%	15%
Incompletely vaccinated	0%	4%	31%	43%	5%	0%	0%	0%	11%
Unvaccinated	100%	96%	0%	0%	0%	0%	0%	0%	43%
Unknown	0%	0%	71%	46%	75%	36%	0%	38%	30%
Reported vaccination status**									
Vaccinated	0%	4%	58%	93%	85%	100%	100%	86%	45%
Unvaccinated	100%	96%	36%	4%	10%	0%	0%	7%	52%
Unknown	0%	0%	7%	4%	5%	0%	0%	7%	3%
Symptoms									
Coughing	98%	98%	100%	100%	95%	100%	100%	100%	99%
Paroxysmal coughing	65%	54%	69%	68%	85%	55%	40%	62%	64%
Whooping	17%	12%	13%	7%	10%	18%	40%	24%	15%
Vomiting	67%	54%	53%	61%	55%	55%	60%	69%	60%
Fever	13%	12%	9%	11%	25%	36%	40%	48%	19%
Complications									
Death	0%	0%	0%	0%	0%	0%	0%	0%	0%
Collapse	12%	7%	9%	14%	10%	0%	0%	7%	9%
Convulsion	0%	0%	2%	0%	0%	0%	0%	0%	0.4%
Encephalopathy	4%	0%	0%	0%	0%	0%	0%	0%	0.8%
Apnoea	29%	12%	16%	11%	20%	0%	0%	0%	15%
Pneumonia	2%	4%	2%	4%	0%	18%	20%	7%	4%
Cyanosis	73%	68%	64%	68%	55%	27%	0%	21%	59%
Artificial respiration	8%	2%	2%	0%	0%	18%	0%	0%	3%
Administration of oxygen	67%	49%	56%	21%	30%	27%	0%	7%	43%

Other									
Median days hospitalised	14 (1-41)	8 (1-25)	8 (2-54)	7 (1-47)	3.5 (2-27)	2 (1-19)	4 (0-11)	4 (1-16)	8 (0-54)
Median time onset disease and hospital admission	7 (0-60)	8 (0-45)	10 (1-41)	8(1-47)	10 (3-95)	13 (2-52)	24 (9-70)	19 (0-94)	10 (1-95)
Laboratory diagnosis									
Positive PCR/culture	61%	53%	58%	61%	50%	55%	0%	21%	51%
Positive serology	19%	19%	24%	32%	40%	45%	100%	76%	33%
Other***	19%	28%	18%	7%	10%	0%	0%	3%	16%

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

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

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

5 Discussion

5.1 Trends in pertussis incidence according to surveillance sources

Surveillance data
Surveillance data have shown an increase in the incidence of pertussis every two to three years in the Netherlands in recent years, with the years 1996, 1999 and 2001 as epidemic years. The reported incidence of notified cases was highest in 2001, and compared to the epidemic year 1999, the annual incidence calculated from notifications increased with a factor 1.2. However, the annual incidence calculated from positive two- and positive one-point serology and hospital admissions had decreased in 2001 with the factors 0.8, 0.9 and 0.8 respectively, when compared to 1999. After the peak in 2001 the incidence calculated from all surveillance sources was again lower in 2002. In 2002 a dip in the incidence among 3 and 4 year olds was shown. Furthermore, on the one hand as a result of this dip, but on the other hand also independently of the dip, the proportional age distributions showed a shift towards older age groups in 2001 and 2002, compared to previous years. However, hospitalisations occurred mainly among young unvaccinated infants for which the paediatric surveillance showed that among hospitalised cases the disease was most severe, with occasionally complications in the youngest age group.

Interpretation of surveillance data
Although various surveillance sources are relied on to monitor the epidemiology of pertussis in the Netherlands, changes in surveillance sources could have been involved in the trends observed in recent years. These changes should be taken into account when interpreting the observed trends.
Firstly, positive one-point serology has been formally accepted as laboratory confirmation for notification since 1997. This resulted in a less rigid case definition and consequently a larger part of pertussis cases will have been recognised and/or reported since that time. In the period 1993-1998 it was possible to link the database containing positive serology with the notification database. Probably as a result of the increased alertness after the pertussis epidemic in 1996-1997 the proportion of cases with positive serology increased (independently from the increased reporting due to inclusion of positive one-point serology in the notifications). However, it seems likely that since 1998 the alertness has not increased further and has not had large impact on the case-reporting rate. It should be mentioned that in general reporting is not complete thus, the number of notified cases does not reflect the true incidence of (symptomatic) pertussis in the Netherlands. The latter can be derived from comparing the notified cases with the number of patients consulting a GP due to pertussis as is registered in the NIVEL's Continuous Morbidity Registration Centres (CMR sentinel stations). In 2002 according to the CMR 54 persons were reported by the GP's connected to the CMR. This corresponds to an incidence of 40/100000 and consequently the coverage of

the notifications amounts 70%. In 2001 the incidence according to the CMR amounted 120/100000 and therefore the coverage of the notifications was 42%.
Furthermore, the development and implementation of the electronic notification system (OSIRIS) in 2002 has simplified the notification of cases by the MHS to the Health Care Inspectorate and although the notification rate will not have increased, OSIRIS will have contributed to more completeness of data in the past year.
A highly complicating factor is that, many laboratories, including at least three large regional public health laboratories, have started to perform pertussis-serology with commercial available assays themselves since 1998. Before, only one laboratory (LIS-RIVM) performed serology for the whole country. Thus, the population coverage of serological surveillance of pertussis has decreased (till about 50%) and therefore the incidence based on positive serology will have been underestimated compared to the period before 1998. However, when we correct for decreasing coverage of serology the number of positive serology exceeds the number of notified cases in 1996 (i.e. before the formal acceptance of one-point serology in the notification criteria), while in more recent years both sources show more similar numbers. With respect to the decreasing serology coverage, it should also be noticed that PCR is applied more generally as method of diagnosis (see 3.3), especially among young children. This could both have partly 'replaced' serology-diagnosis or increased the number of pertussis diagnoses. However, the numbers of PCR compared to positive serology are too small to have had a large impact on trends in positive serology.

We assume that surveillance based on hospital admissions is less sensitive to these changes over time. Thus, changes in case reporting or changes in data on positive serology are likely to reflect true changes if they are accompanied by similar trends in hospital admissions.
In 2002 the incidence of hospitalised cases was lower than in 2001 and equal to the incidence in 2000. These changes in hospital admissions are consistent with the increase of the incidence of pertussis every 2 a 3 years as seen in the other surveillance sources.

Taking all the above into account in the interpretation of the surveillance data, the incidence of pertussis is still at a higher level compared to the period before the pertussis epidemic in 1996/97. In contrast to the period 1989-1995 (with peaks in 1989/90 and 1993/94, i.e. every 4 years) epidemic peaks seem to occur every 2-3 years.

5.2 Effect of vaccination changes

The surveillance data reflect the recent changes in the vaccination schedule. Presumably, as a result of the introduction of the booster-vaccination at the age of four years from November 2001 onwards, in all surveillance sources a decrease in pertussis incidence was observed among the 3-4 year olds compared to previous years (3 years old are affected since vaccination is given in the year the child turns 4). Besides, an increase in incidence towards older age groups was observed for the proportional and absolute age-distributions in 2002,

compared to previous years. Apparently, the introduction of a booster-vaccination on the age of four years has resulted in a decrease in the incidence of pertussis among the target age group. Long-term surveillance will be necessary to provide insight into the effect of this booster vaccination on the disease frequency among the population at large.
Long-term surveillance might also reveal the effect of the advance of the vaccine-schedule, which was introduced in 1999. In the current surveillance data we do not see a clear effect of the advanced administration of the first vaccination.
In addition to the above-mentioned positive effects of changes in the vaccine strategy, an increasing trend in vaccine-efficacy, as calculated with the screenings method, was observed particularly for the 1-year-olds from 1997 up to 2002. The estimated vaccine efficacy for the 1-4 year olds is still lower than before the epidemic years 1996 and 1997, but yet higher than in 1996-1998. In the estimated vaccine-efficacy for 1-4-year-olds a positive effect by the booster given at 4-year of age could not be excluded for 2002. However, the higher estimated vaccine-efficacy for 1-year-olds since 1999 as well as the estimations for 1-3,5 year-olds (i.e. excluding those who might have had a booster dose) indicates that estimated vaccine – efficacy has indeed increased. The most likely explanation is the introduction in 1997 of the whole cell vaccine with a higher content of pertussis toxin.
Still the interpretation of the estimated vaccine efficacy remains difficult. Therefore, we would like to stress that presented vaccine-efficacies should not be interpreted as ‘true’ absolute efficacies. They are rather meant to study trends in vaccine-efficacy estimations. Furthermore, some factors might have influenced calculations of vaccine-efficacy in this report. Firstly, vaccination status is calculated from the reported vaccination status and not verified by the number of doses as reported by the registration of health care administrations. Thus, some data might be incorrect. A small change in the number of vaccinated patients can result in a large change in vaccine efficacy estimates. This uncertainty is illustrated by the wide confident-intervals in Table 13. Furthermore, since it was temporarily impossible to distinguish between complete and incomplete vaccinated in 1999, it is possible that people with one or two vaccinations are classified as ‘vaccinated (for age)’. As a result, the percentage completely vaccinated persons in 1999 might be overestimated and thereby the vaccine efficacy underestimated. Moreover, previous estimates predict a lower vaccine-efficacy for cases with positive one-point serology (10, 17). Nowadays, almost all notified cases are confirmed by positive one-point serology. Therefore in comparison to period prior to introduction of positive one-point serology in criteria for notifications vaccine-efficacy is likely to be underestimated. Taking all the above mentioned into account, a real increase in vaccine efficacy seems even more plausible.
Thus in conclusion, although the estimations of vaccine-efficacy is still lower than before the epidemic in 1996-97, an increase in the vaccine efficacy seems likely during the last years.

5.3 Further Research

Because of large variation in case definitions and types of laboratory confirmation, comparing numbers of reported cases in different countries is meaningless. However, in agreement with our findings many other developed countries witness a re-emerging of pertussis since the last decade, even countries that have had high vaccination coverage like in the Netherlands for many years. A study conducted in the UK demonstrated that severe pertussis is often under diagnosed and therefore the real incidence of severe pertussis is much higher than observed. (5) In addition, an increase in the number of deaths due to pertussis among young (unvaccinated) infants was seen in the United States in the 1990s. (6) In line with our findings, studies in other countries report an increase in the incidence of (asymptomatic) pertussis among adults and adolescents. (22, 23) Many studies have demonstrated that those age groups are the main source of infection for infants. (24, 25) Experts therefore propose to introduce booster doses of (acellular) pertussis vaccines at older-child or even adult (maternal) age. (26, 27) Estimations of infection frequency with *B.pertussis* (irrespective of clinical course) in the Netherlands have shown that in contrast to clinical reported pertussis cases (as shown in this report) the infection frequency is highest among adolescents and adults. Particularly with the aim to protect young unvaccinated infants, further development of dynamic pertussis models to obtain insight in (most) effective vaccination strategies, such as maternal vaccination, vaccination at birth or cocooning strategy (vaccination of future parents/care-givers) is desirable. Of course these models should be based on valid data concerning pertussis epidemiology in the Netherlands. With prevention of pertussis among infants as focus, information on the most important sources of infection of these infants (e.g. adults, siblings) is a necessary component in these models and this information is nowadays still unavailable for the Netherlands.

In summary:

- During the last years pertussis has remained endemic with a higher incidence compared to the period prior to the epidemic in 1996-1997. Furthermore a peak in the incidence has occurred every 2 à 3 years (1996, 1999, 2001)

- Since 1997 many laboratories have started to perform pertussis serology with commercial available assays themselves. Therefore, the coverage of serology performed by the LIS-RIVM has decreased from 100% in and before 1996 to <50% in 2002

- In 2002, as a result of the introduction of the booster vaccination for 4-year-olds, a decrease in the incidence of pertussis in the targeted age group can be seen, i.e. among 3 and 4 year olds. In the future the effect for the population at large will become clear.

- Probably as a result of the change in the production process of the vaccine (higher protection according to the mouse-model) the vaccine-efficacy among 1 year olds and 1-4 has slightly increased. Although the efficacy is still lower compared with the period prior to the epidemic in 1996-1997, estimations of vaccine-efficacy, based on the screening-method, indicate an increase of vaccine efficacy in recent years.

- Pediatric surveillance confirms that pertussis is still most severe among young, unvaccinated children. However, also vaccinated older children develop classical and long-lasting pertussis.

- More insight in the main sources of infection of young unvaccinated children in the Netherlands is necessary. This is important for the development of future vaccination strategies, such as maternal vaccination, vaccination at birth or the cocooning strategy.

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Appendix 1: Abbreviations

CBS	Centraal Bureau voor Statistiek / Central Statistics Netherlands
CIE	Centrum voor Infectieziekten Epidemiologie / Centre for Infectious Disease 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
MHS	GGD / Municipal Health Service
NSCK	Nederlands Signalerings-Centrum Kindergeneeskunde / Netherlands Paediatric Surveillance Centre
PCR	Polymerase Chain Reaction
RIVM	Rijksinstituut voor Volksgezondheid en Milieu / National Institute for Public Health and the Environment
SAS	Statistical Analysis Computer Program
SIG/Prismant	Stichting Informatievoorziening Gezondheidszorg / Foundation Information Centre of Health Care
SOP	Standard Operating Procedure
VE	Vaccin effectiviteit / Vaccine-efficacy

Appendix 2: Mailing list

1	Inspecteur-Generaal voor de Gezondheidszorg prof. dr. J.H. Kingma
2	Hoofdinspecteur voor de Preventie, Public Health en Rampenbestrijding (PPR) prof. drs. E.W. Roscam Abbing
3	Directeur-Generaal van de Volksgezondheid, drs. N.C. Oudendijk
4	Inspecteur Infectieziekten van de Inspectie Gezondheidszorg, drs. J.K. van Wijngaarden
5	Voorzitter van de Gezondheidsraad, prof. dr. J.A. Knottnerus
6	Secretaris beraadsgroep Infectie en immuniteit, drs. J. Sekhuis
7	voorzitter commissie herziening RVP, prof. dr. E.J. Ruitenberg
8	secretaris commissie herziening RVP, dr. H. Houweling
9	WHO-GPV
10	WHO-EURO
11-12	GGD- Nederland
13-55	Artsen infectieziektenbestrijding van de GGD's
56	Bureau van de Landelijk Coördinatiestructuur Infectieziektenbestrijding
57-73	Streeklaboratoria
74	Nederlands Instituut voor onderzoek van de Gezondheidszorg
75-90	Leden IGZ-infectieziekten overleg RIVM
91	Nationale Vereniging Thuiszorg
92	Nederlandse Vereniging voor Kindergeneeskunde
93	Nederlandse Vereniging voor Infectieziekten, prof.dr.J.van der Meer
94	Nederlandse Vereniging voor Medische Microbiologie, prof. dr. H. Verbrugh
95	dr. F. van Loock, Wetenschappelijk Instituut voor Volksgezondheid - Louis Pasteur, Brussel
96	Statens Seruminstitut, Copenhagen
97	Department of Infectious Disease Epidemiology, Helsinki
98	Réseau National de Santé Publique Hospital National Saint-Maurice, Saint-Maurice
99	Instituto Superiore di Sanita, Communicable Disease Unit, Lab. of Epidemiology and Biostatistics, Rome
100	Instituto Nacional de Saudé, Lisboa
101	Swedish Institute for Infectious Disease Control, Sweden
102	PHLS/Communicable Disease Surveillance Centre, London
103	Centro National de Epidemiologia
104	prof. dr. J. Huisman
105	prof. dr. J. van der Noordaa
106	prof. dr. S.P. Verloove-Vanhorick, TNO-PG
107	dr. H. Bijkerk
108	dr. H. Cohen

109	Nederlands Signalerings Centrum Kindergeneeskunde, dr. R. Rodrigues-Pereira
110	Depot Nederlandse Publicaties en Nederlandse bibliografie
111	Bibliotheek Gezondheidsraad
112	Directie RIVM
113	dr. ir. A.M. Henken, Directeur Volksgezondheid, RIVM
114	labhoofden sector VGZ-RIVM
115	prof. dr. B. van der Zeijst, NVI
116	drs. M. Dijkman, NVI
117	dr. ir. T de Graaf, NVI
118-121	NVI
122-134	Leden kinkhoestdwarsverbandoverleg
135-145	Medewerkers LTR
146-156	Medewerkers LIS
157-167	Medewerkers CIE
168-172	SBC/Communicatie
173	Bibliotheek RIVM
174	Bureau Rapportenregistratie
175-185	Bureau Rapportenbeheer
186-200	Reserve exemplaren

Appendix 3: Case-definition notification

Case-definition for notifications due to pertussis

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

1.1 Anamnestic one or more of the following symptoms:

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

in combination with

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

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

and in combination with

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

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

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

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

Appendix 4: Methods

A 1 Used data

A 1.1 Notification data

Since 1976 notification of pertussis to the Medical Inspectorate of Health is obligatory by law. In 1988 criteria for notification of pertussis were introduced (Appendix I). Before 1988 no case definition was used. In addition, the availability of laboratory diagnostics has influenced the surveillance of notifications. In 1981 and 1984, respectively, IgA an IgG immunoassays became available. For these reasons in this report the pertussis surveillance is limited from 1989 onwards.
For the period of 1989-2001 MHS completed notification cards which were send to the RIVM and there entered in a database (Registration InFectious diseases (RIF) database). From January 2002 onwards it was possible for the MHS to enter the notification into an electronic notification system (OSIRIS) which transported the notification directly into the RIF database.
The RIF database includes age and date of notification. However, only since 1993 the first day of illness, vaccination status, date of birth and place of residence are also included in the database. Since the change in the Infectious Disease Law in 1999, the date of birth is not reported anymore. In the analysis, the distribution of cases over the years for notifications and serological results is based on the first day of illness. Age at first day of illness is calculated with: date of first illness minus date of birth. Since the date of birth is not reported exactly in the notifications from 1999 onwards, the age at first date of illness cannot be assessed in this manner anymore. To estimate the age at first day of illness an approximation of the date of birth was made as followed:
For people older than two years of age only the year of birth is exactly given. The month of birth is equated with the month of notification and the day of birth is set at the first of that month. Age is estimated based on 30th June with the year of birth. For children ≤ 2years, the date of birth is based on the exact birth year and the first day of the exact month of birth. Age is estimated based on the 15th of the month.
With the approximation of the date of birth the age at first day of illness could be estimated. However, for cases for whom the first day of illness was unknown, this date was estimated by subtracting the median duration between first day of illness and date of notification (calculated from the data that were available) from the date of notification. For the period 1989 to 1992- when the date of onset of symptoms was not collected- the date of first illness was estimated by subtracting the median duration between first day of illness and date of notification in 1993/1994.
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 2002 in the analyses. The analysis of vaccine-efficacy was limited to those aged 1-9 years, since 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).

A 1.2 Serological data 1989-2002

A 1.2.1 Immunoassays

Serology consisted of measurement of IgA antibodies against a crude cell-membrane preparation of *B. pertussis* and IgG antibodies against purified pertussis toxin in ELISA's, according to described methods (1,2). Sera were tested in 1:100 and 1:400 dilution's. Antibody-binding activity in patient sera was quantitatively expressed (units per millilitre) relative to the capability in a reference immunoglobulin preparation that had been obtained from convalescent sera of patients with culture-proven pertussis and preserved for long-term use. The reference preparation was arbitrarily defined to contain 100 U/ml each of IgA and IgG antibodies. The whole cell vaccine does not induce an IgA response, while the IgG response against pertussis toxin is either absent or very low and short lived (median IgG level: 1 U/ml before vaccination and 14 E/ml shortly thereafter).
Until April 1997, to prove a recent infection with *Bordetella pertussis* with serology a significant rise in titres in paired sera has to be shown to be in accordance with the criteria for notification. The first serum sample has to be taken as soon as possible after the first day of illness. For individuals less than one year, 1-4 years of age and > 4 years the time indication for the second blood sampling are minimal six, four and two weeks after the first day of illness, respectively. 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 A1.

In the database patients with an identical last name en date of birth were matched. Based on the test result of two successive samples a conclusion was drawn for the patient. We studied before 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 A1. 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 were so high that no further increase was expected (height-category ≥8) (in the measurement area used). In those cases sending a second serum sample was not recommended and it was reported that is was not possible to prove a recent pertussis infection, but that it was very probable.

b. When for individuals ≥10 years of age the IgA and IgG concentrations in the first serum sample were very low (height-category <=3) and the first day of illness was more than four weeks before the first blood sampling. In those cases sending a second serum sample was 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 was found: in those cases it was reported that a recent pertussis infection is probable and although a second serum sample was asked for definitive proof, often no second serum sample has been received.

In all other cases no conclusion was given but a second serum sample was asked. In those cases the following conclusions were 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.

A 1.2.2 Serological results 1989-2002

In previous years almost all serological tests for pertussis were performed by LIS-RIVM. Recently at least three of the 16 regional public health laboratories and also some other (hospital) laboratories have started to perform serology. Thus, the population coverage of serological surveillance based on serological data of LIS-RIVM has decreased from 100% to about 50%. The coverage in 1996 was assumed to be 100%. For every year the labs that stopped sending their samples to the LIS-RIVM from that year on, were marked. The contribution of these marked labs in 1996 to the total number of samples in 1996 was calculated. This percentage demonstrated the decrease in coverage for that year in comparison with 1996 and hence the coverage in the concerning year was one minus this decrease.
However, all data on pertussis serology obtained by the LIS for patients whose first day of illness was in the period 1989-2002 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.

A 1.2.3 Case-definition serology

In the data analysis the following categories were used (with reference to the above mentioned conclusions):

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).

A 1.2.4 Exclusion criteria

In Table A2 exclusion criteria that were used in the study are given. To draw a conclusion not only the height-category, but also the duration between the first day of illness and blood sampling and the age of the patient were taken into account. The databases used for analysis of the data of 1989-1995 did not include sera of patients whose first day of illness or first date of birth were unknown. The proportion of serum samples for who the first day of illness was unknown amounted to less than 8% in 1989-1995. However, in 1996 the proportion of serum samples for which the first day of illness is unknown increased to 28%. This increase is probably caused by discontinuing the request to the physicians to supply information on the first day of illness when they have not given this information in first instance. Therefore it was decided not to exclude patients with unknown first day of illness from the database of 1996 onwards. For these patients the first day of illness was estimated by the subtracting the median duration between the first day of illness and the date of blood sampling (31 days in 1999 and 2000; 28 days in 2001 and 29 days in 2002) from this last date.

Table A2. 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.

A 1.3 Hospital admissions

Information on the number of hospital admissions due to pertussis (ICD-9-CM 033) in 1989-2002 by age (children younger than 1 age in months; otherwise age in years) and sex were obtained from ‘SIG Zorginformatie’ / ‘Prismant’.

A 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 within the LSI-project. In this study isolates of Bordetella registered in the period 1989-2002 were used. Since 1996, four Public Health Laboratory have routinely performed PCR for pertussis.

A 1.5 Central Bureau of Statistics (CBS)

The age distribution of the Dutch population per year and deaths due to pertussis in the period 1989-2002 were obtained from the CBS.

A 1.6 Paediatric surveillance

Appendix 5 shows the NSCK reports of pertussis in 2001 and 2002. The total number of reports was 155 in 1999 and 98 in 2002. After exclusion of duplicate (11 in 2001 vs. 4 in 2002) or false cases (12 in 2001 vs. 32 in 2002), cases from whom no questionnaire was received (27 in 2001 vs. 12 in 2002), and cases with missing first day of illness or cases with a date of birth>first day illness (1 in 2001 and 5 in 2002) a total of 247 cases (154 in 1999 and 93 in 2002) cases were included in the analysis.
In 2001 for 33 and in 2002 32 children the vaccination status could be verified at the Provincial Immunisation Administrations.
Vaccination status as registered at health care administrations was categorised as ‘incompletely vaccinated’ (1 or 2 doses), ‘vaccinated’ (3 or 4 doses) or ‘unknown’ when no informed consent from the parents was obtained. Since the reporting paediatricians in many cases missed the opportunity to ask informed consent from the parents to verify the vaccination status, a second classification of vaccination status was also used. For those with an unknown vaccination status, the vaccination status was assessed on the report of the paediatrician. Although the number of doses admitted was asked, many paediatricians did not distinguish between incompletely and completely vaccinated. Therefore these two classes were presented together in the second classification of vaccination status. The coverage of the paediatric study was calculated using hospitalisations with pertussis as main diagnosis (ICD-9-CM 033) in the national registry of hospital admissions.

A 2 Datamanagement and analysis

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

A 2.1 Analyses of surveillance data 1989-2002

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 1989-2002. As denominator the population on the first of January for that year was taken. The number of reported cases, patients with positive two-point serology, positive one-point serology and negative serology was calculated per month, based on first day of illness. The proportional distribution of serological results per year was calculated for 1989 to 2002. The number of isolates of *Bordetella pertussis* in the period 1989-2002 as reported by the 16 regional public health laboratories are calculated from the LSI data.
The age-specific incidence in the years 1989-2002 was calculated for notifications, positive one- and two-point serology 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 in the years 1993 to 2002. For 2001 and 2002 the age-specific incidence (in months) calculated from hospitalisations of children younger than 1 year was estimated. Therefore, it was assumed that the number of babies born in that year was distributed equally over the year.
Finally, the proportional age distributions according to notifications, positive one-point and positive two-point serology by first day of illness were calculated for the same age-groups (0 year, 1-4, 5-9, 10-14, 15-19 and ≥ 20 years) in the period 1989-2002 and according to hospital admissions due to pertussis (age groups 0 year, 1-4, 5-9, ≥ 10) in the period 1989-2000 were calculated.
For many cases the vaccination-status of serologically confirmed 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.
Since in 1989-1992 the vaccination status of reported cases on an individual level was not available in a database but only on paper and aggregated by age-group, data on vaccination status are limited to the years 1993 to 2000. Due to the high uncertainty of vaccine coverage

of those aged less than one and ≥ 10 years, the analysis of vaccine-efficacy was restricted to those aged 1-4 and 5-9 years. If possible vaccine efficacy for each age-year was calculated. In general, vaccine coverage was estimated at 96%.
For the estimation of vaccine-efficacy incompletely vaccinated cases were not included. 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.

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Appendix 5: Paediatric surveillance

Table A3 and Table A4 show the results of the paediatric surveillance for 2001 and 2002, respectively.

Table A3. Characteristics of hospitalised cases reported in the paediatric study in 2001

Hospitalised cases									
	0 mnth	1 mnth	2 mnths	3-5 mnths	6-11 mnths	1-2 yrs	3-4 yrs	5-15 yrs	Total
	N=36	N=41	N=30	N=15	N=11	N=2	N=3	N=16	N=154
	23%	27%	19%	10%	7%	1%	2%	10%	100%
Registered vaccination status*									
Vaccinated	0%	0%	0%	13%	18%	100%	100%	63%	12%
Incompletely vaccinated	0%	2%	23%	40%	0%	0%	0%	0%	9%
Unvaccinated	100%	98%	0%	0%	0%	0%	0%	0%	50%
Unknown	0%	0%	77%	47%	82%	0%	0%	38%	29%
Reported vaccination status**									
Vaccinated	0%	2%	57%	93%	91%	100%	100%	94%	40%
Unvaccinated	100%	98%	33%	7%	9%	0%	0%	6%	58%
Unknown	0%	0%	10%	0%	0%	0%	0%	0%	2%
Symptoms									
Coughing	97%	98%	100%	100%	91%	100%	100%	100%	98%
Paroxysmal coughing	61%	46%	77%	60%	91%	0%	33%	56%	60%
Whooping	17%	7%	13%	0%	0%	0%	33%	31%	12%
Vomiting	75%	56%	53%	53%	55%	0%	100%	69%	61%
Fever	17%	17%	13%	0%	27%	50%	67%	63%	21%
Complications									
Death	0%	0%	0%	0%	0%	0%	0%	0%	0%
Collapse	8%	5%	10%	0%	9%	0%	0%	13%	7%
Convulsion	0%	0%	3%	0%	0%	0%	0%	0%	1%

Encephalopathy	6%	0%	0%	0%	0%	0%	0%	0%	1%
Apnoea	39%	12%	13%	7%	9%	0%	0%	0%	16%
Pneumonia	3%	5%	3%	0%	0%	0%	33%	13%	5%
Cyanosis	78%	73%	60%	73%	55%	0%	0%	31%	64%
Artificial respiration	6%	2%	3%	0%	0%	0%	0%	0%	3%
Administration of oxygen	81%	54%	50%	13%	36%	50%	0%	6%	48%
Other									
Median days hospitalised	15 (1-41)	8 (1-31)	7.5 (2-54)	7 (1-36)	3 (2-13)	6 (2-10)	7 (3-11)	2.5 (1-15)	8 (1-54)
Median time (days) between onset disease and hospital admission	7 (1-60)	10 (0-45)	10 (1-41)	10 (2-47)	9 (3-21)	8.5 (4-13)	24 (20-70)	17 (0-94)	10 (0-94)
Laboratory diagnosis									
Positive PCR/culture	61%	51%	63%	53%	55%	0%	0%	19%	51%
Positive serology	22%	17%	23%	40%	37%	100%	100%	81%	34%
Other***	17%	32%	13%	7%	9%	0%	0%	0%	16%

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

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

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

Table A4. Characteristics of hospitalised cases reported in the paediatric study in 2002

Hospitalised cases									
	0 mnth	1 mnth	2 mnths	3-5 mnths	6-11 mnths	1-2 yrs	3-4 yrs	5-15 yrs	Total
	N=16	N=16	N=15	N=13	N=9	N=9	N=2	N=13	N=93
	17%	17%	16%	14%	10%	10%	2%	14%	100%
Registered vaccination status*									
Vaccinated	0%	0%	0%	8%	11%	56%	100%	62%	19%
Incompletely vaccinated	0%	6%	40%	46%	22%	0%	0%	0%	15%
Unvaccinated	100%	94%	0%	0%	0%	0%	0%	0%	33%
Unknown	0%	0%	60%	46%	67%	44%	0%	38%	32%
Reported vaccination status**									
Vaccinated	0%	0%	60%	92%	78%	100%	100%	77%	56%
Unvaccinated	100%	100%	40%	0%	11%	0%	0%	8%	37%
Unknown	0%	0%	0%	8%	11%	0%	0%	15%	5%
									2%
Symptoms									
Coughing	100%	100%	100%	100%	100%	100%	100%	100%	100%
Paroxysmal coughing	75%	75%	53%	77%	78%	67%	50%	69%	69%
Whooping	19%	25%	13%	15%	22%	22%	50%	15%	19%
Vomiting	50%	50%	53%	69%	56%	67%	0%	69%	57%
Fever	6%	0	0	23%	23%	33%	0%	31%	14%
Complications									
Death	0%	0%	0%	0%	0%	0%	0%	0%	0%
Collapse	19%	13%	7%	31%	11%	0%	0%	0%	12%
Convulsion	0%	0%	0%	0%	0%	0%	0%	0%	0%

Encephalopathy	0%	0%	0%	0%	0%	0%	0%	0%	0%
Apnoea	6%	13%	20%	15%	33%	0%	0%	0%	12%
Pneumonia	0%	0%	0%	8%	0%	22%	0%	0%	3%
Cyanosis	63%	56%	73%	62%	56%	33%	100%	8%	51%
Artificial respiration	13%	0%	0%	0%	0%	22%	0%	0%	4%
Administration of oxygen	38%	38%	67%	31%	22%	22%	0%	7%	33%
Other									
Median days hospitalised	8.5 (1-32)	7.5 (2-19)	8 (2-39)	8 (2-47)	4 (2-27)	2 (1-19)	2 (0-4)	6.5 (1-16)	7 (0-47)
Median time (days) between onset disease and hospital admission	9 (1-47)	7 (2-24)	7 (2-30)	6 (1-21)	11 (5-95)	13 (2-52)	16.5 (9-24)	33.5 (5-93)	9 (1-95)
Laboratory diagnosis									
Positive PCR/culture	63%	56%	47%	69%	44%	67%	0%	23%	34%
Positive serology	13%	25%	27%	23%	44%	33%	100%	69%	50%
Other***	25%	19%	27%	8%	11%	0%	0%	8%	16%

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

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

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

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