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TWELVE YEAR REPORT

Pertussis in Göteborg study area

Technical report October 1, 1997 until December 31, 2009, including enhanced surveillance January 1, 2003 until December 31, 2009, with an executive summary

Lennart Nilsson and Gustaf Rydevik
AVDELNINGEN FÖR EPIDEMIOLOGI
SMITTSKYDDSINSTITUTET

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Swedish Institute for Infectious Disease Control

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Författare: NILSSON L, RYDEVIK G

AVDELNINGEN FÖR EPIDEMIOLOGI

Smittskyddsinstitutet

Smittskyddsinstitutet

171 82 Solna

Besöksadress: Nobels väg 18

Telefon: 08-457 23 00

Fax: 08-32 83 30

E-post: smi@smi.ki.se

www.smittskyddsinstitutet.se

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Contents

Abbreviations

DTPa	*Acellular pertussis vaccine*
FHA	*Filamentous haemagglutinin*
GSK	*GlaxoSmithKline*
Hib	Haemophilus influenzae type b
IPV	*Inactivated Polio vaccine*
ITT	*Intention to treat*
MSD	*Merck Sharp & Dome*
NRN	*National Registration Numbers*
Pa	*Acellular pertussis vaccine*
PCR	*Polymerase chain reaction*
PRN	*Pertactin*
Pw	*Whole cell pertussis vaccine*
PT	*Pertussis toxoid*
SMI	*”Smittskyddsinstitutet” = SIIDC, Swedish Institute for Infectious Disease Control*
SmiNet	*Computer-linked reporting system*
SSI	*Statens Seruminstitut (Copenhagen)*

Executive Summary

A. Background

In Sweden pertussis vaccination was withdrawn in 1979. During 1980 to 1995 laboratory confirmed pertussis was voluntarily reported from all bacteriological laboratories with full personal identifiers. 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, and 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 and/or laboratory confirmed by culture, PCR or serology are reported to the Swedish Institute for Infectious Disease Control through a computer-linked reporting system (SmiNet).

The epidemiology of pertussis in vaccinated cohorts, i.e. children born from 1996, has been studied since October 1st 1997 within an enhanced surveillance project, identifying laboratory verified cases through the routine reporting system (1, 2).

One area of Sweden, called the Göteborg study area (see Material and Method section), located within the region of Västra Götaland (see Material and Method section, Figure A (M&M) and Table A (exec sum)), was excluded from the enhanced follow-up until 2003 because pertussis surveillance was done in this study area within a clinical trial setting (3-5), including a mass vaccination project. Fifty-six percent of children in the area, born 1990 through 1995, were vaccinated within this project during the years 1997-2000 (5).

During four of the most recent twelve years it has been obvious from the yearly national epidemiological reports that there have been more laboratory reported cases of pertussis in the Västra Götaland region in relation to population size than in the rest of Sweden, Figure A (exec sum). The number of cases in this region was clearly in excess of the expected numbers during 2001-2004 with a marked peak in 2004.

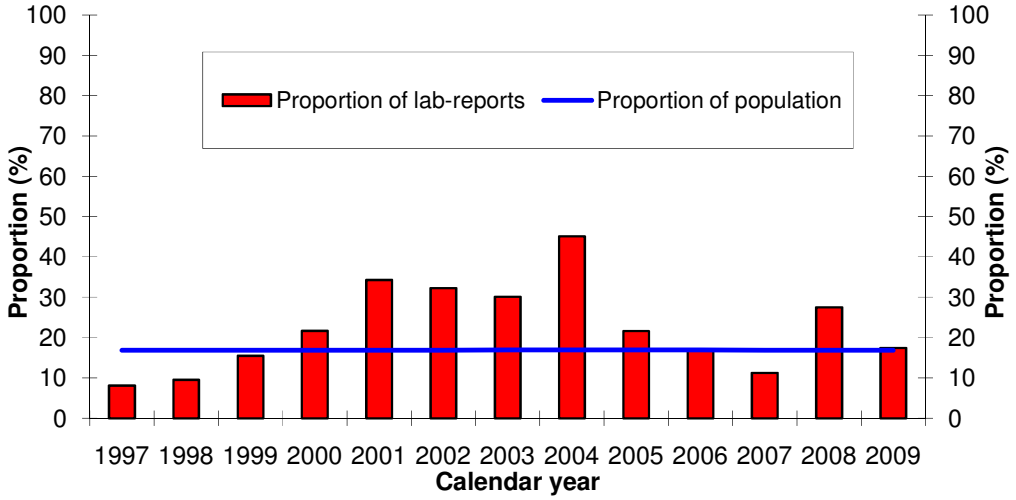


Figure A (exec sum). Proportion of laboratory reported cases of pertussis from the region of Västra Götaland (based on numbers in table 1:2b) and proportion of population in this region during the years 1997-2009 (based on mean population figures from Statistics Sweden). Nota bene: This is the proportion from the whole of Västra Götaland and not only for the Göteborg Study area analysed from the SMI-net data, see Material and Method section, Figure A (M&M) and Table A (M&M).

Göteborg study area (without Kungsbacka) is located in the Västra Götaland region and represents about 50.4% of its population. During the process of collecting and analysing the enhanced surveillance data, it became obvious that most of the pertussis reports in the Västra Götaland region were from the part representing the Göteborg study area, Table A (exec sum). For other areas of Sweden there were only minor differences when comparing proportions of laboratory reported cases in relation to proportion of population size ("index"-column of Table A (exec sum)).

Area	Population		Laboratory confirmed cases		Index
	Number in 1000	Percent of total	Number	% of total	Percent of cases divided by percent of population
Göteborg study area	862	9.3%	1303	34.0%	3.7
V Götaland exc Göteborg	775	8.3%	297	7.7%	0.9
Stockholm	2000	21.5%	668	17.4%	0.8
Skåne	1223	13.2%	365	9.5%	0.7
"South"	1183	12.7%	343	8.9%	0.7
Middle-east"	1023	11.0%	255	6.6%	0.6
"Middle-west"	1078	11.6%	315	8.2%	0.7
"North"	1154	12.4%	291	7.6%	0.6
Total	**9299**	**100.0%**	**3837**	**100.0%**	**1.0**

Table A (exec sum). Number of laboratory confirmed cases from October 1, 1997 until December 31, 2009 for children born January 1, 1996 until December 31, 2009, in different areas of Sweden in relation to population size of the area. The "measure" in column "Index" is percent of laboratory confirmed cases divided by percent of population in respective area of Sweden.

Also, in comparison with other demographic closer areas, the other two more crowded areas in Sweden, the peak incidence is most clear for the year 2004.

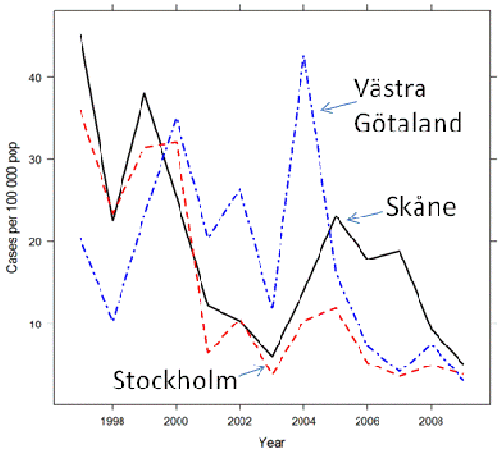


Figure B (exec sum). Laboratory reported pertussis incidence in the counties of Västra Götaland, Skåne and Stockholm; the three most crowded counties in Sweden 1997-2009.

B. Chapter 2, Results from the Göteborg study area

Enhanced pertussis surveillance in children from Göteborg study area followed from January 1, 2003 to 31, December 2009 and born January 1, 1996 to 31, December 2009

During the 7-year period of surveillance, January 1, 2003 until December 31, 2009, there were 617 followed episodes of laboratory confirmed pertussis within the Göteborg study area among 616 children born January 1, 1996 until December 31, 2009, with onset of symptoms from January 1, 2003 until December 31, 2009. Detailed vaccination history and information on coughing period, including duration of spasmodic cough, is available for all 617 episodes of pertussis. Data on hospital stay and complications are available for 614 episodes. Information on antibiotic treatment is available for 615 episodes, whereof 4 were excluded from analyses because of incomplete antibiotic course. The remaining 611 were used in the statistical analyses of antibiotic treatment during the episode.

Age-specific incidence in relation to vaccination data and clinical outcome

Tables 2.6 – 2.9 of chapter 2 present total number of person-years, number of laboratory confirmed pertussis cases and incidence figures with 95% confidence intervals for children in Göteborg study area and the rest of Sweden as well as relative risk results comparing the two areas. All results are presented in age-groups corresponding to the vaccination intervals in the vaccination program and also for one-year age-groups from 1 year of age. These analyses are based on episodes during the 7-year period January 1, 2003 until December 31, 2009.

In all tables an intent-to-treat or a per-protocol approach was used, with analyses according to age and 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. We have therefore included all children born January 1. 1996 through December 31. 2009 with culture-, or PCR-reported pertussis after three doses, regardless of age at episode and from 2009 also serology is added.

The analyses are also done according to different pertussis case definitions. The two main definitions used are all laboratory reported cases regardless of severity (Table 2.6 and 2.8), and the WHO definition of typical pertussis (Table 2.7 and 2.9), i.e. 21 days of more of paroxysmal cough. In addition, some analyses are performed using the current reporting definitions of 2 weeks or more of coughing of any kind.

We refer to chapter 2.4 for the detailed results of the comparisons between the two areas. As a summary: We observe larger risks of being a reported pertussis case for children in the Göteborg study area compared to the rest of Sweden in nearly all comparisons (Table 2:6 – 2:9). Table B (exec sum) below present some other comparisons between the two areas, with data from chapter 2 and done here as a complement to the results in chapter 2. About 10.1% of newborns in Sweden during the years 1996-2009 were born in the Göteborg study area and in the last column, named "Index", the percentage of pertussis cases in the Göteborg study area of total number of cases in Sweden, is therefore divided by 10.1.

Category of pertussis case & first Table in Section 2 where comparison data are presented	Total number of cases in Sweden	Number of cases in the Göteborg area	Percent of total number of cases that occured in Göteborg	Index. Proportion contributed by G. in relation to proportion of newborn children (11.3)
All reported cases(Table 2:5)	1996	617	30.9	3.0
Unvaccinated children(Table 2:2 and 2:3)	560	104	18.6	1.6
Unvaccinated children > = 1year old(Table 2:3)	120	16	13.3	1.2
Vaccinated with one dose(Table 2:5)	193	55	28.5	2.5
Vaccinated with two doses(Table 2:5)	143	83	58.0	5.1
Vaccinated with three doses(Table 2:5)	1100	375	34.1	3.0
Cough < 14 days - spasmodic or non-spasmodic	63	39	61.9	5.5
No spasmodic cough	399	205	51.4	4.6
Spasmodic cough 21 days(Table 2:7)	1478	350	23.7	2.1

Table B (exec sum). Some comparisons, related to different background or outcome parameters, of number of pertussis cases occurring during January 1, 2003 until December 31, 2009, for children born from January 1, 1996 until December 31, 2009, in Göteborg in relation to the rest of Sweden.

For the 5-year period of follow-up, there were considerable, and statistically 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 more cases in the Göteborg study area (or fewer cases in the rest of Sweden) taken differences between population sizes into account. In comparison with the total number of reports, some of the proportions (vaccinated with two doses, vaccinated with three doses, cough <14 days, no spasmodic cough) were higher whereas other (unvaccinated children, spasmodic cough 21 days) were not as highly different from the Sweden material. Note that the reporting of pertussis in unvaccinated infants 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 results for hospitalization and complications. The overall incidence of hospitalization for pertussis were higher in the Göteborg study area, but there were proportionally fewer hospital admissions per pertussis case among children with reported pertussis in this area than in the rest of Sweden (See also figure in chapter 2.5). The proportions of unimmunised children with laboratory-confirmed pertussis that were hospitalized in the Göteborg study area and in the rest of Sweden were respectively 37% and 55% There was furthermore proportionally fewer episodes with a longer hospital stay in Göteborg study area with 28% (13 of 47 children hospitalized) of Göteborg children hospitalized for more than one week whereas 40% (128 of 323) had a hospital stay of one week or more in the rest of the country (not significant). Also the proportion of all laboratory reported cases 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 C (exec sum) summarizes the overall incidence per 100,000 person years of culture/PCR-confirmed pertussis and from 2008 also serology-confirmed, 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 no significantly different hospitalization rate in any age group in the Göteborg study area in comparison with the rest of Sweden. This is a change from the ten year report, possibly signaling a normalization of the hospitalization rates in Göteborg, (see also Figure 2:6). The complication rates were, however, significantly higher in the Göteborg study area after two doses or more.

Pertussis incidence per 100,000 person years (95% C.I.)								
	All pertussis cases as described below		Episodes with >21 days of cough		Hospital admissions		Complications	
Age groups	Göte-borg	Rest of Sweden	Göteborg	Rest of Sweden	Göte-borg	Rest of Sweden	Göte-borg	Rest of Sweden
0-< 3 mo	411 (325-513)	186 (166-208)	242 (177-323)	166 (147-187)	190 (133-263)	139 (122-158)	111 (68-169)	85 (71-100)
3-< 5 mo	358 (261-479)	136 (115-159)	175 (110-265)	119 (99-141)	48 (18-104)	56 (43-72)	64 (27-125)	29 (20-41)
5-< 12 mo	214 (172-262)	23 (19-29)	78 (54-109)	18 (14-23)	2 (0-13)	5 (3-8)	14 (5-30)	3 (2-6)
≥12 mo	64 (58-70)	15 (14-16)	39 (35-45)	12 (11-13)	1 (0-2)	0 (0-0)	5 (3-7)	1 (1-2)

Table C (exec sum). 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 January 1, 1996 until December 31, 2009 and **followed from January.1, 2003 until December 31, 2009**, in the Göteborg study area and in the rest of Sweden (95% confidence interval within brackets). From 2008 serology is added as diagnosis of pertussis.

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 (51% and 46%). However, the proportions of infants treated in the age-group 3-<5 months, were slightly higher in the Göteborg study area as compared to the rest of Sweden. 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.

C. Chapter 3, Göteborg additional analyses

These analyses include the whole 12-year period October 1. 1997 until December 31. 2009. There were 622 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 617 cases mentioned in the Material and Method, section G, and 31 cases since jan 1, 2003 where vaccination data and/or clinical details were lacking.
In all, the twelve-year Part 1 of chapter 3 (3.2-3.3) analyses included 1270 laboratory reported cases in the Göteborg area from October 1, 1997 until December 31, 2009 in children born January 1, 1996 until December 31, 2009. Detailed vaccination data are available for 1 232 (97%) of these cases, included in the Part 2 of chapter 3 (3.4-3.6) analyses.

Age-specific incidence in relation to national vaccination schedule

Tables 2:7 (chapter 2) and 3:3 (chapter 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 2:7 presents data for a 7- year period, January 1, 2003 until December 31, 2009, while table 3:3 presents data from the overall twelve-year period October 1. 1997 until December 31. 2009. 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 7 year surveillance group (2:7) and in the additional 12-year analyses (3:3). 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 years, but Göteborg children at this age still had a 4.2 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 an increase until a maximum after infancy at about 6-7 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 an increase from about 6-7 years. In each age group, but that for nine year of age, 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 chapter 2 and 3, e.g. Table 2:8 and Table 3:10.

Age-specific incidence per calendar year

Table 3:2a and b (chapter 3.2) summarizes the age at laboratory report, and the reporting year, for 1,270 Göteborg cases as well as for 2,404 pertussis reports from the rest of Sweden with a sample taken during the twelve-year period of follow-up. These tables include children lacking clinical data. Table D (exec sum), below, provides age-specific incidence, by calendar year of laboratory diagnosis, based on the counts in table 1:2.b. Denominator data were derived from Statistics Sweden per calendar year (mid-point population counts for the municipalities included in the Göteborg study area, see Figure A and B in Material & Method section).

Table D.a. Sweden excluding Göteborg study area, incidence rates

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
0	114	95	160	192	72	141	76	178	134	90	75	41	41
1	28	21	19	25	15	13	9	17	12	10	6	13	7
2		18	35	20	14	30	10	26	7	13	6	9	2
3			58	35	16	20	7	13	17	8	7	6	8
4				62	19	33	15	25	18	9	9	6	2
5					23	35	12	31	24	20	5	3	9
6						57	19	33	36	22	23	12	8
7							14	51	44	26	22	16	5
8								83	39	21	16	19	9
9									71	18	25	29	5
10										14	10	20	6
11											5	5	4
12												7	1
13													5

Table D.b. Göteborg study area, incidence rates.

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
0	134	147	478	757	569	962	440	1134	240	149	81	107	26
1	174	78	170	648	215	339	95	388	108	38	9	36	18
2		43	56	237	284	305	120	285	61	10	19	0	0
3			131	245	204	216	23	175	74	10	10	19	0
4				218	145	192	80	316	44	11	20	20	10
5					130	245	34	466	68	11	32	0	10
6						217	100	509	159	23	11	0	0
7							109	445	136	46	34	11	0
8								392	89	45	0	0	0
9									22	11	0	23	23
10										109	11	11	0
11											0	0	0
12												22	0
13													0

Table D, a and b (exec sum). Age-specific incidence rates of culture- or PCR- and from 2008 serology-confirmed cases of pertussis in area, Sweden excluding Göteborg study area and in b Göteborg study area from October 1. 1997 until December 31. 2009, by attained age (in years) and calendar year of laboratory diagnosis, among children born January 1. 1996 until December 31. 2009. Age is calculated at date for the positive sample. The year 2004 in Göteborg study area with very high pertussis incidence is high-lighted in red also for the rest of of Sweden.

Since the data collection started on October 1. 1997, and ended on December 31. 2009, the person-time accrued in the underlying populations in 1997 was multiplied by 0.25 (representing 3/12 year of observation). In the calendar years when the studied cohort 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, (the last for each year), the denominators are multiplied by 0.5.

Table D, a and b (exec sum) 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 project, with some increase also in those above 1 year. From the year of 2005 the age-specific incidences in the Göteborg study area have decreased.
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 1997-2009 age-specific incidence rates for the whole region of Västra Götaland (with an overall population of about twice that of Göteborg) are shown in figure 1:2 .

Pertussis incidence in Göteborg area before and after 1996

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 [3] and the Stockholm I efficacy trial [8] 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.

Figure E (exec sum) below shows the number of positive samples per month at the Göteborg bacteriological laboratory, catchment area, mainly Göteborg, from 1990 to March 2001. The figure also includes numbers of positive samples for the rest of Sweden (data from figure 1:2 of the main report [1] subtracted 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 (10.1%).

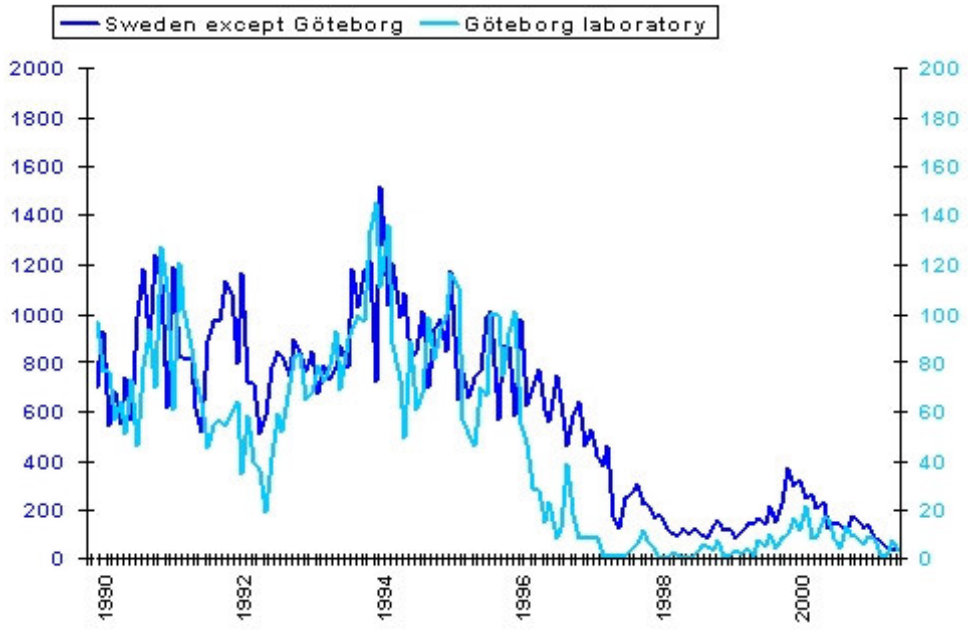


Figure E (exec sum). Number of culture- and PCR-confirmed pertussis cases per month from January 1990 to March 2001 reported from microbiological laboratories in Sweden except the Göteborg laboratory, and from the Göteborg laboratory.

D. 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 E (exec sum)=, 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 twelve years there were 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 A (exec sum). 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 5-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 (chapter 2)
- the 12-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 12-year age-specific calculations of pertussis in vaccinated children by use of the retrospectively collected and validated vaccination data (Chapter 3).

A comparison of number of laboratory confirmed pertussis reports in children born after 1995 during the 12 year period, taking population size into account, indicate only minor differences between different areas of Sweden outside the Göteborg study area. However, the "large city areas" of Stockholm and Skåne have in 2009 higher incidences of pertussis than the rest of Sweden (main 12-year report, Figure 1:7).

As shown in Tables 3:3-3:5, the age-specific incidence rates of confirmed pertussis during the 12 year period is around 2-13 times higher in the Göteborg study area compared to the rest of the country. The vast majority of the Göteborg reports are from the outbreak years 2000-2004,

with 30% of the reports (368/1261) 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 chapters 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.

Note that the Chapter 3 only give overall information on the number of culture- and PCR-confirmed cases of pertussis in children born in 1996 or later during the twelve year-period, with no details of severity at onset of the pertussis episode. From the 7-year enhanced surveillance period, in Chapter 2, i.e. 2003-2009 (including the peak year 2004) it seems that significantly 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. In fact, the relatively small difference between the proportion of cases meeting the WHO case definition in vaccinated and unimmunised children in the rest of Sweden is not in accordance with data in the randomised controlled trials in 1992-5 and 1993-96, and hence suggests an underreporting of mild cases among vaccinated children in these areas [1].

Chapter 1 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, The time difference in implementation of PCR technique in routine reporting of *Bordetella pertussis* can probably, but only to a small extent, contribute to the higher number of cases reported from the county of Västra Götaland during parts of the twelve year period.

Laboratory denominator data, provided by courtesy of the departments 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 county of Västra Götaland , but there are no differences in the number of samples yielding a positive result. There is, however, a difference within the county of Västra Götaland 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 county of Västra Götaland..

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 pertussis vaccine which was used in the Göteborg study area during 1996-1999, both for vaccination of infants and for the catch-up vaccination 1996-2000 was not used anywhere else in Sweden. Following a transition period, all children in the Göteborg study area were from late spring 2000 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 chapters 2 and 3 that there have been 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 during the Göteborg mass vaccination project and the local epidemiological monitoring stopped when the project stopped in early spring 2000.

In summary: The present observational study cannot explain the excess of reports in the Göteborg study area during the years 2000-2004, both among unvaccinated, partly vaccinated infants and among vaccinated children in different age-groups. 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 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. This outbreak illustrates the importance of long-term follow-up of vaccination strategies, and also that surveillance of pertussis in unvaccinated infants is a useful tool in monitoring trends in the epidemiology of pertussis.

It 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 coverage 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 [1]. A higher level of awareness in the Göteborg study area was indicated during the period 2003-2008 by the higher proportion of more mild cases than in the rest of Sweden and also by the lower proportion of hospitalization rate among unvaccinated infants with pertussis in the Göteborg area. We do, however, find it unlikely that a higher level of awareness in itself can fully explain the large number of pertussis.

It cannot be excluded that the monocomponent pertussis 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.

Another aspect that cannot be elaborated without further studies is the role of strain variations. From previous years in the enhanced surveillance, when also strain characterisation was included in the study design, it became obvious that strains appear and disappear in waves, with or without differences in clinical pattern of disease. Internationally, pertussis is reemerging in vaccinated populations, and it has been proposed and also provided evidence for that one explanation is antigenic divergence between vaccine strains and circulating strains (19). In the Netherlands, the resurgence of pertussis has been associated with the rise of *B. pertussis* strains with a novel promoter region for pertussis toxin (ptxP3) (21). The P3 strains are found in higher frequency in areas where a monocomponent vaccine is used (20). As for the Göteborg outbreak it is not known whether or not there were differences in circulating strains as compared to the rest of Sweden. Frozen strains collected from the Göteborg study area during the outbreak years are to some extent available for further characterization studies which could allow comparisons with previous results from the rest of Sweden. This has recently been described but so far not published (20).

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 A 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 to normal during 2005-2009, the age-specific incidence in Göteborg infants was still about twice as high as that of what is reported from the rest of the country until 2007. We find it likely that a difference of this magnitude could be explained by increased awareness, in contrast to the much larger differences noted during the outbreak years.

E. 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 and from 2008 also serology-confirmed, with sampling rates varying

geographically and over time, according to the awareness of pertussis, local clinical practice, level of suspicion and laboratory experience.

Comparisons between Göteborg and other areas in Sweden should be taken with caution and the surveillance study in the Göteborg study area [2-4] is likely to have a higher detection rate of pertussis than most parts in the rest of the country. The detection of proportionally milder cases, as demonstrated in Chapter 2.5-2.8, 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 twelve year period October 1. 1997 to December 31. 2009. 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. The influence of *Bordetella pertussis* strain variations is not known, but could be explored by characterization of strains collected both from the Göteborg study area and the rest of Sweden.

Material and Method

A. Routine reporting system

Within the enhanced surveillance project, all culture- or PCR-verified cases of pertussis in Sweden in children born January 1, 1996 until December 31, 2009 were identified from the national computer-linked reporting system. From 2008 also serology data are analysed. Basic data, i.e. National Registration Number (NRN), place of residence and laboratory date were entered into a separate surveillance database. For all children from the Göteborg study area (Figure A and Table A (M&M), beneath) there was also a "flag" entered in the database. Routine reports based on serology (but from 2008, see above) or immune-fluorescence, and clinical reports without laboratory confirmation were not included in the study database. Hence the study database includes information on birth date and sampling date for all culture- or PCR-verified pertussis in children born from 1996, regardless of area of residence – making it possible to calculate age of child at sampling date for all records in the surveillance database.

Enhanced surveillance program

During the first 5 ¼ years of the surveillance project, October 1. 1997 until December 31. 2002, children from the Göteborg study area entered in the surveillance database, were excluded from the follow-up of clinical and vaccination data. Children from the rest of Sweden were followed-up in detail by telephone interviews to parents and child/school health care nurses, if the child was born after 1995 or participated in the nationwide pertussis trial I and II, and had a laboratory-reported episode of pertussis no earlier than October 1. 1997. Vaccination data, as well as detailed clinical data, including information on hospitalisations, complications and antibiotic treatment, were collected and entered in the surveillance database. During the next 7 years of enhanced surveillance, January 1, 2003 until December 31, 2009, also laboratory-reported cases of pertussis from the Göteborg study area were followed-up in detail, if the child was born after 1995. Hence the study database includes detailed information from 7 years of enhanced surveillance of children in the Göteborg study area, January 1. 2003 through December 31. 2009, and detailed information from 12 years of surveillance in the rest of Sweden, October 1, 1997 through December 31, 2009.

Göteborg study area in relation to the counties of Västra Götaland and Halland and mean number of inhabitants (mean of 31 Dec 2008 and 2009).

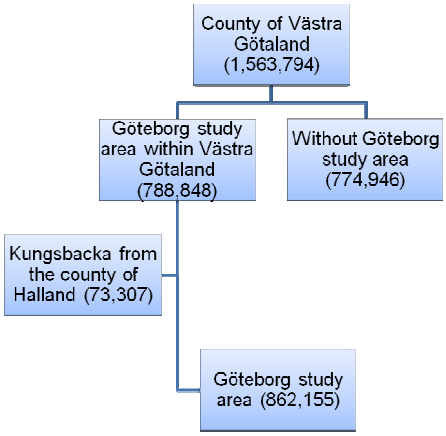


Figure A (M&M). Description of the Göteborg study area in relation to the two counties Västra Götaland and Halland.

County	Municipality	Inhabitants
Halland	Kungsbacka	73,307
Västra Götaland	Göteborg	503,764
"	Kungälv	40,498
"	Mölndal	60,097
"	Partille	34,092
"	Öckerö	12,271
"	Härryda	33,793
"	Ale	27,358
"	Lerum	38,193
"	Stenungsund	23,820
"	Tjörn	14,962
Total	**Göteborg study area**	**862,155**

Table A (M&M). Municipalities participating in the Göteborg study area, inhabitants in mean 2009 and the Göteborg mass-vaccination project.

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. To fill this "gap" we have, in 2006-2007, 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, enhanced surveillance data for Göteborg study area children, born January 1. 1996 until December 31. 2009, are presented in three ways in this report:

i) 7 years of enhanced surveillance information (i.e. with detailed clinical and vaccination data for episodes with onset of disease from **January 1. 2003 until December 31. 2009**), including a comparison with the corresponding data from the rest of Sweden (**Chapter 2**).
ii) 12 years of information on age at sampling date for all culture and PCR-reported cases of pertussis for the whole twelve-year period and serology from 2008 (laboratory sampling date between **October 1. 1997 until December 31. 2009**, without clinical and vaccination data), including a comparison with the corresponding data from the rest of Sweden **(Chapter 3.2-3.4**)
iii) 12 years of information on vaccination status at sampling date for all culture, serology- and PCR-reported cases of pertussis for the whole twelve-year period, with retrospectively collected vaccination data for the Göteborg children with culture- or PCR reports dated **October 1, 1997 until December 31, 2002 and prospectively collected vaccination data for episodes dated January 1. 2003 until December 31. 2009**, (i.e. individual vaccination data for the whole 12-year period, without any clinical data) including a comparison with the corresponding data from the rest of Sweden, (**Chapter 3.5-3.7**).

B. 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 [16]. Additional analyses according to the EU and WHO case definitions of 2002-2003 [17-18] have been added as appropriate. From 2008 also positive serology for pertussis has been added.

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

C. Person time and incidence calculations

Age-specific incidence rates of pertussis for children born from January 1, 1996 until December 31, 2009 were based on the number of notified pertussis cases during the study period January 1, 2003 until December 31, 2009 as described in the main twelve-year 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 "Twelve year report" [1]. Person time figures for the Göteborg study area are based on population figures for municipalities in Sweden during 1996 until 2009 taken from Statistics Sweden http://www.scb.se. To simplify person-time calculations for different cohorts, we used denominator data based on the following; that the total number of births during a calendar year were equally distributed during the calendar months; that all children were born mid-month and; that for dose-specific incidence rates, vaccinations were given according to the recommended schedule at three, five and twelve month of age.

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 positive serology from 2008 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 years divided by two (data from Statistics Sweden, http://www.scb.se).

D. Göteborg study area, vaccines and vaccination

The Göteborg study area is defined as the city of Göteborg and ten additional surrounding municipalities (Figure A and Table A (M&M) above), corresponding to the study area of the Göteborg pertussis vaccine trial and mass vaccination project (3-5). Nine of these municipalities and the city of Göteborg are geographically located within the region of Västra Götaland, whereas the 10th 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), see Abbreviations on page 5. 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 (5).

From 2007 the Swedish vaccination program includes a pre-school (5-6 years of age) and a school-leaving (14-16 years of age) booster against diphtheria-tetanus-pertussis to children born from 2002, with a catch-up dose against the three diseases to children born 1995-2001 at 10 years of age (7)

The excess in reported cases of pertussis from the county of Västra Götaland during the years 2001-2004 (Figure A (M&M), above) has been explained to a great deal by an excess in reports from the Göteborg study area. The aim of the earlier Göteborg reports were, therefore, 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, with the present report updating this information until December 31. 2009.

E. Chapter 1

Comparisons of performance indicators for the vaccination program and efforts to check differences in awareness are included in chapter 1, presenting the overall reported data from the county of Västra Götaland in comparison with the rest of Sweden. Laboratory denominator data are not included in the present Swedish national reporting system, but by courtesy of the county medical officers in Västra Götaland and some other regions, we have been able to perform some comparisons of data from laboratories within Västra Götaland as well as from the Göteborg study area and from the other large cities Stockholm and Malmö-Lund.

F. Chapter 2

In chapter 2 of this report we present the enhanced surveillance data for children born January 1. 1996 until December 31. 2009 from the Göteborg study area for the 7-year period January 1, 2003 through December 31, 2009, with comparisons to the rest of Sweden. This chapter of the Göteborg report includes age and vaccination data in relation to 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 realise that we do not have, and can never get, any comparable clinical data for pertussis episodes in Göteborg children during the period October 1. 1997 to December 31. 2002, i.e. during 5 ¼ years. During this period the area was excluded from the enhanced surveillance project and detailed clinical information, including date of onset of symptoms, cannot be collected retrospectively. It is therefore not possible to compare the prospectively collected detailed clinical information from the rest of Sweden during this period, with corresponding information from the Göteborg study area.

G. Chapter 3

Information on individual vaccination status can, however, be collected retrospectively from medical records, and this was done during the autumn 2006. Having filled this part of the information gap for the first 5 ¼ years of the enhanced surveillance project, we can present additional analyses and comparisons between the two areas for the whole "twelve-year" period, October 1. 1997 until December 31. 2009. These

additional analyses are presented in chapter 3 of this report and include vaccination data and age at date of the positive laboratory sample. It is to be noted that we cannot perform analyses by varying the case definitions in these analyses – the only "end-point" is a laboratory confirmed case of pertussis.

The plausible explanations to the high number of laboratory reported cases from the Göteborg study area are discussed in the Discussion part of the Executive Summary.

Chapter 1. Overall rates of laboratory reported pertussis in the county of Västra Götaland

The yearly progress reports from the enhanced pertussis surveillance project include a chapter with overall information from the Swedish communicable disease reporting system. Ideally, the present Göteborg report would provide a similar overview for the Göteborg study area. However, the Swedish reporting system is county-based and therefore we can only present overall rates from the whole county of Västra Götaland but not for the Göteborg study area part of this region, representing about half of the Västra Götaland population. Furthermore, the Göteborg study area includes one municipality within Halland county, representing about one quarter of the population in Halland (24.8%). In other words, the national communicable disease reporting system does not allow comparisons of the Göteborg study area with the rest of Sweden.

Nevertheless, and in spite of that the county of Västra Götaland is not a reasonable proxy for the ten Västra Götaland municipalities of the Göteborg study area, we find it valuable to look at the overall number of 3376 laboratory reported cases from Västra Götaland during the 1997-2009 period, as compared to the 13,233 laboratory reported cases from the rest of Sweden during the same time interval. We have also made some efforts to check indicators of different awareness and reporting practices in Västra Götaland and in the rest of Sweden.

In addition, some performance indicators for the vaccination program were obtained within the enhanced surveillance and for these we can compare the Göteborg study area with the rest of Sweden.

Laboratory denominator data are not included in the present Swedish national reporting system. By courtesy of the county medical officers in Västra Götaland and other regions, we have obtained some denominator data that were presented in the nine-year report (5), including some comparisons between laboratories within Västra Götaland as well as a large city comparison of the Göteborg, Stockholm and Malmö-Lund.

1.1 Changes over time in overall number of laboratory reported cases

Figure 1:1 demonstrate the overall difference in number of reported cases during 1997-2009. The county of Västra Götaland started at a lower level of reporting, having achieved a reduction in number of laboratory reported cases already in 1996 (Figure E (Exec sum). Then there was a peak within the region corresponding in time to the 1999-2000 peak in all of Sweden. From 2001 through 2004, the *number* of reports from Västra Götaland region was more or less equal to, sometimes even higher than, the number from the rest of Sweden, in spite of that the population in VG region represents 16,8% – 1/6 – of the Swedish population. Figure 1:1 also indicate that there were peaks in Västra Götaland region earlier than those in Sweden in general during the two remaining of the three nationwide peaks, i.e. in 2002 and in 2004-2005. For details about laboratory reported pertussis in different age groups, see Table 1:2, giving the age-specific incidences in 1997-2009 and 1:3 giving the incidence in infants during the years 1986-2009..

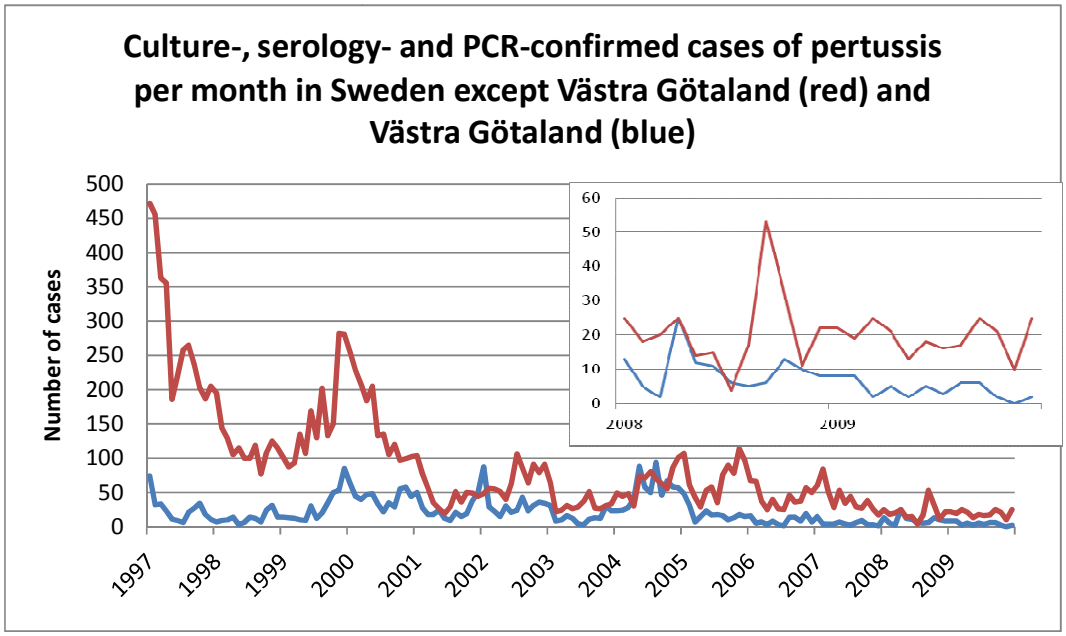


Figure 1:1 Number of laboratory reported cases of pertussis per month from January 1997 through December 2009 in Västra Götaland region (blue line) and the rest of Sweden (red line). Inserted – last two years.

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

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

The mean age-specific incidence of laboratory reported pertussis during the 12 years period 1997-2009, i.e. after the introduction of acellular vaccines, decreased as dramatically in Västra Götaland region as in the whole country (Figure E in Exec sum), and mainly in toddlers and pre-school children. There were, however, differences in the youngest age-groups, i.e. in infants as well as in toddlers, in Västra Götaland region as compared to the rest of Sweden, Figure 1:2.

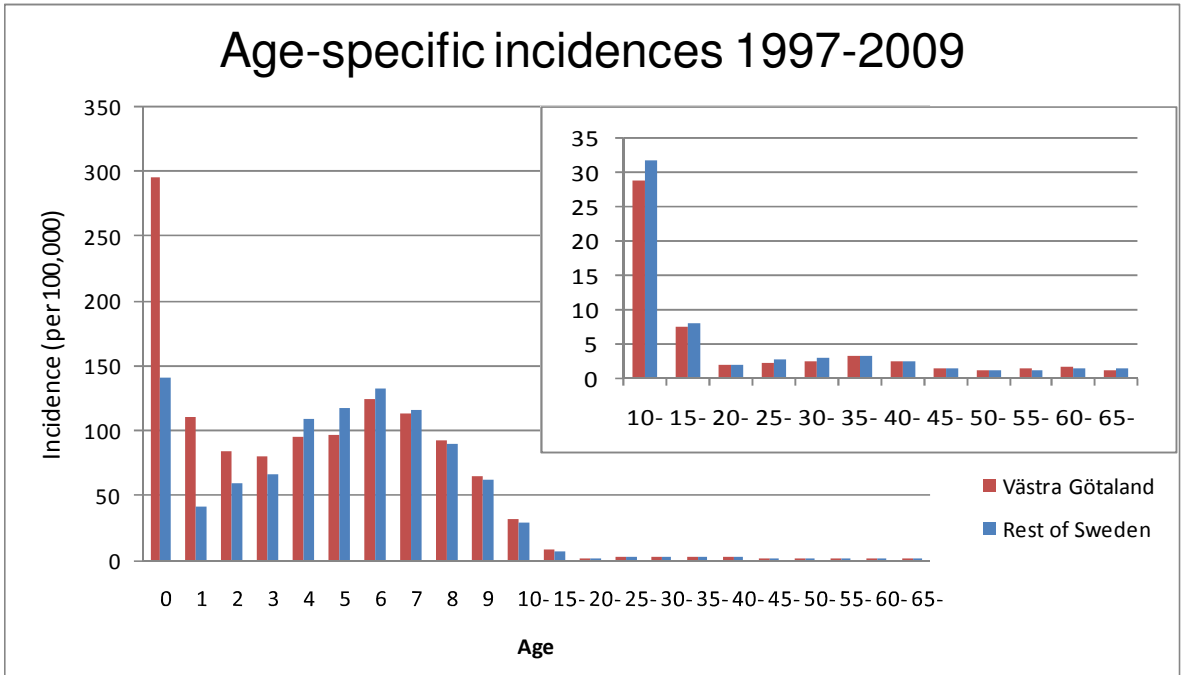


Figure 1:2 Mean incidence in defined age groups during 12 calendar years (1997-2009) in Västra Götaland region and in the rest of Sweden after introduction of DTPa in 1996. Enlarged curves for the age groups 10 years and above are shown in the insertion.

The difference between Västra Götaland region and the rest of Sweden is especially marked in infants (children below 12 months of age). Figure 1:3 provides the age-specific incidence in infants per calendar year in Västra Götaland region and the rest of Sweden during the 1986-2009 period.

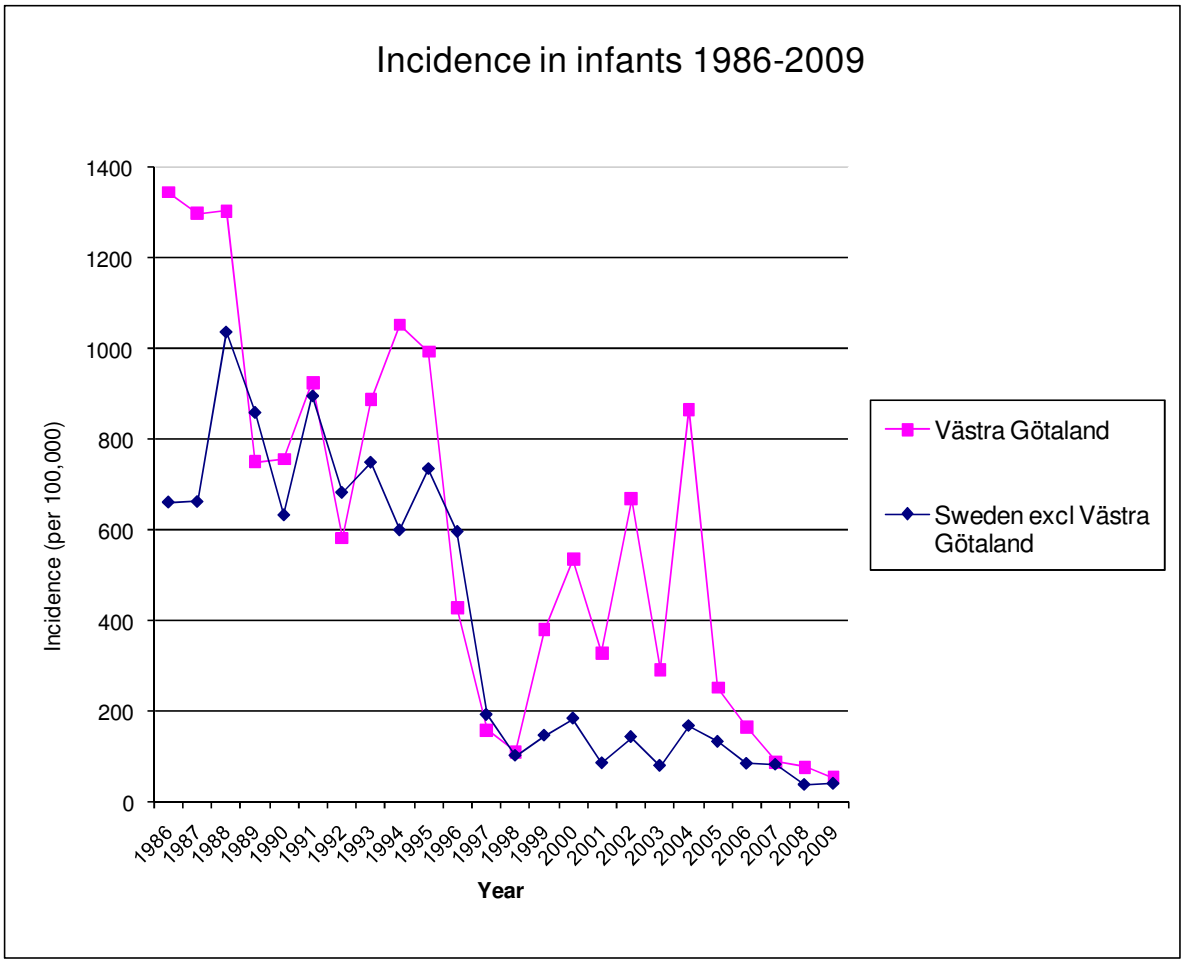


Figure 1:3 Age-specific incidence of laboratory reported pertussis in infants in Västra Götaland region and Sweden excl Västra Götaland during 10 calendar years (1986-95) before, during (1996), and 12 calendar years after (1997-2009) introduction of DTPa in 1996.

The incidence rates in the Västra Götaland region during the outbreak years 1999-2005 were between 250 and 870/100,000 infant person years, i.e. at levels seen in Sweden before introduction of DTPa in 1996, whereas the corresponding rates in the rest of Sweden during the same time period were between 85 and 183/100,000, Table 1:3. In 2007, the age-specific incidence in infancy for the first time was below 100/100,000 in Västra Götaland region.

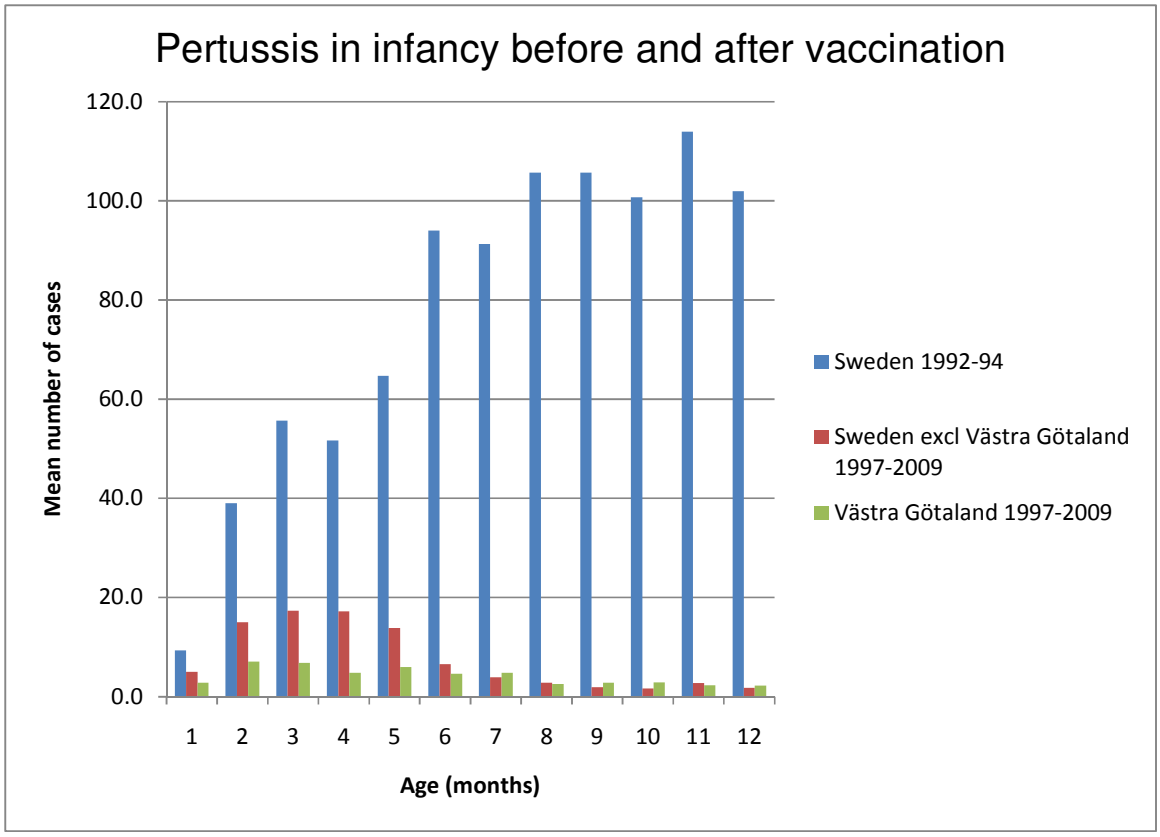


Figure 1:4 The mean number of infants with pertussis in infancy per month reported before (blue) and after (red) introduction of DTPa in 1996. Also, the mean number of infants in the age-groups 0-12 months reported from Västra Götaland region (green) during the years 1997-2009.

Figure 1:4 illustrate the infant age in month at laboratory-reported pertussis before and after 1996, and also the differences in reported number from Västra Götaland region and Sweden as a whole during the years 1997-2009. Carefully note that the comparison of Västra Götaland and the rest of Sweden in figure 1:4 is not adjusted for population size.

1.3 Vaccination coverage and timing of doses

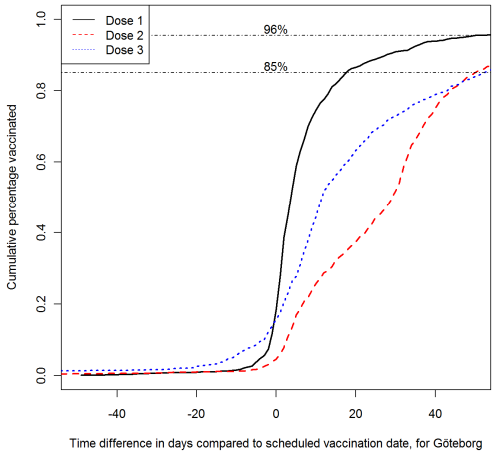
More than 99% of Swedish children attend Child Health Care. The vaccination coverage for the three first doses of Pa is in Sweden measured yearly by checking all child health care medical records. The coverage is consistently around 98.5% over the years and there are no regional differences.

The consistency over time is illustrated in Table 1:1, 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.

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 1997-2009 (Sweden except Göteborg)	94	167	374
Surveillance project from 1997-2009 (Göteborg study area)	94	180	372

Table 1:1 Median age at dose 1-3 in Trial II (1993-94) and during the 1997-2009 enhanced surveillance period in Göteborg study area and the rest of Sweden in children with pertussis. The scheduled ages are 3-5-12 months, corresponding to 90, 150 and 365 days.

There were only small differences in mean age at dose 1-3 in Göteborg and the rest of the country during the years 1997-2009. Furthermore there was no difference in mean age during these twelve years and the period of Trial 2, which was a study conducted throughout Sweden during "ordinary circumstances", i.e. at the infants ordinary child health care centre. The consistency in timing of the three infant doses is further illustrated in Figure 1:5, 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.



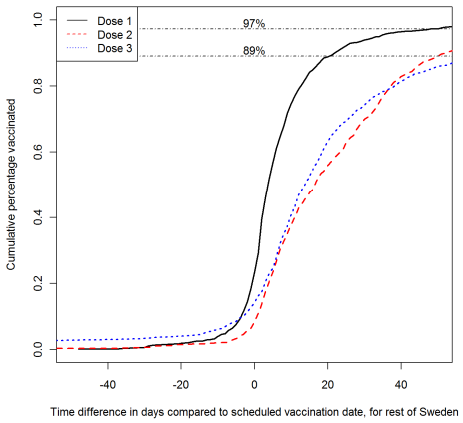


Figure 1:5 a and b Cumulative proportion of children in the Göteborg study area (upper figure) and in the rest of Sweden (lower figure) vaccinated in relation to scheduled day (Day 0) for the doses at 90 days, 150 days and 365 days. Data from the enhanced twelve year surveillance. Vaccination status of children born from January 1. 1996 and until December 31. 2009 with a culture- or PCR-reported episode of pertussis between October 1. 1997 and December 31. 2009.

The "deviations" from scheduled ages were about the same in the Göteborg study area and in the rest of Sweden. However, Dose 2 is administered somewhat later for children in the Göteborg study area compared to the rest of Sweden.

1.4 Catch-up vaccinations

Infants born during the latter part of 1995 were vaccinated against pertussis 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 larger catch-up was only implemented in the area of the Västra Götaland region. In this 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 (5).

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 (5).

1.5 Reporting routines

Pertussis cases are reported either by clinicians or by microbiological laboratories, or both ways, according to the Communicable Disease Act. 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 Västra Götaland region than in the rest of Sweden, Figure 1:6.

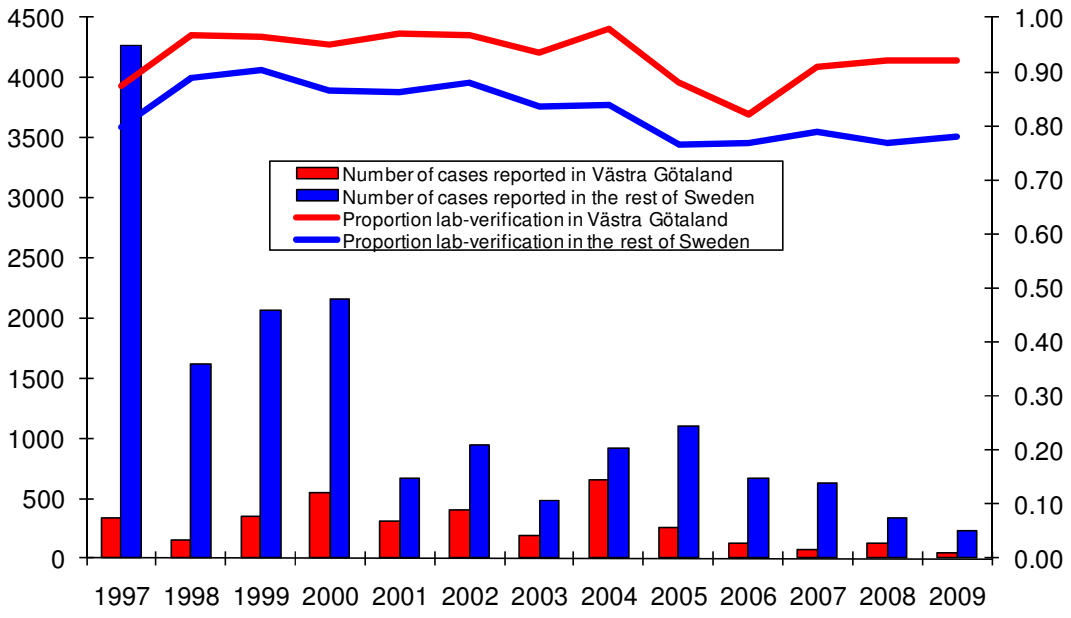


Figure 1:6 The proportion of clinician reported pertussis in relation to the overall number of cases reported 1997-2009 in Göteborg study area and the rest of Sweden.

1.6 Case ascertainment

Confirmation of *B. pertussis* by culture is in Sweden 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 lower than 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 department of communicable disease in Västra Götaland, we obtained nominator and denominator results from the four major laboratories in the region during the period 1997-2006, and also from one smaller private laboratory. These data were presented in the nine year Göteborg report (6).

1.7 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 department of Communicable Disease Control in Stockholm, we 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, see nine year Göteborg report, Table 36 (6). The table also gives the sum of samples analysed within Västra Götaland region and at the Göteborg laboratory during this year.

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 Västra Götaland there was an increased reporting after an illustration of an infant case on the cover of the local newspaper during early summer 2004, see ten year Göteborg report (2).

Table 1:2a Overall and age-specific incidence[5] of laboratory-reported pertussis per 100,000 in the region of Västra Götaland, from 1986 to 1995 before introduction, and 1996 to 2009 after introduction of acellular pertussis vaccine in Sweden. Data on number of reported cases were lost during two months of the year 1990 and therefore the denominator used for incidence was 10/12 of the 1990 population.

	1986	1987	1988	1989	1990*	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
All ages	**162.0**	**178.6**	**183.7**	**108.6**	**101.8**	**124.9**	**102.1**	**141.5**	**160.9**	**150.5**	**62.7**	**20.1**	**10.2**	**23.1**	**34.7**	**20.1**	**26.3**	**11.4**	**41.7**	**15.1**	**6.8**	**4.0**	**7.5**	**3.1**
0	1345.0	1296.6	1301.6	750.3	754.5	925.2	581.8	885.7	1052.1	992.9	**427.9**	**158.1**	**110.1**	**379.2**	**534.1**	**327.9**	**667.7**	**292.4**	**865.6**	**251.8**	**164.9**	**87.5**	**75.6**	**52.9**
1	2178.0	2142.3	2342.3	1279.3	1076.9	1293.1	1047.8	1622.6	1715.9	1617.2	590.6	**118.8**	**50.4**	**115.9**	**383.1**	**129.2**	**217.2**	**62.7**	**248.5**	**82.5**	**29.1**	**11.3**	**38.1**	**10.8**
2	2208.9	2417.2	2492.0	1435.0	1273.1	1649.7	1302.0	1512.5	1943.6	1810.9	602.8	201.2	**35.7**	**50.4**	**141.4**	**168.0**	**192.8**	**57.3**	**206.4**	**36.3**	**23.5**	**11.6**	**5.6**	**5.4**
3	2176.9	2556.9	2468.5	1430.8	1344.7	1713.8	1201.0	1556.5	1952.1	1602.7	649.2	202.8	92.4	**83.2**	**157.0**	**121.5**	**135.0**	**25.6**	**114.2**	**62.4**	**30.1**	**5.9**	**11.5**	**11.2**
4	1742.4	1994.4	1930.9	1370.3	1196.5	1208.7	1053.6	1486.4	1549.4	1647.9	681.7	261.9	106.7	141.2	**148.0**	**106.5**	**121.0**	**51.2**	**191.2**	**19.0**	**12.5**	**18.0**	**17.5**	**5.8**
5	1431.7	1540.0	1614.6	980.3	733.2	869.7	798.2	1246.6	1080.3	1036.4	511.6	174.1	77.7	121.9	249.2	**70.7**	**149.6**	**38.1**	**280.7**	**31.8**	**25.3**	**18.6**	**0**	**5.8**
6	1117.9	1227.0	1079.2	613.0	636.9	744.1	613.5	687.9	622.3	797.7	463.4	130.5	89.6	276.8	217.8	178.1	**146.5**	**55.9**	**322.9**	**101.7**	**6.3**	**25.1**	**24.7**	**0**
7	398.4	740.9	568.5	310.3	261.3	264.3	318.0	434.0	498.2	523.2	268.9	109.8	74.5	192.8	241.8	151.4	150.4	**70.0**	**260.2**	**75.9**	**31.7**	**31.5**	**25.0**	**0**
8	269.1	288.0	399.8	155.3	177.7	247.6	116.3	187.5	282.2	246.6	94.0	69.6	38.1	148.8	201.7	134.8	105.5	59.0	**233.2**	**74.3**	**31.5**	**0.0**	**56.5**	**0**
9	175.1	147.2	159.5	118.0	103.7	79.8	86.3	127.8	139.0	168.0	93.1	15.6	34.7	52.4	139.0	84.1	95.9	60.1	160.2	**52.3**	**12.3**	**6.3**	**75.3**	**18.7**
10	161.7	74.9	101.9	19.0	51.8	73.8	36.7	79.6	24.1	103.4	61.5	16.4	10.4	79.3	109.0	32.3	55.8	14.3	114.8	79.9	**46.3**	**12.2**	**62.3**	**6.2**
11	67.8	65.8	87.1	31.7	7.6	49.2	12.2	30.4	121.2	41.8	5.7	5.6	5.5	52.0	74.1	51.9	32.2	37.1	81.1	39.9	5.3	**11.5**	**6.1**	**6.2**
12	65.8	11.3	11.9	37.1	15.1	25.1	18.4	42.7	18.1	30.0	11.9	11.4	11.1	32.7	41.4	44.2	37.6	27.5	88.0	76.2	24.8	5.3	11.4	0
13	10.8	49.2	28.1	17.8	7.4	18.8	6.3	18.3	30.2	0.0	0.0	0.0	5.7	22.2	48.8	10.3	29.4	32.8	68.5	46.1	14.2	14.9	21.1	5.7
14	10.7	10.8	0.0	11.2	7.1	24.6	6.3	12.5	30.2	0.0	6.0	0.0	0.0	17.1	16.6	10.8	20.5	4.9	42.0	22.8	4.6	9.4	19.7	20.9
15	16.3	21.4	32.3	10.9	13.4	0.0	6.1	6.2	18.5	0.0	0.0	0.0	6.0	17.7	5.7	11.0	10.7	5.1	14.6	18.6	13.6	13.8	28.2	29.4
16	16.4	5.4	21.4	0.0	19.4	5.5	0.0	6.1	18.5	12.3	6.0	5.9	5.9	5.9	41.2	5.6	10.9	5.3	20.3	29.1	4.6	0.0	27.3	4.7
17	10.6	32.7	21.6	0.0	6.4	0.0	5.5	17.5	0.0	6.1	6.1	6.0	0.0	0.0	0.0	0.0	0.0	0.0	10.6	5.1	4.8	13.8	9.0	0
18	0.0	5.3	16.2	0.0	0.0	5.3	5.3	0.0	5.8	0.0	0.0	0.0	0.0	0.0	11.7	0.0	5.8	0.0	16.2	0.0	10.1	4.8	4.6	4.4
19	4.8	9.9	5.2	5.3	0.0	5.2	0.0	5.3	5.4	0.0	5.9	0.0	0.0	5.9	11.7	0.0	0.0	5.8	5.5	10.8	5.3	5.0	0	4.5
20-24	17.5	10.3	13.9	5.6	1.1	4.9	5.0	6.1	13.2	4.1	2.1	1.1	1.1	3.4	1.1	1.1	2.3	0.0	8.8	2.2	0.0	2.1	1.0	1.9
25-29	29.0	31.0	26.5	12.8	20.5	13.8	14.3	13.3	15.3	11.9	4.7	2.9	1.0	2.9	1.9	2.0	2.0	2.0	8.2	3.1	3.1	0.0	5.0	1.0
30-34	20.5	20.4	28.5	16.2	14.6	17.2	22.3	16.1	27.3	13.2	8.2	0.0	0.9	0.9	4.6	2.8	4.7	1.0	12.4	5.7	1.9	0.0	2.0	1.0
35-39	9.4	12.6	17.8	9.1	8.6	8.2	1.0	9.1	14.1	15.1	8.1	0.0	3.0	0.0	7.6	1.8	4.5	3.5	7.1	7.3	0.0	0.0	3.8	1.9
40-44	4.9	5.6	8.3	4.6	5.5	3.8	7.7	4.9	9.1	3.1	0.0	0.0	0.0	0.0	1.0	2.0	4.0	2.0	10.7	3.8	2.7	0.0	6.2	0
45-49	3.8	3.7	4.7	3.3	6.3	1.0	0.9	3.7	7.4	1.9	2.8	1.0	1.0	0.0	0.0	0.0	2.0	2.0	4.0	2.0	1.0	1.0	2.0	1.0
50-54	9.9	8.5	15.3	2.7	7.9	7.7	7.5	7.1	3.4	3.2	2.0	1.9	0.0	0.9	0.0	1.0	2.0	0.0	2.0	3.1	2.1	1.0	0	2.0
55-59	4.1	8.3	2.8	1.4	8.6	1.4	5.8	12.8	9.7	2.7	2.6	0.0	0.0	0.0	2.2	0.0	1.0	1.9	3.8	1.0	2.9	0.0	0	1.0
60-64	3.8	13.2	5.4	1.4	5.1	12.8	11.5	5.8	3.0	6.0	1.5	1.5	0.0	0.0	1.4	0.0	0.0	1.3	2.4	4.5	1.1	1.0	2.0	1.0
65+	3.6	3.6	4.3	1.6	0.9	3.1	4.6	3.5	4.6	3.8	1.9	0.8	0.4	0.8	1.2	0.8	0.8	0.8	0.8	0.4	0.8	0.8	0.4	0.7

[5] Note! Age specific incidence figures in black bold (upper right corner of table) concern children born 1996 or later, i.e. children born after introduction of Pa vaccine in Sweden: Note that the age specific incidence figures concern individuals from two yearly birth cohorts Figures in red represent children born 1995 (latter part) or 1996 (early part), i.e. those born at time of introduction of Pa vaccines. Most of these were vaccinated. All other incidence figures concern birth cohorts born before introduction of Pa vaccine in Sweden. For vaccine coverage per birth cohort, see main report (1) figure A (M&M).

Table 1:2b Number of laboratory reported cases[6] of pertussis from the region of Västra Götaland in defined age-groups from 1986 to 1995 before introduction and 1996 to 2008 after introduction of acellular pertussis vaccine in Sweden. Data on reported cases for the year 1990 represents only ten months, because data from two of the 1990 months were accidently lost during a process of data transferral between two national computer databases.

	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
	2269	**2514**	**2600**	**1548**	**1219**	**1804**	**1482**	**2066**	**2367**	**2227**	**930**	**299**	**151**	**343**	**518**	**301**	**395**	**173**	**633**	**231**	**105**	**62**	**116**	**49**
0	229	228	242	147	130	197	123	183	208	183	**72**	**25**	**17**	**58**	**82**	**51**	**106**	**48**	**146**	**43**	**29**	**16**	**14**	**10**
1	361	368	414	238	176	267	223	343	354	320	109	**20**	**8**	**18**	**59**	**20**	**34**	**10**	**41**	**14**	**5**	**2**	**7**	**2**
2	351	402	429	254	198	324	268	321	411	374	119	37	**6**	**8**	**22**	**26**	**30**	**9**	**33**	**6**	**4**	**2**	**1**	**1**
3	343	408	412	247	199	320	236	321	417	341	134	40	17	**14**	**25**	**19**	**21**	**4**	**18**	**10**	**5**	**1**	**2**	**2**
4	277	316	310	230	173	215	197	293	322	354	145	54	21	26	**25**	**17**	**19**	**8**	**30**	**3**	**2**	**3**	**3**	**1**
5	228	246	257	158	103	151	142	234	215	217	110	37	16	24	46	**12**	**24**	**6**	**44**	**5**	**4**	**3**	**0**	**1**
6	178	196	173	98	86	126	107	123	118	160	97	28	19	57	43	33	**25**	**9**	**51**	**16**	**1**	**4**	**4**	**0**
7	62	118	91	50	35	43	54	76	90	100	54	23	16	41	50	30	28	**12**	**42**	**12**	**5**	**5**	**4**	**0**
8	42	45	64	25	24	40	19	32	50	45	18	14	8	32	43	28	21	11	**40**	**12**	**5**	**0**	**9**	**0**
9	28	23	25	19	14	13	14	21	24	30	17	3	7	11	30	18	20	12	30	**9**	**2**	**1**	**12**	**3**
10	27	12	16	3	7	12	6	13	4	18	11	3	2	16	23	7	12	3	23	15	**8**	**2**	**10**	**1**
11	12	11	14	5	1	8	2	5	20	7	1	1	1	10	15	11	7	8	17	8	1	**2**	**1**	**1**
12	12	2	2	6	2	4	3	7	3	5	2	2	2	6	8	9	8	6	19	16	5	1	2	0
13	2	9	5	3	1	3	1	3	5	0	0	0	1	4	9	2	6	7	15	10	3	3	4	1
14	2	2		2	1	4	1	2	5	0	1	0	0	3	3	2	4	1	9	5	1	2	4	4
15	3	4	6	2	2	0	1	1	3	0	0	0	1	3	1	2	2	1	3	4	3	3	6	6
16	3	1	4	0	3	1	0	1	3	2	1	1	1	1	7	1	2	1	4	6	1	0	6	1
17	2	6	4	0	1	0	1	3	0	1	1	1	0	0	0	0	0	0	2	1	1	3	2	0
18	0	1	3	0	0	1	1	0	1	0	0	0	0	0	2	0	1	0	3	0	2	1	1	1
19	1	2	1	1	0	1	0	1	1	0	1	0	0	1	2	0	0	1	1	2	1	1	0	1
20-24	18	11	15	6	1	5	5	6	13	4	2	1	1	3	1	1	2	0	8	2	0	2	1	2
25-29	28	30	26	13	18	15	16	15	17	13	5	3	1	3	2	2	2	2	8	3	3	0	5	1
30-34	20	20	28	16	12	17	22	16	28	14	9	0	1	1	5	3	5	1	13	6	2	0	2	1
35-39	10	13	18	9	7	8	1	9	14	15	8	0	3	0	8	2	5	4	8	8	0	0	4	2
40-44	5	6	9	5	5	4	8	5	9	3	0	0	0	0	1	2	4	2	11	4	3	0	7	0
45-49	3	3	4	3	5	1	1	4	8	2	3	1	1	0	0	0	2	2	4	2	1	1	2	1
50-54	7	6	11	2	5	6	6	6	3	3	2	2	0	1	0	1	2	0	2	3	2	1	0	2
55-59	3	6	2	1	5	1	4	9	7	2	2	0	0	0	2	0	1	2	4	1	3	0	0	1
60-64	3	10	4	1	3	9	8	4	2	4	1	1	0	0	1	0	0	1	2	4	1	1	2	1
65+	9	9	11	4	2	8	12	9	12	10	5	2	1	2	3	2	2	2	2	1	2	2	1	

[6] Note! Age specific numbers in black bold (upper right corner of table) concern children born 1996 or later, i.e. children born after introduction of Pa vaccine in Sweden: Note that the age specific numbers concern individuals from two yearly birth cohorts. Figures in red represent children born 1995 (latter part) or 1996 (early part), i.e. those born at time of introduction of Pa vaccines. Most of these were vaccinated. All other numbers concern birth cohorts born before introduction of Pa vaccine in Sweden. For vaccine coverage per birth cohort, see main report (1) figure A (M&M).

Chapter 2: Enhanced pertussis surveillance in Göteborg study area

2.1 Laboratory confirmed pertussis cases in the enhanced surveillance reports Jan 1, 2003 to Dec 31, 2009.

This section analyses cases in the database as of April 2010 that have a reported onset of cough between January 1, 2003 until December 31, 2009 and were born between January 1, 1996 until December 31, 2009. For analytical purposes, they are split up into two groups: those born in the Göteborg study area, and those born in the rest of Sweden (Figure 2:1).
Cases lacking clinical data, or cases with a date of sample after Jan 1. 2003 but a start of cough before that time are excluded (5.2% of the cases from Göteborg and 6.1% of the cases from the rest of Sweden had to be excluded in this manner).
Figure 2:1 shows an overview of the data pertaining to the above mention inclusion and exclusion criteria.
One child from the Göteborg study area occurs twice in the analysed data. The child had two pertussis episodes after January 1. 2003, the first one occurred at 9 months and the second episode at 24 months of age.

In Sections 2.2 – 2.3 first laboratory confirmed cases from the Göteborg study area per year and birth cohort is shown. Therafter the pertussis cases are shown in relation to number of pertussis doses.

In Sections 2.4-2.8, we use the clinical data on pertussis episodes to 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 laboratory confirmed pertussis and we compare the results between the two areas of Sweden. In section 2.5 we present results on hospitalisation. The corresponding results for any complication due to the pertussis illness during the pertussis episode and the duration of spasmodic cough are found in sections 2.6 and 2.7. Treatment with antibiotics is covered in section 2.8.

There are laboratory reports in the database for ten children who died due to the pertussis illness. Two of these were from Göteborg study area. For ethical reasons the parents of these ten children have not been contacted and hence there are no clinical data collected from the parents. However, vaccination status and gestational age was checked with medical personnel, see main (eleven year) report, section 2.B.2 (1).

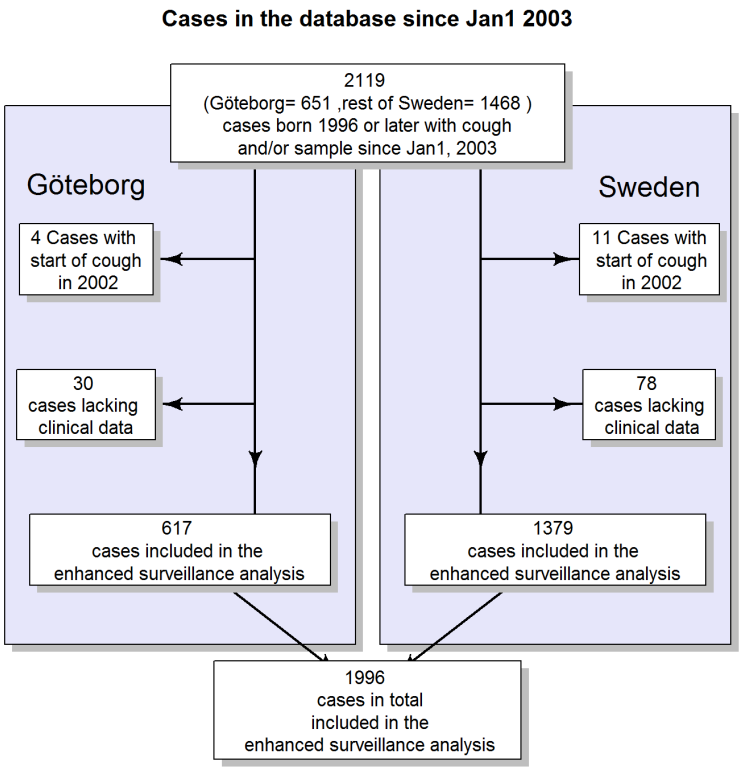


Figure 2:1 Cases in the database under consideration for the enhanced surveillance analysis comparing Göteborg study area and the rest of Sweden **Jan 1, 2003 until Dec 31, 2009.**

2.2 Laboratory confirmed pertussis cases per calendar year & birth cohort Jan 1, 2003 to Dec 31, 2009

All 1,996 laboratory confirmed cases of pertussis were divided by birth-cohorts and calendar years for onset of cough or, for the 14 children without cough (9 from the Göteborg study area) for date of the positive sample (Table 2:1, Figure 2:2 and 2:3).

Pertussis cases 2003-2009

Birth Cohort	2003	2004	2005	2006	2007	2008	2009	Total
1996	7 (14)	34 (60)	3 (41)	6 (14)	0 (3)	1 (6)	0 (2)	51 (140)
1997	7 (7)	35 (25)	15 (26)	2 (16)	1 (14)	0 (9)	0 (0)	60 (97)
1998	4 (12)	41 (34)	11 (40)	3 (21)	0 (13)	1 (25)	0 (3)	60 (148)
1999	9 (8)	39 (18)	10 (25)	6 (12)	1 (18)	2 (21)	2 (4)	69 (106)
2000	5 (7)	12 (21)	4 (14)	2 (24)	0 (18)	0 (15)	0 (4)	23 (103)
2001	8 (8)	28 (16)	4 (13)	1 (10)	0 (10)	1 (13)	0 (4)	42 (74)
2002	17 (15)	32 (15)	5 (10)	1 (8)	3 (3)	0 (2)	0 (6)	58 (59)
2003	24 (52)	55 (40)	11 (11)	1 (6)	1 (7)	1 (4)	1 (7)	94 (127)
2004		73 (116)	18 (40)	0 (12)	2 (7)	2 (5)	1 (5)	96 (185)
2005			14 (74)	6 (14)	0 (4)	0 (4)	0 (3)	20 (99)
2006				10 (64)	5 (22)	3 (11)	0 (5)	18 (102)
2007					6 (46)	6 (17)	2 (4)	14 (67)
2008						7 (26)	1 (17)	8 (43)
2009							4 (29)	4 (29)
Total	81 (123)	349 (345)	95 (294)	38 (201)	19 (165)	24 (158)	11 (93)	617 (1379)

Table 2:1 Laboratory confirmed cases of pertussis per calender year and birth cohort from January 1. 2003 until December 31. 2009 for children born January 1. 1996 until December 31. 2009. Göteborg study area figures first, and rest of Sweden within brackets.

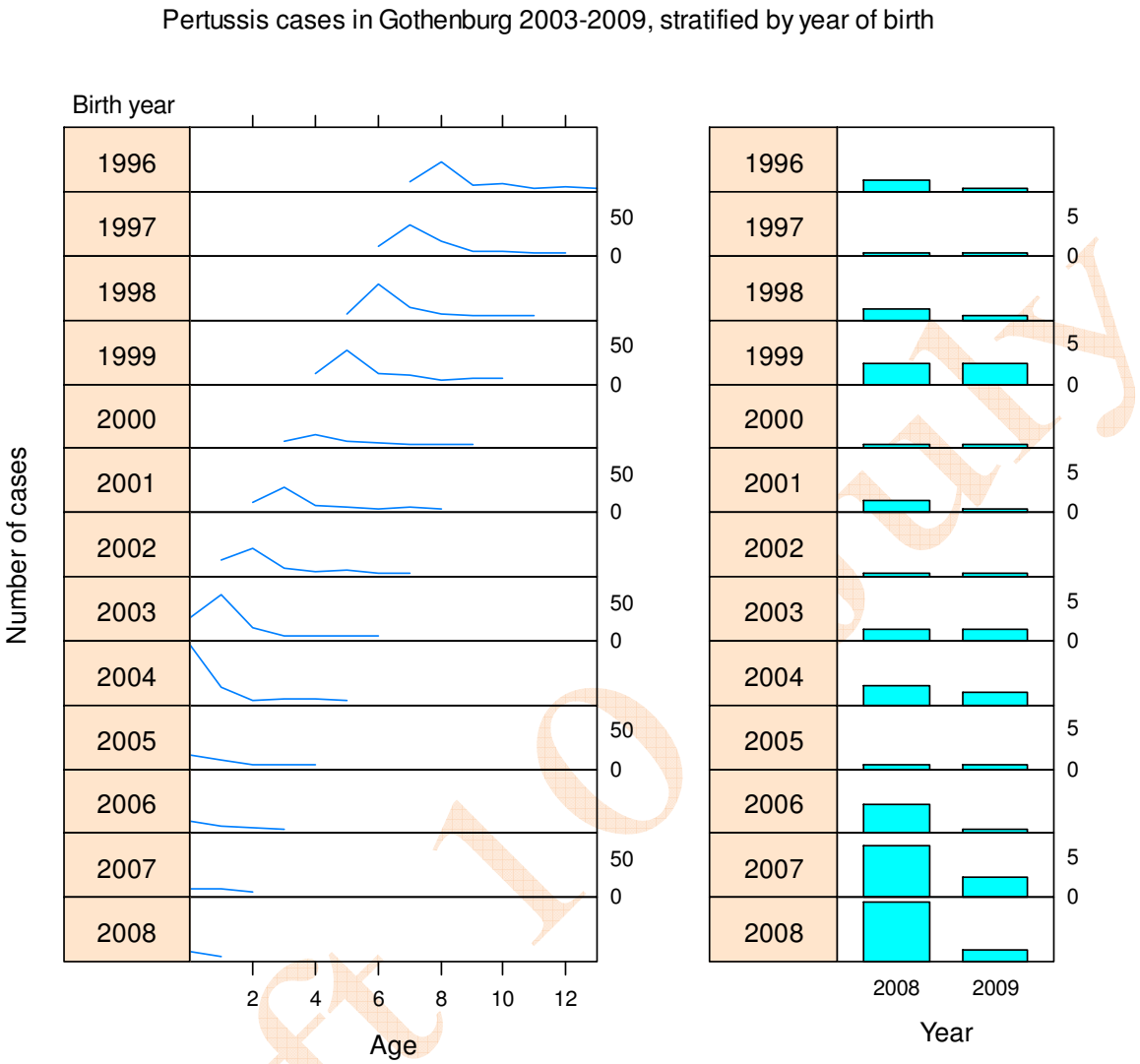


Figure 2:2 Pertussis cases in children born from Jan 1, 1996 until Dec 31, 2009 and followed from Jan 1, 2003 until Dec 31, 2009, stratified by year of birth. The first two columns show the pertussis cases for birth cohorts since 1996. The peak is for all ages in 2004. The next two columns show the last two years for every birth cohort. This is an illustration of Table 2:1.

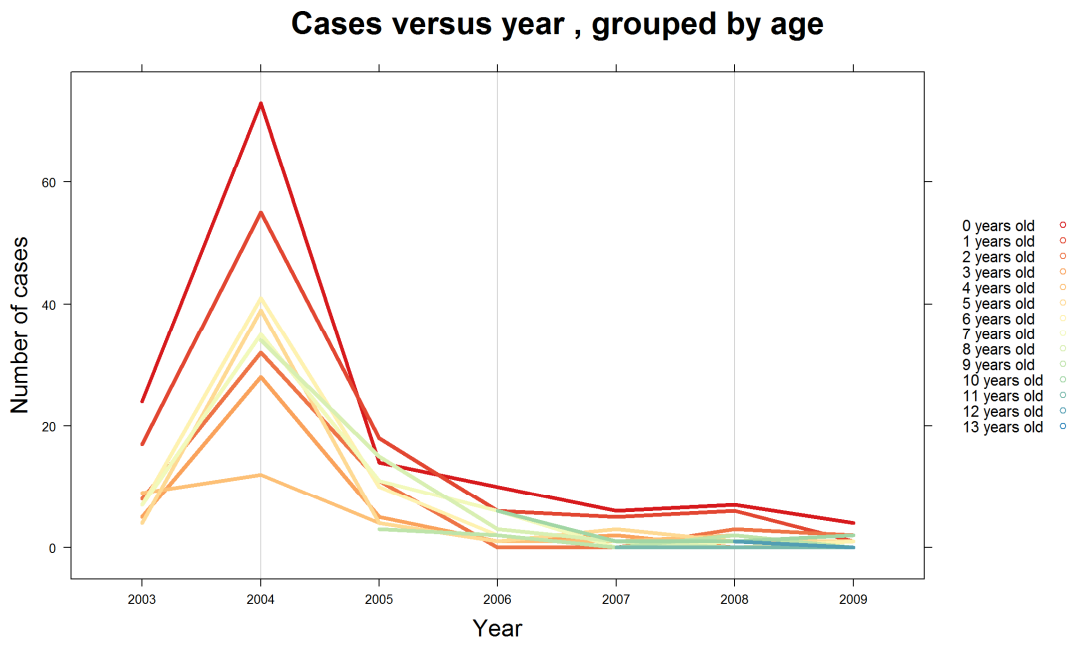


Figure 2:3 Pertussis cases in children born from Jan 1, 1996 until Dec 31, 2009 and followed from Jan 1, 2003 until Dec 31, 2009, stratified by year of birth. This is linked to Table 2:1 and also to Figure 2:2 above illustrating the epidemic in 2004 in all ages.

2.2.1 Laboratory confirmed pertussis cases among unvaccinated children Jan 1, 2003 to Dec 31, 2009.

Among 1,996 followed children with laboratory confirmed pertussis, 560 (28.0%) had not received a pertussis vaccine prior to the illness – for episodes in the Göteborg study area there were 104 (16.9%) and for children in Sweden except Göteborg there were 456 (33.0%) unvaccinated children, Table 2:2.

	Pertussis Cases per year							
Birth Cohort	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**Total**
1996	1 (0)	1 (5)	0 (2)	0 (1)	0 (0)	0 (1)	0 (0)	2 (9)
1997	0 (3)	0 (5)	0 (1)	0 (2)	0 (1)	0 (1)	0 (0)	0 (13)
1998	0 (1)	2 (1)	1 (0)	0 (2)	0 (1)	0 (2)	0 (0)	3 (7)
1999	0 (4)	2 (5)	1 (1)	0 (1)	0 (0)	0 (1)	0 (0)	3 (12)
2000	0 (1)	2 (6)	0 (3)	0 (7)	0 (1)	0 (3)	0 (0)	2 (21)
2001	0 (1)	2 (4)	0 (3)	0 (2)	0 (1)	0 (2)	0 (0)	2 (13)
2002	3 (5)	0 (5)	0 (1)	1 (1)	0 (0)	0 (0)	0 (3)	4 (15)
2003	13 (41)	6 (16)	1 (1)	0 (0)	0 (0)	0 (0)	0 (3)	20 (61)
2004		33 (77)	6 (13)	0 (1)	0 (1)	0 (0)	0 (0)	39 (92)
2005			8 (60)	0 (5)	0 (0)	0 (2)	0 (1)	8 (68)
2006				8 (44)	2 (12)	0 (2)	0 (0)	10 (58)
2007					3 (35)	1 (5)	0 (1)	4 (41)
2008						5 (21)	0 (6)	5 (27)
2009							2 (19)	2 (19)
Total	17 (56)	48 (124)	17 (85)	9 (66)	5 (52)	6 (40)	2 (33)	104 (456)

Table 2:2 Laboratory confirmed cases of pertussis per calender year and birth cohort for unvaccinated children from January 1. 2003 until December 31. 2009 for children born January 1. 1996 until December 31. 2009. Children from the Göteborg study area first, and the rest of Sweden within brackets.

All 560 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 48 days. Spasmodic cough for 21 days or more (episodes according to the WHO-definition) was reported for 84.7% of the episodes – the median duration was 38 days. For 58 (10.4%) 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 104 children from Göteborg study area was 42 and 26 days. The corresponding figures from Sweden except Göteborg were 49 and 39 days. Spasmodic cough for 21 days or more was reported for 62.5% of the Göteborg study area children and for 89.9% of children from the rest of Sweden. No spasmodic cough was reported for 28.9% respectively 6.15% of the episodes. All these differences are statistically significant.

Table 2:3 shows the age distribution of the laboratory confirmed cases at onset of cough for the unimmunised children. Most of the pertussis cases (67.8%) 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 75% of the pertussis cases among unvaccinated occurred before 3 months of age and the proportion in the rest of Sweden was 66.2%. There is no statistically significant difference between the two areas (p-value=0.23).

	Area				Total	
	Göteborg study area		Sweden except Göteborg			
Age in days at onset of cough	Cases	%	Cases	%	Total cases	Total percent
0-30	18	17	92	20	110	20
31-60	31	30	110	24	141	25
61-90	29	28	102	22	131	23
91-120	5	5	29	6	34	6
121-150	2	2	8	2	10	2
151-180	1	1	4	1	5	1
180-365	2	2	7	2	9	2
> 365	16	15	104	23	120	21
Total	104	100	456	100	560	100

Table 2:3 Age distribution among unimmunised children with pertussis in 559 laboratory confirmed cases of pertussis from January 1. 2003 until December 31. 2009 in Göteborg study area and in the rest of Sweden, respectively.

2.2.2 Laboratory confirmed pertussis cases among <u>vaccinated</u> children Jan 1, 2003 to Dec 31, 2009.

Among 1,996 reported children 1,436 (72.3%) had received at least one dose of a pertussis vaccine prior to onset of the pertussis episode – 1100 children had received 3-4 doses, 143 had received 2 doses and 194 had received only one dose of pertussis vaccine.

For children in the Göteborg study area 375 (60.9%), 83 (13.3%) and 55 (8.9%) had received three, two or one dose of a pertussis vaccine prior to onset of the pertussis episode. Corresponding figures for Sweden except Göteborg were; 725 (52.6%), 60 (4.4%) and 138 (10.0%) – (p-value<0.0001). Thus, relatively more children in the Göteborg study area were vaccinated with two or more doses before the episode of pertussis. Table 2:4 give the figures for 1,243 children vaccinated with two or more doses before the episode.

Cohort	2003	2004	2005	2006	2007	2008	2009	Total
1996	6 (14)	33 (55)	3 (38)	6 (13)	0 (3)	1 (5)	0 (2)	49 (130)
1997	7 (4)	34 (20)	15 (25)	2 (14)	1 (13)	0 (8)	0 (0)	59 (84)
1998	4 (11)	39 (33)	9 (40)	3 (19)	0 (12)	1 (23)	0 (3)	56 (141)
1999	9 (4)	36 (13)	9 (24)	6 (11)	1 (18)	2 (20)	2 (4)	65 (94)
2000	5 (6)	10 (14)	4 (11)	2 (17)	0 (17)	0 (12)	0 (4)	21 (81)
2001	8 (7)	26 (11)	4 (10)	1 (8)	0 (9)	1 (11)	0 (4)	40 (60)
2002	12 (3)	32 (10)	5 (9)	0 (7)	3 (3)	0 (2)	0 (3)	52 (37)
2003	4 (2)	44 (17)	10 (10)	1 (6)	1 (7)	1 (4)	1 (4)	62 (50)
2004		17 (4)	9 (16)	0 (11)	2 (6)	2 (5)	1 (5)	31 (47)
2005			3 (0)	6 (5)	0 (4)	0 (2)	0 (2)	9 (13)
2006				0 (4)	2 (6)	3 (9)	0 (5)	5 (24)
2007					1 (0)	5 (12)	2 (3)	8 (15)
2008						0 (1)	0 (8)	0 (9)
2009							1 (0)	1 (0)
Total	55 (51)	271 (177)	71 (183)	27 (115)	11 (98)	16 (114)	7 (47)	458 (785)

Table 2:4 Laboratory confirmed pertussis per calender year and birth cohort from January 1. 2003 until December 31. 2009 for children born January 1. 1996 until December 31. 2009 and vaccinated with two or more doses of pertussis vaccine. Göteborg study area first, and rest of Sweden within brackets.

All children but nine vaccinated with two or more doses were coughing during the pertussis episode. The minimum duration of cough, if cough, was 2 days – the median duration of cough was 47 days. Spasmodic cough for 21 days or more (WHO-definition) was reported for 68.6% of the episodes compared to 85.1% for the unimmunised children – the median duration in immunised children was 35 days. For 25.6% of the episodes there was no spasmodic cough compared to 10.1% for the unimmunised children.

There were differences between the two areas. The median duration of cough and spasmodic cough among 458 children from Göteborg study area was 42 and 24 days. The corresponding figures from Sweden except Göteborg were higher; 50 and 35 days. Spasmodic cough for 21 days or more was reported for 55.6% of the Göteborg children and for 76.2% of children from the rest of Sweden. No spasmodic cough was reported for 34.6% respectively 20.4% of the episodes. All these differences are statistically significant.

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

The proportion of population in the Göteborg study area is 10.1% of the total amount of follow-up during 2003-2009. Taken population sizes from 1996 until 2009 and follow-up time from 2003 until 2009 in the two areas into account, many more pertussis cases are reported in the Göteborg study area for most of the birth cohorts from 1996 and for each of the follow-up years from 2003 until 2006, compared to the number of cases reported in the rest of Sweden both for unvaccinated and vaccinated children.

The overall proportion of children with spasmodic cough for 21 or more days was 62.5% (unvaccinated) and 55.6% (vaccinated) for children in the Göteborg study area and 90.7% respectively 76.2% for children in the rest of Sweden. The proportion of children without spasmodic cough during the pertussis illness was 28.9% (unvaccinated) and 34.6% (vaccinated) in the Göteborg study area and 6.15% respectively 20.4% 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.

2.3 Laboratory confirmed pertussis cases in children and number of doses from Jan 1, 2003 until Dec 31, 2009

For this cohort of children there were 1,996

reports of laboratory confirmed pertussis with an onset of the episode from January 1. 2003 until December 31. 2009 for which we have data on both vaccinations and the clinical outcome. There were 617 cases among children in the Göteborg study area, whereof 104 unvaccinated, and 1,379, whereof 456 unvaccinated, among children in the rest of Sweden, Table 2:5.

Birth Cohort	Number of doses	Sweden except Göteborg	Göteborg area	Total
1996	0	9 (8)	2 (2)	11 (10)
	1	1 (1)	0 (0)	1 (1)
	2	0 (0)	1 (1)	1 (1)
	3	130 (99)	48 (33)	178 (132)
1997	0	13 (12)	0 (0)	13 (12)
	1	0 (0)	1 (1)	1 (1)
	2	0 (0)	0 (0)	0 (0)
	3	84 (70)	59 (41)	143 (111)
1998	0	7 (6)	3 (3)	10 (9)
	1	0 (0)	1 (1)	1 (1)
	2	0 (0)	1 (1)	1 (1)
	3	141 (109)	55 (37)	196 (146)
1999	0	12 (11)	3 (2)	15 (13)
	1	0 (0)	1 (0)	1 (0)
	2	0 (0)	1 (1)	1 (1)
	3	94 (72)	64 (44)	158 (116)
2000	0	21 (21)	2 (1)	23 (22)
	1	1 (1)	0 (0)	1 (1)
	2	0 (0)	0 (0)	0 (0)
	3	81 (59)	21 (12)	102 (71)
2001	0	13 (13)	2 (2)	15 (15)
	1	1 (1)	0 (0)	1 (1)
	2	0 (0)	0 (0)	0 (0)
	3	60 (47)	40 (15)	100 (62)
2002	0	15 (14)	4 (2)	19 (16)
	1	7 (6)	2 (0)	9 (6)
	2	1 (1)	8 (2)	9 (3)
	3	36 (27)	44 (19)	80 (46)
2003	0	61 (51)	20 (9)	81 (60)
	1	16 (13)	12 (5)	28 (18)
	2	14 (11)	38 (9)	52 (20)
	3	36 (29)	24 (13)	60 (42)
2004	0	92 (81)	39 (20)	131 (101)
	1	46 (41)	26 (14)	72 (55)
	2	18 (14)	21 (10)	39 (24)
	3	29 (20)	10 (6)	39 (26)
2005	0	68 (60)	8 (5)	76 (65)
	1	18 (16)	3 (2)	21 (18)
	2	4 (2)	6 (1)	10 (3)
	3	9 (7)	3 (2)	12 (9)
2006	0	58 (54)	10 (10)	68 (64)
	1	20 (18)	3 (1)	23 (19)
	2	8 (4)	2 (1)	10 (5)
	3	16 (10)	3 (1)	19 (11)
2007	0	41 (40)	4 (3)	45 (43)
	1	11 (10)	2 (2)	13 (12)

	2	10 (9)	4 (3)	14 (12)
	3	5 (3)	4 (3)	9 (6)
2008	0	27 (23)	5 (4)	32 (27)
	1	7 (6)	3 (3)	10 (9)
	2	5 (3)	0 (0)	5 (3)
	3	4 (2)	0 (0)	4 (2)
2009	0	19 (16)	2 (2)	21 (18)
	1	10 (7)	1 (1)	11 (8)
	2	0 (0)	1 (0)	1 (0)
	3	0 (0)	0 (0)	0 (0)
Subtotal	0	456 (410)	104 (65)	560 (475)
	1	138 (120)	55 (30)	193 (150)
	2	60 (44)	83 (29)	143 (73)
	3	725 (554)	375 (226)	1100 (780)
Total	-	1379 (1128)	617 (350)	1996 (1478)

Table 2:5. Laboratory confirmed pertussis, 1 Jan 2003-Dec 1 2009, among children born after 1. Jan 1996. Cases fulfilling the WHO definition in brackets

2.4 Laboratory confirmed pertussis incidence Jan 1, 2003 until Dec 31, 2009

See chapter 2A in the main twelve year report [1] and in Appendix 1 for population figures from January 1. 1996 until December 31. 2009 in the two compared areas and Material and Method section for 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 7 year periods of follow-up children in the Göteborg study area have been followed for approximately 521 thousand years and children in the rest of Sweden for 4.7 million years.

Tables in this section present total number of person-years, total number of laboratory confirmed pertussis cases and incidence figures with 95% confidence intervals for children in each of the two areas of Sweden divided in age/vaccination-groups 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);
The interval after 1 year of age is also divided in one-year age intervals of follow-up for which the same information is given.

The relative risk for a 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.

Four incidence tables are presented: Table 2:6 presents results for total number of laboratory confirmed pertussis cases, irrespective of clinical status, whereas in Table 2:7 the same analyses are done for children with 21 or more days of spasmodic cough. The approach in Tables 2:6-2:7 is an intent to treat, i.e. the overall effect of the vaccination program is studied by use of two different clinical case definitions. In Tables 2:8 and 2:9 corresponding analyses are done for children vaccinated with two or more than two doses prior to onset of cough (vaccine failures). The approach in Tables 2:8-2:9 is hence a "per protocol" analyses, i.e. the effect in children who are vaccinated according to the national program.

Table 2:6 presents all children born from January 1. 1996 until December 31. 2009 who had a pertussis episode with onset of episode between January 1. 2003 and December 31. 2009, i.e. the 617 episodes from Göteborg study area and 1379 episodes from the rest of Sweden during the 7 year period of enhanced surveillance. In each age group (but one), the number of cases reported from Göteborg were high in relation to population size in the area, with 227 infant cases and 390 cases in children aged 1 year or more reported in this area. From the rest of Sweden there were 550 infant cases and 829 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.

Age.at.onset of pertussis; vaccine- or age group	Person years of follow-up	Number of laboratory confirmed cases	Incidence per 100,000 person-years	95% confidence interval	Relative risk in Göteborg compared with Sweden except Göteborg
Before Dose 1 (0-90days)	18,982 (164,484)	78 (304)	411 (185)	325-513 (165-207)	2.22 (1.71-2.86)
Between 1 and 2 doses (91-150days)	12,577 (109,180)	62 (175)	493 (160)	378-632 (137-186)	3.08 (2.26-4.13)
Between 2 and 3 doses (151-365days)	43,525 (379,130)	87 (71)	200 (19)	160-247 (15-24)	10.67 (7.71-14.82)
After Dose 3 and/or during 1 year of age	74,000 (647,512)	61 (55)	82 (8)	63-106 (6-11)	9.7 (6.63-14.24)
During 2 years of age	71,833 (632,004)	42 (59)	58 (9)	42-79 (7-12)	6.26 (4.11-9.46)
During 3 years of age	69,551 (616,678)	27 (57)	39 (9)	26-56 (7-12)	4.2 (2.55-6.75)
During 4 years of age	67,556 (603,388)	46 (67)	68 (11)	50-91 (9-14)	6.13 (4.12-9.06)
During 5 years of age	65,955 (593,437)	47 (83)	71 (14)	52-95 (11-17)	5.1 (3.48-7.37)
During 6 years of age	64,763 (587,339)	66 (118)	102 (20)	79-130 (17-24)	5.07 (3.69-6.91)
During 7 years of age	59,526 (542,560)	60 (138)	101 (25)	77-130 (21-30)	3.96 (2.88-5.4)
During 8 years of age	49,921 (456,974)	27 (117)	54 (26)	36-79 (21-31)	2.11 (1.34-3.23)
During 9 years of age	40,656 (373,973)	6 (87)	15 (23)	5-32 (19-29)	0.63 (0.23-1.44)
During 10 years of age	31,670 (292,406)	7 (33)	22 (11)	9-46 (8-16)	1.96 (0.73-4.5)
During 11 years of age	22,765 (211,501)	0 (10)	0 (5)	0-16 (2-9)	0 (0-4.14)
During 12 years of age	13,783 (129,259)	1 (5)	7 (4)	0-40 (1-9)	1.88 (0.04-16.76)

Table 2:6 Incidence of pertussis among children, comparing the Göteborg area (primary numbers) and the rest of Sweden (in brackets). The children are born from **January 1. 1996 until December 31. 2009**, and followed from **January 1. 2003 until December 31. 2009** with culture-, or PCR-confirmed *B.pertussis* with positive serology from 2008. Person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person-years of follow-up and relative risk of having a laboratory-verified episode of *B.pertussis* in age-/vaccine-groups at onset of the pertussis episode is analysed; 0-<3 months of age (before Dose 1); 3-<5 months of age (between Dose 1 and 2); 5-<12 months of age (between Dose 2 and 3); and after 12 months of age (after Dose 3) in ten age intervals. 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). Age interval in the heading classifies unimmunised children.

In both Göteborg study area and the rest of Sweden the highest incidences were reported in the two 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 years, but even at this age Göteborg children had a 4.2 times higher risk of being reported as a laboratory verified case of pertussis in comparison with the rest of the country. Major differences were also found comparing the two areas for children with 21 or more days of spasmodic cough regardless of vaccination status, Table 2:7.

Age at onset of pertussis; in vaccine- or age groups	Person years of follow-up	Number of laboratory confirmed cases	Incidence per 100,000 person-years	95% confidence interval	Relative risk in Göteborg compared to Sweden without Göteborg
Before Dose 1 (0-90days)	18,982 (164,484)	46 (271)	242 (165)	177-323 (146-186)	1.47 (1.05-2.02)
Between 1 and 2 doses (91-150days)	12,577 (109,180)	32 (152)	254 (139)	174-359 (118-163)	1.83 (1.21-2.69)
Between 2 and 3 doses (151-365days)	43,525 (379,130)	33 (55)	76 (15)	52-106 (11-19)	5.23 (3.29-8.19)
After Dose 3 and/or during 1 year of age	74,000 (647,512)	28 (38)	38 (6)	25-55 (4-8)	6.45 (3.81-10.79)
During 2 years of age	71,833 (632,004)	18 (48)	25 (8)	15-40 (6-10)	3.3 (1.81-5.78)
During 3 years of age	69,551 (616,678)	14 (43)	20 (7)	11-34 (5-9)	2.89 (1.46-5.38)
During 4 years of age	67,556 (603,388)	28 (51)	41 (8)	28-60 (6-11)	4.9 (2.98-7.92)
During 5 years of age	65,955 (593,437)	34 (62)	52 (10)	36-72 (8-13)	4.93 (3.15-7.61)
During 6 years of age	64,763 (587,339)	48 (96)	74 (16)	55-98 (13-20)	4.53 (3.14-6.48)
During 7 years of age	59,526 (542,560)	38 (110)	64 (20)	45-88 (17-24)	3.15 (2.12-4.59)
During 8 years of age	49,921 (456,974)	19 (94)	38 (21)	23-59 (17-25)	1.85 (1.07-3.05)
During 9 years of age	40,656 (373,973)	5 (69)	12 (18)	4-29 (14-23)	0.67 (0.21-1.63)
During 10 years of age	31,670 (292,406)	7 (28)	22 (10)	9-46 (6-14)	2.31 (0.85-5.41)
During 11 years of age	22,765 (211,501)	0 (7)	0 (3)	0-16 (1-7)	0 (0-6.45)
During 12 years of age	13,783 (129,259)	0 (4)	0 (3)	0-27 (1-8)	0 (0-14.21)

Table 2:7 Incidence of pertussis with more than 20 days of cough, comparing the Göteborg area (primary numbers and the rest of Sweden (in brackets). Children born **from January 1. 1996 until December 31. 2009**, and followed from **January 1. 2003 until December 31. 2009** with observed Culture-, or PCR-confirmed *B. pertussis* and **with 21 or more days of spasmodic cough** and from 2008 a positive serology is added. Person-years of follow-up, number of laboratory confirmed cases, incidence per 100 000 person-years of follow-up and relative risk

of having a laboratory-verified episode of *B.pertussis* for children in Sweden except Göteborg study area is compared to children in the Göteborg study area in different age-/vaccine-groups at onset of the pertussis episode. 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). Age interval in the heading classifies unimmunised children.

In Tables 2:8 and 2:9 vaccine failures, i.e. children vaccinated with 2 or more doses prior to the laboratory positive pertussis episode, are studied. There were 458 such episodes reported for children from the Göteborg study area, whereof 255 with 21 or more days with spasmodic cough, and 785 reported for children from the rest of the country, whereof 598 with 21 or more days of spasmodic cough.

Age at onset of pertussis in vaccine- or age groups	Person years of follow-up	Number of laboratoryconfirmed cases	Incidence per 100,000 person-years	95% confidence interval	Relative risk in Göteborg compared to Sweden without Göteborg
Between 2 and 3 doses (151-365days)	43,525 (379,130)	84 (60)	193 (16)	154-239 (12-20)	12.19 (8.65-17.28)
After Dose 3 and/or during 1 year of age	74,000 (647,512)	59 (42)	80 (6)	61-103 (5-9)	12.29 (8.14-18.72)
During 2 years of age	71,833 (632,004)	41 (49)	57 (8)	41-77 (6-10)	7.36 (4.74-11.38)
During 3 years of age	69,551 (616,678)	25 (49)	36 (8)	23-53 (6-11)	4.52 (2.68-7.47)
During 4 years of age	67,556 (603,388)	42 (52)	62 (9)	45-84 (6-11)	7.21 (4.69-11.05)
During 5 years of age	65,955 (593,437)	45 (68)	68 (11)	50-91 (9-15)	5.95 (3.99-8.81)
During 6 years of age	64,763 (587,339)	62 (105)	96 (18)	73-123 (15-22)	5.36 (3.85-7.4)
During 7 years of age	59,526 (542,560)	60 (125)	101 (23)	77-130 (19-27)	4.38 (3.16-6)
During 8 years of age	49,921 (456,974)	26 (108)	52 (24)	34-76 (19-29)	2.2 (1.38-3.41)
During 9 years of age	40,656 (373,973)	6 (81)	15 (22)	5-32 (17-27)	0.68 (0.24-1.55)
During 10 years of age	31,670 (292,406)	7 (33)	22 (11)	9-46 (8-16)	1.96 (0.73-4.5)
During 11 years of age	22,765 (211,501)	0 (8)	0 (4)	0-16 (2-7)	0 (0-5.44)
During 12 years of age	13,783 (129,259)	1 (5)	7 (4)	0-40 (1-9)	1.88 (0.04-16.76)

Table 2:8 Incidence of pertussis among children with 2 or more doses of vaccine, comparing the Göteborg area (primary numbers and the rest of Sweden (in brackets). Children born **from January 1. 1996 until December 31. 2009**, and followed from **January 1. 2003 until December 31. 2009** with observed Culture-, or

PCR-confirmed *B.pertussis* (from 2008 also positive serology) and **vaccinated with two or more doses of a pertussis vaccine** prior to the date for onset of the episode. Person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person-years of follow-up and relative risk of having a laboratory-verified episode of *B.pertussis* is analysed (for children in Sweden except Göteborg study area compared to children in the Göteborg study area) in the following age-/vaccine-groups at onset of the pertussis episode; between Dose 2 and 3; and after 12 months of age (after Dose 3) in twelve age intervals. 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).

Age at onset of pertussis in vaccine- or age groups	Person years of follow-up	Number of laboratory confirmed cases	Incidence per100,000 person-years	95% confidence interval	Relative risk in Göteborg compared to Sweden without Göteborg
Between 2 and 3 doses (151-365 days)	43,525 (379,130)	30 (44)	69 (12)	47-98 (8-16)	5.94 (3.61-9.66)
After Dose 3 and/or during 1 year of age	74,000 (647,512)	26 (27)	35 (4)	23-51 (3-6)	8.43 (4.72-15)
During 2 years of age	71,833 (632,004)	17 (38)	24 (6)	14-38 (4-8)	3.94 (2.08-7.14)
During 3 years of age	69,551 (616,678)	12 (36)	17 (6)	9-30 (4-8)	2.96 (1.4-5.81)
During 4 years of age	67,556 (603,388)	25 (36)	37 (6)	24-55 (4-8)	6.2 (3.57-10.62)
During 5 years of age	65,955 (593,437)	32 (49)	49 (8)	33-68 (6-11)	5.88 (3.64-9.36)
During 6 years of age	64,763 (587,339)	45 (83)	69 (14)	51-93 (11-18)	4.92 (3.34-7.15)
During 7 years of age	59,526 (542,560)	38 (98)	64 (18)	45-88 (15-22)	3.53 (2.36-5.19)
During 8 years of age	49,921 (456,974)	18 (86)	36 (19)	21-57 (15-23)	1.92 (1.08-3.21)
During 9 years of age	40,656 (373,973)	5 (64)	12 (17)	4-29 (13-22)	0.72 (0.23-1.77)
During 10 years of age	31,670 (292,406)	7 (28)	22 (10)	9-46 (6-14)	2.31 (0.85-5.41)
During 11 years of age	22,765 (211,501)	0 (5)	0 (2)	0-16 (1-6)	0 (0-10.14)
During 12 years of age	13,783 (129,259)	0 (4)	0 (3)	0-27 (1-8)	0 (0-14.21)

Table 2:9 Incidence of pertussis fulfilling the WHO criteria among children with 2 or more doses of vaccine, comparing the Göteborg area (primary numbers and the rest of Sweden (in brackets) Children born from **January 1. 1996 until December 31. 2009**, and followed from **January 1. 2003 until December 31. 2009** with observed Culture- or PCR-confirmed *B.pertussis* and **with 21 or more days of spasmodic cough** and **vaccinated with 2 or more doses of a pertussis vaccine** prior to the date for onset of the episode. Serology-confirmed pertussis has been added as a diagnostic citerium since 2008. Person-years of follow-up, number of laboratory confirmed cases, incidence per 100 000 person-years of follow-up and relative risk of having a laboratory-verified episode of *B.pertussis* (for children in Sweden except Göteborg study area compared to children in the Göteborg study area) in the following age-/vaccine-groups at onset of the pertussis episode; between Dose 2 and 3; and after 12 months of age (after Dose 3) in twelve age intervals. 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).

2.4.1 Comments to the incidence and risk tables

We noted earlier, section 2.2.1-2.2.3, that there were more "mild" pertussis cases reported for children in the Göteborg study area compared to Sweden except Göteborg, both among unvaccinated and vaccinated children. For comparison of "severe" cases, only cases with 21 or more days of spasmodic cough were included in Tables 2:7 and 2:9.

The pattern of "over-risk" noted for children in the Göteborg study area in Tables 2:6 and 2:8 was also seen for typical pertussis, Tables 2:7 and 2:9. For example; the relative risk for typical pertussis during the first year after 3 doses was 6.5 (95% CI 3.8-10.8) for children in the Göteborg study area compared to children in Sweden except Göteborg. Thus, there were also more "severe" cases of pertussis reported for children in the Göteborg study area.

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

2.5 Hospital admission for pertussis

2.5.1 Hospital admission and age at the pertussis episode

Threehundred-and-seventy (19%) of 1996 children had a hospital admission during the pertussis episode. "Only" 47 (8%) children in the Göteborg study area were hospitalised during the pertussis episode compared to 323 (23%) children in the rest of the country. This difference was statistically significant. Hospitalisation rates (hospitalisations for pertussis/ all pertussis cases) for children in the Göteborg study area were significantly lower compared to the rates in Sweden except Göteborg in all age groups but the last (Table 2:10).

The age specific incidence rate of hospitalisation due to pertussis is highest, 190 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 (Figure 2:4).

	0-90 days	91-150 days	151-365days	> 365 days	Sum
Sweden excl. Göteborg study area	229/306 (75%)	61/148 (41%)	18/89 (20%)	15/836 (2%)	323/1379 (23%)
Göteborg study area	36/78 (46%)	6/45 (13%)	1/95 (1%)	4/399 (1%)	47/617 (8%)
Total	265/384 (69%)	67/193 (35%)	19/184 (10%)	19/1235 (2%)	370/1996 (19%)

Table 2:10 Hospital admissions in Göteborg compared to the rest of Sweden. Number of hospital admission/Total number of episodes and percent of pertussis episodes with a hospital admission due to pertussis, by age at onset of cough among children born from January 1. 1996 until December 31. 2009, during surveillance from January 1. 2003 until December 31. 2009.

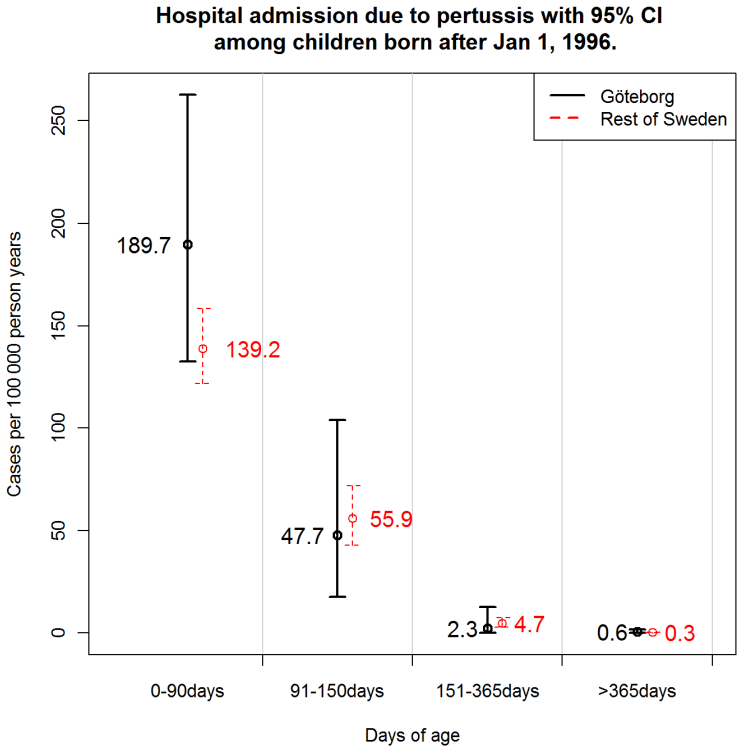


Figure 2:4: Age specific incidence of hospital admissions due to pertussis, among children born after 1 jan 1996 in Göteborg study area and in the rest of Sweden.

The age specific incidence rate of hospitalisation due to pertussis, for children in the rest of Sweden, is highest, 139 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 in the rest of Sweden were comparable for children in the Göteborg study area in all age groups but significantly lower for children in the youngest age-group. However, 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.

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

Hospital admissions were also studied in relation to age. Detailed data for the duration of hospital stay and vaccination status at start of the pertussis episode are given in Table 2:11 and Figure 2:5 for children in the Göteborg study area and percentage of hospitalized children was lower before 2007 in Göteborg study area than in rest of Sweden and is thereafter been equalized (Figure 2:6).

Doses before episode of pertussis	Days of hospital admission	0-30days	31-60days	61-90days	91-150days	151-365days	>365days	Sum
0 doses	0 days	9 (50%)	13 (42%)	20(69%)	5(71%)	3(100%)	16 (100%)	66 (63%)
	1-7 days	6(33%)	12 (39%)	8(28%)	1(14%)	(0%)	(0%)	27(26%)
	> 8 days	3(17%)	6 (19%)	1(3%)	1(14%)	(0%)	(0%)	11(11%)
1 dose	0 days				34(89%)	14 (100%)	3(100%)	51(93%)
	1-7 days				3(8%)	(0%)	(0%)	3(5%)
	> 8 days				1(3%)	(0%)	(0%)	1(2%)
2 or more doses	0 days					77 (99%)	376 (99%)	453 (99%)
	1-7 days					1 (1%)	3 (1%)	4 (1%)
	> 8 days					(0%)	1 (0%)	1 (0%)

Table 2:11. Duration of hospital stay due to the pertussis among children from the Göteborg study area, born from January 1. 1996 until December 31. 2009 and surveyed from January 1. 2003 until December 31.2009, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

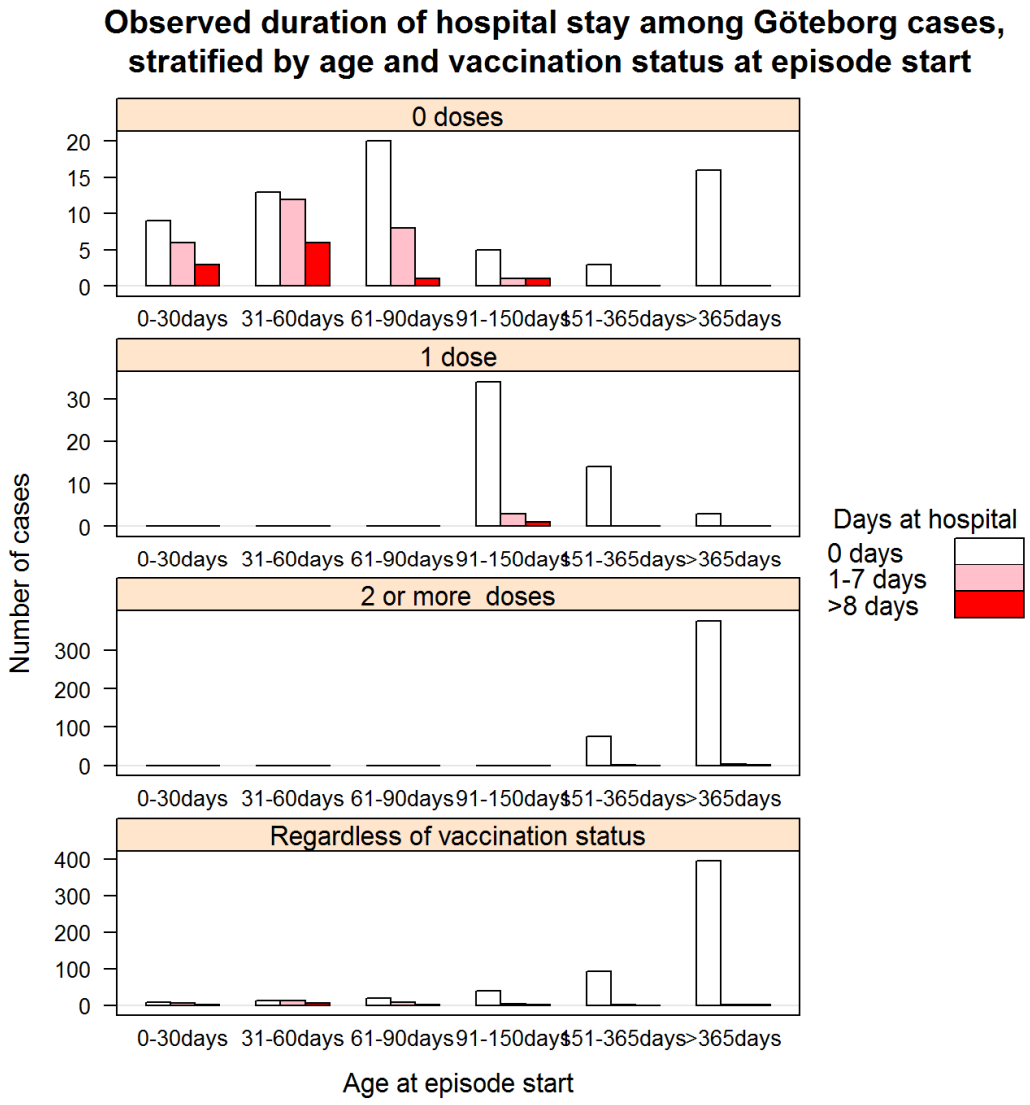


Figure 2:5 Illustration of the duration of hospital stay due to the pertussis among children from the Göteborg study area, born from January 1, 1996 until December 31, 2009 and surveyed from January 1, 2003 until December 31, 2009, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode. See also table 2:11 above.

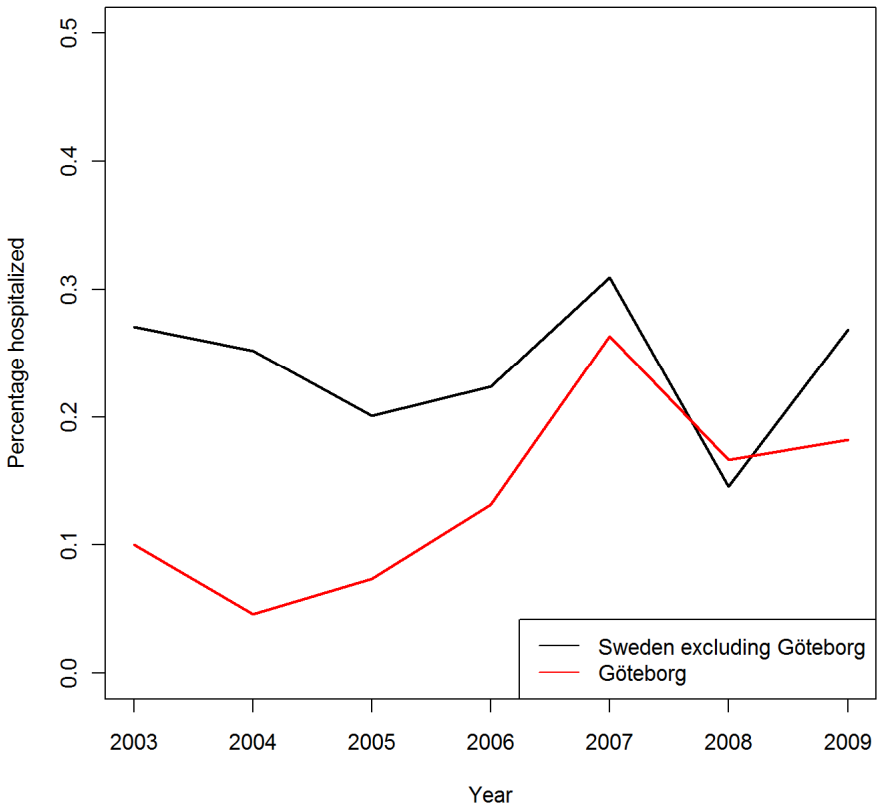


Figure 2:6 Percentage of hospitalized children born during the years 2003-2009 in Göteborg study area and the rest of Sweden. It indicates that the hospitalization being much lower in the Göteborg study area than in the rest of Sweden has now normalized.

A corresponding table for (1,379) children outside Göteborg study area is not included in the present report because the hospital admission proportions for children outside the Göteborg study area were nearly the same as was reported in Table 1:11 of the main twelve-year report (1) for 2,284 children outside the Göteborg study area. However, the figures that we refer to in the text that follow concern the 1,378 children.

The overall rate of hospital admission for unimmunised children from the Göteborg study area was 37%. For hospitalised children 29% (11 of 38 children) of the hospital admissions had a duration longer than one week, Table 2:11. The corresponding figures for children from the rest of Sweden were significantly higher. The overall hospitalisation rate was 54% and for hospitalised 46% (115 of 252 children) of the episodes had a duration longer than one week.

The rate of hospital admission among unimmunised children aged 0-30, 31-60 and 61-90 days at beginning of the pertussis episode was 50% (9/18), 58% (18/31) and 31% (9/29), 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% (2/7), 0% (0/3) and 0% (0/16) respectively for children from the Göteborg study area, Table 1:11. Again the rates for children from the rest of Sweden were significantly higher 90%, 72% and 65% for the three youngest age-groups 0-30, 31-60 and 61-90 days and 51%, 36% and 0% in the three 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, 138 children whereof 34% (47 children) hospitalised, and for children who have received two or more doses of a pertussis vaccine before the pertussis episode, 785 children whereof 3% (21 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 twelve-year report (1).

For children from the Göteborg study area there were only 7% (4 of 55 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% (5 of 457) 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.

2.6 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 1,984 of 1,996 children born from January 1, 1996 until December 31, 2009 with vaccination and follow-up information for a laboratory confirmed pertussis from January 1, 2003 until December 31, 2009.

A respiratory complication (with apnea, n=130, without apnea, n=113) was reported for 243 (12%) and a dehydration for 147 (7.4%) of the children. Uncommon complications, i.e. neurological complications were reported for 4 (0.2%) children, and other serious complications for 1 child from the Göteborg study area. For respiratory complications and dehydration there were statistically significant differences between the Göteborg and the rest of Sweden.

The figures for respiratory complications were 50 (8.2%) and 193 (14.1%), for dehydration 24 (3.9%) and 123 (9.0%), and for neurological complications 1 (0.2%) and 4 (0.3%) for children in the Göteborg study area and the rest of Sweden, respectively.

2.6.1 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. 325 children (16.5%) had at least one complication due to the pertussis disease during their pertussis episode and 1,659 (83.5%) had no complication at all.

	0-90 days	91-150 days	151-365days	> 365 days	Sum
Sweden excl. Göteborg	139/306 (45%)	32/146 (22%)	12/87 (14%)	77/831 (9%)	260/1370 (19%)
Göteborg	21/78 (27%)	8/45 (18%)	6/92 (7%)	30/398 (8%)	65/613 (11%)
Total	160/384 (42%)	40/191 (21%)	18/179 (10%)	107/1228 (9%)	325/1982 (16%)

Table 2:12 Complications in Göteborg compared to the rest of Sweden. Number of cases with any complication/total number of episodes and percent with any complication due to pertussis by age at onset of cough among children born from January 1. 1996 until December 31. 2009, during surveillance from January 1. 2003 until December 31. 2009.

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Sixty-five children (10.6%) from the Göteborg study area and 260 (19.0%) 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, were lower in all age-groups and significantly lower for children from the Göteborg study area in the youngest age-group.

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 2:7.

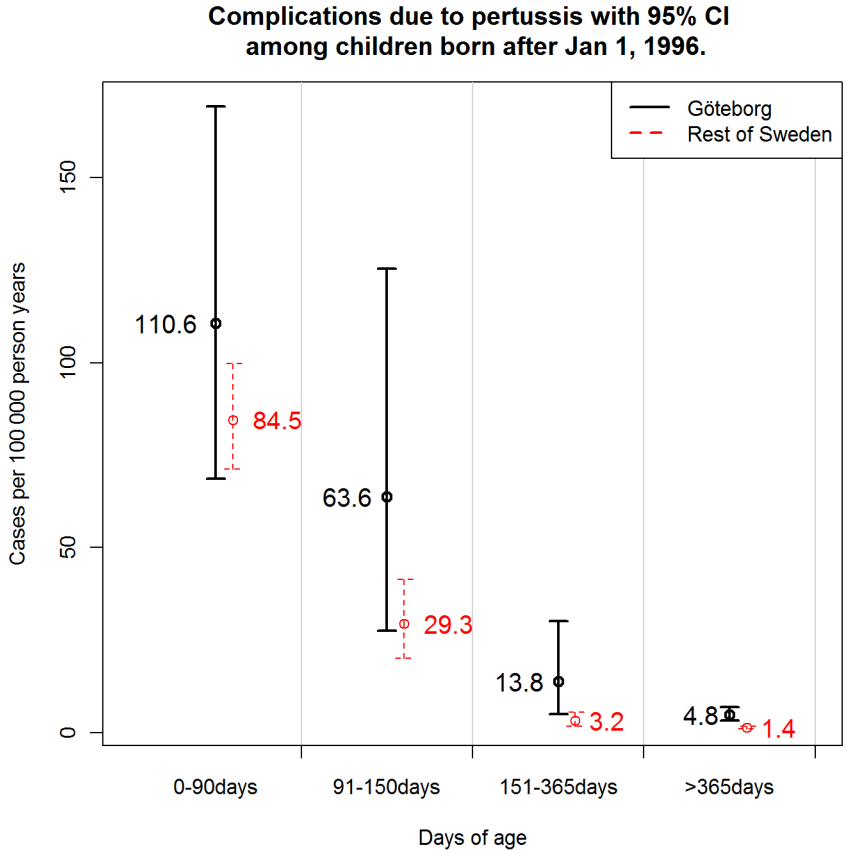

Figure 2:7 Age specific incidence of any complication due to the pertussis disease, per 100,000 years of follow-up regardless of vaccination status for children born from January 1. 1996 until December 31. 2009 with a laboratory confirmed *B. pertussis* from January 1. 2003 until December 31. 2009 for children from the Göteborg study area and children in the rest of Sweden

The age specific incidence rate of any complication due to pertussis is highest, 111 per 100,000 years of follow-up, for children 0-<3 months of age and decreases, by increasing age, to 4.8 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, 84.5 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 of any complication were higher for children in the Göteborg study area in all age groups, but, given the pertussis disease, more children outside the Göteborg study area also had a complication during the pertussis episode.

2.6.2 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 2:13 and Figure 2:8. The corresponding

proportions for the 1,369 children outside the Göteborg study area (data not shown in table) were nearly the same as was reported in the main twelve-year report for 2,284 children outside the Göteborg study area. The figures that we refer to in the text that follow concern the 1369 children.

		Age at episode start						
No of doses before pertussis	Compli-cations	0-30 days	31-60 days	61-90 days	91-150 days	151-365 days	> 365 days	Sum
0 doses	No	13 (72%)	21 (68%)	23 (79%)	5 (71%)	2 (67%)	13 (81%)	77 (74%)
	Yes	5 (28%)	10 (32%)	6 (21%)	2 (29%)	1 (33%)	3 (19%)	27 (26%)
1 dose	No				32 (84%)	13(93%)	1 (33%)	46 (84%)
	Yes				6 (16%)	1 (7%)	2 (67%)	9 (16%)
2 or more doses	No					72 (95%)	354 (93%)	426 (94%)
	Yes					4(5%)	25(7%)	29(6%)

Table 2:13 Any complication due to the pertussis disease among children from the Göteborg study area born from January 1. 1996 until December 31. 2009, and surveyed from January 1. 2003 until December 31. 2009, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode. This is also illustrated in figure 2:8, below.

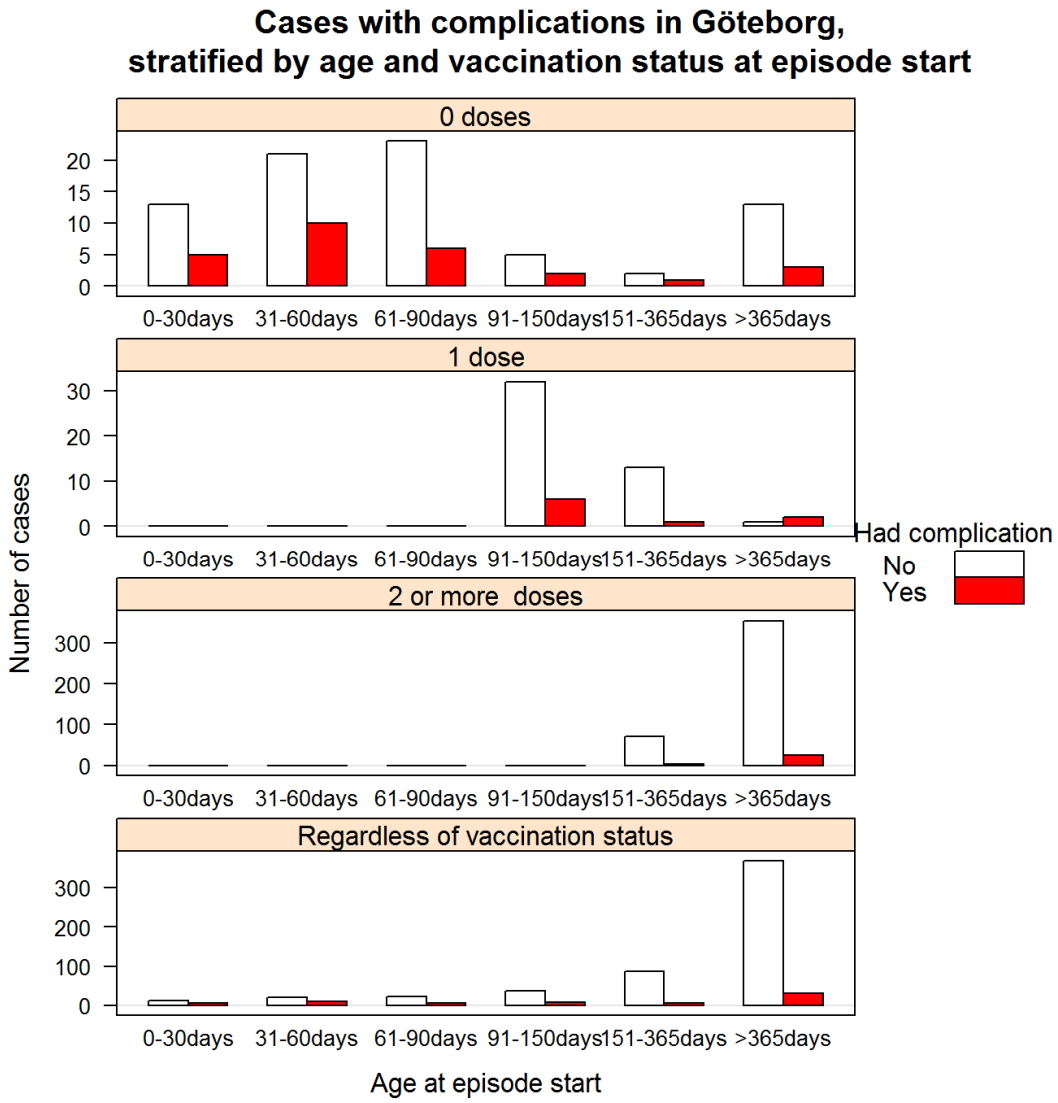

Figure 2:8: Illustration of any complication due to the pertussis disease among children from the Göteborg study area born from January 1, 1996 until December 31, 2009, and surveyed from January 1, 2003 until December 31, 2009, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

The overall rate of any complication for unvaccinated Göteborg study area children was 25%. The corresponding figure for children from the rest of Sweden was significantly higher, at 35%. 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 28% (5/18), 32% (10/31) and 21% (6/29). 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 19% (6/26).

The corresponding complication rates for children outside the Göteborg study area were; 57%, 42%, 38% and 16% in the four 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 16% (9/55), and 6.4% (29/454) for children vaccinated with 2 or more doses before the pertussis episode. For

children from the rest of Sweden the corresponding figures were 20% respectively 9.4%.

Finally (and for obvious reasons), there was also a strong association between any complication and a hospital stay during the pertussis episode. 68%, 208 of 325, of children with at least one complication also had a hospital admission due to the disease during the episode. For 1669 children without any complication the hospitalisation rate was 9.7% ($p<0.001$). For children with any complication 49% of the hospital admissions had a duration of 8 days or longer. For children without any complication 24% 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, 40% in the Göteborg study area and 70% in the rest of Sweden also had a hospital admission during the pertussis episode. The observed difference of hospitalisation rate between the two areas was statistically significant.

2.7 Spasmodic cough during the pertussis episode

Data on spasmodic cough were available for all 1994 children born January 1. 1996 until December 31. 2009 with a pertussis episode from January 1. 2003 until December 31. 2009. Data on duration of regular cough was missing for 21 children; three children did not have any cough. 1595 children (80.0%) had spasmodic cough during the pertussis episode and 399 (20.0%) reported no spasmodic cough.

	0-90days	91-150days	151-365days	> 365days	Sum
Sweden excl. Göteborg	273/306 (89%)	130/148 (88%)	68/89 (76%)	656/835 (79%)	1127/1378 (82%)
Göteborg	46/78(59%)	22/45(49%)	35/94(37%)	246/399(62%)	349/616(57%)
Total	319/384(83%)	152/193(79%)	103/183(56%)	902/1234(73%)	1476/1994(74%)

Table 2:14 Children with more than 20 days of spasmodic cough in Göteborg study area compared to the rest of Sweden. The table shows the number of pertussis cases with spasmodic cough for 21 days or more in relation to total number of episodes and percent with cough for 21 days or more. The table is divided in age groups at onset of cough among children born from January 1. 1996 until December 31. 2009, during surveillance from January 1. 2003 until December 31. 2009.

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

One thousand four-hundred and seventy-six (74.0%) of the children had spasmodic cough for 21 or more days during the pertussis episode. The figures for three weeks or more of spasmodic cough were 349 (56.7%) for children in the Göteborg study area compared to 1127 (81.8%) for children in the rest of the country, a statistically significant difference. 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 2:14).

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 2:9).

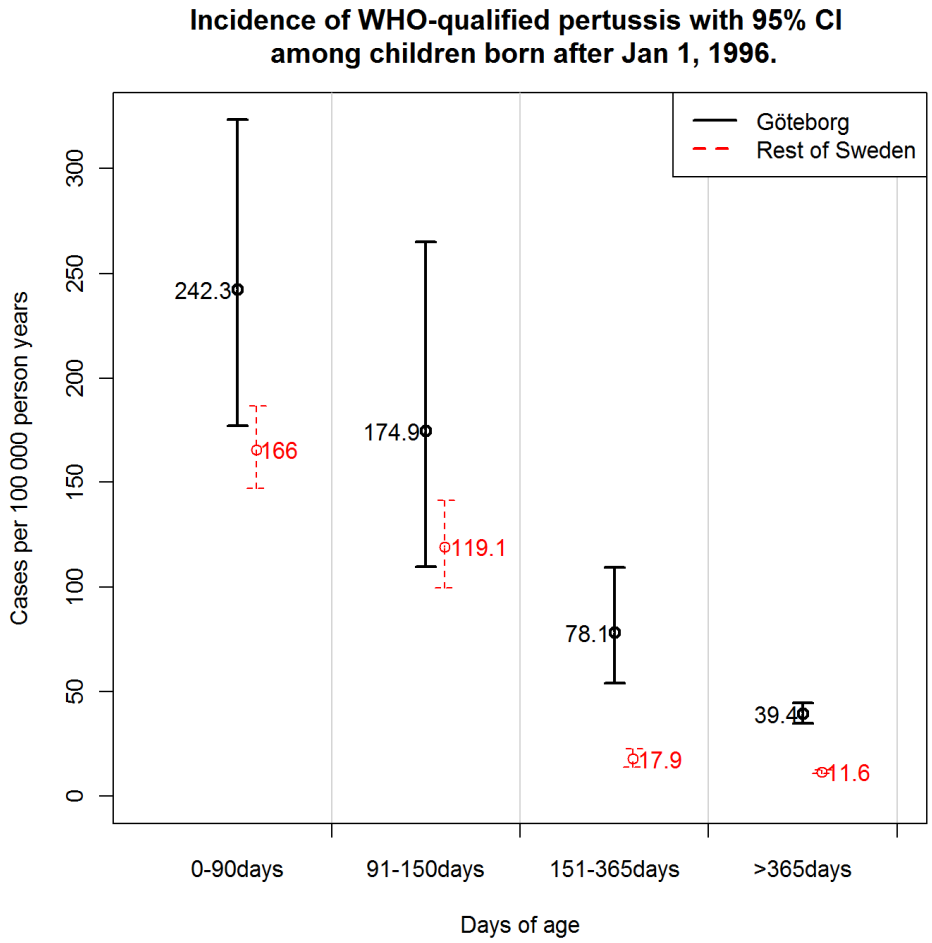

Figure 2:9 Age specific incidence of spasmodic cough for 21 or more days due to the pertussis disease, per 100,000 years of follow-up regardless of vaccination status for children born from January 1. 1996 until December 31. 2009 with a laboratory confirmed *B. pertussis* reported from January 1. 2003 until December 31. 2009 for children in the Göteborg study area and children in the rest of Sweden.

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 high also for the elderly children.

2.7.2 Duration of spasmodic cough, age and vaccination status at the pertussis episodeDuration of spasmodic cough was also studied in relation to age as well as vaccination status at onset of the pertussis episode. Detailed data are given in Table 2:15 for children from the Göteborg study area. Detailed data for children outside the Göteborg study area were presented in the main twelve-year report (Table 2:B.3 – see discussion in chapter 2.B.3. The figures in the text that follows concern the 1,378 children in the Sweden without the Göteborg study area that had a pertussis episode from Jan 1. 2003 to 31 Dec 2009.

Number of doses	Days of spasmodic cough	Age at episode start	0-30days	31-60days	61-90days	91-150days	151-365days	>365days	Sum
0 doses	0 days		7 (44%)	6 (21%)	10 (38%)	3 (43%)	(0%)	2 (13%)	28 (29%)
	1-20 days		2(13%)	4 (14%)	1 (4%)	2 (29%)	(0%)	(0%)	9(9%)
	>20days		7(44%)	19 (66%)	15 (58%)	2 (29%)	2 (100%)	14 (88%)	59 (61%)
1 dose	0 days					14 (41%)	2(14%)	1 (33%)	17 (33%)
	1-20 days					4 (12%)	4 (29%)	(0%)	8 (16%)
	>20days					16 (47%)	8 (57%)	2 (67%)	26 (51%)
2 or more doses	0 days						33 (45%)	121 (34%)	154 (35%)
	1-20 days						18 (25%)	22 (6%)	40 (9%)
	>20days						22 (30%)	218 (60%)	240 (55%)

Table 2:15 Duration of spasmodic cough due to pertussis disease among children born from January 1, 1996 until December 31, 2009, during surveillance from January 1, 2003 until December 31, 2009, 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.

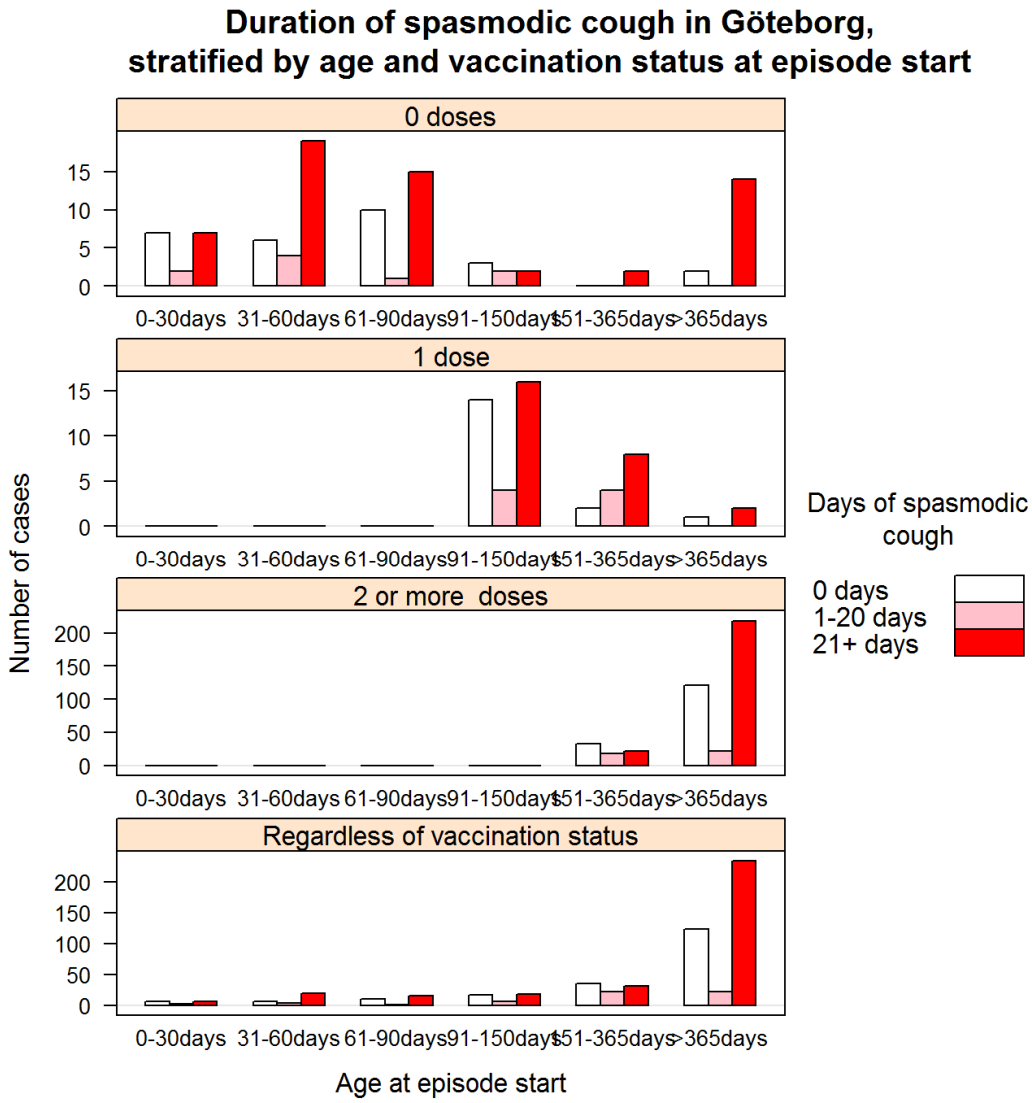

Figure 2:10: Duration of cough versus age and vaccination status, among children born after 1. Jan 1996 in the Göteborg study area, which contracted Pertussis after Jan 1. 2003. See also table 2:15.

The overall rate of children with 21 or more days of spasmodic cough for unvaccinated children from the Göteborg study area was 63%. The corresponding figure for children from the rest of Sweden was significantly higher at 90%.

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 50%, 65% and 59% respectively. Since there are very few children in each age group from 3 months of age they are combined and for children older than 3 months of age the rate was 73%. The corresponding rates for children outside the Göteborg study area were all significantly higher; 90%, 89%, 89% and 91% in the four 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 55% and among those vaccinated with 2 or more doses 55% as well for children from the Göteborg study area and significantly higher, 89% respectively 76%, for children from the rest of Sweden.

2.8 *Duration of cough and antibiotic treatment*

As stated in section 2.7, data on cough and spasmodic cough were available for all 1994 children born from January 1. 1996 until December 31. 2009 and under surveillance from January 1. 2003 until December 31. 2009, whereof were 760 infants. All children but 24 were coughing during their pertussis episode; of these, 14 were infants. Five of the infants were less than 3 months old. Of these, three had one or more apneas.

Applying the EU clinical case definition of pertussis with 2 weeks or more of coughing (any type) in conjunction with positive laboratory sample, in all 1910/1994 (95.8%) would fulfil this definition.
Among the 63 cases that would not fulfil the EU definition, 21 were infants and 42 were children one year or older. All but one infants had received erythromycin or trimetoprim-sulfametoxazol, whereas eleven of the 42 children were not treated with antibiotics. Twelve of the infants were unvaccinated, 3 had received one dose and 6 had received two doses. All 42 children had received three doses.

2.8.1 Duration of cough, spasmodic cough and antibiotic treatment

For 737 of the episodes, no antibiotic treatment was reported. Of these, 91 were episodes for infants. Before further statistical analysis 23 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.

Figures 2:11 and 2:12 presents 561 children from the Göteborg study area and 1182 children from Sweden except the Göteborg study area. There were 379 children aged 0-90 days at onset of the episode, without any pertussis vaccination prior to onset, 147 children aged 91-150 days at onset of the episode, with one dose of a pertussis vaccine prior to onset, 131 children aged 151-365 days at onset of the episode, with two doses of a pertussis vaccine prior to onset, and 1086 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 168/189 (88.9%) infants were treated, in the rest of Sweden 408/468 (87.2%). The proportions treated were highest in the youngest, i.e. those below 3 months of age, with 69/77 (89.6 %), treated in the Göteborg study area and 277/302 (91.7%) in the rest of Sweden. The proportion of infants treated remained high in the Göteborg study area also for the age-group 3 to below 5 months (35/37, i.e. 94.6 %) but there was a slight decrease in the rest of Sweden (85/110, i.e. 77.3 %). From 5 to below 12 months the proportion treated in Göteborg was 64/75 (85,3%) and 46/56 (82.1%) in the rest of Sweden. Among those aged one year or more at onset of cough during the episode, 192/372 (51.6%) of Göteborg study area children were treated and so were 328/714 (45.9%) of the children from the rest of Sweden.

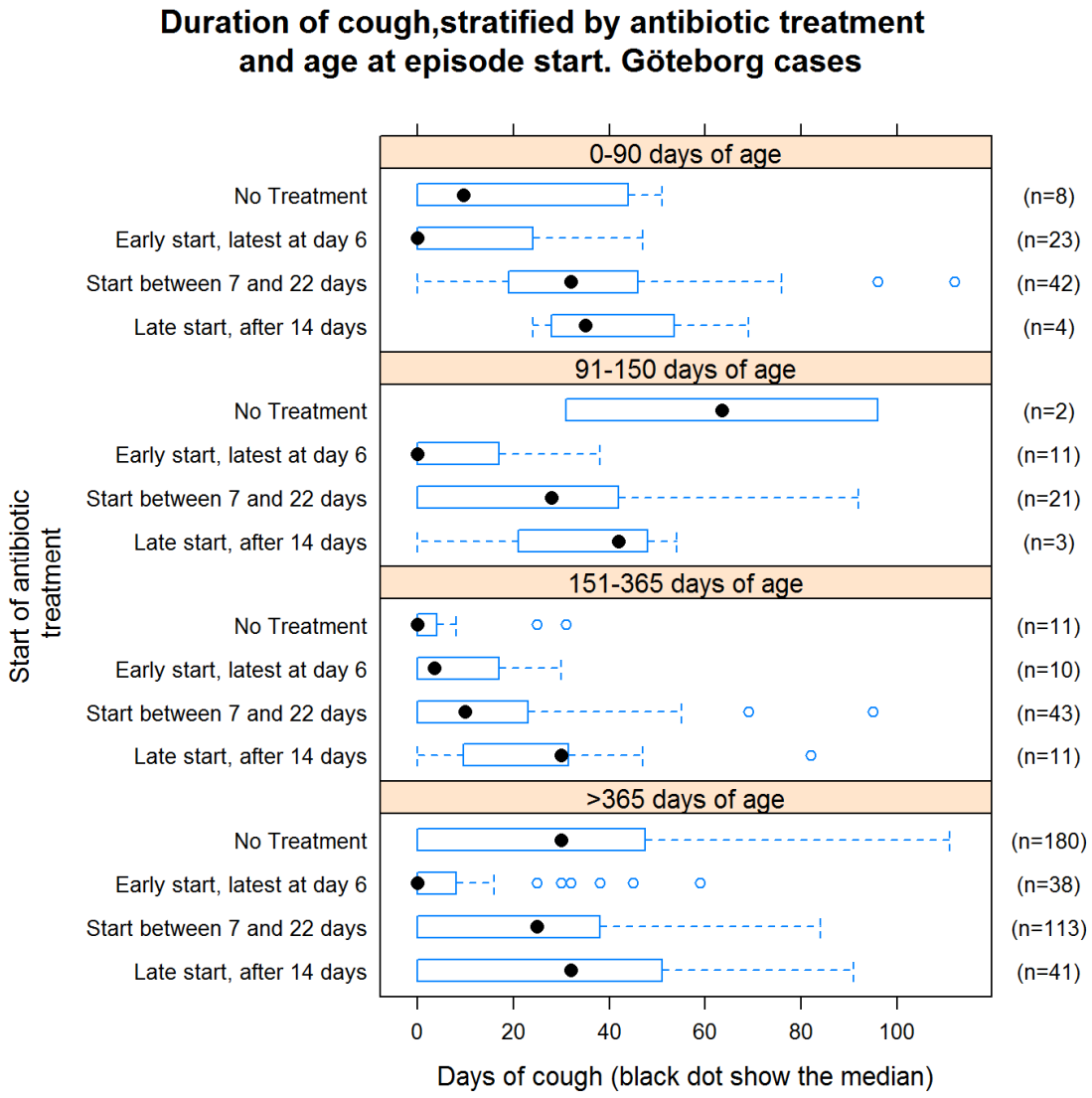

Figure 2:11: Children with pertussis and duration of cough versus age and antibiotic treatment, among children born from Jan 1. 1996 to Dec 31 2009 in the Göteborg study area, which contracted pertussis from Jan 1. 2003 to 31 Dec 2009. Boxes show 1st and 4th quartile, whiskers extend the most extreme point, or at most 1.5 times the interquartile range.

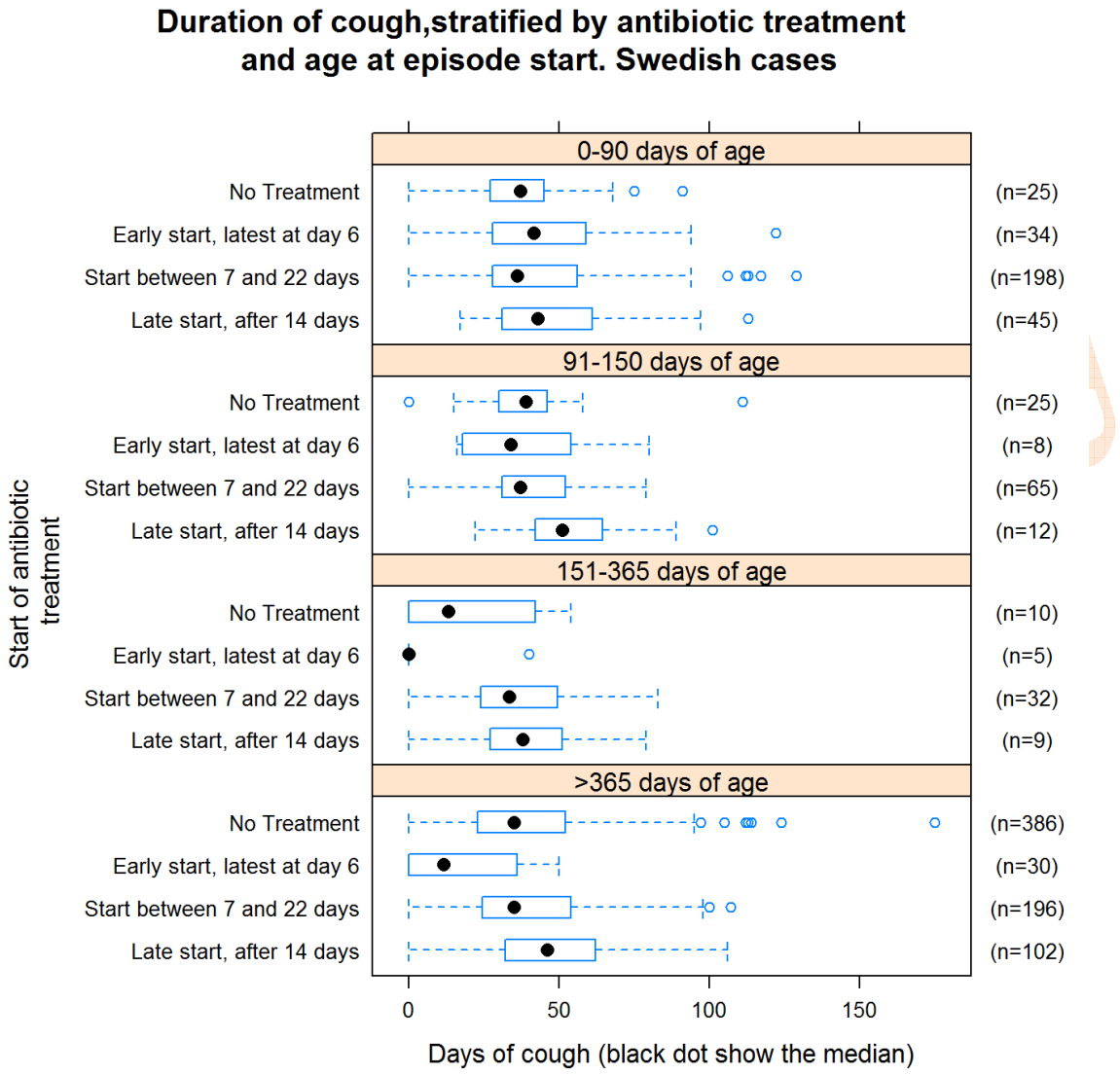

Figure 2:12: Children with pertussis and duration of cough versus age and antibiotic treatment, among children born Jan 1, 1996 to Dec 31, 2009 in Sweden outside the Göteborg study area, which contracted Pertussis from Jan 1,. 2003 to 31, Dec 2009.

An early start of the antibiotic treatment, within the first week (≤6 days) after onset of cough during the episode was, in most age groups and for both the Göteborg study area and the rest of Sweden, 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.

Chapter 3 :Additional analyses from the Göteborg study area

3.1 Pertussis reports used for the 12 year additional analyses Oct 1, 1997 until Dec 31, 2009

In the beginning of March 2010 there were 1,416 episodes reported in the surveillance database sampled before jan 1, 2010, from children in the Göteborg study area, whereof 1,270 was sampled from October 1. 1997 until December 31. 2009 among children born from January 1. 1996 until December 31. 2009. From other parts of Sweden there were 2,404 episodes reported in the surveillance database for the same birth period and the same calendar period. (In the main 12 y report 115 of those episodes were not included since they lacked clinical follow-up data.) In Sections 3.2-3.5, we use all these 3,674 reports (1,270 from Göteborg study area and 2,404 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 3:1 – 3:5 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 626 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 626 cases. In summary, information on vaccination status at date for the positive sample exists for 1,232 (96.9%) of the 1,270 episodes for children from the Göteborg area, and for 2,366 (98.3%) of the 2,404 episodes for children from other parts of Sweden. In Sections 3.6-3.7, we use these 3,598 reports 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 3:10 – 3:12 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.

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3.2 Laboratory-confirmed pertussis cases per calendar year & birth cohort Oct 1, 1997 until Dec 31, 2009

In Table 3:1a and 3:1b all 3,674 culture- or PCR-reported cases from October 1. 1997 until December 31. 2009, in children born from January 1. 1996 until December 31. 2009 are shown for the Göteborg study area and the rest of Sweden and from 2008 also confirmed via serology. In Table 3:2a and 3:2b results are given, for the same groups of children, but for one-year age groups and year of positive sample.

Göteborg study area

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Sum
1996	3	3	7	21	9	23	7	37	4	6	0	1	0	121
1997	2	7	7	17	12	15	8	38	15	2	1	0	0	124
1998		12	27	40	26	23	2	46	10	4	0	1	0	191
1999			27	65	24	21	8	40	10	4	3	2	2	206
2000				34	30	33	6	13	4	1	1	0	0	122
2001					32	53	10	29	6	1	0	1	0	132
2002						49	20	32	5	0	4	0	0	110
2003							28	59	11	2	2	1	1	104
2004								74	18	1	2	3	1	99
2005									11	9	0	0	0	20
2006										10	5	2	0	17
2007											5	7	2	14
2008												7	1	8
2009													2	2
Sum	5	22	68	177	133	217	89	368	94	40	23	25	9	1270

Table 3:1a Cases of pertussis per age and year of sample. Göteborg study area. Number of positive samples, per area, according to year of birth and year of positive sample. See also in the text above

Sweden excl Göteborg study area

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Sum
1996	5	17	39	45	19	40	19	59	47	14	3	5	3	315
1997	22	32	19	24	17	32	7	27	26	14	18	7	2	247
1998		54	45	16	7	17	12	32	42	23	15	24	5	292
1999			94	72	12	20	9	18	24	15	19	19	4	306
2000				89	34	16	7	20	16	22	19	14	5	242
2001					32	23	9	16	14	10	9	15	5	133
2002						103	21	18	11	8	4	2	7	174
2003							49	48	10	7	7	4	6	131
2004								121	46	14	7	5	5	198
2005									80	18	5	5	3	111
2006										68	26	11	5	110
2007											49	19	3	71
2008												27	18	45
2009													29	29
Sum	27	103	197	246	121	251	133	359	316	213	181	157	100	2404

Table 3:1b Laboratory confirmed pertussis cases stratified by age and year in Sweden excl Göteborg study area. See also in the text above.

Taken population sizes for the two areas into account, in mean 11.4% of the children were born in the Göteborg study area and 88.6% in the rest of Sweden, the number of cases for each birth-cohort (but 2007) and for each calendar year, are higher than expected for the Göteborg study area compared to the rest of Sweden.

Göteborg study area

Age	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Sum
0	3	13	42	67	52	91	43	115	25	16	9	12	3	491
1	2	7	15	57	19	31	9	38	11	4	1	4	2	200
2		2	5	21	25	27	11	27	6	1	2	0	0	127
3			6	22	18	19	2	16	7	1	1	2	0	94
4				10	13	17	7	28	4	1	2	2	1	85
5					6	22	3	41	6	1	3	0	1	83
6						10	9	45	14	2	1	0	0	81
7							5	40	12	4	3	1	0	65
8								18	8	4	0	0	0	30
9									1	1	0	2	2	6
10										5	1	1	0	7
11											0	0	0	0
12												1	0	1
13													0	0
Sum	5	22	68	177	133	217	89	368	94	40	23	25	9	1270

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Table 3:2a Laboratory confirmed pertussis cases in Göteborg study area, according to year of age in one-year classes from 1997-2009.

Sweden excluding Göteborg study area.

Age	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Sum
0	24	77	128	154	59	119	67	160	122	84	72	40	41	1147
1	3	18	15	20	12	11	8	15	11	9	6	12	7	147
2		8	29	16	11	24	8	22	6	12	5	8	2	151
3			25	29	13	16	6	11	14	7	6	5	7	139
4				27	16	27	12	20	15	8	8	5	2	140
5					10	29	10	25	19	16	4	3	8	124
6						25	16	27	29	18	19	10	7	151
7							6	43	36	21	18	13	4	141
8								36	33	17	13	15	7	121
9									31	15	20	23	4	93
10										6	8	16	5	35
11											2	4	3	9
12												3	1	4
13													2	2
Sum	27	103	197	246	121	251	133	359	316	213	181	157	100	2404

Table 3:2b Laboratory confirmed pertussis cases in Sweden excl Göteborg study area, according to year of age in one-year classes, and year of pertussis.

3.3 Laboratory confirmed pertussis cases, incidence and relative risk calculations Oct 1, 1997 until Dec 31, 2009 stratified by year of birth

In Table 3:3, 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 December 31. 2009, for pertussis episodes which occurred from October 1. 1997 until December 31. 2009 in two areas of Sweden – Sweden except Göteborg, and the Göteborg study area.

In Tables 3:4 and 3:5 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 represent a transition cohort with mixed vaccinations within the 3-5-12 month schedule. As for Table 3:3 vaccination status is not used in these two tables.

Göteborg study area, and Sweden excl Göteborg study area born 1996-2009

Onset of pertussis	Person years of follow-up	Number of lab conf pertussis cases	Incidence per 100,000	95% confidence interval	Relative risk
0-< 3 months	30,875 (271,812)	150 (493)	486 (181)	411-570 (166-198)	2.68 (2.22-3.22)
3-< 5 months	20,478 (180,574)	104 (381)	508 (211)	415-615 (190-233)	2.41 (1.92-3)
5-< 12 months	71,017 (628,159)	237 (273)	334 (43)	293-379 (38-49)	7.68 (6.42-9.17)
During 1 years of age	119,511 (1,063,828)	200 (147)	167 (14)	145-192 (12-16)	12.1 (9.74-15.01)
During 2 years of age	110,808 (990,972)	127 (151)	115 (15)	96-136 (13-18)	7.52 (5.89-9.59)
During 3 years of age	99,696 (895,416)	94 (139)	94 (16)	76-115 (13-18)	6.07 (4.62-7.95)
During 4 years of age	88,950 (802,530)	85 (140)	96 (17)	76-118 (15-21)	5.48 (4.13-7.22)
During 5 years of age	78,534 (711,804)	83 (123)	106 (17)	84-131 (14-21)	6.12 (4.57-8.15)
During 6 years of age	68,382 (621,912)	81 (151)	118 (24)	94-147 (21-28)	4.88 (3.68-6.43)
During 7 years of age	58,608 (534,198)	65 (140)	111 (26)	86-141 (22-31)	4.23 (3.1-5.72)
During 8 years of age	49,158 (450,006)	30 (122)	61 (27)	41-87 (23-32)	2.25 (1.46-3.38)
During 9 years of age	40,026 (368,184)	6 (93)	15 (25)	6-33 (20-31)	0.59 (0.21-1.34)
During 10 years of age	31164 (287,742)	7 (36)	22 (13)	9-46 (9-17)	1.8 (0.67-4.09)
During 11 years of age	22,380 (207,930)	0 (9)	0 (4)	0-16 (2-8)	0 (0-4.71)
During 12 years of age	13,542 (127,002)	1 (6)	7 (5)	0-41 (2-10)	1.56 (0.03-12.9)

Table 3:3 . **Incidence of pertussis among children in Göteborg and rest of Sweden (in brackets), born from Jan. 1. 1996 until Dec. 31. 2009. Stratified by onset of pertussis**. Children followed from **October 1. 1997 until December 31. 2009** with observed culture or PCR-confirmed *B.pertussis.*with serology-confirmed pertussis added 2008. Person-years of follow-up, Number of laboratory confirmed cases, incidence per 100,000 person-years of follow-up and relative risk of having a laboratory-verified episode of *B.pertussis* for children in Sweden except the Göteborg study area compared to children in this area) in the following age-groups at the pertussis episode; 0-<3 months of age; 3-<5 months of age; 5-<12 months of age; and after 12 months of age in ten age intervals. Age is calculated at the date of the positive sample.

Göteborg and Sweden excl Göteborg study area, born 1996-1998

Onset of pertussis	Person years	Number of lab conf pertussis cases	Incidence per 100,000	95% confidence interval	Relative risk
0-< 3 months	3037 (27,705)	5 (38)	165 (137)	53-384 (97-188)	1.2 (0.37-3.05)
3-< 5 months	2332 (21,305)	7 (42)	300 (197)	121-618 (142-266)	1.52 (0.58-3.42)
5-< 12 months	10,105 (92,572)	19 (55)	188 (59)	113-294 (45-77)	3.16 (1.77-5.42)
During 1 years of age	24,231 (223,792)	49 (49)	202 (22)	150-267 (16-29)	9.24 (6.09-14.0)
During 2 years of age	26,796 (248,028)	38 (57)	142 (23)	100-195 (17-30)	6.17 (3.98-9.47)
During 3 years of age	26,796 (248,028)	58 (75)	216 (30)	164-280 (24-38)	7.16 (4.99-10.2)
During 4 years of age	26,796 (248,028)	40 (76)	149 (31)	107-203 (24-38)	4.87 (3.24-7.24)
During 5 years of age	26,796 (248,028)	49 (60)	183 (24)	135-242 (18-31)	7.56 (5.07-11.2)
During 6 years of age	26,796 (248,028)	72 (83)	269 (33)	210-338 (27-41)	8.03 (5.77-11.1)
During 7 years of age	26,796 (248,028)	59 (97)	220 (39)	168-284 (32-48)	5.63 (4-7.86)
During 8 years of age	26,796 (248,028)	30 (93)	112 (37)	76-160 (30-46)	2.99 (1.91-4.55)
During 9 years of age	26,796 (248,028)	2 (79)	7 (32)	1-27 (25-40)	0.23 (0.03-0.87)
During 10 years of age	26,796 (248,028)	7 (35)	26 (14)	11-54 (10-20)	1.85 (0.69-4.23)
During 11 years of age	22,380 (207,930)	0 (9)	0 (4)	0-16 (2-8)	0 (0-4.71)
During 12 years of age	13,542 (127,002)	1 (6)	7 (5)	0-41 (2-10)	1.56 (0.03-12.88)

Table 3:4. Incidence of pertussis among children in Göteborg and rest of Sweden (in brackets), born from Jan. 1. 1996 until Dec. 31. 1998. Stratified by onset of pertussis. Children followed from **October 1. 1997 until December 31. 2009,** with observed Culture- or PCR-confirmed *B.pertussis* and with serology added 2008. Person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person-years of follow-up and relative risk of having a laboratory-verified episode of *B.pertussis* (for children in Sweden except Göteborg study area) compared to children in the Göteborg study area). Age is calculated at the date of the positive sample.

. Born 2000-2009

Onset of pertussis	Person years of follow-up	Number of lab conf pertussis cases	Incidence per 100,000	95% confidence interval	Relative risk
0-< 3 months	27,838 (244,108)	136 (402)	489 (165)	410-578 (149-182)	2.97 (2.42-3.61)
3-< 5 months	18,146 (159,269)	83 (287)	457 (180)	364-567 (160-202)	2.54 (1.96-3.25)
5-< 12 months	60,912 (535,587)	181 (164)	297 (31)	255-344 (26-36)	9.7 (7.81-12.1)
During 1 years of age	95,280 (840,036)	110 (86)	115 (10)	95-139 (8-13)	11.28 (8.43-15.1)
During 2 years of age	84,012 (742,944)	60 (75)	71 (10)	54-92 (8-13)	7.07 (4.95-10.1)
During 3 years of age	72,900 (647,388)	28 (53)	38 (8)	26-56 (6-11)	4.69 (2.86-7.55)
During 4 years of age	62,154 (554,502)	21 (53)	34 (10)	21-52 (7-13)	3.53 (2.03-5.96)
During 5 years of age	51,738 (463,776)	7 (40)	14 (9)	5-28 (6-12)	1.57 (0.59-3.54)
During 6 years of age	41,586 (373,884)	1 (47)	2 (13)	0-13 (9-17)	0.19 (0-1.12)
During 7 years of age	31,812 (286,170)	1 (23)	3 (8)	0-18 (5-12)	0.39 (0.01-2.41)
During 8 years of age	22,362 (201,978)	0 (13)	0 (6)	0-16 (3-11)	0 (0-2.96)
During 9 years of age	13,230 (120,156)	0 (1)	0 (1)	0-28 (0-5)	0 (0-354.2)
During 10 years of age	4368 (39,714)	0 (0)	0 (0)	0-84 (0-9)	NaN (0-Inf)

Table 3:5. Incidence of pertussis among children in Göteborg and rest of Sweden (in brackets), born from Jan. 1. 2000 until Dec. 31. 2009. Stratified by onset of pertussis. Children followed from **January 1. 2000 until December 31. 2009** with observed Culture-, or PCR-confirmed *B.pertussis* and serology-confirmation from 2008. Person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person-years of follow-up and relative risk of having a laboratory-verified episode of *B.pertussis* (for children in Sweden except Göteborg study area) compared to children in the Göteborg study area) in the following age-groups at the pertussis episode; 0-<3 months of age; 3-<5 months of age; 5-<12 months of age; and after 12 months of age in six age intervals. Age is calculated at the date of the positive sample.

3.3 Comments to incidence and risk tables

Also in this larger group (Table 3:3), the number of cases reported from Göteborg was high in relation to population size in the area, with 491 reported infant cases and 779 cases in children aged 1 year or more. From the rest of Sweden there were 1.147 infant cases and 1.257 cases in children aged from 1 year.

For children born from January 1. 1996 until December 31. 1998 (Table 3:4), in each age-group from 5-<12 months until 8 years of age there was a statistically significant higher risk (RR=3.2 – RR=9.2) 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 5.2 (95% C.I. 4.6 – 5.9) and the incidence figures per 100,000 years of follow-up was 134 for children in the Göteborg study area and 26 for children living outside that area.

Corresponding Table 3:5 presents result for 628 and 1,244 children born January 1. 2000 until December 31. 2009 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=2.7 – RR=11.3) 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 5.2 (95% C.I. 4.4 – 6.1) and the incidence figures per 100,000 years of follow-up was 45 for children in the Göteborg study area and 9 for children living outside that area.

3.4 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 December 31. 2009 among children born from January 1. 1996 until December 31. 2009 from children for whom we have access to vaccination history at date for the positive sample. From 2008 also serology-confimed cases are analysed. In total 1,232 reports from Göteborg study area and 2,366 from the rest of Sweden are described. 894 respectively 1,206 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 3:6).

Number of doses	Göteborg study area	Göteborg, percent between areas	Sweden except Göteborg study area	Sweden except Göteborg, percent between areasa	Total number of cases
0	203 (16%)	19%	844 (36%)	81%	1047
1	135 (11%)	30%	316 (13%)	70%	451
2	199 (16%)	55%	166 (7%)	45%	365
3	695 (56%)	40%	1040 (44%)	60%	1735
Sum	1232 (100%)	34%	2366 (100%)	66%	3598

Table 3:6 Vaccination history at date of the positive sample for children in Göteborg study area and in Sweden except Göteborg, for children born January 1. 1996 until December 31. 2009 and for culture or PCR positive pertussis episodes from October 1. 1997 until December 31. 2009. From 2008 also serology-confirmed cases are described.

Figures in Table 3:6 further confirm conclusion in section 2.4 that relatively more cases are reported among not vaccinated in Sweden except Göteborg (36% vs 16%) and, consequently, relatively more cases were reported among vaccinated in the Göteborg study area, specifically there was a higher percentage of cases who had received at least two doses of a pertussis vaccine (72% vs 51%) before the date of the positive sample. Figures in column "Percent between area" (nearly "equal" to those of Table A (exec sum)), taking the follow-up time for children in the Göteborg study area (10.1% of the total amount of follow-up) into account, tell the same story. The "overrepresentation" of reported pertussis cases

in children from the Göteborg study area varies between a multiple of 1.8 (for not vaccinated) and 5.7 (for those vaccinated with two doses).

3.5 Lab. confirmed pertussis in children born Jan. 1. 1996 until Dec. 31. 2009 and immunization status

For those birth cohorts of children there were 3,598 reports of laboratory confirmed pertussis from October 1. 1997 until December 31. 2009 for which we have data on vaccination status prior to the date of the positive sample, Table 3:7.

Birth Cohort	Number of doses	Sweden except Göteborg	Göteborg area	Total
1996	0	4	29	33
	1	1	2	3
	2	4	5	9
	3	110	275	385
1997	0	3	43	46
	1	2	11	13
	2	4	19	23
	3	110	171	281
1998	0	12	62	74
	1	10	27	37
	2	17	21	38
	3	146	182	328
1999	0	18	113	131
	1	24	45	69
	2	30	25	55
	3	127	118	245
2000	0	19	107	126
	1	13	32	45
	2	22	9	31
	3	61	91	152
2001	0	23	40	63
	1	18	16	34
	2	32	11	43
	3	52	64	116
2002	0	32	93	125
	1	18	36	54
	2	16	4	20
	3	44	37	81
2003	0	24	62	86
	1	12	17	29
	2	40	15	55
	3	25	35	60
2004	0	41	97	138
	1	26	51	77
	2	21	20	41
	3	10	30	40
2005	0	8	70	78
	1	3	18	21
	2	6	5	11
	3	3	10	13
2006	0	10	60	70
	1	3	22	25

	2	2	9	11
	3	2	16	18
2007	0	4	42	46
	1	2	11	13
	2	4	10	14
	3	4	5	9
2008	0	5	27	32
	1	3	8	11
	2	0	5	5
	3	0	4	4
2009	0	1	19	20
	1	1	10	11
	2	0	0	0
	3	0	0	0
Subtotal	0	204	864	1068
	1	136	306	442
	2	198	158	356
	3	694	1038	1732
Total	-	1232	2366	3598

Table 3:7 Number of reported laboratory confirmed cases of pertussis by number of doses prior to the positive sample and per area, Oct 1, 1997-Dec 1, 2009, among children born from Jan 1, 1996 until Dec 31, 2009..

Since we lack proper information of onset of the pertussis episode, i.e. 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. From the enhanced surveillance reports we know that onset of cough generally occurs one to two weeks before the sample was taken.

Table 3:8 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 3:3.

Age at sample	Unvaccinated in Göteborg study area	Vaccinated with one dose in Göteborg study area	Unvaccinated in Sweden excl Göteborg study area	Vaccinated with one dose in Sweden excl Göteborg study area
0-< 3 months	146 (100%)	0 (0%)	485 (100%)	0 (0%)
3-< 5 months	24 (24%)	76 (76%)	147 (40%)	224 (60%)
5-< 12 months	4 (7%)	51 (93%)	41 (32%)	86 (68%)
During 1 years of age	4 (67%)	2 (33%)	36 (97%)	1 (3%)
During 2 years of age	5 (83%)	1 (17%)	25 (100%)	0 (0%)
During 3 years of age	3 (100%)	0 (0%)	20 (91%)	2 (9%)
During 4 years of age	5 (100%)	0 (0%)	24 (92%)	2 (8%)
During 5 years of age	5 (83%)	1 (17%)	20 (100%)	0 (0%)
During 6 years of age	6 (67%)	3 (33%)	13 (100%)	0 (0%)
During 7 years of age	0 (0%)	1 (100%)	15 (100%)	0 (0%)
During 8 years of age	1 (100%)	0 (0%)	9 (100%)	0 (0%)
During 9 years of age	0	0	6 (86%)	1 (14%)
During 10 years of age	0	0	1 (100%)	0 (0%)
During 11 years of age	0	0	1 (100%)	0 (0%)
During 12 years of age	0	0	1 (100%)	0 (0%)
Sum	203 (60%)	135 (40%)	844 (73%)	316 (27%)

Table 3:8 Number of reported laboratory confirmed cases of pertussis from October 1. 1997 until December 31. 2009 per birth-cohort from January 1. 1996 until December 31. 2009, for unvaccinated and for children vaccinated with one dose prior to the date of the positive sample per age-group and per area for the pertussis episode.

Most of the pertussis cases among unvaccinated children occurred, as expected, in the two youngest age-groups – 83.7% and 74.9% in Sweden except Göteborg respectively in the Göteborg study area. In Sweden except Göteborg 171 cases (20.2%) occurred with a date for the positive sample, after one year of age. In the Göteborg study area there were 29 cases (14.3%) 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, before the second dose. However, 38% and 27%, respectively, of the one-dose vaccinated cases prior to the positive

sample occurred in the age interval 5 - < 12 months (where a dose 2 should have been given).

As seen in Table 3:9 most of the one-dose vaccinated cases occurring in the age interval 5 - <12 months 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.

Age at sample	Unvaccinated in Göteborg study area	Vaccinated with one dose in Göteborg study area	Unvaccinated in Sweden excl Göteborg study area	Vaccinated with one dose in Sweden excl Göteborg study area
0-< 1 months	24(100%)	0(0%)	72(100%)	0(0%)
1-< 2 months	62(100%)	0(0%)	200(100%)	0(0%)
2-< 3 months	60(100%)	0(0%)	213(100%)	0(0%)
3-< 4 months	18(43%)	24(57%)	124(59%)	86(41%)
4-< 5 months	6(10%)	52(90%)	23(14%)	138(86%)
5-< 6 months	1(3%)	30(97%)	12(18%)	56(82%)
6-< 12 months	3(12%)	21(88%)	29(49%)	30(51%)
After 1 years of age	29(78%)	8(22%)	171(97%)	6(3%)
Sum	203(60%)	135(40%)	844(73%)	316(27%)

Table 3:9 Number of reported laboratory confirmed cases of pertussis from October 1. 1997 until December 31. 2009 per birth-cohort from January 1. 1996 until December 31. 2009, 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.

3.6 Age-specific incidence, relative risk for children with at least two doses stratified by period of birth

In Table 3:10 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 December 31. 2009 for pertussis episodes which occurred from October 1. 1997 until December 31. 2009 in two areas of Sweden – Sweden except Göteborg, and the Göteborg study area, for children who had received at least two doses of a pertussis vaccine prior to the date for the positive sample.

In Tables 3:11 and 3:12 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 represent a transition cohort with mixed vaccinations within the 3-5-12 month schedule.

Onset of pertussis	Person years of follow-up	Number of laboratory confirmed cases	Incidence per 100,000	95% confidence interval	Relative risk
Before Dose 1	30,875 (271,812)	0 (0)	0 (0)	0-12 (0-1)	NaN (0-Inf)
Between 1 and 2 doses	20,478 (180,574)	2 (10)	10 (6)	1-35 (3-10)	1.76 (0.19-8.28)
Between 2 and 3 doses	71,017 (628,159)	198 (158)	279 (25)	241-320 (21-29)	11.08 (8.95-13.8)
After Dose 3 and during 1 year of age	119,511 (1,063,828)	170 (83)	142 (8)	122-165 (6-10)	18.23 (13.9-24)
During 2 years of age	110,808 (990,972)	114 (122)	103 (12)	85-124 (10-15)	8.36 (6.42-10.9)
During 3 years of age	99,696 (895,416)	86 (116)	86 (13)	69-107 (11-16)	6.66 (4.98-8.88)
During 4 years of age	88,950 (802,530)	76 (112)	85 (14)	67-107 (11-17)	6.12 (4.51-8.27)
During 5 years of age	78,534 (711,804)	75 (103)	96 (14)	75-120 (12-18)	6.6 (4.83-8.97)
During 6 years of age	68,382 (621,912)	68 (135)	99 (22)	77-126 (18-26)	4.58 (3.37-6.18)
During 7 years of age	58,608 (534,198)	62 (122)	106 (23)	81-136 (19-27)	4.63 (3.36-6.34)
During 8 years of age	49,158 (450,006)	29 (111)	59 (25)	40-85 (20-30)	2.39 (1.53-3.63)
During 9 years of age	40,026 (368,184)	6 (86)	15 (23)	6-33 (19-29)	0.64 (0.23-1.45)
During 10 years of age	31,164 (287,742)	7 (35)	22 (12)	9-46 (8-17)	1.85 (0.69-4.22)
During 11 years of age	22,380 (207,930)	0 (8)	0 (4)	0-16 (2-8)	0 (0-5.44)
During 12 years of age	13,542 (127,002)	1 (5)	7 (4)	0-41 (1-9)	1.88 (0.04-16.8)
Overall, after 365 days of age	780,759 (7,061,524)	694 (1038)	89 (15)	82-96 (14-16)	6.05 (5.49-6.66)

Table 3:10 Incidence of pertussis among children in Göteborg and rest of Sweden (in brackets),. Children born from **January 1. 1996 until December 31. 2009**, and followed from **October 1. 1997 until December 31. 2009** with observed Culture- or PCR-confirmed and from 2008 also serology-confirmed *B.pertussis* and **vaccinated with two or more doses of a pertussis vaccine** prior to the date for onset of the episode. Person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person-years of follow-up and relative risk of having a laboratory-verified episode of *B.pertussis* (for children in Sweden except Göteborg study area) compared to children in the Göteborg study area) in the following age-/vaccine-groups at the pertussis episode; between Dose 2 and 3; and after 12 months of age (after Dose 3) in ten one-year age intervals. Age is calculated at the date of the positive culture or PCR sample or 2008 also serology.

Onset of f pertussis	Person years of follow-up	Number of laboratory confirmed cases of pertussis	Incidence per 100,000	95% confidence interval	Relative risk
Before Dose 1	3037 (27,705)	0 (0)	0 (0)	0-121 (0-13)	NaN (0-Inf)
Between 1 and 2 doses	2332 (21,305)	0 (2)	0 (9)	0-158 (1-34)	0 (0-48.64)
Between 2 and 3 doses	10,105 (92,572)	25 (45)	247 (49)	160-365 (35-65)	5.09 (2.9-8.5)
After Dose 3 & during 1 year of age	24,231 (223,792)	42 (29)	173 (13)	125-234 (9-19)	13.38 (8.1-22.3)
During 2 years of age	26,796 (248,028)	35 (50)	131 (20)	91-182 (15-27)	6.48 (4.0-10.2)
During 3 years of age	26,796 (248,028)	55 (64)	205 (26)	155-267 (20-33)	7.95 (5.4-11.6)
During 4 years of age	26,796 (248,028)	35 (65)	131 (26)	91-182 (20-33)	4.98 (3.2-7.7)
During 5 years of age	26,796 (248,028)	44 (53)	164 (21)	119-220 (16-28)	7.68 (5.0-11.7)
During 6 years of age	26,796 (248,028)	60 (80)	224 (32)	171-288 (26-40)	6.94 (4.8-9.9)
During 7 years of age	26,796 (248,028)	56 (84)	209 (34)	158-271 (27-42)	6.17 (4.3-8.8)
During 8 years of age	26,796 (248,028)	29 (83)	108 (33)	72-155 (27-41)	3.23 (2.0-5.0)
During 9 years of age	26,796 (248,028)	2 (73)	7 (29)	1-27 (23-37)	0.25 (0.0-1.0)
During 10 years of age	26,796 (248,028)	7 (34)	26 (14)	11-54 (9-19)	1.91 (0.7-4.4)
During 11 years of age	22,380 (207,930)	0 (8)	0 (4)	0-16 (2-8)	0 (0-5.5)
During 12 years of age	13,542 (127,002)	1 (5)	7 (4)	0-41 (1-9)	1.88 (0.0-16.8)
Overall, after 365 days of age	301,317 (2,790,976)	366 (628)	121 (23)	109-135 (21-24)	5.4 (4.7-6.2)

Table 3:11 Incidence of pertussis among children in Göteborg and rest of Sweden (in brackets), born from Jan. 1. 1996 until Dec. 31. 1998. Stratified by onset of pertussis. Children followed from **October 1, 1997 until December 31. 2009** with observed culture- or PCR-confirmed *B.pertussis* and **vaccinated with two or more doses of a pertussis vaccine** prior to the date for onset of the episode. Person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person-years of follow-up and relative risk of having a laboratory-verified episode of *B.pertussis* (for children in Sweden except the Göteborg study area compared to children in the Göteborg study area) in the following age-/vaccine-groups at the pertussis episode; between Dose 2 and 3; and after 12 months of age (after Dose 3) in ten one-year intervals. Age is calculated at the date of the positive culture or PCR sample, or, from 2008 serology analyses..

Onset off pertussis	Person years of follows-up	Number of laboratory confirmed cases	Incidence per 100,000	95% confidence interval	Relative risk
Between 2 and 3 doses	55,816 (489,254)	143 (88)	256 (18)	216-302 (14-22)	14.24 (10.8-18.8)
After Dose 3 and during 1 year of age	86.544 (760,608)	95 (48)	110 (6)	89-134 (5-8)	17.39 (12.1-25.2)
During 2 years of age	75,276 (663,516)	55 (59)	73 (9)	55-95 (7-11)	8.22 (5.59-12.1)
During 3 years of age	64,164 (567,960)	25 (44)	39 (8)	25-58 (6-10)	5.03 (2.95-8.4)
During 4 years of age	53,418 (475,074)	18 (41)	34 (9)	20-53 (6-12)	3.9 (2.11-6.95)
During 5 years of age	43,002 (384,348)	6 (32)	14 (8)	5-30 (6-12)	1.68 (0.57-4.06)
During 6 years of age	32,850 (294,456)	1 (35)	3 (12)	0-17 (8-17)	0.26 (0.01-1.52)
During 7 years of age	23,076 (206742)	1 (20)	4 (10)	0-24 (6-15)	0.45 (0.01-2.8)
During 8 years of age	13,626 (122,550)	0 (12)	0 (10)	0-27 (5-17)	0 (0-3.24)
During 9 years of age	4494 (40,728)	0 (1)	0 (2)	0-82 (0-14)	0 (0-353.45)
Overall, after 365 days of age	396,450 (3,515,982)	201 (292)	51 (8)	44-58 (7-9)	6.1 (5.08-7.33)

Table 3:12 Incidence of pertussis among children in Göteborg and rest of Sweden (in brackets), born from Jan. 1. 2000 until Dec. 31. 2009. Stratified by onset of pertussis. Children followed from **January 1. 2000 until December 31. 2009** with observed Culture- or PCR-confirmed *B.pertussis* and **vaccinated with two or more doses of a pertussis vaccine** prior to the date for onset of the episode. Person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person-years of follow-up and relative risk of having a laboratory-verified episode of *B.pertussis* (for children in Sweden except the Göteborg study area compared to children in the Göteborg study area) in the following age-/vaccine-groups at the pertussis episode; between Dose 2 and 3; and after 12 months of age (after Dose 3) in six age intervals. Age is calculated at the date of the positive culture or PCR sample, or, from 2008 also serology is added as a diagnosis of pertussis.

3.6.1 Comments to incidence and risk tables

For children born from January 1. 1996 until December 31. 2009 and vaccinated with at least two doses of a pertussis vaccine prior to the date for the positive sample (Table 3:10), in each age-group from 5-<12 until 8 years of age, there was a statistically significant higher risk (RR=2.4 – RR=18.2) 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 6.05 (95% C.I. 5.49-6.7) and the incidence figures per 100,000 years of follow-up was 89 for children in the Göteborg study area and 15 for children living outside that area. One can also note that the excess in risk in Göteborg study area slowly decreases by rising age.

Corresponding Table 3:11 presents result for 391 and 675 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 29 children in the Göteborg study area in

Table 3:11 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=3.2 – RR=13.4) of contracting 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 5.4 (95% C.I. 4.73 – 6.15) and the incidence figures per 100,000 years of follow-up was 121 for children in the Göteborg study area and 23 for children living outside that area. One can also note that the excess in risk in Göteborg study area slowly decreases by age. The corresponding intent-to-treat table, Table 3:4, gives the same picture.

Table 3:12 presents result for 344 and 380 children born January 1. 2000 until December 31. 2009 with 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 8 children in the Göteborg study area in Table 3:12 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=3.9 – RR=17.4) 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 6.1 (95% C.I. 5.1-7.3) and the incidence figures per 100,000 years of follow-up was 51 for children in the Göteborg study area and 8 for children living outside that area. One can also note that the excess in risk in Göteborg study area slowly decreases by age. The corresponding intent-to-treat table, Table 3:5, gives the same picture but with lower relative risks.

Chapter 4 Plan for continued work

Study objectives for 2010:
To continue the work in studying the long-term effects of a general infant acellular pertussis vaccination program implemented in 1996, with addition of a pre-school booster from 2007, on age-specific incidence in vaccinated cohorts and in the general population.
To find background data and evaluate suitable intervals between booster vaccinations.

Analyses will 2010 also focus on:
- pertussis in infants and boostered age cohorts, in order to monitor the impact of preschool booster on age-specific incidence in infants, and the duration of protection from pre-school booster.

- Additional studies may be added to the project as decided by the yearly steering committee meetings: Mathematical modelling, capture-recapture analyzes of booster effects or other additional analyses.

- Yearly progress reports will, as previously, summarise overall number and age-specific incidence of laboratory confirmed cases, detailed analyses in vaccinated cohorts, including hospital admission rates, and number of cases in trial cohorts, and procurement of vaccine per county will be provided. In addition, case-contact information has been added for infants from 1. January 2009. Progress reports will be based on data collected per calendar year.

Scientific publications and presentations:

Manuscripts planned during project year 12 include

1. - A clinical paper concerning incidences of one and two doses of pertussis vaccine and is planned for submission September/October 2010.
2. - A 12-year surveillance project paper will be presented to the Steeering Committee as a draft in October/November and part of it was presented as a poster at ESPID 2010.
3. An evaluation of the booster effect of pertussis vaccination will be written during autumn 2010 and was also presented as a poster and poster session at ESPID 2010
4. - A surveillance paper from the 11-year report from the Göteborg study area.

Also planned is

5. - a presentation of clinical information, including data from 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.

Chapter 5 Administration

Contracts for the project Pertussis surveillance in Sweden have been agreed for continued follow-up of clinical epidemiology during the years by the manufacturers, Sanofi-Pasteur-MSD, Lyon, France; Sanofi-Pasteur, Canada, and Glaxo SmithKline, Rixensart, Belgium.

The Advisory Group meets 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 Appendices 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.

Chapter 6 Acknowledgments

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