JULI 2007

SMITTSKYDDSINSTITUTETS RAPPORTSERIE NR 2:2007

NINE YEAR REPORT

Pertussis in Göteborg study area

Technical report October 1997 – September 2006, including enhanced surveillance January 2003 - September 2006, with an executive summary

AV Carlsson RM, Gustafsson L

AVDELNINGEN FÖR EPIDEMIOLOGI, SMITTSKYDDSINSTITUTET, SOLNA

SMITTSKYDDSINSTITUTET
Swedish Institute for Infectious Disease Control

Smittskyddsinstitutet är en statlig expertmyndighet som har till uppgift att bevaka det epidemiologiska läget i fråga om smittsamma sjukdomar bland människor och främja skyddet mot sådana sjukdomar.
Rapportserien syftar till att sprida information av myndighetens arbets- och forskningsfält. I varje rapport belyses centrala och aktuella frågeställningar inom smittskyddsarbetet. Innehållet i de vetenskapliga rapporter som publiceras ansvarar den enskilde författaren för och ska inte tolkas som ett uttryck för SMI:s allmänna uppfattning.
Rapporterna distribueras via Smittskyddsinstitutets webbplats och trycks endast i undantagsfall.

Författare: [1]CARLSSON RM, [1]GUSTAFSSON L

[1]Smittskyddsinstitutet

171 82 Solna

AVDELNINGEN FÖR EPIDEMIOLOGI

Smittskyddsinstitutet
ISSN-nummer 1400-3473
SMI-rapport Nr 2:2007

Besöksadress: Nobels väg 18
Telefon: 08-457 23 00
Fax: 08-32 83 30
E-post: smi@smi.ki.se
www.smittskyddsinstitutet.se

Contents

1 Executive Summary

1.1 Introduction

In Sweden pertussis vaccination was withdrawn in 1979. Following a 17 year hiatus without general vaccination, pertussis vaccination of infants was again included in the national vaccination program after licensure of the new acellular vaccines in January 1996.

During 1980 to 1995 laboratory confirmed pertussis was voluntarily reported from all bacteriological laboratories with full personal identifiers. Because of reintroduction of pertussis vaccination in 1996, pertussis was included in the Communicable Disease Act in 1997.

Since then, the national epidemiology of pertussis in all age-groups is studied annually by analysing the obligatory reporting. Cases of pertussis, either clinically suspected or/and laboratory confirmed by culture, PCR or serology are reported to the Swedish Institute for Infectious Disease Control through a computer-linked reporting system (SmiNet). Basic data in this routine reporting system include, for example, the national registration numbers (NRN), but there are limited or no clinical or vaccination data available from the routine reports. The NRN are individually unique Swedish person identifiers that includes information on date of birth, sex and current place of residence including county. Laboratory reports include laboratory method and (normally) date of sampling and/or date of positive result.

The national pertussis epidemiology in vaccinated cohorts, i.e. children born from 1996, has been studied since October 1st 1997 within an enhanced surveillance project, in which detailed data on vaccination status and clinical outcome are collected and entered in a separate study database. For a general summary of the enhanced surveillance project, see the main nine year report [1]. One area of Sweden, called the Göteborg study area, was originally excluded from the enhanced follow-up part of the surveillance project because pertussis surveillance in this area was already done within a clinical trial setting [2,3], including a mass vaccination project during a 3-4 year period. In all 56 percent of all children in the Göteborg area, born in 1990 through 1995, were vaccinated within this project during the years 1997-2000 [4]. From January 1, 2003 also the Göteborg study area (Table 5, section 2.2) is included in the enhanced follow-up.

During four to five of the most recent ten years it has been obvious from the yearly national epidemiological reports that there have been more laboratory reported cases of pertussis in the region of Västra Götaland (VG) in relation to population size than in the rest of Sweden, with a maximum during the year 2004, Figure 1. Note that the region consists of two parts, i.e. the Göteborg study area and the rest of VG region (representing about 47 and 53% of the region population, respectively).

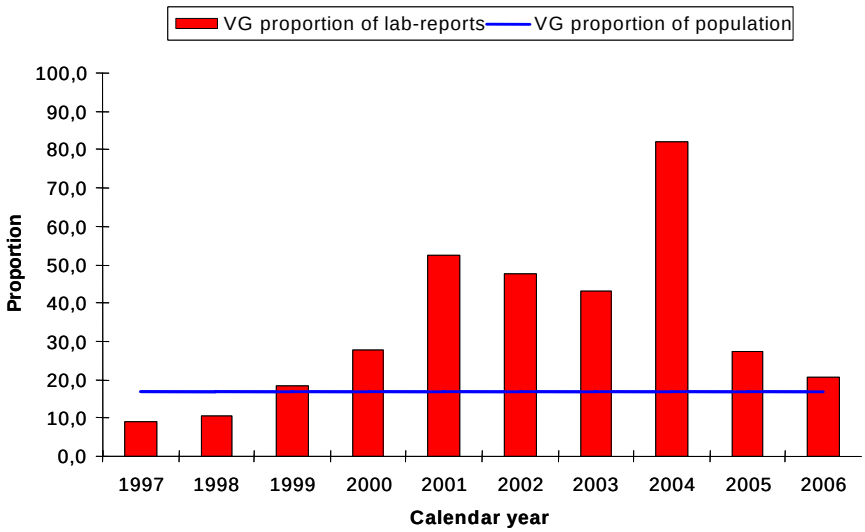


Figure 1 Proportion of number of laboratory reported cases of pertussis from the region of Västra Götaland (based on numbers in table 37B), and proportion of population in this region during the years 1997-2006 (based on mean population figures from Statistics Sweden).

In relation to population size, the VG region hence reported proportionally fewer cases during the years 1997-1998, but from year 2000 until 2005 the number of reports increased and was indeed clearly in excess of the expected numbers during those years, specifically during 2001-2004, with a marked peak in 2004.

During the process of collecting and analysing the enhanced surveillance data, it has also become obvious that most of these pertussis reports in the VG region were from the Göteborg study area part, Table 1. Population figures (2004 mid year population) are taken from Table 4 in the main nine year report [1] and laboratory confirmed cases are from Section 3 of the present report. The calculation for Sweden except the Göteborg study area give an index (percent of cases divided by percent of population).

Table 1 The number of laboratory confirmed cases between October 1, 1997 until September 30, 2006 for children born January 1, 1996 until September 30, 2006, in relation to population size of the Göteborg study area and other parts of Sweden

Area	Population		Laboratory confirmed cases		Index
	Number in 1000	%	Number	%	% of cases divided by % of population
Göteborg study area	782	8,7	1 202	38,6	4,4
Stockholm	1 867	20,8	492	15,8	0,8
Skåne	1 157	12,9	251	8,1	0,6
V. Götaland exc. Gbg	804	8,9	217	7,0	0,8
"South"	1 163	12,9	302	9,7	0,8
"Middle-east"	978	10,9	179	5,7	0,5
"Middle-west"	1 084	12,1	263	8,4	0,7
"North"	1 158	12,9	212	6,8	0,5
Total	8 993	100	3 118	100	1

Thus, there are only minor differences in number of laboratory confirmed pertussis reports, taking population size into account, between different areas of Sweden but the Göteborg study area.

Therefore, the aim of the present report is to present detailed pertussis epidemiology data for the Göteborg study area in comparison with the rest of Sweden, and to provide and discuss a list of plausible explanations to the differences noted.

In Section 2 of this report we present the enhanced surveillance data from the Göteborg study area for the 3 ¾ year period January 1, 2003 through September 30, 2006, with comparisons to the rest of Sweden. This part of the report include vaccination data in relation to age at date of onset of symptoms, and also in relation to detailed clinical information including different case definitions (i.e. different grades of severity of disease).

It is important to realize that we do not have clinical data from the period October 1, 1997 to December 31, 2002. Therefore, we present alternative types of analyses for the whole nine year period October 1, 1997 until September 30, 2006 in Section 3. To fill the gap in available data on vaccination status and clinical course in the Gothenburg study area during the first 5 ¼ years of this period we have retrospectively collected vaccination data for children born from 1996 with laboratory-reported pertussis in this area during this time period previously not followed within the enhanced surveillance, and we have analysed vaccination data in relation to age date of laboratory sampling for the whole nine year period. It is to be noted that we cannot calculate age at onset of symptoms, nor can we perform analyses by varying the case definitions in this type of analyses.

An effort to check indicators of differences in awareness is included in Section 4, presenting the overall reported data from the region of VG in comparison with the rest of Sweden, including performance indicators for the vaccination program. Laboratory denominator data are not included in the present Swedish national reporting system, but by courtesy of the county medical officers in VG and other

regions, we have included an effort to compare laboratories within VG as well as a large city comparison of the Göteborg study area in comparison with Stockholm and Malmö-Lund.

The plausible explanations to the high number of laboratory reported cases from the Göteborg study area are briefly discussed in section 1.4.

1.2 Materials and methods

Within the enhanced surveillance project, all culture- or PCR-verified cases of pertussis in Sweden in children born in 1996 and onwards have been identified from the national computer-linked reporting system, and basic data (NRN, place of residence, laboratory date) for all these children have been entered into a separate surveillance database. Routine reports based on serology or clinical reports without laboratory confirmation were not at all included in the study database. Hence the study database includes general information for all culture- or PCR-verified pertussis in children born from 1996, regardless of area of residence. For all children from the Göteborg study area there was also a "flag" entered in the database.

During the first 5 ¼ years of the project (October 1, 1997 through December 31, 2002) children from the Göteborg study area entered in the surveillance database were excluded from further follow-up. Children from the rest of Sweden born after 1995 with a pertussis report from October 1, 1997 or later as well as children in the Göteborg study area born after 1995 with a pertussis report from January 1, 2003 were followed-up in detail by telephone interviews to parents and child/school health care nurse. Vaccination data, as well as detailed clinical data (including information on hospitalisations, complications and antibiotic treatment) were collected and entered in the surveillance database. Hence the study database, in October 2006, include detailed information from 3 ¾ year of surveillance in the Göteborg study area (January 1, 2003 through September 30, 2006) plus detailed information from 9 years of surveillance in the rest of Sweden (October 1, 1997 through September 30, 2006).

Thus, for children from the Göteborg study area there was originally no clinical data or vaccination history collected as supplementary information to the positive laboratory reports with a sampling date from October 1, 1997 until December 31, 2002. However, the exact age of the child at the day for the positive sample could be calculated from the NRN.

In addition, we have in 2006-07 retrospectively collected the vaccination information for almost all of these children. This was mainly done by collecting the individual vaccination data from the individual medical records by telephone to the Child or School Health Care nurses, and also by collecting the individual vaccination data from the computerised files of the Göteborg mass vaccination study.

In summary, we use data for Göteborg study area children in three ways in this report:

i) 3 ¾ year of enhanced surveillance information (i.e. detailed clinical and vaccination data for episodes with onset of disease occurring between January 1, 2003, until September 30, 2006), including a comparison with the corresponding data from the rest of Sweden (Section 2)
ii) information on laboratory reported pertussis for the whole nine year period (laboratory sampling date between October 1997 until September 30, 2006), including a comparison with the corresponding data from the rest of Sweden (Part 1 of section 3)
iii) retrospectively collected individual vaccination data from Göteborg children with laboratory reports dated October 1, 1997 until December 31, 2002, including a comparison with the corresponding data from the rest of Sweden (Part 2 of section 3).

1.2.1 Göteborg study area, vaccines and vaccination

The Göteborg area is defined as the city of Göteborg and nine additional surrounding municipalities (Table 5, section 2.2), corresponding to the study area of the Göteborg pertussis vaccine trial and mass vaccination project [2,3,4]. Eight of these municipalities and the city of Göteborg are geographically located within the region of Västra Götaland, whereas the 9th municipality (Kungsbacka) is located within the county of Halland.

In the Göteborg study area, a trivalent one-component DTPa* with only PT* (DiTeKik®, SSI) was used within the ordinary vaccination program from January 1996 and until spring 1999, when it was replaced by a pentavalent two-component DTPa-IPV-Hib* with PT and FHA* (Pentavac®, Sanofi Pasteur MSD). During the same period (from 1996 and until spring 2000), there was in this area a mass vaccination project, offering general and free catch-up during the years 1996-1999 by use of monovalent one-component Pa vaccine (Kikhostevaccin, SSI) to all children born in the 1990:s [3]. From the autumn 2005 the national program included a pertussis booster at 10 years of age to children born from 1995. However, no child in the study database has yet reported any booster dose prior to the episode.

1.3 Results

1.3.1 Göteborg enhanced surveillance (Section 2)

During the 3 ¾ year period of surveillance (starting January 2003) there were 549 followed episodes of laboratory confirmed pertussis within the Göteborg area among 548 children born 1996 or later, with onset of symptoms from January 1, 2003 and until September 30, 2006. Detailed vaccination history and information on coughing period, including duration of spasmodic cough, is available for all 549 episodes of pertussis. Data on hospital stay and complications are available for 547 and 546 episodes, respectively, and information on antibiotic treatment is available for 547 episodes, whereof 52 were excluded from analyses because of incomplete antibiotic course or deviation from vaccination schedule. The remaining 495 were used in the statistical analyses.

1.3.2 Göteborg additional analyses (Section 3)

These analyses include the whole 9 year period (starting October 1997). There were 625 culture- or PCR-reported cases of pertussis during the 5 ¼ year period when the Göteborg study area was not included in the enhanced surveillance, i.e. from October 1, 1997 and until December 31, 2002. Individual vaccination status was retrospectively collected for all but 7 of these children. The analyses also include the 549 cases mentioned in section 1.3.1, with addition of those 28 cases from the enhanced period where vaccination data and/or clinical details was lacking.

In all the nine year analyses include 1 202 laboratory reported cases in the Göteborg area from October 1, 1997, and until September 30, 2006 in children born 1996 or later, with detailed vaccination history available for 1 167 (97.1%) of these cases.

1.3.2 Age-specific incidence in relation to vaccination data and clinical outcome for children born in 1996 through September 2006

The tables of Section 2 present total number of person-years, total number of laboratory confirmed pertussis cases and incidence figures with 95% confidence intervals for children in Göteborg study area and the rest of Sweden, divided in age-groups corresponding to the vaccination intervals in the national vaccination program. These analyses are based on the 3 ¾ year period starting January 1, 2003.

In all tables a per-protocol approach was used, with analyses according to vaccination status at date for onset of cough during the pertussis episode. The number of children with pertussis during the period between second and third dose, and the number of toddlers with pertussis after three doses represent vaccine failures. There is at present no consensus on the upper age limit for the definition of vaccine failure after primary immunisation, and we have therefore included all children born 1996 through September 2006 with culture- or PCR-reported pertussis after three doses.

The analyses are also done according to different pertussis case definitions. The two main definitions used are all laboratory reported cases regardless of severity, and the WHO definition of typical pertussis, i.e. 21

* DTPa = diphtheria-tetanus-acellular pertussis vaccine,
DTPa-IPV-Hib = diphtheria-tetanus-acellular pertussis-inactivated polio and Haemophilus influenzae type b vaccine,
PT = pertussis toxoid, FHA = filamentous haemagglutinin

days of more of paroxysmal cough (See Section 2.1.3). In addition, some analyses are performed using the current reporting definitions of 2 weeks or more of coughing any kind.

For the 3 ¾ year period, there were considerable, and statically significant, differences between the two areas comparing laboratory confirmed pertussis cases for whom we have both vaccination and clinical data. For all categories (regardless of parameter chosen for comparison) there are a more or less over-representation of cases in the Göteborg study area (or under-representation of cases in the rest of Sweden) taken population sizes into account.

Table 2 summarizes some comparisons done between the two areas. About 9,1% of newborns in Sweden during the years 1996-2006 were born in the Göteborg study area and in the last column the percentage of pertussis cases in the Göteborg study area, of total number of cases, is divided by 9.1.

Table 2 Some comparisons, related to different background or outcome parameters, of number of pertussis cases occurring during January 1, 2003 until September 30, 2006, for children born from January 1, 1996 until September 30, 2006, in Göteborg in relation to the rest of Sweden.

Category of pertussis case	Total no. of cases	Children in the Göteborg study area		
		Number of cases	Percent of total number of cases in Sweden	Percent adjusted to population size
All reported cases	1 455	549	37.8	4.2
Unvaccinated children	397	88	22.2	2.4
Unvaccinated children > 1 y	54	14	17.7	1.9
Vaccinated with one dose	152	47	30.9	3.4
Vaccinated with two doses	114	76	66.7	7.3
Vaccinated with three doses	792	338	42.7	4.7
Cough <14 days	64	43	67.2	7.4
No spasmodic cough	322	193	59.9	6.6
Spasmodic cough ≥21 days	1 038	299	28.8	3.2

Note that the reporting of pertussis in unvaccinated infants and in unvaccinated children aged 1 year or more is approximately twice as high in the Göteborg study area than in the rest of Sweden. Note also that the most marked differences in reporting are in milder cases, i.e. in cases with cough < 14 days or cases with no spasmodic cough at all.

A more frequent reporting of milder cases in the Göteborg study area is also reflected by data on hospitalization and complications. There were proportionally fewer hospital admissions among unimmunized children with laboratory-confirmed pertussis in the Göteborg study area in comparison with the rest of Sweden (respectively 33% and 54%). The hospital stay was furthermore shorter in Göteborg study area with 24% (7 of 29) of Göteborg children hospitalized for more than one week whereas 44% (73 of 166) had a hospital stay of one week or more in the rest of the country. Also the proportion of all laboratory reported with a complication was lower in the Göteborg study area than in the rest of Sweden, with significant differences in proportions with respiratory complications or dehydration.

Table 3 summarizes the overall incidence per 100 000 person years of culture/PCR-confirmed pertussis, episodes with > 21 days of cough, hospital admissions and complications in the age groups surveyed. The number of events recorded per 100 000 person years in different age groups indicate a significantly higher hospitalization rate in the youngest and unvaccinated infants (below 3 months of age) in the Göteborg study area in comparison with the rest of Sweden, but the incidence of hospitalizations in children vaccinated with one dose or more was similar in the two areas.

Table 3. Incidence of all reported culture/PCR-confirmed cases of pertussis, reported cases with >21 days of cough, hospital admissions and complications in children born from 1996 and onwards and followed from January, 2003 until September 30, 2006, in the Göteborg study area and in the rest of Sweden (95% confidence interval within parenthesis).

	Number of events per 100 000 person years (95% C.I.)							
	Culture/PCR-confirmed pertussis		Episodes with >21 days of cough		Hospital admissions		Complications	
Age groups	Gbg	Rest of Sweden	Gbg	Rest of Sweden	Gbg	Rest of Sweden	Gbg	Rest of Sweden
0 - <3 months	754	243	411	211	313 (206-456)	175 (147-205)	197 (115-316)	120 (98-144)
3 - <5 months	663	185	279	166	87 (28-204)	73 (53-99)	122 (49-252)	45 (30-67)
5 - <12 months	434	31	151	24	5 (0-19)	6 (3-11)	25 (8-59)	4 (2-8)
≥12 months	145	21	88	17	0.8 (0-2.9)	0.3 (0.1-0.6)	11 (7-16)	1.9 (1.4-2.5)

Interestingly, there were no significant differences in the overall frequency of antibiotic treatment in infant cases (90% and 87%) or in children with pertussis at age 1 year or more (52 and 48%). However, the proportion of infants treated in the age-groups 3-<5 months and 5-<12 months, were slightly higher in the Göteborg study area as compared to the rest of Sweden, Table 22. The current recommendation is to prescribe antibiotics to all infants with pertussis, already as post-exposure prophylaxis to infants below 6 months and in the form of early treatment to infants aged 6-12 months. As already noted in the main report, antibiotic treatment within a week after onset of coughing was associated with significantly shorter duration of period with paroxysmal coughing.

1.3.4 Age-specific incidence in relation to national vaccination schedule for children born in 1996 through September 2006

The tables 12 (Section 2) and 25 (Section 3) present total number of person-years, total number of laboratory confirmed pertussis cases and incidence figures with 95% confidence intervals for children in the Göteborg study area and the rest of Sweden, divided into age-groups corresponding to the vaccination intervals in the national vaccination program.

Table 12 presents data for a 3 ¾ year period, starting January 1, 2003, while table 25 presents data from the overall nine year period starting October 1, 1997. In both tables an intent-to-treat approach was used, i.e. all children were included regardless of whether they were vaccinated or not, and also regardless of severity of disease.

In spite of different methods for calculation of age, the same kind of decline pattern was seen in the 3 ¾ year surveillance group (Table 12) and in the additional nine year analyses (Table 25). In both tables, the highest incidence in the Göteborg study area and in the rest of Sweden were reported in the youngest age-groups, with a marked decline from 5 months of age in the rest of Sweden and a slight decline in this age-group in the Göteborg study area, and in both areas a further decline from 12 months of age. In the Göteborg study area the decline continued until a lowest incidence at 3-4 years, but Göteborg children at this age still had a 7.5 times higher risk of being reported as a laboratory verified case of pertussis as compared to the rest of the country. From this age there was in Göteborg a slight increase until a maximum after infancy at about 6-8 years of age. This is in contrast to the rest of Sweden, where age-specific incidence rates dropped more markedly during the infancy year and remained at this low level until a slight increase from about 5-6 years. In each age group, but the last one, children living in the Göteborg study area were at a much higher risk for being reported as a laboratory confirmed case of pertussis compared to children living in the rest of the country. The same pattern is found in the other incidence tables of section 2 and 3, e.g. Table 14 and Table 32.

1.3.5 Age-specific incidence per calendar year for children born in 1996 through September 2006

Table 24 (Section 3.3) summarizes the age at laboratory report, and the reporting year, for all the 1 202 Göteborg cases as well as the 1 916 reports from the rest of Sweden during the nine year period. Table 4 provides age-specific incidence, by calendar year of laboratory diagnosis, based on the counts in table 24. Denominator data were derived from Statistics Sweden per calendar year (mean of the mid-point population counts for the municipalities included in the Göteborg study area, table 5, section 2.2). Since the data collection started on October 1, 1997, and ended on September 30, 2006, the person-time accrued in the underlying populations in 1997 was multiplied by 0.25, and in 2006 by 0.75 (representing . respectively 3/12 and 9/12 year of observation). In the calendar years when the studied cohort (born in 1996 or later) first entered the various strata of attained age, the calendar observation period for this age group was, on average, 1/2 year. For the transition age groups, in *italics in the table,* the denominators are multiplied by 0.5.

Table 4 Age-specific incidence rates of culture- or PCR-confirmed cases of pertussis from October 1,1997 to September 30, 2006, by attained age (in years) and calendar year of laboratory diagnosis, among children born in 1996 through September 2006. Age is calculated at date for the positive sample.

			1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Göteborg study area	**Year of age**	**0**	141	154	498	789	596	1 007	459	1 186	252	169
		1	*103*	82	177	673	223	356	100	406	114	40
		2		*45*	59	248	295	306	127	301	65	14
		3			*136*	257	212	225	24	185	78	0
		4				*226*	152	200	83	331	46	15
		5					*135*	257	35	486	71	16
		6						*225*	105	533	166	16
		7							*112*	469	142	48
		8								*405*	94	32
		9									*23*	16
Sweden except Gbg	**Year of age**	**0**	114	95	159	191	72	140	76	177	133	88
		1	*15*	21	18	23	15	13	9	17	12	9
		2		*18*	34	19	13	29	10	25	7	14
		3			*55*	34	16	19	7	13	16	9
		4				*59*	19	32	15	24	18	11
		5					*22*	33	12	30	23	25
		6						*57*	19	32	34	25
		7							*13*	48	44	29
		8								*80*	37	17
		9									*69*	14

Figure 1 and table 4 show that there was a marked increase in age-specific incidence in infants already in 1999 for children in the Göteborg study area, i.e. during the last phase of the mass vaccination trial, with some increase also in those above 1 year. From the year of 2005 the age-specific incidences decreased to expected levels.

The age-specific incidence rates in earlier birth cohorts than children born after 1995 are not known in the

Göteborg study area, since the reports of communicable diseases are only grouped at county level in the national database SmiNet and since those age-groups are not covered by the enhanced surveillance project. The 1997-2006 age-specific incidence rates for the whole region of Västra Götaland (with an overall population of about twice that of Göteborg) are shown in figures 7-8, Section 4.

1.3.6 Pertussis incidence in the Göteborg and/or Västra Götaland before and after 1996 (introduction of acellular pertussis vaccines)

Although data from routine notifications according to the communicable disease act are available only for the Västra Götaland region (not for the Göteborg study area), some information from this area is available: Considering that the Göteborg efficacy trial [2] and the Stockholm I efficacy trial [5] were related in time and study design, including case ascertainment routines, the rates of culture-confirmed cases in the placebo-groups of the two trials can be compared. The Göteborg trial started 3-4 months before Stockholm I, and the follow-up in the Göteborg study area stopped about 6 months before the follow-up was terminated in Stockholm, rendering the Göteborg study a slightly shorter follow-up period. The Göteborg placebo group included 1726 children, with 154 culture confirmed cases reported during the follow-up (8.9%). The corresponding group in Stockholm included 2574 children, and 296 culture-confirmed cases were detected (11.5%). Taking the slightly shorter follow-up in the Göteborg study area into account, we consider the incidence of culture-confirmed cases similar in the two trials.

By courtesy of dr Birger Trollfors, we have information on number of positive samples per month at the Göteborg bacteriological laboratory, catchment area mainly Göteborg, from 1986 to March 2001, figure 2. The figure also includes numbers of positive samples for the rest of Sweden (data from figure A of the main report [1] substracted with the Göteborg data). The number of Göteborg reports for these years seems proportionate to the population of the Göteborg study area, with a scale on the right x-axis is 1/10 of the scale of the left x-axis, corresponding to the fact that the Göteborg study area has about 1/10 of the Swedish population.

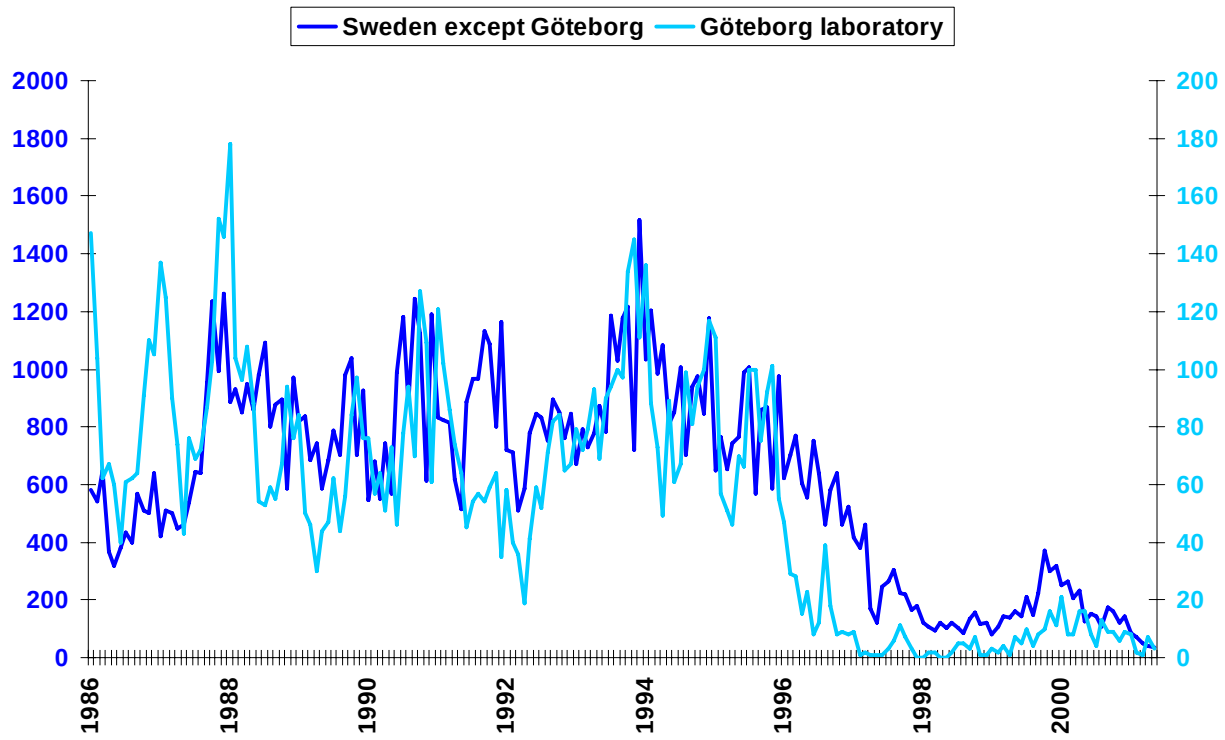


Figure 2 Number of culture- and PCR-confirmed pertussis cases per month area from January 1986 to March 2001 reported from microbiological laboratories in Sweden except the Göteborg laboratory, and from the Göteborg laboratory.

1.4 Discussion

In general, there has been a dramatic decrease in the incidence of pertussis in Sweden after introduction of acellular pertussis vaccines in 1996, Figure 2, and the overall incidence of reported pertussis has since 2000 stabilized at a low level corresponding to the incidence rates in the late sixties when an efficacious whole-cell DTP was used.

However, there are still variations in incidence rates over time and geographically. During four to five of the most recent ten years there have been more laboratory reported cases of pertussis in the Göteborg study area of the Västra Götaland region in relation to population size than in the rest of Sweden, with a maximum during the year 2004, Figure 1. The aim of the present report is to present detailed pertussis epidemiology data from the Göteborg study area in comparison with the rest of Sweden, and to provide and discuss a list of plausible explanations to the differences noted.

The present technical report from the Göteborg study area summarises

- the 3¾-year of enhanced surveillance from this area in comparison with the corresponding information from the rest of Sweden, including age-specific calculations by use of date of onset of symptoms (Section 2)
- the 9 year age-specific estimates of pertussis incidence (laboratory confirmed cases) by use of sampling date for both Göteborg and the rest of Sweden, including the 9 year age-specific calculations of pertussis in vaccinated children by use of the retrospectively collected and validated vaccination data (Section 3).

A comparison of number of laboratory confirmed pertussis reports in children born after 1995 during the nine year period, taking population size into account, indicate only minor differences between different areas of Sweden outside the Göteborg study area. Therefore it is not worth the effort to perform extensive comparisons of the Göteborg study area with for instance the other "large city areas", e.g. Stockholm or Skåne.

As shown in Tables 25-27, Section 3.4, the age-specific incidence rates of confirmed pertussis during the 9 year period is 5-20 times higher in the Göteborg study area compared to the rest of the country, irrespective of period and vaccine use. The vast majority of the Göteborg reports are from the outbreak years 2000-2004, with 31% of the reports (368/1202) reported during the peak year 2004.

The age-specific incidence in unvaccinated infants was significantly higher in the Göteborg study area in comparison with the rest of Sweden, and all incidence tables in sections 2 and 3 demonstrate much higher age-specific incidence rates, compared to the rest of Sweden, in most age-groups above 5 months of age who have received at least two doses of a pertussis vaccine prior to the pertussis episode. This observation holds regardless of whether monocomponent or two-component vaccine was given prior to the positive pertussis episode and regardless of severity of the disease.

Note that the sections 3.3-3.7 only give overall information on the number of culture- and PCR-confirmed cases of pertussis in children born in 1996 or later during the nine year-period, with no details of severity at onset of the pertussis episode. From the 3 ¾ year enhanced surveillance period (including the peak year 2004) it seems that more mild cases are reported from the Göteborg study area, as indicated by shorter duration of cough and spasmodic cough, and by lower proportion of hospitalisations and complications among the cases reported in this area in comparison to the corresponding proportion among laboratory reported cases from the rest of Sweden.

Section 4 further describes the reporting system in Sweden. A higher proportion of cases are laboratory-verified in the region of Västra Götaland in comparison with the rest of Sweden, but this small difference cannot on its own explain the observed differences. There is also a slight difference in use of laboratory methods, since the Göteborg laboratory was among the first in Sweden to implement PCR technique for detection of *Bordetella pertussis*, although many other laboratories today use the PCR in routine reporting. The time difference in implementation can probably, but only to a small extent, contribute to the higher

number of cases reported from the VG region during parts of the nine year period.

Laboratory denominator data, provided by courtesy of the dept of communicable diseases in the region of Västra Götaland, Stockholm and Malmö, indicate that there is a higher sampling rate in relation to population size in the VG region, but there are no differences in the number of samples yielding a positive result. There is, however, a difference within the VG region with more samples submitted to the Microbiological Laboratory in Göteborg, with Göteborg city and surrounding communities as main catchment area, than in the rest of the VG region.

There are no indications that there are any differences in terms of delivery of the national vaccination program. The timing and coverage were similar in the Göteborg study area in comparison to the rest of Sweden.

The overall vaccination program did, however, differ in this region during the first 3-4 years after 1996 since free catch-up was offered to all and given to 56% of all children up to 7 years of age. Free catch-up vaccination was not offered to children born in 1990-1995 in other parts of Sweden. Also, the monocomponent vaccine which was used in the Göteborg study area during 1996-1999, both for vaccination of infants and for the catch-up vaccination (including one more year), was not used anywhere else in Sweden. Since 1999 children in the Göteborg study area are vaccinated with a pertussis vaccine, which is used also in other parts of Sweden (in about 50% of counties).

It is obvious from the data in Sections 2 and 3 that there are much more reports of laboratory-verified pertussis from the Göteborg study area than from the rest of Sweden. This local increase in incidence was not noted within the Göteborg mass vaccination project [4, 5] because the monitoring of local epidemiology of pertussis stopped when the project stopped in early spring 2000, i.e. at the same time as the out-break started.

In summary: The present observational study cannot fully explain the excess of reports in the Göteborg study area. There are only minor differences in the reporting system and use of laboratory methods, there are no differences in number of samples yielding positive result comparing some areas of Sweden and there are no differences in implementation of the infant vaccination program in the region of Västra Götaland in comparison in the rest of Sweden. There was, however, a difference in the overall vaccination program with free catch-up to children implemented in the Göteborg study area during the years 1997-2000. One likely part of the explanation is a higher level of awareness, as indicated by the higher proportion of more mild cases among the reports, and by the lower proportion of hospitalization rate among reported infant cases for children from the Göteborg area.

Noteworthy is that the age-specific incidences in infants, i.e. the age-group most likely to reflect ongoing circulation of pertussis, indicate that the outbreak started already during the last phase of the mass vaccination project in 1999-2000, with rapidly increasing age-specific incidences in infants until peaks with more than 1,000/100,000 infant years during the years 2002 and 2004, whereafter the outbreak declined. These maximum age-specific incidence rates in infants were about five times higher than in the rest of the country, where peaks of, respectively, 191 and 177/100,000 person years were noted during the years 2000 and 2004.

It is therefore likely that there is a true difference in pertussis incidence indicating a large and long-lasting outbreak of the pertussis disease during these years in the Göteborg study area, as indicated by high age-specific incidence in unvaccinated as well as in partly vaccinated infants.

I is known from the literature that epidemics have a facilitating effect on notification by the presence of large numbers of cases in the community, perhaps mediated in part also by press overage with a possible time difference during the course of the epidemic. Also, outbreak settings may have a different age-distribution when compared to non-outbreak endemic settings [6]. We do, however, find it unlikely that a higher level of awareness in itself can fully explain the much larger number of pertussis cases than expected reported from the Göteborg study area during most years of the nine year period of follow-up, most obvious for the years 2000-2004, both among unvaccinated and partly vaccinated infants and among vaccinated children in different age-groups.

It cannot be excluded that vaccine and vaccination factors, including duration of protection, have contributed to the observed differences in overall number of laboratory cases, in age-specific incidences and in severity of disease as compared to the non-outbreak endemic setting in the rest of the country. As previously noted, the type and design of this observational study cannot address questions on the mechanisms causing these differences between an outbreak setting and ordinary endemic setting.

Mathematic modeling could possibly be one of the additional tools that might help in understanding the epidemiology of pertussis, but as for the Göteborg study area such an attempt would require information also on pertussis in the catch-up vaccinated cohorts.

Interestingly, the year 2004 was a peak year also in the rest of the country, and to some extent in other Nordic countries. It is therefore possible that Figure 1 demonstrates the combined effect of a national (or Nordic) peak in 2004 and a large local outbreak in the Göteborg study area during the years 2001-2004.

Noteworthy is that although the situation in the Göteborg study area seems to have returned almost to normal during 2005-2006, the age-specific incidence in Göteborg infants is still about twice as high as that of what is reported from the rest of the country, but we do not consider it unlikely that a difference of this magnitude might be explained solely by increased awareness.

1.5 Caveats

Our analysis is subject to important limitations. The study design in the enhanced surveillance, including the additional analyses, is open and non-randomised. Case ascertainment is based on routine surveillance of culture- and PCR-confirmed pertussis, with sampling rates varying geographically and over time, according to the awareness of pertussis, local clinical practice, level of suspicion and laboratory experience.

Any comparisons between Göteborg and other areas in Sweden should take this into account and also that the Göteborg study area through careful clinical and laboratory follow-up in clinical trials and mass-vaccination studies performed during more than a decade [2,3,4] is likely to have a higher detection rate of pertussis then most parts in the rest of the country. The detection of proportionally more milder cases, as demonstrated in Section 2.4, 2.6-2.9, may support this hypothesis. In addition, an outbreak will in itself increase awareness of disease, and hence influence the reporting of milder cases, those where the physician do not normally suspect pertussis.

There are also other problems with surveillance by analysis of laboratory confirmed cases, mainly the differential sensitivity of culture-confirmation in vaccinated compared to unvaccinated individuals, and also differential sensitivity in culture- and PCR-confirmation. Confirmation by PCR has earlier than elsewhere in Sweden replaced culture-confirmation in the Göteborg study area, which may, to some extent, spuriously decrease observed differences between pre and post vaccination periods and may also confound comparisons over time regarding, e.g., waning protection.

Another important limitation is that all vaccinated Göteborg cohorts are not included in the pertussis surveillance. The vaccination regimen in this area included a catch-up strategy involving children born from 1990-1995 and these cohorts are not followed-up with regard to episodes of laboratory-verified pertussis during the nine year period October 1, 1997 to September 30, 2006. This means that we cannot address the possible influence of pertussis in these catch-up vaccinated cohorts on the overall situation in the Göteborg study area.

Finally, it needs to be pointed out that this report is clinical, with no analyses of microbiological epidemiology. From previous years in the enhanced surveillance, when also strain characterisation was included in the study design, it is obvious that strains appear and disappear in waves, with or without differences in clinical pattern of disease. It is not known whether or not there have been any major differences in circulating strains during the outbreak years as compared to previous years in the Göteborg study area or as compared to the rest of Sweden. Further analyses could be made, since there are strains collected both from the Göteborg study area and the rest of Sweden.

2 Enhanced pertussis surveillance in Göteborg study area

2.1 Material and methods

2.1.1 Background, routine reporting system

During 1980 to1995 laboratory confirmed pertussis was voluntarily reported from all bacteriological laboratories with full personal identifiers. Pertussis was included in the Communicable Disease Act in 1997. Since then, all cases of pertussis, either clinically suspected or/and laboratory confirmed by culture, PCR or serology were reported to the Swedish Institute for Infectious Disease Control through a computer-linked reporting system. Basic data in this routine reporting system include for example the unique Swedish person identifier and place of residence including county, but there are limited or no clinical or vaccination data. Laboratory reports include laboratory method and (normally) date of sampling and/or date of positive result.

2.1.2 Enhanced surveillance program

Briefly, all cases of culture or PCR-confirmed pertussis occurring in Sweden in children born since 1996 were identified via the national register of reports according to the Communicable Disease Act from October 1, 1997. All reports except those from Göteborg area between this date and December 31, 2002, were followed-up in detail. Vaccination data as well as clinical data (including data on hospitalisation, complications and antibiotic treatment) were collected by telephone interview according to the same routines as in the nation-wide efficacy trial [7,8]. Detailed description of the enhanced surveillance program and the routine reporting system are found in previous main progress reports [9,10,11,12,13,14,15] and publications [16,17,18,19], with a nine year report updating these results until September 30, 2006 [1].

From January 1, 2003, until September 30, 2006, also cases in the Göteborg study area were included in the enhanced followed-up. The present report is the first enhanced surveillance progress from this area. The results are presented for episodes occurring in Göteborg study area (549 episodes) respectively in Sweden except Göteborg study area (906 episodes) during the 3 ¼-year period from January 1, 2003 until September 30, 2006, for children born from 1996 until September 30, 2006 for whom we have access to clinical follow-up and vaccination data, Sections 2.3-2.10.

2.1.3 Pertussis case definitions

An episode of pertussis was defined by (primary case definition) detection of *B. pertussis* by culture- or PCR in a sample obtained >6 months after a previous positive sample, and regardless of symptoms. Typical pertussis was defined as culture- or PCR-confirmed pertussis with twenty-one days or more of spasmodic cough, corresponding to the WHO pertussis case definition of 1991, established for use in the efficacy trials in order to reduce observer bias [20]. Additional analyses according to the EU and WHO case definitions of 2002-2003 [21, 22] have been added as appropriate.

The start of an episode was defined as first day of cough (if no cough day of sampling). In the present technical report also analyses according to sampling date have been added as appropriate.

2.1.4 Person time and incidence calculations

Age-specific incidence rates of pertussis for children born from January 1, 1996 until September 30, 2006 were based on the number of notified pertussis cases during the study period January 1, 2003, to September 30, 2006 as described in the main report [1].

We computed person time of observation by using data on yearly birth cohort size and months of surveillance for pertussis disease. Person time figures, for Sweden except the Göteborg study area, are

taken from the "Nine year report" [1]. Person time figures for the Göteborg study area are derived from those for Sweden except Göteborg. Municipality specific figures from Statistics Sweden showed that, in mean for children born 1996 or later, **9.1**% of the children were born in the Göteborg study area. To simplify person-time calculations for different cohorts, we used denominator data based on the following; that the total number of births were equally distributed during the calendar months, that children were born mid-month, and that, for dose-specific incidence rates, vaccinations were given on the recommended schedule in the middle of the third, fifth and twelfth month after the day of birth.

In addition, annual overall incidences and age-specific incidences of pertussis in the region of Västra Götaland were based on the number of notified culture- or PCR-confirmed pertussis in the whole population of the region and in all age groups, based on age at sampling/notification, and on the corresponding mid-year populations derived from the mean of population figures at two consecutive new years divided by two (data from Statistics Sweden, http://www.scb.se).

2.2 Göteborg study area, vaccines and vaccinated cohorts

2.2.1 Göteborg study area

The Göteborg study area is defined as the city of Göteborg and nine additional surrounding municipalities (Table 5), corresponding to the study area of the Göteborg pertussis trial [2] the same area as the mass vaccination project [4].

Table 5 Municipalities participating in the Göteborg mass-vaccination project

County	**Municipality**	**Mean population 2004**
Halland	Kungsbacka	68 331
Västra Götaland	Göteborg	479 899
”	Mölndal	57 791
”	Härryda	31 582
”	Partille	33 381
”	Öckerö	12 238
”	Stenungsund	22 655
”	Tjörn	15 086
”	Ale	26 279
”	Lerum	36 207

Total population, 2004 (mean population, Statistics Sweden), in the Göteborg study area was about 783 thousand people, i.e. 8.7% of the Swedish population. All but one (Kungsbacka) of the municipalities in the Göteborg study area belong to the region of Västra Götaland, a region with a total population of 1 519 thousand people, i.e. 16.9% of the Swedish population. Thus Västra Götaland can be divided in two parts, municipalities participating or not participating in the Göteborg mass-vaccination project, with population sizes 715 respectively 804 thousand people, i.e. 8.0% and 8.9% of the Swedish population mid 2004.

2.2.2 Vaccines used from 1996 in Göteborg study area

2.2.2.1 General vaccination at 3-5-12 months

Figure 1 of the main nine year report illustrates the procurement of vaccines by county 1996 –2006 [1]. In the nine municipalities of Västra Götaland and the one (Kungsbacka) of Halland, a trivalent one-component DTPa with only PT (DiTeKik®, SSI) was used within the ordinary vaccination program from 1996 until February 1999, when three municipalities (Ale, Lerum, Kungsbacka) switched to a pentavalent two-component DTPa-IPV-Hib with PT and FHA (Pentavac®, Sanofi Pasteur MSD). The remaining six municipalities continued with DiTeKik® until February 2000. By March or April 2000 all municipalities in the Göteborg study area used Pentavac®. Children who had received one or two doses with DiTeKik® got the remaining doses with Pentavac® during a period that followed after the change of vaccine.

From 1999 Kungsbacka has followed the routines of Halland. They used Pentavac until 2000, then the corresponding pentavalent three-component combination vaccine from GSK (Infanrix-Polio+Hib) for one year, again Pentavac for two years, then again Infanrix-Polio+Hib for three years, and the latest switch was to Pentavac® in spring 2006.

The corresponding hexavalent vaccines has to a small extent been used to infants at risk for hepatitis B, but most of these were vaccinated with monovalent hepatitis B vaccine administered separately or concomitantly with the pentavalent vaccine.

2.2.2.2 Catch-up

General and free catch-up by use of monovalent one-component Pa vaccine (Kikhostevacin, SSI) was in the Göteborg study area offered to all children born in the 1990:s during the mass vaccination project. There were also vaccine trials including vaccination with either DiTeKik or Kikhostevaccin, SSI. In all, about 56% of all children until about seven years of age were vaccinated during the years 1996-1999 [3].

2.2.2.3 School boosters

A school booster to children born from 1995 was implemented autumn 2005. No child born 1996 with a pertussis episode during 2005-2006 had yet received this booster dose during the present follow/up period.

2.2.3 Vaccinated birth cohorts in the Göteborg study area

2.2.3.1 Summary of vaccinated birth cohorts

The table 6 summarises vaccines used in different cohorts, and data available in the study database concerning laboratory reports, vaccination data and clinical information. To each cohort there is a short description and an estimate of the vaccination rate.

Table 6 Birth cohorts in the Göteborg study area

1990-5	Children born 1990-1995. Almost 70,000 were vaccinated with DiTeKik® or monovalent one-component vaccine (Kikhostevaccin®, SSI) either within vaccine trials or during the years 1997-2000 within the Göteborg mass vaccination study. Vaccination coverage 3 doses in these cohorts is about 60% (detailed vaccination coverage and information on laboratory reports was collected within the mass vaccination project until spring 2000). Information on laboratory reports in these cohorts is missing thereafter.
1996-8	Children born 1996-1998, vaccinated with DiTeKik®. Vaccine coverage for three doses Pa at 2 years of age is above 98%, according to the statistics from the Child Health Centres from 1999-2001. Information on laboratory reports is lacking for the period 1996-97.09. Detailed clinical information in relation to laboratory reports is missing for the period 199710-20021231.
1999	Children born 1999, vaccinated with DiTeKik® and/or Pentavac®. Vaccine coverage for three doses Pa at 2 years of age is above 98%, according to the statistics from the Child Health Centres from 2002. Detailed clinical information is missing for laboratory confirmed pertussis during the period 1999-20021231
2000-2002	Children born 2000-2002, vaccinated with Pentavac®. Vaccine coverage for three doses Pa at 2 years of age is above 98%, according to the statistics form the Child Health Centres from 2003-2005. Detailed clinical information is missing for laboratory confirmed pertussis during the period 2000-20021231
2003-2005	Children born 2003-2005. Part of the 2005 cohort still not fully immunized. Vaccine coverage for three doses Pa at 2 years of age is above 98% for the cohorts born 2003, according to the statistics form the Child Health Centres from 2006. These are the first one-year birth-cohorts completely covered by the Part 1 analyses in this report.
2006:1-9	Children born January to September 2006, still not fully immunised.

2.2.3.2 Followed birth cohorts within the enhanced surveillance

The analyses include enhanced follow-up from January 1, 2003, until September 30, 2006, of children born 1996 or later and residing in the Göteborg study area at time of pertussis. These children are followed continuously from 1 January 2003 in the same way as children from other parts of the country are followed continuously from 1 October 1997.

2.2.3.3 Birth cohorts in the additional analyses

In Section 3, results from the Göteborg study area are summarized for the whole nine year period and each annual birth cohort is presented with the corresponding age cohorts from the study areas in the rest of Sweden. Available data from the Göteborg study area are also grouped in two groups, which can be characterized as follows. The 1996-1998 cohort, most infants vaccinated with DiTeKik® during a period when toddlers were catch-up vaccinated with monovalent Pa vaccine, and the 2000-2006.9 cohort, most infants vaccinated with Pentavac®, without catch-up of older siblings.

2.3 Laboratory confirmed pertussis cases used for the 3 ¾ year report

In the middle of December 2006 there were 581 pertussis episodes entered in the surveillance database with a date for the positive sample from January 1, 2003 or later for children in the Göteborg study area. Four of those children with an onset of cough during 2002 were excluded and for 28 (4.9%) of remaining 577 children clinical data had not been possible to collect. Thus, for **549** episodes in 548 children both clinical and vaccination data were entered in the surveillance database for children in the Göteborg study area with an onset of the episode from January 1, 2003 until September 30, 2006.

There was one child from the Göteborg study area with two pertussis episodes after January 2003, the first one occurred at9 months and the second episode at 24 months of age.

From other parts of Sweden there were 971 pertussis episodes entered in the database with a date for the positive sample from January 1, 2003 or later for children born January 1, 1996 until September 30, 2006. Eleven of those children with an onset of cough during 2002 were excluded and for 54 (6.0%) of remaining 960 children clinical data had not been possible to collect. For **906** episodes both clinical and vaccination data were entered in the surveillance database for the episodes for children in other parts of Sweden with an onset of the pertussis episode from January 1, 2003 until September 30, 2006.

In Sections 2.3-2.10, we use data from 549 + 906 = 1 455 pertussis episodes and we estimate and compare pertussis incidence, severeness of the illness and use of antibiotics for children living in the Göteborg study area respectively in the rest of Sweden.

In sections 2.4 – 2.6 we present number of pertussis cases per area, per birth cohort and calendar period and per vaccination status of the child, and the pertussis incidences for different age groups for the 1 455 episodes of laboratory confirmed pertussis and we compare the results from the two areas of Sweden. In section 2.7 we present results on hospitalisation for children for whom we have data on length of hospitalisation (1 452). The corresponding results for any complication (1 450) due to the pertussis illness during the pertussis episode and the duration of spasmodic cough (1 455) are found in sections 2.8 and 2.9. Treatment with antibiotics is covered in section 2.10.

There are laboratory reports in the database for nine children (two from the Göteborg study area) who died due to the pertussis. For ethical reasons the parents of these nine children have not been contacted and hence there are no clinical data, except for limited information obtained from medical personnel. A national summary about deaths due to pertussis is provided in the main (nine year) report, section 2.17[1].

2.4 Laboratory confirmed pertussis per calendar period & birth cohort

All 1 455 laboratory confirmed cases of pertussis were divided by the followed birth-cohorts and mentioned calendar periods for onset of cough (or, if no cough - 11 children, whereof 9 from the Göteborg study area - during the episode, for date of the positive sample) as well as on the two areas.

Table 7 Total number of reported laboratory confirmed cases of pertussis from January 1, 2003 until September 30, 2006 per birth-cohort, period of onset of cough and area for pertussis episode.

Birth-cohort	Area	2003	2004	2005	2006 Q1-Q3	Total
1996	**Sweden except Gbg**	**14**	**60**	**41**	**8**	**123**
	Göteborg study area	***7***	***34***	***3***	***5***	***49***
1997	**Sweden except Gbg**	**7**	**25**	**26**	**8**	**66**
	Göteborg study area	***7***	***36***	***14***	***2***	***59***
1998	**Sweden except Gbg**	**12**	**34**	**40**	**14**	**100**
	Göteborg study area	***3***	***42***	***11***	***1***	***57***
1999	**Sweden except Gbg**	**8**	**18**	**25**	**10**	**61**
	Göteborg study area	***9***	***39***	***10***	***2***	***60***
2000	**Sweden except Gbg**	**7**	**21**	**14**	**20**	**62**
	Göteborg study area	***5***	***12***	***4***	***1***	***22***
2001	**Sweden except Gbg**	**8**	**16**	**13**	**9**	**46**
	Göteborg study area	***8***	***28***	***4***	***1***	***41***
2002	**Sweden except Gbg**	**15**	**15**	**10**	**6**	**46**
	Göteborg study area	***17***	***32***	***5***	***0***	***54***
2003	**Sweden except Gbg**	**52**	**40**	**11**	**4**	**107**
	Göteborg study area	***24***	***55***	***11***	***0***	***90***
2004	**Sweden except Gbg**	**-**	**116**	**40**	**9**	**165**
	Göteborg study area		***73***	***18***	***0***	***91***
2005	**Sweden except Gbg**	**-**	**-**	**74**	**13**	**87**
	Göteborg study area			***14***	***5***	***19***
2006 Q1-Q3	**Sweden except Gbg**	**-**	**-**	**-**	**43**	**43**
	Göteborg study area				***7***	***7***
Total	**Sweden except Gbg**	**123**	**345**	**294**	**144**	**906**
	Göteborg study area	***80***	***351***	***94***	***24***	***549***

2.4.1 Laboratory confirmed pertussis among unvaccinated children

Among 1 455 followed children with laboratory confirmed pertussis, 397 (27.3%) had not received a pertussis vaccine prior to the illness – for episodes in the Göteborg study area there were 88 (16.0%) and for children in Sweden except Göteborg there were 309 (34.1%) unvaccinated children, Table 8.

Table 8 Number of reported laboratory confirmed cases of pertussis from January 1, 2003 until September 30, 2006 per birth-cohort, period of onset of cough and area for the pertussis episode among children who had not received any pertussis vaccine before onset of cough.

Birth-cohort	Area	2003	2004	2005	2006 Q1-Q3	Total
1996	**Sweden except Gbg**	**0**	**5**	**2**	**1**	**8**
	Göteborg study area	***1***	***1***	***0***	***0***	***2***
1997	**Sweden except Gbg**	**3**	**5**	**1**	**1**	**10**
	Göteborg study area	***0***	***0***	***0***	***0***	***0***
1998	**Sweden except Gbg**	**1**	**1**	**0**	**1**	**3**
	Göteborg study area	***0***	***2***	***1***	***0***	***3***
1999	**Sweden except Gbg**	**4**	**5**	**1**	**1**	**11**
	Göteborg study area	***0***	***2***	***1***	***0***	***3***
2000	**Sweden except Gbg**	**1**	**6**	**3**	**4**	**14**
	Göteborg study area	***0***	***2***	***0***	***0***	***2***
2001	**Sweden except Gbg**	**1**	**4**	**3**	**2**	**10**
	Göteborg study area	***0***	***2***	***0***	***0***	***2***
2002	**Sweden except Gbg**	**5**	**5**	**1**	**1**	**12**
	Göteborg study area	***3***	***0***	***0***	***0***	***3***
2003	**Sweden except Gbg**	**41**	**16**	**1**	**0**	**58**
	Göteborg study area	***13***	***6***	***1***	***0***	***20***
2004	**Sweden except Gbg**	**-**	**77**	**13**	**1**	**91**
	Göteborg study area		***33***	***6***	***0***	***39***
2005	**Sweden except Gbg**	**-**	**-**	**60**	**5**	**65**
	Göteborg study area			***8***	***0***	***8***
2006 Q1-Q3	**Sweden except Gbg**	**-**	**-**	**-**	**27**	**27**
	Göteborg study area				***6***	***6***
Total	**Sweden except Gbg**	**56**	**124**	**85**	**44**	**309**
	Göteborg study area	***17***	***48***	***17***	***6***	***88***

All 397 episodes, but four – three from the Göteborg study area, among the unimmunised children were symptomatic according to the clinical follow-up. The minimum duration of cough, if cough, was 7 days - the median duration was 45 days. Spasmodic cough for 21 days or more (episodes according to the WHO-definition) was reported for 82.4% of the episodes - the median duration was 34 days. For 46 (11.6%) of the episodes there were no spasmodic cough at all.

There were differences between the two areas. The median duration of cough and spasmodic cough among the 88 children from Göteborg study area was 40 and 25 days, the corresponding figures from Sweden except Gbg was 47 and 37 days. Spasmodic cough for 21 days or more was reported for 58.0% of the Göteborg study area children and for 89.0% of children from the rest of Sweden. For 31.8% respectively 5.8% of the episodes no spasmodic cough was reported. All these differences are statistically significant.

Table 9 shows the age distribution of the laboratory confirmed cases at onset of cough for the unimmunised children. Most of the pertussis cases (69%) in this subgroup occurred before three months of age, i.e. before the scheduled first dose of a DTPa-containing vaccine. In the Göteborg study area nearly 74% of the pertussis cases among unvaccinated occurred before 3 months of age and the proportion in the rest of Sweden was 67%. There is no statistically significant difference between the two areas (p-value=0.82).

Table 9 Age at onset of cough for 397 laboratory confirmed cases of pertussis from January 1, 2003 until September 30, 2006 per area among unvaccinated children.

		Area				Total	
		Göteborg study area		Sweden except Gbg			
		Number	%	Number	%	Number	%
Age in days at onset of cough	0-30	15	17.0	52	16.8	67	16.9
	31-60	25	28.4	80	25.9	105	26.4
	61-90	25	28.4	75	24.3	100	25.2
	91-120	5	5.7	17	5.5	22	5.5
	121-150	2	2.3	7	2.3	9	2.3
	151-180	0	.0	4	1.3	4	1.0
	181-365	2	2.3	4	1.3	6	1.5
	≥366	14	15.9	70	22.7	84	21.2
Total		88	100.0	309	100.0	397	100.0

2.4.2 Laboratory confirmed pertussis among vaccinated children

Among 1 455 reported children 1 058 (72.7%) had received at least one dose of a pertussis vaccine prior to onset of the pertussis episode - 792 children had received 3-4 doses, 114 had received 2 doses and 152 had received only one dose of pertussis vaccine.

Among children in the Göteborg study area 338 (61.6%), 76 (13.8%) and 47 (8.6%) had received three, two or one dose of a pertussis vaccine prior to onset of the pertussis episode. Corresponding figures for Sweden except Gbg were; 454 (50.1%), 38 (4.2%) and 105 (11.6%) – (p-value<0.000). Thus, relatively more children in the Göteborg study area were vaccinated with two or more doses before the episode. Table 10 give the figures for 906 children vaccinated with two or more doses before the episode.

Table 10 Number of reported laboratory confirmed cases of pertussis from January 1, 2003 until September 30, 2006 per birth-cohort, period of onset of cough and area for the pertussis episode among children vaccinated with two or more doses.

Birth-cohort	Area	2003	2004	2005	2006 Q1-Q3	Total
1996	**Sweden except Gbg**	**14**	**55**	**38**	**7**	**114**
	Göteborg study area	***6***	***33***	***3***	***5***	***47***
1997	**Sweden except Gbg**	**4**	**20**	**25**	**7**	**56**
	Göteborg study area	***7***	***35***	***14***	***2***	***58***
1998	**Sweden except Gbg**	**11**	**33**	**40**	**13**	**97**
	Göteborg study area	***3***	***40***	***9***	***1***	***53***
1999	**Sweden except Gbg**	**4**	**13**	**24**	**9**	**50**
	Göteborg study area	***9***	***36***	***9***	***2***	***56***
2000	**Sweden except Gbg**	**6**	**14**	**11**	**16**	**47**
	Göteborg study area	***5***	***10***	***4***	***1***	***20***
2001	**Sweden except Gbg**	**7**	**11**	**10**	**7**	**35**
	Göteborg study area	***8***	***26***	***4***	***1***	***39***
2002	**Sweden except Gbg**	**3**	**10**	**9**	**5**	**27**
	Göteborg study area	***12***	***32***	***5***	***0***	***49***
2003	**Sweden except Gbg**	**2**	**17**	**10**	**4**	**33**
	Göteborg study area	***4***	***44***	***10***	***0***	***58***
2004	**Sweden except Gbg**	**-**	**4**	**16**	**8**	**28**
	Göteborg study area		***17***	***9***	***0***	***26***
2005	**Sweden except Gbg**	**-**	**-**	**0**	**4**	**4**
	Göteborg study area			***3***	***5***	***8***
2006 Q1-Q3	**Sweden except Gbg**	**-**	**-**	**-**	**1**	**1**
	Göteborg study area				***0***	***0***
Total	**Sweden except Gbg**	**51**	**177**	**183**	**81**	**492**
	Göteborg study area	***54***	***273***	***70***	***17***	***414***

All children but five vaccinated with two or more doses were coughing during the pertussis episode. The minimum duration of cough, if cough, was 4 days – the median duration was 45 days. Spasmodic cough for 21 days or more (WHO-definition) was reported for 65.7% of the episodes compared to 82.4% for the unimmunised children – the median duration was 30 days. For 28.1% of the episodes there was no spasmodic cough compared to 11.6% for the unimmunised children.

There were differences between the two areas. The median duration of cough and spasmodic cough among 414 children from Göteborg study area was 39 and 24 days. The corresponding figures from Sweden except Gbg was higher; 48 and 34 days. Spasmodic cough for 21 days or more was reported for 54.3% of the Göteborg children and for 75.2% of children from the rest of Sweden. For 36% respectively 21.5% of the episodes no spasmodic cough was reported. All these differences are statistically significant.

2.4.3 Some comparisons between cases from the Göteborg study area and the rest of Sweden

Taken population sizes into account, in mean **9.1**% newborns in the Göteborg study area and 90.9% in the rest of Sweden during 1996-2006, there were many more pertussis cases are reported in the Göteborg study area for each birth cohort from 1996 and for each of the follow-up years from 2003, compared to the number of cases reported in the rest of Sweden both for unvaccinated and vaccinated children.
The proportion of children with spasmodic cough for 21 or more days was 58.0% (unvaccinated) and 54.3% (vaccinated) for children in the Göteborg study area and 89.0% respectively 75.2% for children in the rest of Sweden. The proportion of children **without** spasmodic cough during the pertussis illness was 31.8% (unvaccinated) and 36.0% (vaccinated) in the Göteborg study area and 5.8% respectively 21.5% for children in the rest of the country. Thus, proportionally more "mild" pertussis cases are reported in the Göteborg study area both among unvaccinated and vaccinated children (Table 2).

Summing up so far: There are considerable, and statically significant, differences between the two areas comparing laboratory confirmed pertussis cases for whom we have both vaccination and clinical data. For all categories in Table 2 there are a more or less over-representation of cases in the Göteborg study area.

2.5 Laboratory confirmed pertussis in children born 1996 – Sept. 30, 2006

For this cohort of children there were 1 455 reports of laboratory confirmed pertussis with an onset of the episode from January 1, 2003 until September 30, 2006 for which we have data on both vaccinations and the clinical outcome. There were 549 cases among children in the Göteborg study area, whereof 88 unvaccinated, and 906, whereof 309 unvaccinated, among children in the rest of Sweden, Table 11.

Table 11 Number of reported laboratory confirmed cases from January 1, 2003 until September 30, 2006 per birth-cohort from 1996 to September 30, 2006, number of vaccine doses prior to the episode and area of episode. The number of cases with 21 or more days of spasmodic cough is given in parenthesis.

Birth-cohort	No. of doses of pertussis vaccine	Sweden except Göteborg		Göteborg study area		Total
		Not vaccinated No. (≥21)	Vaccinated No. (≥21)	Not vaccinated No. (≥21)	Vaccinated No. (≥21)	No. (≥21)
1996	0	8	-	2	-	10 (9)
	1		1		0	1 (1)
	2		0		1	1 (1)
	3		114		46	160 (117)
1997	0	10	-	0	-	10 (9)
	1	-	0	-	1	1 (1)
	2	-	0	-	0	0 (0)
	3	-	56	-	58	114 (86)
1998	0	3	-	3	-	6 (6)
	1	-	0	-	1	1 (1)
	2	-	0	-	1	1 (1)
	3	-	97	-	52	149 (111)
1999	0	11	-	3	-	14 (12)
	1	-	0	-	1	1 (0)
	2	-	0	-	1	1 (1)
	3	-	50	-	55	105 (73)
2000	0	14		2	-	16 (15)
	1	-	1	-	0	1 (1)
	2	-	0	-	0	0 (0)
	3	-	47	-	20	67 (43)
2001	0	10		2		12 (12)
	1	-	1	-	0	1 (1)
	2	-	0	-	0	0 (0)
	3	-	35	-	39	74 (40)
2002	0	12		3		15 (12)
	1	-	7	-	2	9 (6)
	2	-	1	-	8	9 (3)
	3	-	26	-	41	67 (35)
2003	0	58	-	20	-	78 (58)
	1	-	16	-	12	28 (18)
	2	-	14	-	38	52 (20)
	3	-	19	-	20	39 (25)
2004	0	91		39		130 (101)
	1		46	-	26	72 (55)
	2		18	-	21	39 (24)
	3		10	-	5	15 (11)
2005	0	65	-	8	-	73 (62)
	1		18	-	3	21 (18)
	2		4	-	6	10 (3)
	3		0	-	2	2 (1)
2006.09	0	27	-	6	-	33 (31)
	1		15	-	1	16 (14)
	2		1	-	0	1 (0)
Total	0	309	-	88	-	397 (327)
Total	1	-	105 (93)		47 (23)	152 (116)
Total	2	-	38 (28)		76 (25)	114 (53)
Total	3	-	454 (342)		338 (200)	792 (542)
Total	0 – 3	309 (276)	597 (463)	88 (51)	461 (248)	1455 (1038)

2.6 Person-time & incidence in children born 1996 – September 30, 2006

See sections 2.11 and 2.13 in the main nine year report [1] for population figures from 1996 until September 30, 2006 in Sweden and section 2.1.4 for the general principles for calculation of person time of follow-up. In Sections 2.6-2.10 all person-time of follow-up before January 1, 2003 are excluded. During the remaining 3 ¾ year period of follow-up children in the Göteborg study area have been followed for approximately 281 825 person-years and children in the rest of Sweden for 2 815 145 years.

The tables present total number of person-years, total number of laboratory confirmed pertussis cases and incidence figures with 95% confidence intervals for children in the each of the two areas of Sweden that we compare divided in four combinations of ages corresponding to the vaccination intervals in the national vaccination program;
- Before dose 1(<3 months of age);
- Between Dose 1 and Dose 2 (3 - <5 months of age);
- Between Dose 2 and Dose 3 (5 - < 12 months of age);
- Between Dose 3 (12 months of age) and Dose 4 (10 years of age).

The relative risk for reported laboratory positive pertussis episode in the Göteborg study area compared to the rest of Sweden and a 95% confidence interval for the relative risk is also calculated for each age/vaccination interval. The interval after 1 year of age is also divided in 9 one-year age intervals of follow-up for which the same information is given.

Table 12 presents these data for the total number of laboratory confirmed pertussis cases (irrespective of clinical status and vaccination status), whereas in Table 13 the same analyses are done for children with 21 or more days of spasmodic cough (irrespective of vaccination status). The approach in Tables 12-13 is an intent to treat, i.e. the overall effect of the vaccination program in the studied cohorts by use of two different case definitions (Table 12, all laboratory reported cases, Table 13, all laboratory-reported cases of typical pertussis).

In Tables 14 and 15 the corresponding analyses are done, but for children vaccinated with two or more than two doses prior to onset of cough (vaccine failures). The approach in Tables 14-15 is hence a per protocol analyses, i.e. the effect of the vaccination program in children who are vaccinated according to the recommendations in the national program. Also these analyses are done according to two different case definitions; Table 14 presents all vaccinated and laboratory reported cases, whereas table 15 presents all vaccinated and laboratory reported cases of typical pertussis.

Table 12 presents all children born from 1996 and onwards who had a pertussis episode between January 1, 2003 and September 20, 2006, and regardless of vaccination status at onset of episode, i.e. the 549 episodes from Göteborg study area and also 906 episodes from the rest of Sweden during the same 3 ¾ year period of enhanced surveillance. In each age group (but the last one), the number of cases reported from Göteborg were high in relation to population size in the area, with 197 infant cases and 352 cases in children aged 1 year or more reported in this area. From the rest of Sweden there were 382 infant cases and 524 cases in children aged from 1 year. The relationship between number of children born in the Göteborg study area and born in the rest of Sweden was about 1 to 10.

In both Göteborg and the rest of Sweden the highest incidences were reported in the youngest age-groups, with a marked decline from 5 months of age, and a further decline from 12 months of age. In Göteborg there was a further decline until lowest incidence at 3-4 years, but at this age Göteborg children still had a 6.7 times higher risk of being reported as a laboratory verified case of pertussis in comparison with the rest of the country. From this age there was in Göteborg a slight increase until a maximum after infancy at 6-8 years of age. This is in contrast to the rest of Sweden, where the age-specific incidences dropped more markedly during the infancy year and stayed low until a slight increase starts at about 5 years.

Major differences were also found, when comparing children from the two areas with 21 or more days of spasmodic cough regardless of vaccination status, Table 13, and when comparing children vaccinated with

two or more doses before onset of episode in Göteborg study area versus rest of Sweden (both for any and typical pertussis), Tables 14-15.

Table 12 Total person-time of follow-up, number of observed culture- or PCR-confirmed cases, incidence per 100 000 person years and relative risk of having a reported laboratory-verified episode of pertussis in the different age-groups for children born from January 1, 1996 until September 30, 2006, followed from January 1, 2003 until September 30, 2006 in two areas of Sweden – Sweden except Gbg (except the Göteborg study area) and the Göteborg study area. Age-specific incidences per 100 000 person-years are given for the period < 3 months of age (before scheduled age for Dose 1), the period 3 - <5 months of age (after scheduled age for Dose 1 and before Dose 2), the period 5 - <12 months of age (after scheduled age for Dose 2 and before Dose 3) and thereafter in one-year periods from 12 months of age (after scheduled age for Dose 3). Age is calculated at the date for onset of cough during the episode (for cases without cough the date for the positive sample is used).

Period or Age	Person time of follow-up in years	Number of laboratory confirmed cases	Incidence per 100 000 person years and 95% confidence interval	Relative risk Göteborg compared to Sweden except Gbg
Before Dose 1 or <3 months	-	-	-	-
Sweden except Gbg	86 065	207	241 (209-276)	-
Göteborg study area	*8 615*	*65*	*754 (583-961)*	***3.1 (2.4 - 4.1)***
Between Dose1 and 2 or 3-<5 months	-	-	-	-
Sweden except Gbg	57 235	129	225 (190-270)	-
Göteborg study area	*5 730*	*54*	*942 (709-1230)*	***4.2 (3.0 – 5.7)***
Between Dose 2 and 3 or 5-<12 months	-	-	-	-
Sweden except Gbg	198 085	46	23 (17-31)	-
Göteborg study area	*19 830*	*78*	*393 (311-491)*	***16.9 (11.8 – 24.4)***
After Dose 3 or 12-<24 months	-	-	-	-
Sweden except Gbg	331 500	33	10 (7-14)	-
Göteborg study area	*33 185*	*54*	*163 (122-212)*	***16.3 (10.6 – 25.2)***
24-<36 months	-	-	-	-
Sweden except Gbg	321 300	41	13 (9-17)	-
Göteborg study area	*32 165*	*39*	*121 (86-166)*	***9.5 (6.1 – 14.8)***
36-<48 months	-	-	-	-
Sweden except Gbg	311 100	36	12 (8-16)	-
Göteborg study area	*31 145*	*24*	*77 (49-115)*	***6.7 (4.0 – 11.2)***
48<60 months	-	-	-	-
Sweden except Gbg	306 000	52	17 (13-22)	-
Göteborg study area	*30 635*	*40*	*131 (93-178)*	***7.7 (5.1 – 11.6)***
60<72 months	-	-	-	-
Sweden except Gbg	306 775	71	23 (18-29)	-
Göteborg study area	*30 710*	*44*	*143 (104-192)*	***6.2 (4.3 – 9.0)***
72- <84 months	-	-	-	-
Sweden except Gbg	309 450	80	26 (20-32)	-
Göteborg study area	*30 980*	*66*	*213 (165-271)*	***8.2 (5.9 – 11.4)***
84-<96 months	-	-	-	-
Sweden except Gbg	270 030	100	37 (30-45)	-
Göteborg study area	*27 035*	*54*	*199 (150-261)*	***5.4 (3.9 – 7.5)***
96-<108 months	-	-	-	-
Sweden except Gbg	188 430	74	39 (31-49)	-
Göteborg study area	*18 865*	*25*	*133 (86-196)*	***3.4 (2.1 – 5.3)***
≥108 months	-	-	-	**-**
Sweden except Gbg	129 175	37	29 (20-39)	**-**
Göteborg study area	*12 930*	*6*	*46 (17-101)*	***1.6 (0.7 – 3.8)***
All ≥12 months	-	-	-	-
Sweden except Gbg	2 473 760	524	21 (19-23)	-
Göteborg study area	*247 650*	*352*	*142 (128-157)*	***6.7 (5.9 – 7.7)***

Table 13 Total person-time of follow-up, number of observed culture- or PCR-confirmed cases with 21 or more days of spasmodic cough, incidence per 100 000 person years and relative risk of having a reported laboratory-verified episode of pertussis in the different age-groups for children born from January 1, 1996 until September 30, 2006, followed from January 1, 2003 until September 30, 2006 in two areas of Sweden – Sweden except Gbg (except the Göteborg study area) and the Göteborg study area. Age-specific incidences per 100 000 person-years are given for the period < 3 months of age (before scheduled age for Dose 1), the period 3 - <5 months of age (after scheduled age for Dose 1 and before Dose 2), the period 5 - <12 months of age (after scheduled age for Dose 2 and before Dose 3) and thereafter in one-year periods from 12 months of age (after scheduled age for Dose 3). Age is calculated at the date for onset of cough during the episode (for cases without cough the date for the positive sample is used)

Period or Age	Person time of follow-up in years	Number of laboratory confirmed cases	Incidence per 100 000 person years and 95% confidence interval	Relative risk Göteborg study area compared to Sweden except Gbg
Before Dose 1 or <3 months				
Sweden except Gbg	86 065	180	209 (180-242)	-
Göteborg study area	*8 615*	*35*	*406 (283-565)*	***1.9 (1.4 – 2.8)***
Between Dose1 and 2 or 3-<5 months	-	-	-	-
Sweden except Gbg	57 235	114	199 (164-236)	-
Göteborg study area	*5 730*	*25*	*436 (283-644)*	***2.2 (1.4 – 3.4)***
Between Dose 2 and 3 or 5-<12 months	-	-	-	-
Sweden except Gbg	198 085	36	18 (13-25)	-
Göteborg study area	*19 830*	*27*	*136 (90-198)*	***7.5 (4.5 – 12.3)***
After Dose 3 or 12-<24 months	-	-	-	-
Sweden except Gbg	331 500	26	8 (5-11)	-
Göteborg study area	*33 185*	*24*	*72 (46-108)*	***9.2 (5.3 – 16.1)***
24-<36 months	-	-	-	-
Sweden except Gbg	321 300	34	11 (7-15)	-
Göteborg study area	*32 165*	*17*	*53 (31-85)*	***5.0 (2.8 – 8.9)***
36-<48 months	-	-	-	-
Sweden except Gbg	311 100	29	9 (6-13)	-
Göteborg study area	*31 145*	*12*	*39 (20-67)*	***4.1 (2.1 – 8.1)***
48<60 months	-	-	-	-
Sweden except Gbg	306 000	37	12 (9-17)	-
Göteborg study area	*30 635*	*22*	*72 (45-109)*	***5.9 (3.5 – 10.1)***
60<72 months	-	-	-	-
Sweden except Gbg	306 775	53	17 (13-23)	-
Göteborg study area	*30 710*	*32*	*104 (71-147)*	***6.0 (3.9 – 9.4)***
72- <84 months	-	-	-	-
Sweden except Gbg	309 450	64	21 (16-26)	-
Göteborg study area	*30 980*	*47*	*152 (111-202)*	***7.3 (5.0 – 10.7)***
84-<96 months	-	-	-	-
Sweden except Gbg	270 030	79	29 (23-36)	-
Göteborg study area	*27 035*	*33*	*122 (84-171)*	***4.2 (2.8 – 6.3)***
96-<108 months	-	-	-	-
Sweden except Gbg	188 430	61	32 (25-42)	-
Göteborg study area	*18 865*	*19*	*101 (61-157)*	***3.1 (1.9 – 5.2)***
≥108 months	-	-	-	**-**
Sweden except Gbg	129 175	26	20 (13-29)	**-**
Göteborg study area	*12 930*	*6*	*46 (17-101)*	***2.3 (0.9 – 5.6)***
All ≥12 months	-	-	-	-
Sweden except Gbg	2 473 760	409	17 (15-19)	-
Göteborg study area	*247 650*	*212*	*86 (74-98)*	***5.2 (4.4 – 6.1)***

Table 14 Total person-time of follow-up, number of observed culture- or PCR-confirmed, incidence per 100 000 person years and relative risk of having a reported laboratory-verified episode of pertussis in the different age-groups for children born from January 1, 1996 until September 30, 2006, followed from January 1, 2003 until September 30, 2006 in two areas of Sweden – Sweden except Gbg (except the Göteborg study area) and the Göteborg study area – for children vaccinated with two or more doses of a pertussis vaccine prior to date of the positive sample. Age-specific incidences per 100 000 person-years are given for the scheduled age period between Dose 2 and 3 (5 - <12 months) and thereafter in one-year periods after Dose 3 from 12 months of age. Age is calculated at the date for onset of cough during the episode (for cases without cough the date for the positive sample is used)

Period or Age	Person time of follow-up in years	Number of laboratory confirmed cases	Incidence per 100 000 person years and 95% confidence interval	Relative risk Göteborg study area compared to Sweden except Gbg
Between Dose 2 and 3	-	-	-	-
Sweden except Gbg	198 085	38	19 (14-26)	-
Göteborg study area	*19 830*	*76*	*383 (302-480)*	***20.0 (13.5 – 29.5)***
After Dose 3				-
12-<24 months	-	-	-	
Sweden except Gbg	331 500	24	7 (5-11)	-
Göteborg study area	*33 185*	*53*	*160 (120-209)*	***22.1 (13.6 – 35.7)***
24-<36 months	-	-	-	-
Sweden except Gbg	321 300	34	11 (7-15)	-
Göteborg study area	*32 165*	*38*	*118 (31-160)*	***11.2 (6.7 – 18.6)***
36-<48 months	-	-	-	-
Sweden except Gbg	311 100	30	10 (6-14)	-
Göteborg study area	*31 145*	*22*	*71 (44-107)*	***7.3 (4.2 – 12.7)***
48<60 months	-	-	-	-
Sweden except Gbg	306 000	37	12 (9-17)	-
Göteborg study area	*30 635*	*37*	*121 (85-166)*	***10.0 (6.3 – 15.8)***
60<72 months	-	-	-	-
Sweden except Gbg	306 775	59	19 (15-25)	-
Göteborg study area	*30 710*	*42*	*137 (99-185)*	***7.1 (4.8 – 10.6)***
72- <84 months	-	-	-	-
Sweden except Gbg	309 450	76	25 (19-31)	-
Göteborg study area	*30 980*	*62*	*200 (153-257)*	***8.6 (6.2 – 12.0)***
84-<96 months	-	-	-	-
Sweden except Gbg	270 030	91	34 (27-41)	-
Göteborg study area	*27 035*	*54*	*200 (150-261)*	***5.9 (4.2 – 8.3)***
96-<108 months	-	-	-	-
Sweden except Gbg	188 430	68	36 (28-46)	-
Göteborg study area	*18 865*	*24*	*127 (82-189)*	***3.5 (2.2 – 5.6)***
≥108 months	-	-	-	**-**
Sweden except Gbg	129 175	35	27 (19-38)	**-**
Göteborg study area	*12 930*	*6*	*46 (17-101)*	***1.7 (0.7 – 4.1)***
All ≥12 months	-	-	-	-
Sweden except Gbg	2 473 760	454	18 (17-20)	-
Göteborg study area	*247 650*	*338*	*136 (122-152)*	***7.4 (6.5 – 8.6)***

Table 15 Total person-time of follow-up, number of observed culture- or PCR-confirmed cases with 21 or more days of spasmodic cough, incidence per 100 000 person years and relative risk of having a reported laboratory-verified episode of pertussis in the different age-groups for children vaccinated with 2 or more doses of a pertussis vaccine prior to onset of cough.... ....(For complete legend see Table 14).

Period or Age	Person time of follow-up in years	Number of laboratory confirmed cases	Incidence per 100 000 person years and 95% confidence interval	Relative risk Göteborg study area compared to Sweden except Gbg
Between Dose 2 and 3	-	-	-	-
Sweden except Gbg	198 085	28	14 (9-20)	-
Göteborg study area	*19 830*	*25*	*126 (82-186)*	***8.9 (5.2 – 15.3)***
After Dose 3				-
12-<24 months	-	-	-	
Sweden except Gbg	331 500	17	5 (3-8)	-
Göteborg study area	*33 185*	*23*	*69 (46-104)*	***13.5 (7.2 – 25.3)***
24-<36 months	-	-	-	-
Sweden except Gbg	321 300	27	8 (5-12)	-
Göteborg study area	*32 165*	*16*	*50 (28-81)*	***5.9 (3.2 – 11.0)***
36-<48 months	-	-	-	-
Sweden except Gbg	311 100	23	7 (5-11)	-
Göteborg study area	*31 145*	*10*	*32 (15-59)*	***4.3 (2.1 – 9.1)***
48<60 months	-	-	-	-
Sweden except Gbg	306 000	22	7 (5-11)	-
Göteborg study area	*30 635*	*20*	*65 (40-101)*	***9.1 (5.0 – 16.6)***
60<72 months	-	-	-	-
Sweden except Gbg	306 775	42	14 (10-19)	-
Göteborg study area	*30 710*	*30*	*98 (66-139)*	***7.1 (4.5 – 11.4)***
72- <84 months	-	-	-	-
Sweden except Gbg	309 450	60	19(15-25)	-
Göteborg study area	*30 980*	*44*	*142 (103-190)*	***7.3 (5.0 – 10.8)***
84-<96 months	-	-	-	-
Sweden except Gbg	270 030	71	26 (21-33)	-
Göteborg study area	*27 035*	*33*	*122 (84-171)*	***4.6 (3.1 – 7.0)***
96-<108 months	-	-	-	-
Sweden except Gbg	188 430	56	30 (22-39)	-
Göteborg study area	*18 865*	*18*	*95 (57-151)*	***3.2 (1.9 – 5.5)***
≥108 months	-	-	-	**-**
Sweden except Gbg	129 175	24	19 (12-28)	**-**
Göteborg study area	*12 930*	*6*	*46 (17-101)*	***2.5 (1.0 – 6.0)***
All ≥12- months	-	-	-	-
Sweden except Gbg	2 473 760	342	14 (12-15)	-
Göteborg study area	*247 650*	*200*	*81 (70-93)*	***5.8 (4.9 – 7.0)***

2.6.1 Comments to the incidence and risk tables

From 12 months of age, when 96% of the pertussis case in the Göteborg study area and 87% of the cases in the rest of Sweden had received 3 doses of a pertussis vaccine prior to onset of the episode, the risk of having a laboratory reported pertussis episode for a child in the Göteborg study area was nearly 7 times that for a child living outside that area in Sweden, RR=6.7 and 95% C.I. 5.9 – 7.7.

We noted earlier, se section 2.4.1-2.4.2, that there were many more "mild" pertussis cases reported for children in the Göteborg study area compared to Sweden except Göteborg, both among unvaccinated and vaccinated children. Therefore, in Tables 13 and 15, only cases with 21 or more days of spasmodic cough were included. The pattern of "over-risk" noted for children in the Göteborg study area in Table 12 and 14 was also seen in Tables 13 and 15, however the levels of the relative risks were lower, but still high,

even in the later mentioned tables. For example, the relative risk for a laboratory reported typical pertussis from 12 months of age was 5.2 (95% C.I. 4.4 – 6.1) for all children and 5.8 (95% C.I. 4.9 – 7.0) for vaccinated children in the Göteborg study area compared to children in Sweden except Göteborg. Thus, taken the population sizes in the two compared areas into account, there were also more "severe" cases of pertussis reported for children in the Göteborg study area.

In Tables 14 and 15 vaccine failures, i.e. children vaccinated with 2 or more doses prior to the laboratory positive pertussis episode, were studied. There were 414 such episodes reported for children from the Göteborg study area, whereof 225 with 21 or more days with spasmodic cough, and 492 reported for children from the rest of the country, whereof 370 with 21 or more days of spasmodic cough.

Comparing the relative risk figures in Table 14 with those in Table 12 the relative risk of having a laboratory-confirmed and reported episode of pertussis was higher in all age groups when only vaccinated children were included. The risk for a vaccinated child in the Göteborg study area to have a reported laboratory confirmed pertussis was 3.5 to 22 time higher (depending on the age-group) compared to the risk for a child outside that area. All relative risks in Table 14, but the last one, were statistically significant (RR=3.5 – RR=22.1).

Table 15 where only the "severe" pertussis cases were included can be compared with both Tables 13 and 14. When the "mild" pertussis cases were excluded, Table 15 vs. Table 13, relative risks are lower in each age group, but still they are high and statistically significant (RR=2.5 – RR=13.5). When unvaccinated children were excluded, Table 15 vs. Table 14, the relative risk was higher in each age group. For instance, from 12 months of age the risk for a vaccinated child of having a laboratory-confirmed episode of pertussis with 21 or more days of spasmodic cough was about 6 times higher for a child in the Göteborg study area compared to a child in the rest of Sweden, RR=5.8 95% C.I. 4.9 - 7.0.

Thus, we can also conclude that, taken the population sizes of the two compared areas into account:

1. More "severe" laboratory positive pertussis cases were reported for children in the Göteborg study area in nearly all age groups studied.
2. More cases, both "mild" and "severe", were reported for children from the Göteborg study area vaccinated with two or more doses of a pertussis vaccine prior to the pertussis episode .

Caveats in comparing the two areas of Sweden, as well as different reasons for the large differences observed, are discussed in Section 1.4.

2.7 Hospital admission for pertussis

Data on hospitalisation, defined as at least one night at hospital due to the pertussis disease during the episode, was available for 1 452 of 1 455 children born from 1996 until September 30, 2006 with an episode from January 1, 2003 until September 30, 2006 in the two areas of Sweden.

2.7.1 Hospital admission and age at the pertussis episode

Table 16 Number of hospital admission, total number of episodes, xx/yy, and percent with a hospital admission due to pertussis by age at onset of cough among children born from 1996 until September 30, 2006, during surveillance from January 1, 2003 until September 30, 2006

Hospital admission	0 - < 3 months		3 - <5 months		5 -<12 months		≥12months		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Sweden e. Gbg area	151/209	*72*	42/106	*40*	12/62	*19*	7/528	*1*	212/905	*23*
Göteborg st.area	27/65	*42*	5/38	*13*	1/85	*1*	2/359	*1*	35/547	*6*
Total hosp. Adm.	178/274	*65*	47/144	*33*	13/147	*9*	9/887	*1*	247/1452	*17*

Two hundred and forty-seven (17%) of the children had a hospital admission during the pertussis episode and 1 205 had none. Only 35 (6.4%) children in the Göteborg study area were hospitalised during the pertussis episode compared to 212 (23.4%) children in the rest of the country, this difference was

statistically significant. Hospitalisation rates for children in the Göteborg study area were significantly lower for children from the Göteborg study area in all age groups but the last (Table 16).

Age specific incidence rates of hospitalisation due to pertussis per 100 000 years of follow up in the four age groups are shown in Figure 3 (solid lines). For comparison the figure also gives the age specific incidence rates for all pertussis in the area (dotted lines). Person time of follow up for incidence calculations for the four age groups was taken from Table 12.

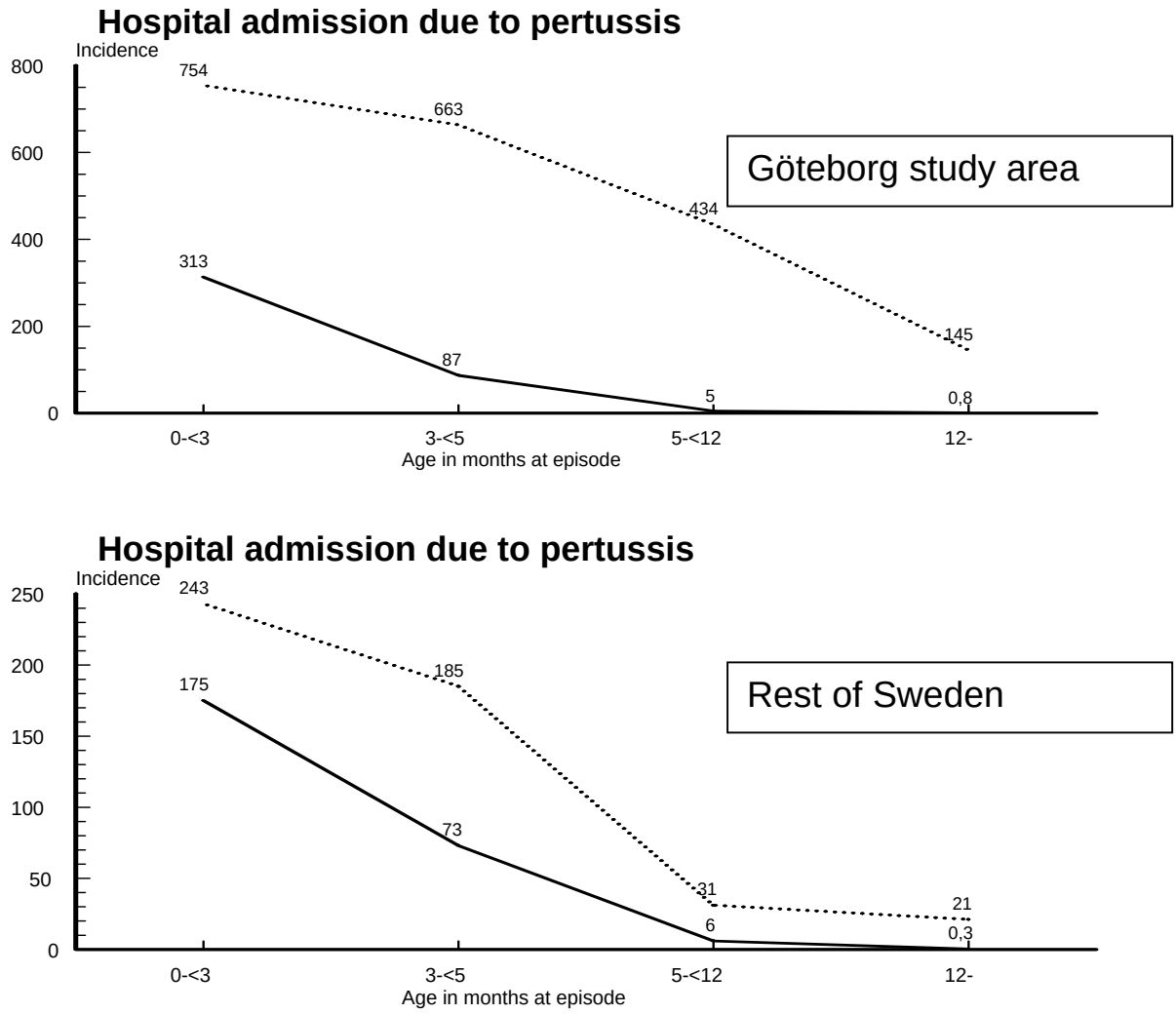


Figure 3 Age specific incidence of hospital admission due to the pertussis disease, solid lines, and age specific incidence of all pertussis, dotted lines, per 100 000 years of follow-up regardless of vaccination status for children born from 1996 to September 30, 2006 with a laboratory confirmed *B. pertussis*-from January 1, 2003 until September 30, 2006 for children in the Göteborg study area (upper diagram) and children in the rest of Sweden (lower diagram).

The age specific incidence rate of hospitalisation due to pertussis is highest, 313 per 100 000 years of follow-up, for children 0-<3 months of age and decreases, by increasing age, to less than 1 per 100 000 years for children above one year of age at the pertussis episode for children in the Göteborg study area.

The age specific incidence rate of hospitalisation due to pertussis, for children in the rest of Sweden, is highest, 175 per 100 000 years of follow-up, for children 0-<3 months of age and decreases, by increasing age, to less than 0.5 per 100 000 years for children above one year of age at the pertussis episode. The incidence rates of hospitalisation were lower for children in the Göteborg study area in all age groups, but, given an episode of pertussis, more children outside the Göteborg study area had a hospital stay during the pertussis episode.

Thus, the risk of also suffering a hospital admission due to the disease was highest among children below three months of age at beginning of the pertussis episode. Obviously circulating pertussis in the country has not decreased to a level that offers sufficient protection for the youngest unvaccinated infants.

2.7.2 Duration of hospital stay, age and vaccination status at the pertussis episode

Hospital admissions were also studied in relation to age, duration of hospital stay as well as vaccination status at start of the pertussis episode. Detailed data are given in Table 17 for children in the Göteborg study area.

Table 17 Duration of hospital stay due to the pertussis among children from the Göteborg study area, born from 1996 until September 30, 2006 and surveyed from January 1, 2003 until September 30, 2006, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

No of doses of a pertussis vaccine prior to the episode			Age of child at beginning of the pertussis episode							Total no. of children
			0-30 days	31-60 days	61-90 days	91-150 days	151-180 days	181-365 days	366- days	
Unimmunised children	**Duration of hospital stay**	**0 days**	9	11	18	5	0	2	14	**59**
		1-7 days	6	9	6	1	0	0	0	**22**
		8- days	0	5	1	1	0	0	0	**7**
	Total no. of children		**15**	**25**	**25**	**7**	**0**	**2**	**14**	**88**
	Total no. and rate of children with a hospital stay		***6 40%***	***14 56%***	***7 28%***	***2 29%***	***0 0%***	***0 0%***	***0 0%***	***29 33%***
Children vaccinated with one dose	**Duration of hospital stay**	**0 days**	-	-	-	28	9	4	3	**44**
		1-7 days	-	-	-	2	0	0	0	**2**
		8- days	-	-	-	1	0	0	0	**1**
	Total no. of children		-	-	-	**31**	**9**	**4**	**3**	**47**
	Total no. and rate of children with a hospital stay		-	-	-	***3 10%***	***0 0%***	***0 0%***	***0 0%***	***3 6%***
Children vaccinated with two or more doses	**Duration of hospital stay**	**0 days**	-	-	-	-	4	65	340	**409**
		1-7 days	-	-	-	-	0	1	2	**3**
		8- days	-	-	-	-	0	0	0	**0**
	Total no. of children		-	-	-	-	**4**	**66**	**342**	**412**
	Total no. and rate of children with a hospital stay		-	-	-	-	***0 0%***	***1 2%***	***2 1%***	***3 1%***
All children regardless of vaccination status	**Duration of hospital stay**	**0 days**	9	11	18	33	13	71	357	**512**
		1-7 days	6	9	6	3	0	1	2	**27**
		8- days	0	5	1	2	0	0	0	**8**
	Total no. of children		**15**	**25**	**25**	**38**	**13**	**72**	**359**	**547**
	Total no. and rate of children with a hospital stay		***6 40%***	***14 56%***	***7 28%***	***5 13%***	***0 0%***	***1 1%***	***2 1%***	***35 6%***

A corresponding table for the 905 children outside Göteborg study area is not included in the present report because the hospital admission proportions for 905 children outside the Göteborg study area were

nearly the same as was reported in Table 11 of the main nine year report [1] for 1 819 children outside the Göteborg study area. However, the figures that we refer to in the text that follow concern the 905 children.

The overall rate of hospital admission for **unimmunised** children from the Göteborg study area was 33%. For hospitalised children 24%, 7 of 29 children, of the hospital admissions had a duration longer than one week, Table 17. The corresponding figures for children from the rest of Sweden were significantly higher, the overall rate was 54% and for hospitalised 44%, 73 of 166 children, had a duration longer than one week.

The age specific rate of hospital admission among **unimmunised** children aged 0-30, 31-60 and 61-90 days at beginning of the pertussis episode was 40%, 56% and 28% respectively. For unimmunised children between 3-<5 and 5-<12 months and above 1 year of age, the rate of hospital admission was lower 29%, 0% and respectively 0% for children from the Göteborg study area, Table 17. Again the rates for children from the rest of Sweden were significantly higher 92%, 70% and 61% for the three youngest age-groups 0-30, 31-60 and 61-90 days and higher 54%, 38% and 0% in the tree older age-groups.

This downward trend by age in hospitalisation rate was also observed for **vaccinated** children from the rest of Sweden, both for children vaccinated with only one dose, 105 children whereof 31% (33 children) hospitalised, and for children who have received two or more doses of a pertussis vaccine before the pertussis episode, 491 children whereof 3% (13 children) hospitalised, but the levels for these trends are lower when compared to those for the unvaccinated children – for detailed figures and further discussion of hospitalisation for children outside the Göteborg study area see the main nine year report [1].

For children from the Göteborg study area there were only 6%, 3 of 47, children vaccinated with only one dose before the episode who were hospitalised and for those with at least two doses of a pertussis vaccine before the episode 1%, 3 of 412, were hospitalised – thus the two hospitalisation rates for vaccinated children from the rest of Sweden were also significantly higher. No trend of rate by age was observed for vaccinated children from the Göteborg study area.

2.8 Complications during the pertussis episode

Data on respiratory complication, neurological complication, dehydration with > 5 % loss of weight or other serious complications during the pertussis episode were registered in the database for 1 450 of 1 455 children born from 1996 until September 30, 2006 with vaccination and follow-up information for a laboratory confirmed pertussis from January 1, 2003 until September 30, 2006.

A respiratory complication (with apnea, n=101, without apnea, n=80) was reported for 181 (12%) and a dehydration for 110 (8%) of the children. Uncommon complications, i.e. neurological and other serious complications, were reported for 4 (0.3%) and 0 of the children respectively. For respiratory complications and dehydration there were statistically significant differences between the Göteborg and the rest of Sweden. The figures were respiratory complications 44 (8.1%) and 137 (15.2%), dehydration 19 (3.5%) and 91 (10.1%), neurological complications 1 (0.2%) and 3 (0.3%).

2.8.1 Any complication and age at the pertussis episode

To analyse the association between complications during the pertussis episode and age and/or vaccination status of the child at the episode, children were grouped in two groups; children with at least one noted complication and children without any complication during the pertussis episode.

Two hundred and forty-one children (15.5%) had at least one complication due to the pertussis disease during their pertussis episode and 1 209 (83.4%) had no complication at all. Fifty-six children (10.3%) from the Göteborg study area and 185 (20.5%) from Sweden outside the Göteborg study area had at least one complication during the pertussis episode – this difference was statistically significant. Rates of any complication due to the pertussis disease for children in the Göteborg study area was lower in all age-groups and significantly lower for children from the Göteborg study area in the youngest age-group.

Table 18 Number of cases with any complication, total number of episodes, xx/yy, and percent with any complication due to pertussis by age at onset of cough among children born from 1996 until September 30, 2006, during surveillance from January 1, 2003 until September 30, 2006

Any complication	0 - < 3 months		3 - <5 months		5 -<12 months		≥12 months		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Sweden e. Gbg area	103/209	*49*	26/106	*25*	8/62	*13*	48/527	*9*	185/904	*21*
Göteborg st. area	17/64	*27*	7/38	*18*	5/85	*6*	27/359	*8*	56/546	*10*
Total any complic.	120/273	*44*	33/144	*23*	13/147	*9*	75/886	*8*	241/1450	*16*

Age specific incidence rates of any complication due to pertussis per 100 000 years of follow up in the four age groups are shown in Figure 4 (solid lines). For comparison the figure also gives the age specific incidence rates for all pertussis (dotted lines).

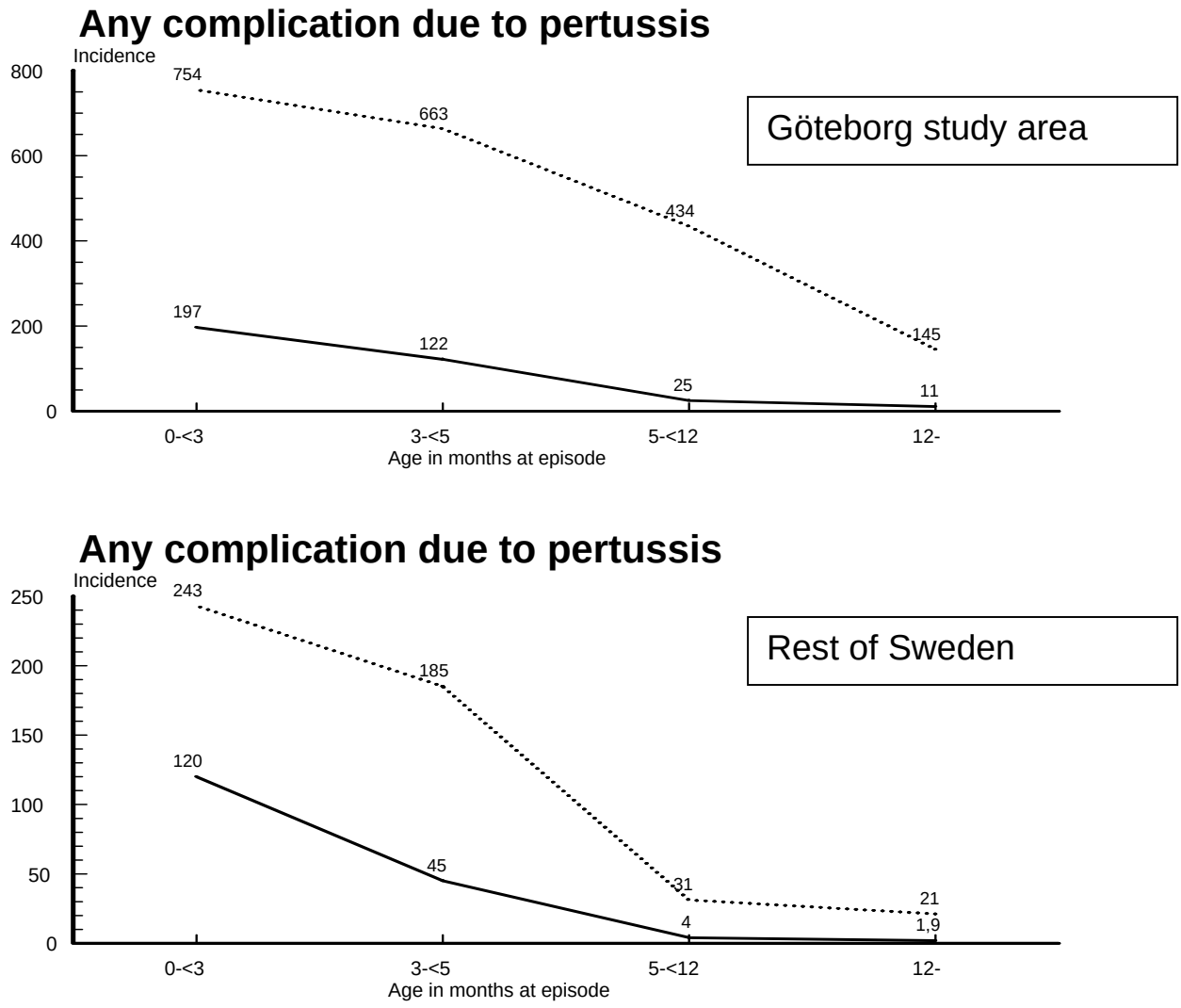


Figure 4 Age specific incidence of any complication due to the pertussis disease, solid lines, and age specific incidence of all pertussis, dotted lines, per 100 000 years of follow-up regardless of vaccination status for children born from 1996 to September 30, 2006 with a laboratory confirmed *B. pertussis* from January 1, 2003 until September 30, 2006 for children from the Göteborg study area (upper diagram) and children in the rest of Sweden (lower diagram)

The age specific incidence rate of any complication due to pertussis is highest, 197 per 100 000 years of follow-up, for children 0-<3 months of age and decreases, by increasing age, to 11 per 100 000 years for children above one year of age at the pertussis episode, for children in the Göteborg area.

The age specific incidence rate of any complication due to pertussis, among children in the rest of Sweden, is highest, 120 per 100 000 years of follow-up, for children 0-<3 months of age and decreases, by increasing age, to less than 2 per 100 000 years for children above one year of age at the pertussis episode.

Thus, there is an association between age of child at beginning of the pertussis episode and, if a pertussis disease, the risk of also suffering at least one complication due to the disease. The incidence rates were lower for children in the Göteborg study area in all age groups, but, given the pertussis disease, more children outside the Göteborg study area had a complication during the pertussis episode.

2.8.2 Any complication, age and vaccination status at the pertussis episode

The event "any complication" was also studied in relation to age as well as vaccination status at beginning of the episode. Detailed data for children from the Göteborg study area are given in Table 19. The corresponding proportions for the 904 children outside the Göteborg study area (data not shown in table) were nearly the same as was reported in the main nine year report (Table 12) for 1 818 children outside the Göteborg study area. The figures that we refer to in the text that follow concern the 904 children.

Table 19 Any complication due to the pertussis disease among children from the Göteborg study area born from 1996 until September 30, 2006, and surveyed from January 1, 2003 until September 30, 2006, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

No of doses of a pertussis vaccine prior to the episode			**Age of child at beginning of the pertussis episode**							**Total no. of children**
			0-30 days	**31-60 days**	**61-90 days**	**91-150 days**	**151-180 days**	**181-365 days**	**366- days**	
Unimmunised children	**Any complication**	**No**	12	15	20	5	0	1	11	**64**
		Yes	3	9	5	2	0	1	3	**23**
	Total no. of children		**15**	**24**	**25**	**7**	**0**	**2**	**14**	**87**
	Rate of children with any complication		***20%***	***38%***	***20%***	***29%***	***0%***	***50%***	***21%***	***26%***
Children vaccinated with one dose	**Any complication**	**No**	-	-	-	26	9	3	1	**39**
		Yes	-	-	-	5	0	1	2	**8**
	Total no. of children		-	-	-	**31**	**9**	**4**	**3**	**47**
	Rate of children with any complication		-	-	-	***16%***	***0%***	***25%***	***67%***	***17%***
Children vaccinated with two or more doses	**Any complication**	**No**	-	-	-	-	4	63	320	**387**
		Yes	-	-	-	-	0	3	22	**25**
	Total no. of children		-	-	-	-	**4**	**66**	**342**	**412**
	Rate of children with any complication		-	-	-	-	***0%***	***5%***	***6%***	***6%***
All children regardless of vaccination status	**Any complication**	**No**	12	15	20	31	13	67	332	**490**
		Yes	3	9	5	7	0	5	27	**56**
	Total no. of children		**15**	**24**	**25**	**38**	**13**	**72**	**359**	**546**
	Rate of children with any complication		***20%***	***38%***	***20%***	***18%***	***0%***	***7%***	***8%***	***10%***

The overall rate of any complication for unvaccinated Göteborg study area children was 26%. The corresponding figure for children from the rest of Sweden was significantly higher 37%. For

unimmunised children from the Göteborg study area aged 0-30, 31-60 and 61-90 days at the beginning of the pertussis episode the complication rate was 20%, 38% and 20% respectively. Since there are very few children in each age groups from 3 months of age these age-groups were combined. For children older than 3 months of age the rate of any complication was 26%.

The corresponding complication rates for children outside the Göteborg study area were; 63%, 45% 40% and 14% in the different age groups mentioned above – only for the youngest the observed difference was statistically significant. This downward trend of complication rate by increasing age are not observed for the vaccinated children, neither for children vaccinated with only one dose nor for children who have received two or more doses of a pertussis vaccine before the pertussis episode. Regardless of age the rate of any complication for children from the Göteborg study area vaccinated with one dose was 17%, and 6% for children vaccinated with 2 or more doses before the pertussis episode, and for children from the rest of Sweden the corresponding figures were 22% respectively 10%.

Finally (and for obvious reasons), there was also a strong association between any complication and a hospital stay during the pertussis episode. Sixty-three percent, 153 of 241, of children with at least one complication also had a hospital admission due to the disease during the episode. For 1 209 children without any complication the hospitalisation rate was 7.7% ($p<0.001$). For children with any complication 46% of the hospital admissions had a duration 8 days or longer. For children without any complication 19% of the hospital admissions were longer than 8 days ($p<0.001$).

Again the figures for children from the Göteborg study area were quite different from those for Sweden except Göteborg. For children with any complication, 38% in the Göteborg study area and 71% in the rest of Sweden also had a hospital admission during the pertussis episode. For children without any complication the figures were 2.7% and 11.1% in the two areas. Both observed differences of hospitalisation rates between the two areas were statistically significant.

2.9 Spasmodic cough during the pertussis episode

Data on cough and spasmodic cough were available for all 1 455 children born 1996 until September 2006 with a pertussis episode from January 1, 2003 until September 30, 2006. All children but 11 were coughing during their pertussis episode. One thousand one hundred and thirty-three (77.9%) had spasmodic cough during the pertussis episode and 322 (22.1%) reported no spasmodic cough.

2.9.1 Spasmodic cough for 21 or more days and age at the pertussis episode

Table 20 Number of pertussis cases with spasmodic cough for 21 days or more, total number of episodes, xx/yy, and percent with cough for 21 days or more by age at onset of cough among children born from 1996 until September 30, 2006, during surveillance from January 1, 2003 until September 30, 2006

Spasmodic cough for 21 or more days	0 - < 3 months		3 - <5 months		5 -<12 months		≥12 months		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Sweden e. Gbg area	182/209	*87*	95/106	*90*	48/62	*77*	414/529	*78*	739/906	*82*
Göteborg st. area	35/65	*54*	16/38	*42*	30/86	*35*	218/360	*61*	299/549	*54*
Total >=21 days	217/274	*79*	111/144	*77*	78/148	*53*	632/889	*71*	1 038/1455	*71*

One thousand and thirty-eight (71.3%) of the children had spasmodic cough for 21 or more days during the pertussis episode. The figures for a long duration of spasmodic cough were 299 (54.5%) for children in the Göteborg study area compared to 739 (81.6%) for children in the rest of the country, this difference was statistically significant. There were also significantly fewer cases with spasmodic cough for 21 or more days reported for Göteborg study area children in all age-groups (Table 20). Age specific incidence rates of spasmodic cough for 21 days or longer due to pertussis per 100 000 years of follow up in the four age groups are shown in Figure 5 (solid lines), and age specific incidence rates for all pertussis (dotted lines).

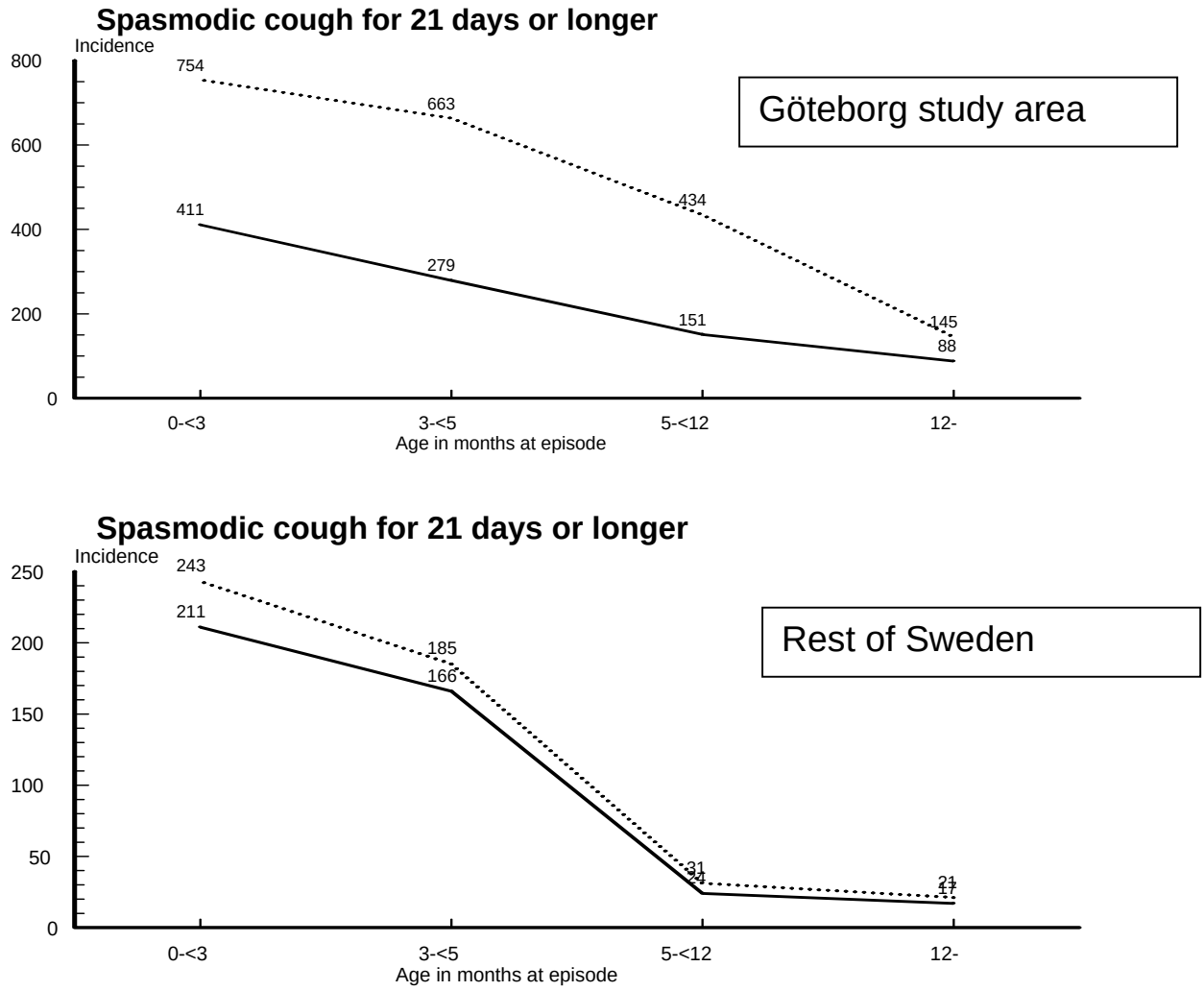


Figure 5 Age specific incidence of spasmodic cough for 21 or more days due to the pertussis disease, solid lines, and age specific incidence of all pertussis, dotted lines, per 100 000 years of follow-up regardless of vaccination status for children born from 1996 to September 30, 2006 with a laboratory confirmed *B. pertussis* reported from January 1, 2003 until September 30, 2006 for children in the Göteborg study area (upper diagram) and children in the rest of Sweden (lower diagram).

The age specific incidence rate of pertussis with 21 or more days of spasmodic cough was highest, 411 per 100 000 years of follow-up, for children 0 to <3 months of age and decreases to 88 per 100 000 years for children above one year of age at the pertussis episode, for children in the Göteborg area.

The age specific incidence rate, for children in the rest of Sweden, is highest, 211 per 100 000 years of follow-up, for children 0-<3 months of age and decreases, by increasing age, to 17 per 100 000 years for children above one year of age at the pertussis episode. The incidence rates were lower than for children in the Göteborg study area in all age groups, but, given an episode of pertussis, more children outside the Göteborg study area had a long duration of spasmodic cough during the pertussis episode.

There was a "weak" association between age of child at beginning of the pertussis episode and the risk of also suffering a long duration of spasmodic cough during the pertussis disease. The risk for a long duration of spasmodic cough was even high for the elderly children.

2.9.2 Duration of spasmodic cough, age and vaccination status at the pertussis episode

Duration of spasmodic cough was also studied in relation to age as well as vaccination status at start of the pertussis episode. Detailed data are given in Table 21 for children from the Göteborg study area. Detailed

data for children outside the Göteborg study area were presented in the main nine year report (Table 13) – see discussion in section 2.6.2. The figures in the text that follow concern the 906 children in this report.

Table 21 Duration of spasmodic cough due to the pertussis disease among children born from 1996 until September 30, 2006, during surveillance from January 1, 2003 until September 30, 2006, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode for children from the Göteborg study area.

Number of doses of a pertussis vaccine prior to the episode			Age of child at beginning of the pertussis episode							Total no. of children
			0-30 days	31-60 days	61-90 days	91-150 days	151-180 days	181-365 days	366- days	
Unimmunised children	**Duration of spasmodic cough**	**0 days**	7	6	10	3	0	0	2	**28**
		1-20 days	2	4	1	2	0	0	0	**9**
		21- days	6	15	14	2	0	2	12	**51**
	Total number of children		**15**	**25**	**25**	**7**	**0**	**2**	**14**	**88**
	Rate of children with spasmodic cough for 21 days or longer		***40%***	***60%***	***56%***	***29%***	***0%***	***100%***	***86%***	***58%***
Children vaccinated with one dose	**Duration of spasmodic cough**	**0 days**	-	-	-	13	1	1	1	**16**
		1-20 days	-	-	-	4	4	0	0	**8**
		21- days	-	-	-	14	4	3	2	**23**
	Total number of children		-	-	-	**31**	**9**	**4**	**3**	**47**
	Rate of children with spasmodic cough for 21 days or longer		-	-	-	***45%***	***44%***	***75%***	***67%***	***49%***
Children vaccinated with two or more doses	**Duration of spasmodic cough**	**0 days**	-	-	-	-	3	29	117	**149**
		1-20 days	-	-	-	-	1	17	22	**40**
		21- days	-	-	-	-	0	21	204	**225**
	Total number of children		-	-	-	-	**4**	**67**	**343**	**414**
	Rate of children with spasmodic cough for 21 days or longer		-	-	-	-	***0%***	***31%***	***59%***	***54%***
All children regardless of vaccination status	**Duration of spasmodic cough**	**0 days**	7	6	10	16	4	30	120	**193**
		1-20 days	2	4	1	6	5	17	22	**57**
		21- days	6	15	14	16	4	26	218	**299**
	Total number of children		**15**	**25**	**25**	**38**	**13**	**73**	**360**	**549**
	Rate of children with spasmodic cough for 21 days or longer		***40%***	***60%***	***56%***	***42%***	***31%***	***36%***	***61%***	***54%***

The overall rate of children with 21 or more days of spasmodic cough for unvaccinated children from the Göteborg study area was 58%. The corresponding figure for children from the rest of Sweden was significantly higher 89%.

For unvaccinated children from the Göteborg study area aged 0-30, 31-60 and 61-90 days at the beginning of the pertussis episode the rate was 40%, 60% and 56% respectively. Since there are very few children in each age groups from 3 months of age they are combined and for children older than 3 months of age the rate was 70%. The corresponding rates for children outside the Göteborg study area were all significantly higher; 88%, 74%, 87% and 94% in the different age groups mentioned above.

Regardless of age the rate of children with 21 or more days of spasmodic cough among vaccinated with one dose was 49% and among those vaccinated with 2 or more doses 54% for children from the Göteborg study area and significantly higher, 89% respectively 75%, for children from the rest of Sweden.

2.10 Duration of cough and antibiotic treatment

As stated in section 2.9, data on cough and spasmodic cough were available for all 1 455 children born from 1996 until September 30, 2006 and under surveillance from January 1, 2003 until September 30, 2006, whereof 566 were infants. All children but 11 were coughing during their pertussis episode, including 2 infants.

Applying the EU clinical case definition of pertussis with 2 weeks of more of coughing (any type) in conjunction with positive laboratory sample, in all 1 391/1 455 (95.6%) would fulfil this definition. Among the 64 cases that would not fulfil the EU definition, 27 were infants and 37 were children one year or older. All but three infants had received erythromycin or trimetoprim-sulfametoxazol, whereas seven of the 37 children were not treated with antibiotics. Fourteen of those infants were unvaccinated, 5 had received one dose and 8 had received two doses. All 37 children had received three doses.

2.10.1 Duration of cough, spasmodic cough and antibiotic treatment

There was information on antibiotic treatment, or not, including date at start of treatment for 1451 of 1455 children, including 564 of 566 infants. No treatment at all was reported for 525 cases, whereof 10 were infants. Before further statistical analysis 14 treated cases with a short erythromycin treatment, 1 – 6 days, were first excluded. Most often the described treatment period was shortened due to diarrhoea etc.

Table 22 presents 1 259 children, whereof 495 were from the Göteborg study area and 764 from Sweden except the Göteborg study area. There were 269 children aged 0-90 days at onset of the episode, without any pertussis vaccination prior to onset, 111 children aged 91-150 days at onset of the episode, with one dose of a pertussis vaccine prior to onset, 105 children aged 151-365 days at onset of the episode, with two doses of a pertussis vaccine prior to onset, and for 764 children one year or older at onset of the episode, with three or more doses prior to onset. Children below one year of age were in general treated with antibiotics. In the Göteborg study area 147/163 (90%) of infants were treated, in the rest of Sweden 280/322 (87%). The proportions treated were highest in the youngest, i.e those below 3 months of age, with 57/63 (90.4 %), treated in the Göteborg study area and 188/206 (91.3 %) in the rest of Sweden. The proportion of infants treated remained high in the Göteborg area also for the age-group 3 to below 5 months (30/31, i.e. 96.8 %) but there was a slight decrease in the rest of Sweden (62/80, i.e. 77.5 %). From 5 to below 12 months the proportion treated in Göteborg was 60/69 (87.0%) and 30/36 (83.3%) in Göteborg and the rest of Sweden. Among those aged one year or more at onset of cough during the episode, 173/332 (52%) of Göteborg study area children were treated and so were 210/442 (48%) of the children from the rest of Sweden.

An early start of the antibiotic treatment, within the first week (<=6 days) after onset of cough during the episode was, in all age groups and for each area, associated with a shorter duration of cough compared to both "no antibiotic treatment" and a late start, later than two weeks after onset. The same was true, with some exceptions, for spasmodic cough.

Table 22 Duration of cough and spasmodic cough due to the pertussis disease among children born from 1996 until September 30, 2006 and under surveillance from January 1, 2003 until September 30, 2006, by age at onset of cough and start of antibiotic treatment in relation to onset of the pertussis episode.

Age at beginning of episode	Day after onset of cough for start of antibiotic treatment with Erytromycin etc. during the pertussis episode	Area								
		Göteborg study area			Sweden except Göteborg			Sweden		
		Duration, days of cough		Duration, days of spasmodic cough	Duration, days of cough		Duration, days of spasmodic cough	Duration, days of cough		Duration, days of spasmodic cough
		N	Median	Median	N	Median	Median	N	Median	Median
0-90 days	**No treatment**	6	30.5	9.5	18	47	32	24	43.5	30.5
	Start day ≤6	***20***	***25***	***0***	***24***	***41.5***	***38***	***44***	***33.5***	***24***
	Start day 7-13	15	44	27	63	44	35	78	44	33
	Start day ≥ 14	22	43.5	32	101	48	37	123	47	37
	Total	63	38	24	206	46	36	269	44	33
91-150 days	**No treatment**	1	164	96	18	49.5	40	19	51	41
	Start day ≤6	***11***	***22***	***0***	***4***	***32***	***25.5***	***15***	***24***	***14***
	Start day 7-13	10	41	6.5	20	41.5	35	30	41.5	32
	Start day ≥ 14	9	47	41	38	50.5	41.5	47	47	41
	Total	31	42	14	80	47	37	111	46	36
151-365 days	**No treatment**	9	31	0	6	45	34	15	34	0
	Start day ≤6	***10***	***13.5***	***3.5***	***5***	***33***	***0***	***15***	***19***	***0***
	Start day 7-13	23	28	10	11	45	37	34	30	19.5
	Start day ≥ 14	27	33	14	14	41.5	33	41	37	23
	Total	69	30	8	36	43	31.5	105	32	17
1 year or older	**No treatment**	159	47	29	232	50	34	391	49	32
	Start day ≤6	***37***	***14***	***0***	***24***	***21***	***6.5***	***61***	***15***	***0***
	Start day 7-13	45	30	16	63	41	31	108	37	26.5
	Start day ≥ 14	91	49	32	123	56	42	214	52	36
	Total	332	42	25.5	442	49	35	774	46	31
All ages	**No treatment**	175	45	28	274	49	34.5	449	48	32
	Start day ≤6	***78***	***15***	***0***	***57***	***34***	***30***	***135***	***24***	***7***
	Start day 7-13	93	32	15	157	43	32	250	39.5	29
	Start day ≥ 14	149	46	31	276	51	38	425	48	36
	Total	495	39	23	764	47	35	1259	45	31

3 Additional analyses from the Göteborg study area

3.1 Material and methods

3.1.1 Background, the surveillance database

See also Section 2.1.1 and 2.1.2.

In order to also cover the first 5 ¼ Göteborg years, i.e. the period not included in the enhanced follow-up for children from this area of Sweden, we have made two additional types of analyses, previously not reported or done within the surveillance project.

The first is to use the common information we collected for all children in Sweden in the inclusion process of the enhanced surveillance, i.e. the birth date of the child and the date for the laboratory-confirmed pertussis sample. Thus, all routine reports of laboratory-confirmed pertussis occurring in the Göteborg study area from September 1, 1997 through December 31, 2002, were also entered in the surveillance database but without any clinical follow-up or vaccination data. We have now calculated age at sampling date for these reports, and also for all other reports of laboratory-confirmed pertussis including those followed-up within the enhanced surveillance. By doing this, we can compare nine years of age-specific data from the Göteborg study area and from the rest of Sweden, although without clinical and vaccination data. This is performed in Sections 3.3-3.4.

The second additional type of analyses include a retrospective collection of missing vaccination data from the first 5 ¼ year of culture- or PCR-confirmed reports from the Göteborg study area. This was recently done by telephoning the Child or School Health Care nurses with access to the individual medical record. By combining vaccination data with age at date of sampling, we have estimated age-specific incidence in children vaccinated with at least two doses prior to the date for sampling for the whole nine year period, thereby allowing a comparison between the Göteborg study area and the rest of Sweden for the whole surveillance period for children with known vaccination status. This part is reported in Sections 3.5-3.7.

3.1.2 Person time and incidence calculations

See section 2.1.4

3.1.3 Göteborg study area, vaccines and vaccinated cohorts

See section 2.2

3.2 Pertussis reports used for the 9 year additional analyses

In the middle of December 2006 there were 1 347 episodes reported in the surveillance database from children in the Göteborg study area, whereof 1 202 occurred from October 1, 1997 until September 30, 2006 among children born from January 1, 1996 until September 30, 2006. From other parts of Sweden, in mid December 2006, there were 1 916 episodes reported in the surveillance database for the same birth period and the same calendar period. (In the main 9 y report 91 of those episodes were not included since they lacked clinical follow-up data.) In Sections 3.3-3.4, we use all these 3 118 reports (1 202 from Göteborg study area and 1 916 from the rest of Sweden) for comparison of pertussis incidence in different age-groups between children in the Göteborg study area and in the rest of Sweden. The approach in Tables 25-27 is an intent to treat, i.e. the overall effect of the vaccination program.

From November 2006 until April 2007 we performed a retrospective collection of individual vaccination history for 621 culture- or PCR-confirmed cases of pertussis occurring during the 5 ¼ year period when the Göteborg study area was not included in the enhanced surveillance, i.e. from October 1, 1997 and

until December 31, 2002. The individual vaccination history was collected for all but 7 of the 621 cases. In summary, information on vaccination status at date for the positive sample exists for 1 167 (97.1%) of the 1 202 episodes for children from the Göteborg area, and for 1 886 (98.4%) of the 1 916 episodes for children from other parts of Sweden.

In Sections 3.5-3.7, we use these 3 053 reports (1 167 from Göteborg study area and 1 886 from the rest of Sweden) for comparison of pertussis incidence, for vaccinated children in different age-groups, between the Göteborg study area and the rest of Sweden. The incidence analyses in Tables 27-29 are done for children vaccinated with at least two doses prior to the laboratory report (the vaccine failures). The approach in these tables is more similar to a per protocol analyses, i.e. the tables indicate the effect of the vaccination program in children who are vaccinated according to the recommendations of this program.

3.3 Culture-confirmed pertussis per calendar period & birth cohort

In Table 23 all 3 118 culture or PCR reported cases from October 1, 1997 until September 30, 2006, in children born from 1996 are shown for the Göteborg study area and the rest of Sweden. In Table 24 result are given, for the same groups of children, but for year of age and year of positive sample.

Table 23 Number of positive samples, per area, according to year of birth and year of positive sample.

Area			**Year of laboratory positive sample**										**Total**
			1997	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	
Göteborg study area	**Year of birth**	**1996**	3	3	7	21	9	23	7	37	4	5	119
		1997	2	7	7	17	12	15	8	38	15	2	123
		1998		12	27	40	26	23	2	46	10	2	188
		1999			27	65	24	21	8	40	10	2	197
		2000				34	30	32	6	13	4	1	120
		2001					32	53	10	29	6	1	131
		2002						49	20	32	5	0	106
		2003							28	59	11	1	99
		2004								74	18	1	93
		2005									11	8	19
		2006										7	7
	Total		5	22	68	177	133	216	89	368	94	30	1202
Sweden except Gbg	**Year of birth**	**1996**	5	17	39	45	19	40	19	59	47	8	298
		1997	22	32	19	24	17	32	7	27	26	9	215
		1998		54	45	16	7	17	12	32	42	16	241
		1999			94	72	12	20	9	18	24	14	263
		2000				90	33	16	7	20	16	20	202
		2001					32	23	9	16	14	10	104
		2002						103	21	18	11	7	160
		2003							49	48	10	5	112
		2004								121	46	11	178
		2005									80	17	97
		2006										46	46
	Total		27	103	197	247	120	251	133	359	316	163	1916

Taken population sizes for the two areas into account, in mean 9.1% of the children were born in the Göteborg study area and 90.9% in the rest of Sweden, the number of cases for each birth-cohort and for each calendar year, are higher for the Göteborg study area compared to the rest of Sweden.

Table 24 Number of positive samples, per area, according to year of age, in one-year classes, and year of positive sample for children at date for the positive sample. Figures in italics indicate a transition period, i.e. only half of children of these age-groups were covered by the enhanced surveillance.

Area			Year of laboratory positive sample										Total
			1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	1997
Göteborg study area	Year of age	0	3	13	42	67	52	91	43	115	25	13	464
		1	*2*	7	15	57	19	31	9	38	11	3	192
		2		*2*	5	21	25	26	11	27	6	1	124
		3			*6*	22	18	19	2	16	7	0	90
		4				*10*	13	17	7	28	4	1	80
		5					*6*	22	3	41	6	1	79
		6						*10*	9	45	14	1	79
		7							*5*	40	12	3	60
		8								*18*	8	2	28
		9									*1*	1	2
		≥10										*4*	4
	Total		5	22	68	177	133	216	89	368	94	30	1202
Sweden except Gbg	Year of age	0	24	77	128	155	59	119	67	160	122	62	973
		1	*3*	18	15	19	12	11	8	15	11	6	118
		2		*8*	29	16	11	24	8	22	6	10	134
		3			*25*	29	13	16	6	11	14	6	120
		4				*27*	16	27	12	20	15	7	124
		5					*10*	28	10	25	19	16	108
		6						*26*	16	27	28	16	113
		7							*6*	42	37	18	103
		8								*37*	32	11	80
		9									*32*	10	42
		≥10										*1*	1
	Total		27	103	197	246	121	251	133	359	316	163	1916

3.4 Person-time of follow-up & incidence and relative risk calculations

In Table 25, total person-time of follow-up, number of observed culture- or PCR-confirmed cases, incidence per 100 000 person years and relative risk are calculated, irrespective of vaccination status, for different age-groups for children born from January 1, 1996 until September 30, 2006, for pertussis episodes which occurred from October 1, 1997 until September 30, 2006 in two areas of Sweden – Sweden except Gbg, and the Göteborg study area.

In Tables 26 and 27 the corresponding comparisons are performed for two birth periods; children born 1996–1998, and children born 2000 or later. For children from the Göteborg study area the first birth period means children in a nearly pure DiTeKik® cohort, while in the second birth period most children in this area have received Pentavac®, (except for children in Kungsbacka, approximately 5%, who

received either Infanrix®-Polio-Hib or Pentavac®). The children born 1999 are not included in these tables because they represents a transition cohort with mixed vaccinations within the 3-5-12 month schedule. However, as for Table 25 vaccination status is not used in these two tables.

Table 25 Total person-time of follow-up, number of observed culture- or PCR-confirmed cases, incidence per 100 000 person years and relative risk of having a reported laboratory-verified episode of pertussis in the different age-groups for children born from January 1, 1996 until September 30, 2006, followed from October 1, 1997 until September 30, 2006 in two areas of Sweden – Sweden except Gbg (except the Göteborg study area) and the Göteborg study area. Age-specific incidences per 100 000 person-years are given for the period < 3 months of age (before scheduled age for Dose 1), the period 3 - <5 months of age (after scheduled age of Dose 1 and before Dose 2), the period 5 - <12 months of age (after scheduled age of Dose 2 and before Dose 3) and thereafter in one-year periods from 12 months of age (after scheduled age for Dose 3). Age is calculated at the date for the positive culture or PCR sample.

Age at date for positive culture or PCR sample and area	Person time of follow-up in years	Number of laboratory confirmed cases	Incidence per 100 000 person years and 95% confidence interval	Relative risk Göteborg compared to Sweden except Gbg
<3 months				
Sweden except Gbg	193 565	399	206 (187-227)	-
Göteborg study area	*19 380*	*140*	*722 (608-852)*	***3.5 (2.4 - 4.2)***
3-<5 months	-	-	-	-
Sweden except Gbg	128 785	330	256 (229-285)	-
Göteborg study area	*12 895*	*96*	*744 (603-909)*	***2.9 (2.3 – 3.6)***
5-<12 months	-	-	-	-
Sweden except Gbg	449 130	244	54 (48-61)	-
Göteborg study area	*44 960*	*228*	*507 (443-576)*	***9.3 (7.8 – 11.2)***
12-<24 months	-	-	-	-
Sweden except Gbg	761 405	118	15 (13-19)	-
Göteborg study area	*76 225*	*192*	*252 (210-281)*	***16.3 (12.9 – 20.4)***
24-<36 months	-	-	-	-
Sweden except Gbg	693 330	134	19 (16-23)	-
Göteborg study area	*69 410*	*124*	*179 (148-211)*	***9.2 (7.2 – 11.8)***
36-<48 months	-	-	-	-
Sweden except Gbg	601 530	120	20 (17-24)	-
Göteborg study area	*60 220*	*90*	*149 (120-184)*	***7.5 (5.7 – 9.8)***
48<60 months	-	-	-	-
Sweden except Gbg	514 830	124	24 (20-29)	-
Göteborg study area	*51 540*	*80*	*155 (123-193)*	***6.4 (4.9 – 8.5)***
60<72 months	-	-	-	-
Sweden except Gbg	433 230	108	25 (21-30)	-
Göteborg study area	*43 370*	*79*	*182 (144-227)*	***7.3 (5.5 – 9.8)***
72- <84 months	-	-	-	-
Sweden except Gbg	351 630	113	32 (26-38)	-
Göteborg study area	*35 200*	*79*	*224 (178-280)*	***7.0 (5.2 – 9.3)***
84-<96 months	-	-	-	-
Sweden except Gbg	270 030	103	38 (31-46)	-
Göteborg study area	*27 035*	*60*	*222 (169-286)*	***5.8 (4.2 – 8.0)***
96-<108 months	-	-	-	-
Sweden except Gbg	188 430	80	42 (34-53)	-
Göteborg study area	*18 865*	*28*	*148 (99-215)*	***3.5 (2.3 – 5.4)***
≥108 months	-	-	-	**-**
Sweden except Gbg	129 175	43	33 (24-45)	**-**
Göteborg study area	*12 930*	*6*	*46 (17-101)*	***1.4 (0.6 – 3.3)***
All ≥12 months	-	-	-	-
Sweden except Gbg	3 943 590	943	24 (22-26)	-
Göteborg study area	*394 795*	*738*	*187 (174-201)*	***7,8 (7.1 – 8.6)***

Table 26 Number of observed culture- or PCR-confirmed cases and relative risk in the different age-groups for children born **from January 1, 1996 until December 31, 1998**, followed from October 1, 1997 until September 30, 2006 in two areas of Sweden – Sweden except the Göteborg (Gbg) area and the Göteborg study area. Age-specific incidences per 100 000 person-years are given for the period < 3 months of age (before scheduled age for Dose 1), the period 3 - <5 months of age (after scheduled age for Dose 1 and before Dose 2), the period 5 - <12 months of age (after scheduled age for Dose 2 and before Dose 3) and thereafter in one-year periods from 12 months of age (after scheduled age for Dose 3). Age is calculated at the date for the positive culture or PCR sample

Age at date for positive culture or PCR sample and area	Person time of follow-up in years	Number of laboratory confirmed cases	Incidence per 100 000 person years and 95% confidence interval	Relative risk Göteborg study area compared to Sweden except Gbg	
<3 months					
Sweden except Gbg	28 135	38	135 (96-186)		
Göteborg study area	*2 815*	*5*	*178 (58-415)*	***1.3***	***(0.5 – 3.3)***
3-<5 months	-	-	-		**-**
Sweden except Gbg	21 685	42	194 (140-262)		**-**
Göteborg study area	*2 170*	*7*	*323 (129-664)*	***1.7***	***(0.7 – 3.7)***
5-<12 months	-	-	-		**-**
Sweden except Gbg	94 360	55	58 (44-76)		**-**
Göteborg study area	*9 440*	*19*	*201 (121-315)*	***3.5***	***(2.0 – 5.8)***
12-<24 months	-	-	-		**-**
Sweden except Gbg	225 905	49	22 (16-29)		**-**
Göteborg study area	*22 615*	*49*	*217 (160-287)*	***10.0***	***(6.7 – 14.8)***
24-<36 months	-	-	-		**-**
Sweden except Gbg	249 630	57	23 (17-30)		**-**
Göteborg study area	*24 990*	*38*	*152 (108-209)*	***6.7***	***(4.4 – 10.0)***
36-<48 months	-	-	-		**-**
Sweden except Gbg	249 630	75	30 (24-38)		**-**
Göteborg study area	*24 990*	*58*	*232 (176-300)*	***7.7***	***(5.5 – 10.9)***
48-<60 months	-	-	-		**-**
Sweden except Gbg	249 630	76	30 (24-38)		**-**
Göteborg study area	*24 990*	*40*	*160 (114-218)*	***5.3***	***(3.6 – 7.7)***
60-<72 months	-	-	-		**-**
Sweden except Gbg	249 630	60	24 (18-31)		**-**
Göteborg study area	*24 990*	*49*	*196 (145-259)*	***8.2***	***(5.6 – 11.9)***
72-<84 months	-	-	-		**-**
Sweden except Gbg	249 630	83	33 (26-41)		**-**
Göteborg study area	*24 990*	*72*	*288 (225-363)*	***8.7***	***(6.3 – 11.9)***
84-<96 months	-	-	-		**-**
Sweden except Gbg	247 080	96	39 (31-47)		**-**
Göteborg study area	*24 740*	*59*	*238 (181-307)*	***6.1***	***(4.4 – 8.5)***
96- <108 months	-	-	-		**-**
Sweden except Gbg	188 430	80	42 (34-53)		
Göteborg study area	*18 865*	*28*	*148 (99-215)*	***3.5***	***(2.3 – 5.4)***
≥108 months	-	-	-		**-**
Sweden except Gbg	129 175	43	33 (24-45)		
Göteborg study area	*12 930*	*6*	*46 (17-101)*	***1.4***	***(0.6 – 3.3)***
All ≥12 months	-	-	-		**-**
Sweden except Gbg	2 038 740	619	30 (28-33)		
Göteborg study area	*204 100*	*399*	*195 (177-216)*	***6.4***	***(5.6 – 7.3)***

Table 27 Number of observed culture- or PCR-confirmed cases and relative risk in the different age-groups for children born **from January 1, 2000 until September 30, 2006**, followed from January 1, 2000 until September 30, 2006 in two areas of Sweden – Sweden except the Göteborg (Gbg) area and the Göteborg study area. Age-specific incidences per 100 000 person-years are given for the period < 3 months of age (before scheduled age for Dose 1), the period 3 - <5 months of age (after scheduled age for Dose 1 and before Dose 2), the period 5 - <12 months of age (after scheduled age for Dose 2 and before Dose 3) and thereafter in one-year periods from 12 months of age (after scheduled age for Dose 3). Age is calculated at the date for the positive culture or PCR sample.

Age at date for positive culture or PCR sample and area	Person time of follow-up in years	Number of laboratory confirmed cases	Incidence per 100 000 person years and 95% confidence interval	Relative risk Göteborg study area compared to Sweden except Gbg
<3 months	-	-	-	-
Sweden except Gbg	145 030	308	212 (191-238)	-
Göteborg study area	*14 520*	*126*	*868 (727-1064)*	***4.1 (3.3 – 5.0)***
3-<5 months	-	-	-	-
Sweden except Gbg	93 580	236	252 (221-287)	-
Göteborg study area	*9 360*	*75*	*801 (630-1004)*	***3.2 (2.4 – 4.1)***
5-<12 months	-	-	-	-
Sweden except Gbg	307 170	135	44 (37-52)	-
Göteborg study area	*30 750*	*172*	*559 (479-649)*	***12.7 (10.2 – 15.9)***
12-<24 months	-	-	-	-
Sweden except Gbg	453 900	57	13 (10-16)	-
Göteborg study area	*45 440*	*102*	*224 (183-271)*	***17.9 (12.9 – 24.7)***
24-<36 months	-	-	-	-
Sweden except Gbg	362 100	58	16 (12-21)	-
Göteborg study area	*36 250*	*57*	*157 (119-204)*	***9.8 (6.8 – 14.1)***
36-<48 months	-	-	-	-
Sweden except Gbg	270 300	34	13 (9-18)	
Göteborg study area	*27 060*	*24*	*89 (57-132)*	***7.1 (4.2 – 11.9)***
48- <60 months	-	-	-	-
Sweden except Gbg	183 600	37	20 (14-28)	
Göteborg study area	*18 380*	*16*	*87 (50-141)*	***4.3 (2.4 – 7.8)***
≥60 months	-	-	-	-
Sweden except Gbg	124 950	34	27 (19-38)	
Göteborg study area	*12 510*	*3*	*24 (5-70)*	***0.9 (0.3 – 2.9)***
All ≥12 months	-	-	-	-
Sweden except Gbg	1 394 850	220	16 (13-18)	
Göteborg study area	*139 640*	*202*	*145 (125-165)*	***9.2 (7.6 – 11.1)***

3.4.1 Comments to incidence and risk tables

Also in this larger group (Table 25), the number of cases reported from Göteborg was high in relation to population size, with 464 reported infant cases and 738 cases in children aged 1 year or more. From the rest of Sweden there were 973 infant cases and 943 cases in children aged from 1 year.

For children born from January 1, 1996 until December 31, 1998 (Table 26), in each age-group from 5-<12 until 96-<108 months of age there was a statistically significant higher risk (RR=3.5 – RR=10.0) of receiving pertussis for children in the Göteborg study area compared to children in the rest of the country. From 12 months of age the relative risk was 6.4 (95% C.I. 5.6 – 7.3) and the incidence figures per 100 000 years of follow-up was 195 for children in the Göteborg study area and 30 for children living outside that area. One can also note that the excess risk in Göteborg study area slowly decreases from RR=8.7, for 6 year old children, until RR=1.4, for nine year old children.

Corresponding Table 27 presents result for 575 and 899 children born January 1, 2000 until September 30, 2006 with a laboratory confirmed pertussis for children living in the Göteborg study area respectively in Sweden except Göteborg. In each age group until 4 years of age there was a statistically significant higher

risk (RR=3.2 – RR=17.9) of receiving pertussis for children in the Göteborg study area compared to children in the rest of the country. From 12 months of age the relative risk was 9.2 (95% C.I. 7.6 – 11.1) and the incidence figures per 100 000 years of follow-up was 145 for children in the Göteborg study area and 16 for children living outside that area. One can also note that the excess risk in Göteborg study area slowly decreases from RR=17.9, for one year old children, until RR=0.9, for five year old children. For the very young children the relative risk was 4.1 and 3.2 in the two age groups 0-<3 and 3-<5 months of age.

3.5 Vaccination history at date of positive laboratory sample

For comparison of pertussis incidence for vaccinated children between the Göteborg study area and the rest of Sweden, we use reports of culture- or PCR-confirmed pertussis from October 1, 1997 until September 30, 2006 among children born from January 1, 1996 until September 30, 2006 from children for whom we have access to vaccination history at date for the positive sample – in total 1 167 reports from Göteborg study area and 1 886 from the rest of Sweden. Eight hundred and fifty-one respectively 910 children in the two areas were vaccinated with at least two doses of a pertussis vaccine prior to the date of the laboratory-confirmed pertussis (Table 28).

Table 28 Vaccination history at date of the positive sample for children in Göteborg area and in Sweden except Göteborg, for children born January 1, 1996 until September 30, 2006 and for culture or PCR positive pertussis episodes from October 1, 1997 until September 30, 2006

			Göteborg study area		Sweden except Gbg		Total
				Percent between area		Percent between area	
Number of doses before positive sample	Not vaccinated	Number of episodes	188	21,3	696	78,7	884
		Percent within area	*16,1*	-	*36,9*	-	*29,0*
	One dose	Number of episodes	128	31,4	280	68,6	408
		Percent within area	*11,0*	-	*14,8*	-	*13,4*
	Two doses	Number of episodes	192	57,3	143	42,7	335
		Percent within area	*16,5*	-	*7,6*	-	*11,0*
	Three or more doses	Number of episodes	659	46,2	767	53,8	1426
		Percent within area	*56,5*	-	*40,6*	-	*46,7*
Total		Number of episodes	1167	38,2	1886	61,8	3053

Figures in Table 28 further confirm earlier conclusion in section 2.4 that relatively more cases are reported among not vaccinated in Sweden except Göteborg (36.9% vs 16.1%) and, consequently, relatively more cases were reported among vaccinated in the Göteborg study area, specifically among those who had received at least two doses of a pertussis vaccine (73.0% vs 48.2%) before the date of the positive sample ("*Percent within area*"). Figures in column "Percent between area" (nearly "equal" to those of Table 2 in section 1.3.3), taking the population size of the Göteborg study area (9.1%) into account, tell the same story. The "overrepresentation" of reported pertussis cases in children from the Göteborg study area varies between a multiple of 2.3 (for not vaccinated) and 6.3 (for those vaccinated with two doses).

Since data for the unvaccinated and for those vaccinated with only one dose prior to the date for the positive sample already are represented in the intent-to-treat incidence tables in section 3.4, Tables 25-27 and since tables for the slightly smaller dataset used in sections 3.5-3.7 (65 episodes fewer than used in section 3.4) should be nearly identical to those in Section 3.4, the age-specific incidence tables of section

3.7, will include only children vaccinated with two or more doses prior to the date of the positive sample. Thus, incidence tables in section 3.7 should be regarded as a complement to Section 3.4, Tables 25-27, (the intent-to treat analyses), and to Table 14 of the Section 2 analyses. The last mentioned table gives age-specific incidence for a smaller dataset of episodes occurring from January 1, 2003 for children vaccinated with at least two doses of a pertussis vaccine prior to onset of cough. However, in section 3.6 some descriptive data, for episodes with less than two doses prior to the positive sample, are also given.

For a table of "Year of birth" and "Year of positive sample" we refer to Table 23 (with the slightly larger dataset – 35 and 30 more episodes for children in the Göteborg study area respectively in the rest of Sweden).

3.6 Laboratory confirmed pertussis in children born 1996-Sept. 30, 2006

For this cohort of children there were 3 053 reports of laboratory confirmed pertussis from October 1, 1997 until September 30, 2006 for which we have data on vaccination status prior to the date of the positive sample. There were 1 167 episodes among children in the Göteborg study area, whereof 188 unvaccinated, and 1 886, whereof 696 unvaccinated, among children in the rest of Sweden, Table 29.

Table 29 Number of reported laboratory confirmed cases of pertussis from October 1, 1997 until September 30, 2006 per birth-cohort from January 1,1996 until September 30, 2006, per birth cohort and number of pertussis vaccine doses prior to the positive sample and per area for the pertussis episode

Birth-cohort	Number of doses of a pertussis vaccine	Sweden except Göteborg		Göteborg study area		Total
		Not vaccinated	Vaccinated	Not vaccinated	Vaccinated	
1996	0	28	-	4	-	32
	1		2		1	3
	2		5		4	9
	3		259		108	367
1997	0	37	-	3	-	40
	1	-	13	-	2	15
	2	-	20	-	4	24
	3	-	142	-	109	251
1998	0	55	-	12	-	67
	1	-	28	-	10	38
	2	-	22	-	17	39
	3	-	136	-	143	279
1999	0	109	-	18	-	127
	1	-	46	-	24	70
	2	-	27	-	30	57
	3	-	76	-	118	194
2000	0	96		19	-	115
	1	-	35	-	13	48
	2	-	10	-	22	32
	3	-	58	-	60	118
2001	0	38		23		61
	1	-	16	-	18	34
	2	-	10	-	32	42
	3	-	39	-	51	90
2002	0	88		31		119
	1	-	36	-	18	54
	2	-	5	-	16	21
	3	-	27	-	41	68
2003	0	57	-	24	-	81
	1	-	16	-	11	27
	2	-	18	-	40	58

	3	**-**	**19**	**-**	**22**	**41**
2004	**0**	**93**		**40**		**133**
	1		**54**	**-**	**27**	**81**
	2		**20**	**-**	**21**	**41**
	3		**11**	**-**	**5**	**16**
2005	**0**	**66**	**-**	**8**	**-**	**74**
	1		**18**	**-**	**3**	**21**
	2		**5**	**-**	**6**	**11**
	3		**0**	**-**	**2**	**2**
2006.01-09	**0**	**29**	**-**	**6**	**-**	**35**
	1		**16**	**-**	**1**	**17**
	2		**1**	**-**	**0**	**1**
	3		**-**	**-**	**-**	**-**
Total	**0**	**696**	**-**	**188**	**-**	**884**
Total	**1**	**-**	**280**		**128**	**408**
Total	**2**	**-**	**143**		**192**	**335**
Total	**3**	**-**	**767**		**659**	**1 426**
Total	**0 – 3**	**696**	**1 190**	**188**	**979**	**3 053**

Since we lack proper information of onset of the pertussis episode, i.e. we lack a date for onset of cough for many of the reports, we use the date for the positive sample (available for all reports) as a proxy. Thus, in the Part 3 analyses we calculate the age at "onset" of episode as the difference between that date and the date of birth. Generally onset of cough occurred one to two weeks before the sample was taken.

Table 30 shows the age distribution, at date of the positive sample for unvaccinated children and for children with one dose prior to that date. Age groups are the same as in Table 25.

Table 30 Number of reported laboratory confirmed cases of pertussis from October 1, 1997 until September 30, 2006 per birth-cohort from January 1,1996 until September 30, 2006, for unvaccinated and for children vaccinated with one dose prior to the date for the positive sample per age-group and per area for the pertussis episode

Age at date for the positive culture or PCR sample	**Sweden except Göteborg**				**Göteborg study area**			
	Not vaccinated		**Vaccinated with one dose**		**Not vaccinated**		**Vaccinated with one dose**	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
<3 months	**392**	**56,3**	**0**		**136**	**72,3**	**0**	
3-<5 months	**128**	**18,4**	**196**	**70,0**	**22**	**11,7**	**70**	**54,7**
5-<12 months	**38**	**5,5**	**78**	**27,9**	**3**	**1,6**	**50**	**39,1**
12-<24 months	**33**	**4,7**	**1**	**0,4**	**3**	**1,6**	**2**	**1,6**
24-<36 months	**23**	**3,3**	**0**		**5**	**2,7**	**1**	**0,8**
36-<48 months	**18**	**2,6**	**2**	**0,7**	**3**	**1,6**	**0**	
48-<60 months	**24**	**3,4**	**2**	**0,7**	**5**	**2,7**	**0**	
60-<72 months	**16**	**2,3**	**0**		**4**	**2,1**	**1**	**0,8**
72-<84 months	**5**	**0,7**	**0**		**6**	**3,2**	**3**	**2,3**
84-<96 months	**11**	**1,6**	**0**		**0**		**1**	**0,8**
>=96 months	**8**	**1,2**	**1**	**0,4**	**1**	**0,5**	**0**	
Total	**696**		**280**		**188**		**128**	

Most of the pertussis case among unvaccinated children occurred, as expected, in the two youngest age-groups – 747% and 84.0% in Sweden except Göteborg respectively in the Göteborg study area. In

Sweden except Göteborg 138 cases (19.8%) occurred, with a date for the positive sample, after one year of age. In the Göteborg study area there were 27 cases (14.4%) older than one year.

For vaccinated with only one dose prior to the date of the positive sample very few cases occurred after one year of age and the majority of the one-dose vaccinated pertussis cases occurred before the scheduled date, at five months of age, for the second dose. However, nearly 40% respectively 28% of the one-dose vaccinated cases occurred in the age interval between dose 2 and dose 3 in the two areas.

As seen in Table 31 most of the one-dose vaccinated case occurring "in the age interval for the second pertussis dose" occurred at 5 months of age. Also remember that we use the date for the positive sample for calculation of age – generally that date is one to two weeks after onset of cough at the pertussis episode.

Table 31 Number of reported laboratory confirmed cases of pertussis from October 1, 1997 until September 30, 2006 per birth-cohort from January 1,1996 until September 30, 2006, for unvaccinated and for children vaccinated with one dose prior to the date for the positive sample per age-group and per area for the pertussis episode

Age at date for the positive culture or PCR sample	Sweden except Göteborg				Göteborg study area			
	Not vaccinated		Vaccinated with one dose		Not vaccinated		Vaccinated with one dose	
	No.	%	No.	%	No.	%	No.	%
<1 months	47	6,8	0		22	11,7	0	
1-<2 months	166	23,9	0		58	30,9	0	
2-<3 months	179	25,7	0		56	29,8	0	
3-<4 months	107	15,4	71	25,4	16	8,5	22	17,2
4-<5 months	21	3,0	125	44,6	6	3,2	48	37,5
5-<6 months	11	1,6	49	17,5	0		30	23,4
6-<12 months	27	3,9	29	10,4	3	1,6	20	15,6
>=12 months	138	19,8	6	2,1	27	14,4	8	6,3
Total	696		280		188		128	

3.7 Age-specific incidence, relative risk for children with at least two doses

In Table 32 total person-time of follow-up, number of observed culture- or PCR-confirmed cases, incidence per 100 000 person years of follow-up and relative risk are calculated for different age-groups for children born from January 1, 1996 until September 30, 2006, for pertussis episodes which occurred from October 1, 1997 until September 30, 2006 in two areas of Sweden – Sweden except Gbg, and the Göteborg study area and for children who had received at least two doses of a pertussis vaccine prior to the date for the positive sample.

In Tables 33 and 34 the corresponding comparisons are performed for two birth periods; children born 1996–1998, and children born 2000 or later. For children from the Göteborg study area the first birth period means children in a nearly pure DiTeKik® cohort, while in the second birth period most children in this area have received Pentavac®, (except for children in Kungsbacka, approximately 5%, who received either Infanrix®-Polio-Hib or Pentavac®). Children born 1999 are not included in these two tables because they represents a transition cohort with mixed vaccinations within the 3-5-12 month schedule.

Table 32 Total person-time of follow-up, number of observed culture- or PCR-confirmed cases, incidence per 100 000 person years and relative risk of having a reported laboratory-verified episode of pertussis in the different age-groups for children born from January 1, 1996 until September 30, 2006, followed from October 1, 1997 until September 30, 2006 in two areas of Sweden – Sweden except Gbg (except the Göteborg study area) and the Göteborg study area – for children vaccinated with two or more doses of a pertussis vaccine prior to date of the positive sample. Age-specific incidences per 100 000 person-years are given for the scheduled age period between Dose 2 and 3 (5 - <12 months of age) and thereafter in one-year periods after Dose 3 from 12 months of age. Age is calculated at the date for the positive culture or PCR sample.

Age at date for positive culture or PCR sample and area	Person time of follow-up in years	Number of laboratory confirmed cases	Incidence per 100 000 person years and 95% confidence interval	Relative risk Göteborg compared to Sweden except Gbg
Between Dose 2 and 3				
Sweden except Gbg	449 130	143	32 (27-37)	-
Göteborg study area	*44 960*	*192*	*427 (367-492)*	***13.3 (10.7 – 16.5)***
After Dose 3				
12-<24 months	-	-	-	-
Sweden except Gbg	761 405	66	9 (7-11)	-
Göteborg study area	*76 225*	*164*	*215 (184-249)*	***24.8 (18.6 – 33.0)***
24-<36 months	-	-	-	-
Sweden except Gbg	693 330	107	15 (13-18)	-
Göteborg study area	*69 410*	*112*	*161 (133-193)*	***10.5 8.12 – 13.7)***
36-<48 months	-	-	-	-
Sweden except Gbg	601 530	99	16 (13-20)	-
Göteborg study area	*60 220*	*83*	*138 (110-171)*	***8.4 (6.3 – 11.2)***
48<60 months	-	-	-	-
Sweden except Gbg	514 830	96	19 (15-23)	-
Göteborg study area	*51 540*	*72*	*140 (109-176)*	***7.5 (5.5 – 10.2)***
60<72 months	-	-	-	-
Sweden except Gbg	433 230	92	21 (17-26)	-
Göteborg study area	*43 370*	*72*	*166 (129-210)*	***7.8 (5.7 – 10.6)***
72- <84 months	-	-	-	-
Sweden except Gbg	351 630	106	30 (25-36)	-
Göteborg study area	*35 200*	*66*	*188 (114578-239)*	***6.2 (4.6 – 8.4)***
84-<96 months	-	-	-	-
Sweden except Gbg	270 030	89	33 (26-40)	-
Göteborg study area	*27 035*	*57*	*211 (159-274)*	***6.4 (4.6 – 8.9)***
96-<108 months	-	-	-	-
Sweden except Gbg	188 430	72	38 (30-48)	-
Göteborg study area	*18 865*	*27*	*143 (95-207)*	***3.7 (2.4 – 5.8)***
≥108 months	-	-	-	**-**
Sweden except Gbg	129 175	40	31 (22-42)	**-**
Göteborg study area	*12 930*	*6*	*46 (17-101)*	***1.5 (0.6 – 3.5)***
All ≥12 months	-	-	-	-
Sweden except Gbg	3 943 590	767	19 (18-21167)	-
Göteborg study area	*394 795*	*659*	*187 (154-180)*	***8,6 (7.7 – 9.5)***

Table 33 Number of observed culture- or PCR-confirmed cases and relative risk in the different age-groups for children born **from January 1, 1996 until December 31, 1998**, followed from October 1, 1997 until September 30, 2006 in two areas of Sweden – Sweden except the Göteborg (Gbg) area and the Göteborg study area – for children vaccinated with two or more doses of a pertussis vaccine prior to date of the positive sample. Age-specific incidences per 100 000 person-years are given for the scheduled age period between Dose 2 and 3 (5 - <12 months of age) and thereafter in one-year periods after Dose 3 from 12 months of age. Age is calculated at the date for the positive culture or PCR sample.

Age at date for positive culture or PCR sample and area	Person time of follow-up in years	Number of laboratory confirmed cases	Incidence per 100 000 person years and 95% confidence interval	Relative risk Göteborg study area compared to Sweden except Gbg	
Between Dose 2 and 3					
Sweden except Gbg	94 360	47	50 (36-67)	-	
Göteborg study area	*9 440*	*25*	*265 (169-392)*	***5.3***	***(3.3 – 8.6)***
After Dose 3					
12-<24 months	-	-	-	-	
Sweden except Gbg	225 905	29	13 (8-19)	-	
Göteborg study area	*22 615*	*42*	*186 (133-252)*	***14.5***	***(9.0 – 23.2)***
24-<36 months	-	-	-	-	
Sweden except Gbg	249 630	50	20 (15-26)	-	
Göteborg study area	*24 990*	*35*	*140 (96-196)*	***7.0***	***(4.5 – 10.8)***
36-<48 months	-	-	-	-	
Sweden except Gbg	249 630	64	26 (20-33)	-	
Göteborg study area	*24 990*	*55*	*220 (164-288)*	***8.6***	***(6.0 – 12.3)***
48-<60 months	-	-	-	-	
Sweden except Gbg	249 630	65	26 (20-33)	-	
Göteborg study area	*24 990*	*35*	*140 (96-196)*	***5.4***	***(3.6 – 8.1)***
60-<72 months	-	-	-	-	
Sweden except Gbg	249 630	53	21 (16-28)	-	
Göteborg study area	*24 990*	*44*	*176 (128-236)*	***8.3***	***(5.6 – 12.4)***
72-<84 months	-	-	-	-	
Sweden except Gbg	249 630	80	32 (25-40)	-	
Göteborg study area	*24 990*	*60*	*240 (180-308)*	***7.5***	***(5.8 – 9.7)***
84-<96 months	-	-	-	-	
Sweden except Gbg	247 080	84	34 (27-42)	-	
Göteborg study area	*24 740*	*56*	*226 (170-295)*	***6.7***	***(4.8 – 9.4)***
96- <108 months	-	-	-	-	
Sweden except Gbg	188 430	72	38 (30-48)		
Göteborg study area	*18 865*	*27*	*143 (95-207)*	***3.7***	***(2.4 – 5.8)***
≥108 months	-	-	-	-	
Sweden except Gbg	129 175	40	31 (22-42)		
Göteborg study area	*12 930*	*6*	*46 (17-101)*	***1.5***	***(0.6 – 3.5)***
All ≥12 months	-	-	-	-	
Sweden except Gbg	2 038 740	537	26 (24-29)		
Göteborg study area	*204 100*	*360*	*176 (158-195)*	***6.7***	***(5.9 – 7.7)***

Table 34 Number of observed culture- or PCR-confirmed cases and relative risk in the different age-groups for children born **from January 1, 2000 until September 30, 2006**, followed from January 1, 2000 until September 30, 2006 in two areas of Sweden – Sweden except the Göteborg (Gbg) area and the Göteborg study area – for children vaccinated with two or more doses of a pertussis vaccine prior to date of the positive sample. Age-specific incidences per 100 000 person-years are given for the scheduled age period between Dose 2 and 3 (5 - <12 months of age) and thereafter in one-year periods after Dose 3 from 12 months of age. Age is calculated at the date for the positive culture or PCR sample.

Age at date for positive culture or PCR sample and area	Person time of follow-up in years	Number of laboratory confirmed cases	Incidence per 100 000 person years and 95% confidence interval	Relative risk Göteborg study area compared to Sweden except Gbg	
Between Dose 2 and 3					
Sweden except Gbg	307 170	69	22 (17-28)	-	
Göteborg study area	*30 750*	*137*	*446 (371-527)*	***19.8***	***(14.8 – 26.4)***
After Dose 3					
12-<24 months	-	-	-	-	
Sweden except Gbg	453 900	31	7 (5-10)	-	
Göteborg study area	*45 440*	*89*	*196 (156-242)*	***28.7***	***(19.1 – 43.1)***
24-<36 months	-	-	-	-	
Sweden except Gbg	362 100	44	12 (9-16)	-	
Göteborg study area	*36 250*	*53*	*146 (108-190)*	***12.0***	***(8.0 – 17.9)***
36-<48 months	-	-	-	-	
Sweden except Gbg	270 300	27	10 (7-14)		
Göteborg study area	*27 060*	*22*	*81 (52-122)*	***8.1***	***(4.6 – 14.2)***
48- <60 months	-	-	-	-	
Sweden except Gbg	183 600	25	14 (9-20)		
Göteborg study area	*18 380*	*14*	*76 (44-128)*	***5.6***	***(2.9 – 10.8)***
≥60 months	-	-	-	-	
Sweden except Gbg	124 950	27	22 (14-31)		
Göteborg study area	*12 510*	*3*	*24 (5-70)*	***1.1***	***(0.3 – 3.6)***
All ≥12 months	-	-	-	-	
Sweden except Gbg	1 394 850	154	11 (9-13)		
Göteborg study area	*139 640*	*181*	*130 (111-150)*	***11.7***	***(9.4 – 14.5)***

3.7.1 Comments to incidence and risk tables

For children born from January 1, 1996 until September 30, 2006 and vaccinated with at least two doses of a pertussis vaccine prior to the date for the positive sample (Table 32), in each age-group from 5-<12 until 96-<108 months of age, there was a statistically significant higher risk (RR=3.7 – RR=24.8) of having a laboratory confirmed episode of pertussis for children in the Göteborg study area compared to children in the rest of the country.

From 12 months of age the relative risk was 8.6 (95% C.I. 7.7 – 9.5) and the incidence figures per 100 000 years of follow-up was 167 for children in the Göteborg study area and 19 for children living outside that area. One can also note that the excess risk in Göteborg study area slowly decreases by raising age. Results in Table 32 confirm, with a larger dataset, what already was shown in Table 14 of the Part 1 analyses.

Corresponding Table 33 presents result for 385 and 584 children born January 1, 1996 until December 31, 1998 with a laboratory confirmed pertussis for children living in the Göteborg study area respectively in Sweden except Göteborg. Those children have all received at least two doses of a pertussis vaccine prior to the date of the positive sample. During this birth period children in the Göteborg area were vaccinated with the DiTeKik® vaccine and all but 19 children in the Göteborg study area in Table 33 had received that pertussis vaccine prior to the date for the positive sample.

In each age group until 8 years of age there was a statistically significant higher risk (RR=3.7 – RR=14.5) of receiving pertussis for children in the Göteborg study area compared to children in the rest of the country.

From 12 months of age the relative risk was 6.7 (95% C.I. 5.9 – 7.7) and the incidence figures per 100 000 years of follow-up was 176 for children in the Göteborg study area and 26 for children living outside that area. One can also note that the excess risk in Göteborg study area slowly decreases by age. The corresponding intent-to-treat table, Table 26, gives the same picture.

Table 34 presents result for 318 and 223 children born January 1, 2000 until September 30, 2006 with a laboratory confirmed pertussis for children living in the Göteborg study area respectively in Sweden except Göteborg. Those children have all received at least two doses of a pertussis vaccine prior to the date of the positive sample. During this birth period most children in the Göteborg area were vaccinated with the Pentavac® vaccine and all but 6 children in the Göteborg study area in Table 34 had received that pertussis vaccine prior to the date for the positive sample.

In each age group until 4 years of age there was a statistically significant higher risk (RR=5.6 – RR=28.7) of receiving pertussis for children in the Göteborg study area compared to children in the rest of the country.

From 12 months of age the relative risk was 11.7 (95% C.I. 9.4 – 14.5) and the incidence figures per 100 000 years of follow-up was 130 for children in the Göteborg study area and 11 for children living outside that area. One can also note that the excess risk in Göteborg study area slowly decreases by age. The corresponding intent-to-treat table, Table 27, gives the same picture but with lower relative risks.

4 Overall rates of laboratory confirmed pertussis in Västra Götaland region

The Swedish communicable disease reporting system is county-based. Therefore, general information on reports according to the communicable disease act is only available for the whole region of Västra Götaland, but not for the Göteborg study area part of this region, representing about half of the VG population. We present data on the overall reported data from the region of VG in comparison with the rest of Sweden, as an effort to check indicators of different awareness and different reporting system in different parts of Sweden. We have also included performance indicators for the vaccination program. It is to be carefully noted that the overall VG data represents a mixture of the data from the Göteborg study area and the rest of VG region, and the VG region is therefore not a reasonable proxy for the nine VG municipalities of the Göteborg study area.

Laboratory denominator data are not included in the present Swedish national reporting system, but by courtesy of the county medical officers in VG and other regions, we have included an effort to compare laboratories within VG as well as a large city comparison of the Göteborg study area in comparison with Stockholm and Malmö-Lund

4.1 Changes in age-specific incidence over time

According to the information in Section 1.3.6, there were no major differences in the overall or age-specific incidence of pertussis in the region of Västra Götaland in comparison with the rest of Sweden during the 10 year period 1986-1995, before introduction of acellular vaccination in the general programme in 1996. Therefore, the national incidences are used as a proxy for the VG incidences during this period in the Figure 6 below. This figure compares the mean age-specific incidence in the region of Västra Götaland during the 10 year period 1997-2006 after the introduction of acellular vaccines, with the base-line - the national reports during ten years before introduction of acellular vaccines in the general vaccination program. Incidences in age-groups from 10 years and above are enlarged.

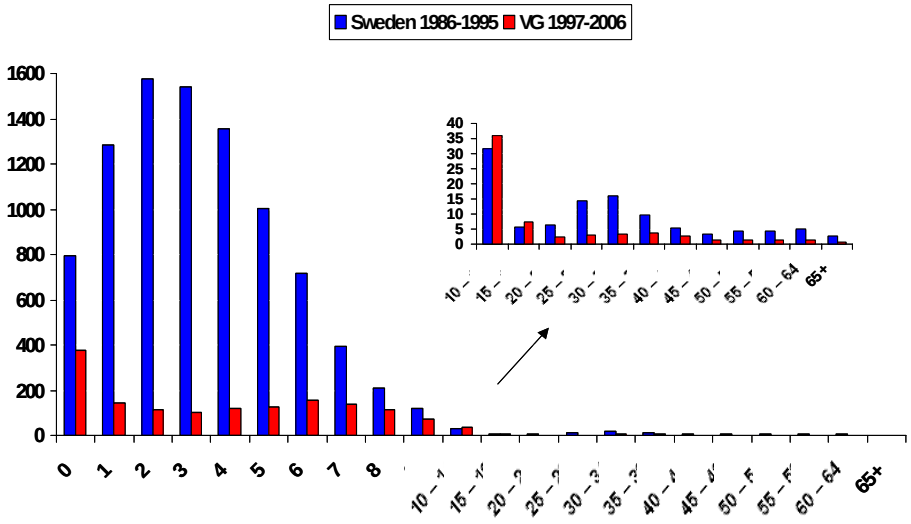


Figure 6 Mean incidence in defined age groups in the whole country during 10 calendar years (1986-95) before and in the VG region during 10 years after (1997-2006) introduction of DTPa in 1996. Enlarged bars for the age groups 10 years and above are shown in the insertion.

The figure demonstrate major changes in the age-specific incidences in toddlers and pre-school children, similar to what was illustrated in Figure 7 of the main nine year report [1]. However, a detailed comparison for the period 1997-2006 reveals differences between the region of Västra Götaland (above) and Sweden (Figure 7, main report), with higher age-specific incidence in infancy during the 1997-2006 period in the region of Västra Götaland.

4.2 Comparison of age-specific incidence in VG and the rest of Sweden

4.2.1 Age-specific incidences in the region of Västra Götaland and the rest of Sweden

A comparison of the mean age-specific incidences in VG and the rest of the country during the years 1997-2006 are found in figure 7. There are differences during early childhood in the two areas, i.e. in infants as well as in toddlers. This difference is especially marked in infants, where yearly age-specific incidence rates in the VG region were between 290 and 670/100,000. The corresponding rates in the rest of Sweden were between 80 and 180/100,000, Table 37A.

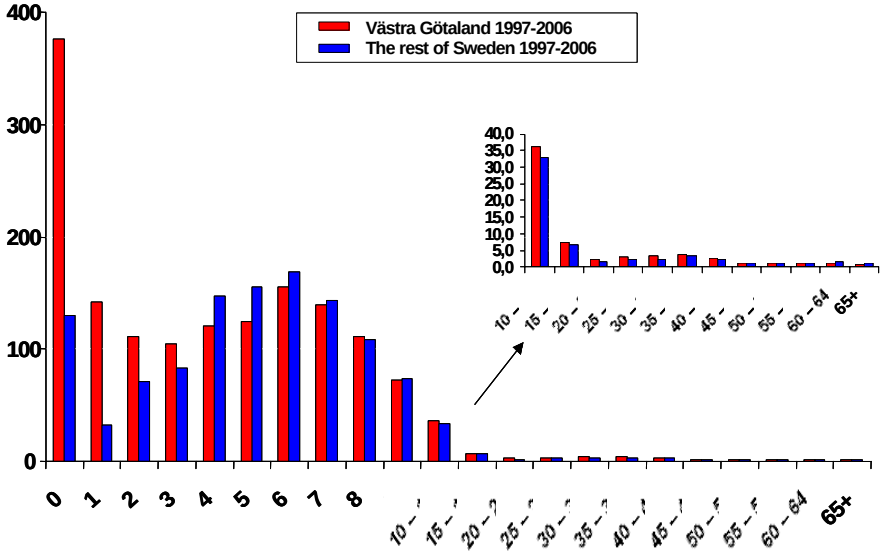


Figure 7 Mean incidence in defined age groups during 10 calendar years (1997-2006) after introduction of DTPa in 1996. Enlarged curves for the age groups 10 years and above are shown in the insertion.

Figure 8 illustrate the age-specific incidence 1997-2006 per calendar year for the VG region. The step-wise decrease seen in the rest of the country (Figure B of the nine year report, [1]), with intermediate levels of incidence during the years 1998-2000 and thereafter lower levels, is not seen.

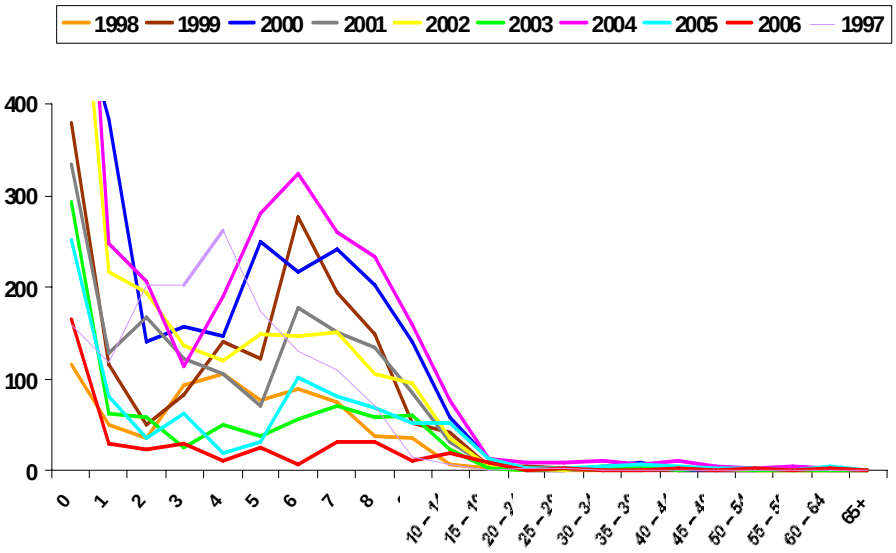


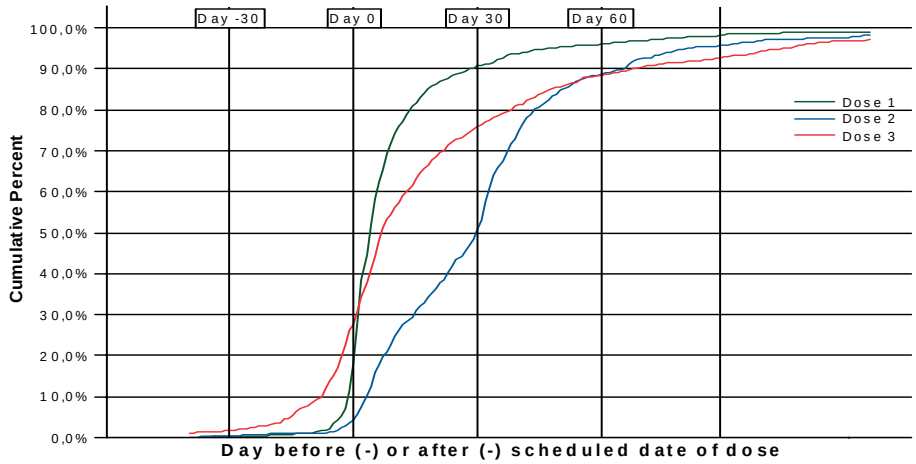
Figure 8 Age-specific incidence rates of laboratory-verified pertussis in the region of Västra Götaland during the period 1997-2006.

Since the national reporting system cannot separate reports from the Göteborg study area, it is not possible to check whether or not the figure represents a mixture of two patterns (i.e. a separate pattern in the Göteborg study area and another similar to the national in the rest of VG region). However, the analyses of age-specific incidence in children born from 1996 (Section 1.3.5, table 4) in the surveillance project reveal very high age-specific rates in the Göteborg study area infants, thus it is likely that the rest of Västra Götaland have age-specific incidences similar to the rest of the country.

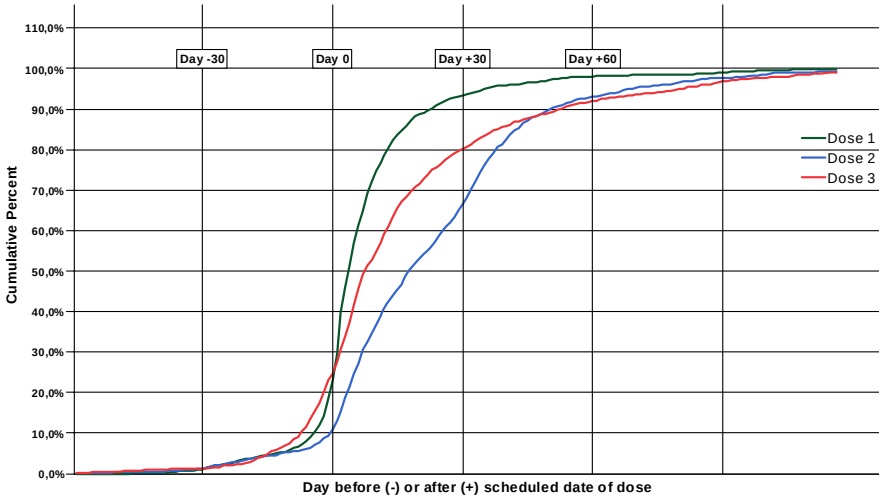
4.3 Vaccination coverage and timing of doses

More than 99% of Swedish children attend Child Health Care. The vaccination coverage for the three first doses of Pa is in Sweden measured yearly by checking all child health care medical records. The coverage is consistently around 98.5% over the years and there are no regional differences.

Timing of the three infant doses is illustrated in Figure 9, by plotting the cumulative proportion of children who have received their first, second and third dose in relation to scheduled age 3-5-12 months. The "deviations" from scheduled ages were about the same in the two areas. However, Dose 2 seems to be administered later for children in the Göteborg study area compared to the rest of Sweden.



Göteborg study area



The rest of Sweden

Figure 9 Cumulative proportion of children in the Göteborg study area (upper figure) in the rest of Sweden (lower figure) vaccinated in relation to scheduled day (Day 0) for the doses at 90 days, 150 days and 365 days. Data from the enhanced nine year surveillance. Vaccination status of children born from 1996 and until September 30, 2006, with a culture- or PCR-reported episode of pertussis between October 1, 1997 and September 30, 2006.

The consistency over time is further illustrated in Table 35, comparing the median ages (in days) at dose 1-3, and in children followed within the enhanced surveillance with the corresponding ages during the nation-wide Trial II in early 1990:s.

Table 35 Median age at dose 1-3 in Trial II (1993-94) and during the 1997-2006 enhanced surveillance period in Göteborg study area and the rest of Sweden. The scheduled ages are 3-5-12 months, corresponding to 90, 150 and 365 days.

Median ages at vaccination (days)	Dose 1 (90 days)	Dose2 (150 days)	Dose 3 (365 days)
Trial 2 (n = 72,698 infants included in 3-5-12 mo schedule)	100	174	386
Surveillance project from 1997-2006 (Sweden except Göteborg)	95	170	372
Surveillance project from 1997-2006 (Göteborg study area)	94	180	372

4.4 Catch-up vaccinations

Infants born during the latter part of 1995 were vaccinated in most parts of the country, because the start of their vaccination program was delayed until the Pa vaccines were licensed in January 1996. At age 2 years, the overall 3-dose coverage for the 1995 cohort was 60%. Toddlers and school children were catch-up vaccinated to some degree in Sweden except Göteborg study area, but a true catch-up was only implemented in this area of the VG region. In this city area, free catch-up vaccinations to more than 65,000 children born in the 1990:s were offered from 1997 to 1999. By spring 2000, about 56% of children born in the 1990:s were vaccinated with three doses of Pa-containing vaccine [4]

The influence of the Göteborg catch-up vaccinations on the long-term circulation of *Bordetella pertussis* is not known. The mass vaccination study reported signs of herd immunity as reflected by a significant reduction of the number of pertussis cases in vaccinated and unvaccinated individuals during the 1997-1999 period, but the follow-up stopped at the same time as the mass vaccination campaign stopped [4, 5].

4.5 Reporting routines

Pertussis cases are reported by clinicians and by microbiological laboratories, or both ways according to the Communicable Disease Act. The laboratory reports are based on culture, PCR or serology, Figure 10. The proportion of laboratory reports (i.e. cases reported both from clinicians and from laboratories, or only from the laboratories) is somewhat higher in the VG region than in the rest of Sweden, Figure 11.

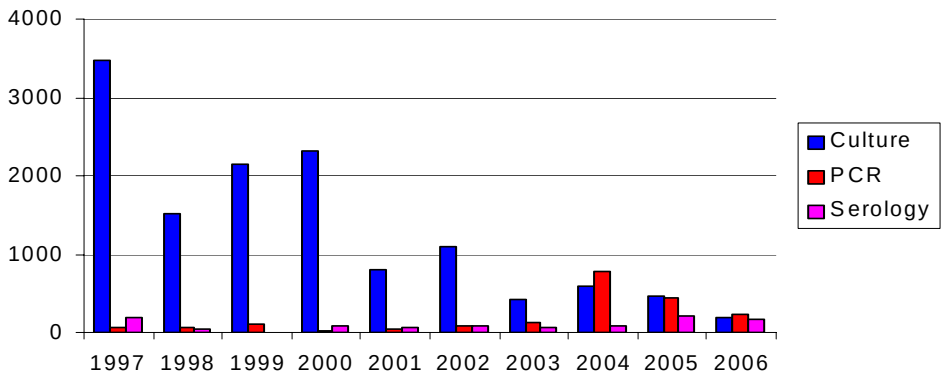


Figure 10 Laboratory methods used for verification of cases reported according to the Communicable Disease Act 1997-2006.

The proportion of laboratory reports (i.e. cases reported both from clinicians and from laboratories, or only from the laboratories) is somewhat higher in the VG region than in the rest of Sweden, Figure 11.

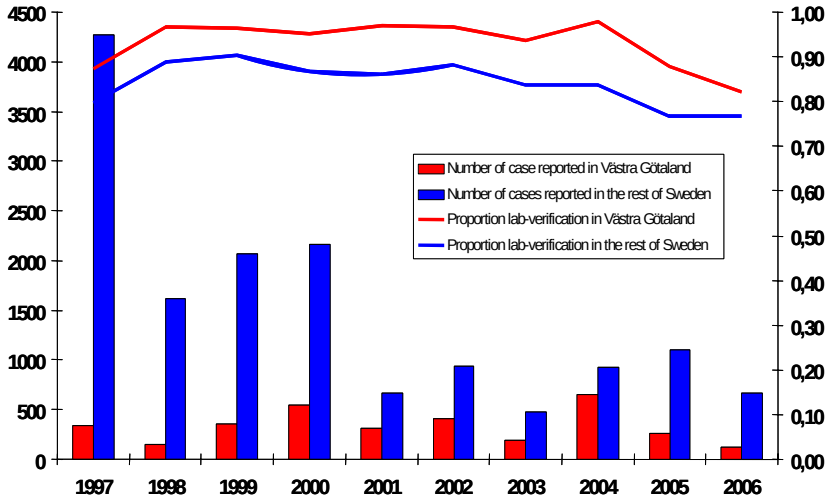


Figure 11 The proportion laboratory reported pertussis in relation to the overall number of cases reported 1997-2006 in Göteborg study area and the rest of Sweden.

4.6 Case ascertainment

Confirmation of *B. pertussis* by culture is in Sweden slowly by slowly becoming replaced by PCR, although many laboratories have continued to perform cultures on PCR-positive samples. In 1997 the proportion of PCR-verified cases was 5% or less. In 2003 around 20% of all laboratory reports were based on PCR and nowadays only about 50% of the pertussis reports are based on culture. It is well known that PCR may have a higher sensitivity in comparison with culture, especially in milder cases and later stage of disease, and the increasing use of PCR may hence increase the reporting of cases.

By courtesy of the dept of communicable disease in Västra Götaland, we have obtained nominator and denominator results form the four major laboratories in the region, and also from one smaller private laboratory. Figure 12 summarizes the total number of samples analyzed, and the proportion of samples that returned a positive result. The table confirms the progressive shift over time from culture to PCR.

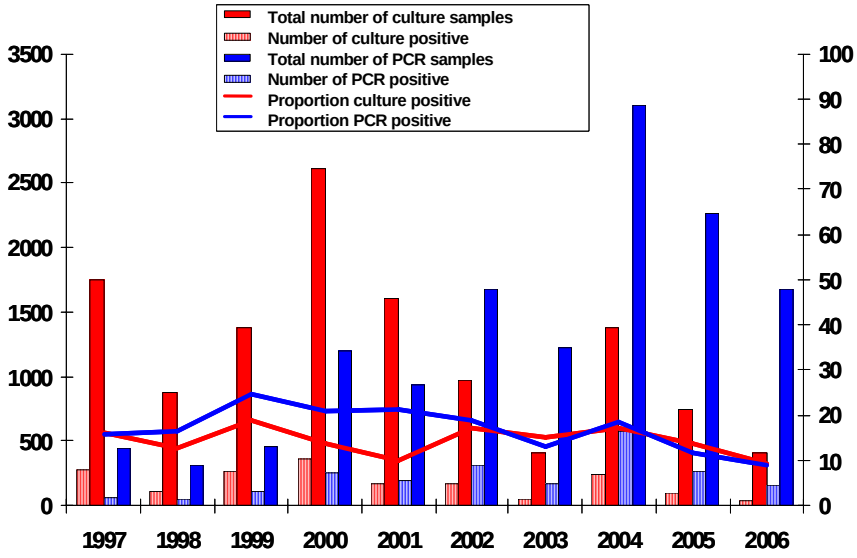


Figure 12 The number of samples analysed 1997-2006 for B. pertussis by culture and by PCR at five microbiological laboratories in VG region, the number and proportion of samples positive.

4.7 Potential differences in awareness

One possibility to address awareness would be to analyse laboratory denominator data, i.e. the number of samples submitted for detection of *B. pertussis* by culture or PCR in different parts of the country. By courtesy of the dept of Communicable Disease Control in Stockholm, we have obtained the total number of samples submitted during the year of 2006 to three major Stockholm laboratories (Capio, Huddinge, Karolinska including Medilab) for detection of *B. pertussis* by culture or PCR, Table 36. The table also gives the sum of samples analysed within VG region and at the Göteborg laboratory during this year.

Table 36 Number of samples submitted to Stockholm, Skåne, VG and Göteborg laboratories during the year 2006, number and proportion of positive results. Population figure are from table 5

	Population (no in thousand)	Number of samples 2006	Number positive	Proportion positive
Stockholm	1 867	1 185	115	9,7
Skåne	1 157	919	96	10,5
VG region without Gbg	804	1 092	98	9,0
Göteborg	782	990	91	9,2

There were no differences in proportion of samples positive. However, considering the population sizes (Table 1), it seems as the sampling frequency is considerably higher in VG region. Assuming that the Göteborg laboratory has a catchment area representing about half the population in VG region, there seem to be no differences in sampling frequency nor in proportion positive during the year 2006. This does not exclude differences during other years of the period 1997-2006.

Figure 13 demonstrates the overall number of samples analysed at the Göteborg laboratory and at the other VG laboratories during this ten year period. The figure demonstrates that there were more samples submitted to the Göteborg laboratory during the years 2000-2005 than to the other VG laboratories, i.e. during the outbreak years, although the proportions positive seems constant. We cannot from these data conclude whether or not there is a higher awareness in this area as compared to in the rest of VG region or in comparison to the rest of Sweden.

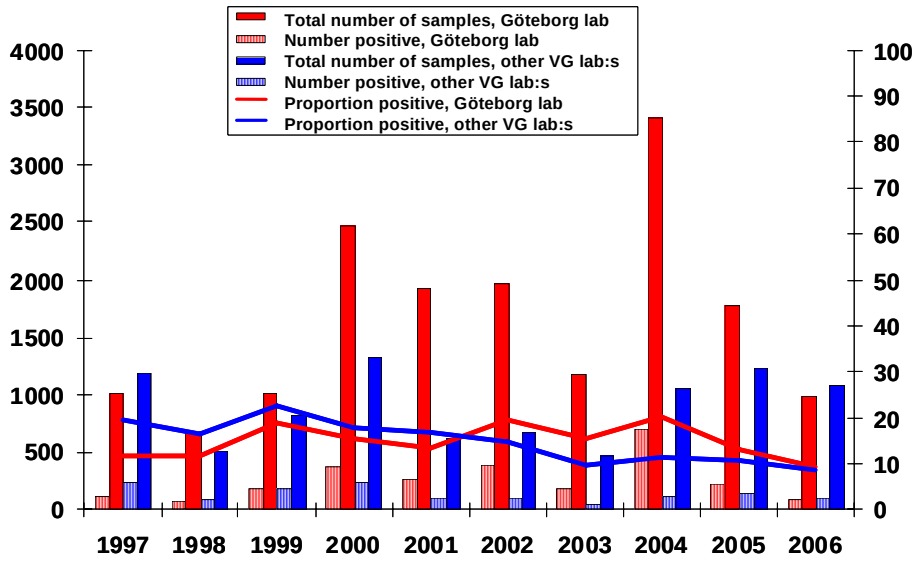


Figure 13 The number of samples analysed for B. pertussis (either by culture or by PCR) at the Bacteriological Laboratory at Sahlgrenska University Hospital (catchment area mainly Göteborg part of VG) and at the other bacteriological laboratories in Skövde, Uddevalla and Borås (catchment area mainly the rest of VG region) during the years 1997-2006.

There are no studies addressing the awareness of pertussis among the reporting physicians, but there are examples of high reporting rates with a timely association to media attention or to medical information campaigns drawing attention to pertussis. In the region of VG there was an increased reporting after an illustration of an infant case on the cover of the local newspaper during early summer 2004, Figure 14.

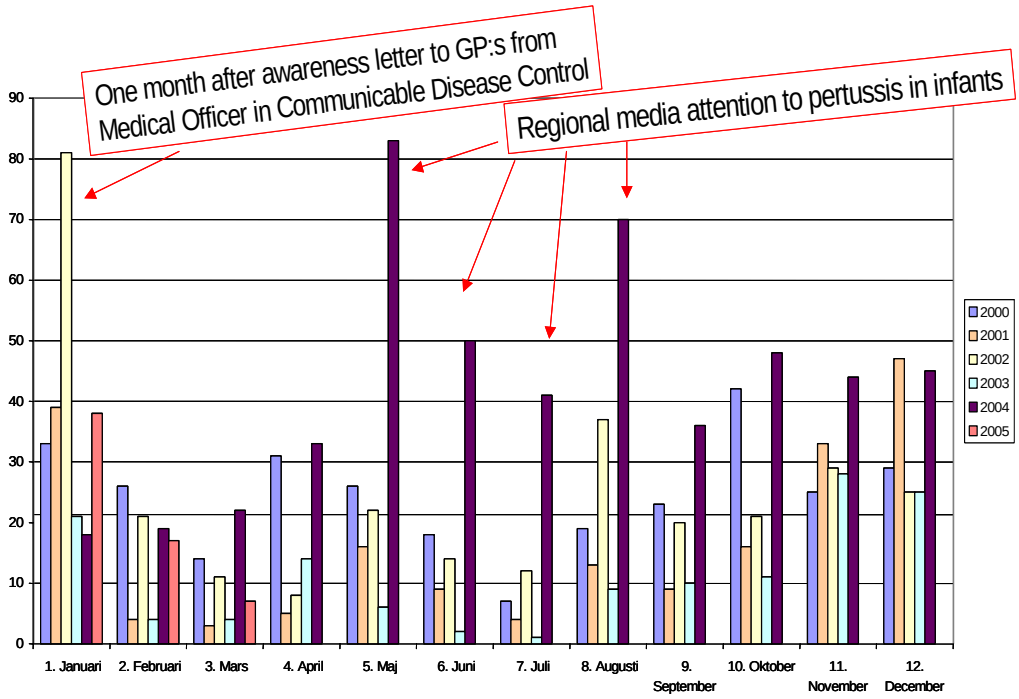


Figure 14 Number of pertussis reports in a VG region during the years 2000-04, with arrows indicating local attention to pertussis in media (by courtesy of Peggy Österberg, dept of Communicable Disease Control, Göteborg, Västra Götaland)

Table 37A Overall and age-specific incidence of notified culture- or PCR-confirmed pertussis per 100,000 for calendar years from 1997 to 2006 in region of Västra Götaland and in the rest of Sweden.

	Region Västra Götaland											Rest of Sweden									
Age, years	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Age, years	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
All	**20,1**	**10,2**	**23,1**	**34,7**	**20,2**	**26,3**	**11,4**	**41,7**	**15,1**	**6,8**	**All**	**46,1**	**19,4**	**25,4**	**25,3**	**7,8**	**11,2**	**5,4**	**10,3**	**11,2**	**6,8**
0	158,1	116,6	379,2	534,1	334,3	667,7	292,4	865,6	251,8	164,9	**0**	192,8	99,6	145,6	183,3	84,6	142,4	78,8	165,7	131,8	83,4
1	118,8	50,4	115,9	383,1	129,2	217,2	62,7	248,5	82,5	29,1	**1**	169,7	22,0	21,4	24,3	17,3	10,5	11,4	15,8	16,6	12,9
2	201,2	35,7	50,4	141,4	168,0	192,8	57,3	206,4	36,3	23,5	**2**	431,5	82,3	31,0	18,6	14,8	30,5	11,7	21,4	9,7	11,8
3	202,8	92,4	83,2	157,0	121,5	135,0	25,6	114,2	62,4	30,1	**3**	333,2	208,9	96,6	34,8	14,6	21,3	6,6	16,8	16,3	3,6
4	261,9	106,7	141,2	148,0	106,5	121,0	51,2	191,2	19,0	12,5	**4**	604,3	138,6	295,6	153,0	14,1	35,6	15,9	26,2	21,9	10,0
5	174,1	77,7	121,9	249,2	70,7	149,6	38,1	280,7	31,8	25,3	**5**	563,0	221,3	172,0	263,6	43,2	33,1	10,5	30,4	26,1	21,8
6	130,5	89,6	276,8	217,8	178,1	146,5	55,9	322,9	101,7	6,3	**6**	426,9	265,6	324,9	214,5	97,6	71,7	20,3	33,9	46,0	26,0
7	109,8	74,5	192,8	241,8	151,4	150,4	70,0	260,2	82,2	31,7	**7**	263,2	150,3	262,4	298,3	72,0	133,7	22,6	50,5	55,9	28,8
8	69,6	38,1	148,8	201,7	134,8	105,5	59,0	233,2	68,1	31,5	**8**	147,4	93,4	212,7	235,8	76,6	73,8	37,4	79,4	47,8	32,3
9	15,6	34,7	52,4	139,0	84,1	95,9	60,1	160,2	52,3	12,3	**9**	66,8	49,7	106,8	169,6	58,5	78,3	22,8	62,5	77,9	27,5
10 – 14	6,9	6,7	41,8	59,7	30,7	35,4	23,6	78,4	52,2	18,2	**10 – 14**	28,0	17,2	37,9	47,9	18,3	34,1	24,0	45,8	51,8	24,0
15 – 19	1,2	2,4	5,9	14,0	3,4	5,6	3,3	13,6	13,1	7,7	**15 – 19**	5,2	5,5	5,0	8,6	2,1	7,1	5,1	7,7	11,7	7,9
20 – 24	2,1	1,1	3,4	1,1	1,1	2,3	0,0	8,8	2,2	0,0	**20 – 24**	1,9	1,1	0,9	3,0	0,5	2,6	1,9	1,2	2,3	2,5
25 – 29	2,9	1,0	2,9	1,9	2,0	2,0	2,0	8,2	3,1	3,1	**25 – 29**	4,8	1,0	2,6	2,4	1,0	1,5	1,9	2,4	2,9	3,1
30 – 34	0,0	0,9	0,9	4,6	2,8	4,7	1,0	12,4	5,7	1,9	**30 – 34**	4,4	1,8	2,6	4,4	1,5	1,4	1,0	2,2	3,2	1,8
35 – 39	0,0	3,0	0,0	7,6	1,8	4,5	3,5	7,1	7,3	0,0	**35 – 39**	4,5	1,6	3,8	4,1	0,8	2,7	1,1	4,6	4,1	4,9
40 – 44	0,0	0,0	0,0	1,0	2,0	3,0	2,0	10,7	3,8	2,7	**40 – 44**	4,3	0,8	1,6	2,7	1,2	1,4	1,2	1,4	5,6	2,2
45 – 49	1,0	1,0	0,0	0,0	0,0	3,0	2,0	4,0	2,0	1,0	**45 – 49**	1,2	0,4	1,6	1,2	0,2	1,6	0,2	0,6	3,7	2,3
50 – 54	1,9	0,0	0,9	0,0	1,0	2,0	0,0	2,0	3,1	2,1	**50 – 54**	1,7	1,3	0,2	0,9	0,6	1,4	0,6	1,2	1,9	2,1
55 – 59	0,0	0,0	0,0	2,2	0,0	1,0	1,9	3,8	1,0	2,0	**55 – 59**	1,2	0,7	1,3	1,2	1,0	1,1	0,9	0,6	0,8	3,1
60 – 64	1,5	0,0	0,0	1,4	0,0	0,0	1,3	2,4	4,5	2,1	**60 – 64**	2,7	0,6	0,8	2,2	0,5	1,8	0,2	0,5	2,6	3,0
65+	0,8	0,4	0,8	1,2	0,8	0,8	0,8	0,8	0,4	0,8	**65+**	1,5	0,6	0,9	0,9	0,0	0,6	0,9	0,9	2,0	1,7

Table 37B Number of culture- or PCR confirmed cases of pertussis in defined age groups for calendar years from 1997 to 2006 after introduction of acellular pertussis vaccine in Sweden in region of Västra Götaland and in the rest of Sweden.

	Region Västra Götaland											Rest of Sweden									
Age, years	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	Age, years	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
All	299	152	343	518	302	395	173	633	231	105	All	3392	1430	1870	1870	577	830	401	771	842	512
0	25	18	58	82	52	106	48	146	43	29	0	148	74	107	136	64	111	64	138	111	72
1	20	8	18	59	20	34	10	41	14	5	1	140	17	16	18	13	8	9	13	14	11
2	37	6	8	22	26	30	9	33	6	4	2	386	68	24	14	11	23	9	17	8	10
3	40	17	14	25	19	21	4	18	10	5	3	317	187	80	27	11	16	5	13	13	3
4	54	21	26	25	17	19	8	30	3	2	4	603	132	265	127	11	27	12	20	17	8
5	37	16	24	46	12	24	6	44	5	4	5	582	221	164	237	36	26	8	23	20	17
6	28	19	57	43	33	25	9	51	16	1	6	448	275	325	205	88	60	16	26	35	20
7	23	16	41	50	30	28	12	42	13	5	7	270	158	272	299	69	121	19	40	43	22
8	14	8	32	43	28	21	11	40	11	5	8	145	96	224	245	77	71	34	67	38	25
9	3	7	11	30	18	20	12	30	9	2	9	63	49	110	179	61	79	22	57	66	22
10 – 14	6	6	39	58	31	37	25	83	54	18	10 – 14	120	76	174	229	91	174	124	236	261	116
15 – 19	1	2	5	12	3	5	3	13	13	8	15 – 19	22	23	21	36	9	31	23	36	57	40
20 – 24	2	1	3	1	1	2	0	8	2	0	20 – 24	9	5	4	13	2	11	8	5	10	11
25 – 29	3	1	3	2	2	2	2	8	3	3	25 – 29	24	5	13	12	5	7	9	11	13	14
30 – 34	0	1	1	5	3	5	1	13	6	2	30 – 34	24	10	14	23	8	7	5	11	16	9
35 – 39	0	3	0	8	2	5	4	8	8	0	35 – 39	22	8	19	21	4	15	6	25	22	26
40 – 44	0	0	0	1	2	3	2	11	4	3	40 – 44	21	4	8	13	6	7	6	7	29	12
45 – 49	1	1	0	0	0	3	2	4	2	1	45 – 49	6	2	8	6	1	8	1	3	18	11
50 – 54	2	0	1	0	1	2	0	2	3	2	50 – 54	9	7	1	5	3	7	3	6	9	10
55 – 59	0	0	0	2	0	1	2	4	1	2	55 – 59	5	3	6	6	5	6	5	3	4	16
60 – 64	1	0	0	1	0	0	1	2	4	2	60 – 64	9	2	3	8	2	7	1	2	12	15
65+	2	1	2	3	2	2	2	2	1	2	65+	19	8	12	11	0	8	12	12	26	22

5 Plan for continued work

The plans for project year ten include

- A scientific manuscript presenting nine year surveillance in Göteborg area, and another with presentation of all clinical information, including cohorts no longer under surveillance (overall clinical presentation of pertussis) and analyses of antibiotic use in relation to severity of disease and duration of symptoms
- Also, the results will be presented at national and international conferences/workshops as appropriate
- Extension of the surveillance period 3 months of 10th year until December 31st 2007
- Preparation of an overall ten year report with the results of the enhanced surveillance in Sweden except Göteborg, and also a 5 year report for Göteborg, in both cases with overall summaries according to primary case definitions (typical pertussis) as well as to current EU and WHO case definitions
- Transferral of the project database to SmiNet, i.e. the national disease reporting system, allowing access for the county medical officers in communicable disease control to enhanced data from their respective counties.
- Closure of the project in its present form, including archiving of all documents
- Planning of a redesigned project design, focusing on effectiveness in children boosted according to the revised national vaccination schedule, and on age-specific incidence in infancy (including clinical and vaccination data)
- An international workshop on pertussis epidemiology during autumn 2008 or spring 2009

6 Administration

Contracts for the project Pertussis surveillance in Sweden have been agreed for continued follow-up of clinical epidemiology during year 2004 to 2006 with the participating manufacturers, Sanofi-Pasteur-MSD, Lyon, Sanofi-Pasteur, Canada, and Glaxo SmithKline, Belgium.

The Advisory Group met annually. Progress reports are prepared as postmarketing follow-up for regulatory agencies. For transparency, it has been agreed that annual progress report is posted on www.smittskyddsinstitutet.se. The two vaccine specific Appendix 2 should also be posted, with a clear note of caution that comparisons between vaccines should not be performed.

The advisory group should in advance approve public presentations of data from the study. Papers should be submitted to peer reviewed journals. The investigators and the Advisory Group will not endorse other uses of the data.

7 Acknowledgements

Financial support was obtained from the National Institute of Allergy and Infectious Diseases, Contract no. N01-AI-15125, from the European Commission, Contract n° QLK2-CT-2001-01819; Eupertstrain, and from the following manufacturers: Sanofi Pasteur Ltd (formerly CLL), Toronto, Canada, Sanofi Pasteur MSD, Lyon, France, and GlaxoSmithKline Bio (formerly SKB Bio), Rixensart, Belgium.

We would like to acknowledge the departments of communicable disease control in Västra Götaland, Stockholm and Skåne, for help in obtaining laboratory denominator data, Birger Trollfors/Elisabet Bergfors in Göteborg for help in validating vaccination history for Göteborg children, and also Olof Nyrén at the dept of medical epidemiology and biostatistics, Karolinska Institute, for support.

8 References

1 Nine year report. Pertussis surveillance in Sweden, progress report October 1997 - September 2006 with an executive summary. Carlsson RM, Gustafsson L. *Smittskyddsinstitutets rapportserie* 1:2007 (available at www.Smittskyddsinstitutet.se).

2 Trollfors B, Taranger J, Lagergård T, Lind I, Sundh V, Zackrisson G, et al. A placebo-controlled trial of a pertussis-toxoid vaccine. New Engl J Med 1995;333:1045-50

3 Taranger J, Trollfors B, Lagergård T, Lind L, Sundh V, Zackrisson G, et al. Unchanged efficacy of a pertussis toxoid vaccine throughout the two years after the third vaccination of infants. Pediatr Infect Dis J. 1997;16:180-4.

4 Taranger J, Trollfors B, Bergfors E, Knutsson N, Sundh V, Lagergård T, et al. Mass vaccination of children with pertussis toxoid – decreased incidence in both vaccinated and nonvaccinated persons. Clin Infect Dis 2001;33:1004-9

5 Robbins JB, Schneerson R, Keith JM, Shiloach J, Miller M, Trollfors B. The rise in pertussis cases urges replacement of chemically-inactivated with genetically-inactivated toxoid for DTP. Vaccine 2007; 25;2811-6

6 Clarkson J, Fine PE. The efficiency of measles and pertussis notification in England and Wales. Int J Epid 1985;14:153-68

7 Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med 1996;334:349-55

8 Olin P, Rasmussen F, Gustafsson L, Hallander HO, Heijbel H. for the Ad Hoc Group for the Study of Pertussis Vaccines: Randomised trial of two-component, three-component and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Lancet 1997;350:1569-77

9 One year report. Pertussis surveillance in Sweden. Progress Report October 1997 – September 1998. Swedish Institute for Infectious Disease Control 1999.

10 Three year report. Pertussis surveillance in Sweden. Progress Report October 1997 – September 2000. Swedish Institute for Infectious Disease Control 2001.

11 Four year report. Pertussis surveillance in Sweden. Progress Report October 1997 – September 2001. Swedish Institute for Infectious Disease Control 3 february 2002.

12 Five year report. Pertussis surveillance in Sweden. Progress Report October 1997 – September 2002. Gustafsson L, Hallander HO, Advani A, Olin P. Swedish Institute for Infectious Disease Control 3 february 2003.

13 Six year report. Pertussis surveillance in Sweden, progress report October 1997 - September 2003 with an executive summary. Gustafsson L, Hallander HO, Advani A, Carlsson RM, Olin P. *Smittskyddsinstitutets rapportserie* 2:2004 (available at www.Smittskyddsinstitutet.se).

14 Gustafsson, L., Hallander, HO, Olin, P, Seven year report, Pertussis surveillance in Sweden, Progress Report October 1997 - September 2004. http://www.smittskyddsinstitutet.se/SMItemplates/Article____5894.aspx, 2005.

15 Eight year report. Pertussis surveillance in Sweden, progress report October 1997 - September 2005 with an executive summary. Carlsson RM, Gustafsson L, Hallander HO. *Smittskyddsinstitutets rapportserie* 4:2006 (available at www.Smittskyddsinstitutet.se).

16 Olin P, Hallander HO: Marked decline in pertussis followed reintroduction of pertussis vaccination in Sweden. EuroSurveillance 1999;4:128-9

17 Olin P, Gustafsson L, Barreto L, Hessel L, Mast C, Van Rie A, Bogaerts H, Storsaeter S. Declining pertussis incidence in Sweden following the introduction of acellular pertussis vaccine. Vaccine 2003;21:2015-21

18 Olin P. [Whooping cough is declining – but the risk for small infants has not been reduced.] Smittskydd 2002 (1)

19 Gustafsson L, Hessel L, Storsaeter J, Olin P. Long-term follow-up of Swedish children vaccinated with acellular pertussis vaccines at 3, 5, and 12 months of age indicates the need for a booster dose at 5 to 7 years of age. Pediatrics 2006;118(3):978-84.

20 WHO meeting on case definition of pertussis. Geneva, 10-11 January 1991. Geneva: WHO, MIN/EPI/PET/91. 1:4-5

21 EU Commission decision 19 March 2002, Decision No 2119/98/EC
22 WHO surveillance definition of feb 2003, WHO/V&B/03.01

Aktuella rapporter i denna serie

Nine Year Report - Pertussis surveillance in Sweden
Progress Report October 1997 - September 2006 with an executive summary
Smittskyddsinstitutets rapportserie 1:2007, 50 sidor (exkl bilagor). Tryckår 2007
Författare: Rose-Marie Carlsson och Lennart Gustafsson

Spridning av smtitkoppor - simuleringsexperiment
Smittskyddsinstitutets rapportserie 5:2006, 38 sidor. Tryckår 2006
Författare: Brouwers L, Mäkilä K, Camitz M

Eight Year Report - Pertussis surveillance in Sweden
Progress Report October 1997 - September 2005 with an executive summary
Smittskyddsinstitutets rapportserie 4:2006, 51 sidor (exkl bilagor). Tryckår 2006
Författare: Carlsson RM, Gustafsson L, Hallander HO

Exploratory analysis of spatial aspects on the Swedish influenza
Smittskyddsinstitutets rapportserie 3:2006, 25 sidor. Tryckår 2006
Författare David Bock och Kjell Pettersson. Statistical Research Unit, Göteborg University.

On statistical surveillance of Swedish influenza incidence. Peak detection
Smittskyddsinstitutets rapportserie 2:2006, 23 sidor. Tryckår 2006
Författare David Bock, Eva Andersson och Marianne Frisén.
Statistical Research Unit, Göteborg University.

Exploratory analysis of Swedish influenza data
Smittskyddsinstitutets rapportserie 1:2006, 53 sidor. Tryckår 2006
Författare Eva Andersson, David Bock och Marianne Frisén,
Research Unit, Göteborg University.

Har vårdpersonal inom den kommunala vården samt på länssjukhuset i Halmstad grundläggande vårdhygienisk kompetens för att förhindra smittspridning?
Uppsats för magisterexamen i Smittskydd och Vårdhygien. Tryckår 2005.
Smittskyddsinstitutets rapportserie 3:2005, 33 sidor (exkl bilagor).
Författare Eva Schöbel.

HIV-epidemin i Sverige.
Epidemiologisk uppföljning av nyupptäckta HIV-patienter 2002-2003 i Sverige
Smittskyddsinstitutets rapportserie 2:2005, 72 sidor. Tryckår 2005
Författare: My Heinrup

Är rätt personer vaccinerade mot TBE?
Smittskyddsinstitutets rapportserie 1:2005, 24 sidor. Tryckår 2005
Författare: Liza Johanesson och Christine Carlswärd
.

Rapporterna distribueras via Smittskyddsinstitutets
webbplats och trycks endast i undantagsfall.

SMITTSKYDDSINSTITUTET
Swedish Institute for Infectious Disease Control