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TEN YEAR REPORT

Pertussis surveillance in Sweden

Progress Report October 1, 1997 – December 31, 2007 with an executive summary

AV Carlsson RM, Gustafsson L
AVDELNINGEN FÖR EPIDEMIOLOGI
SMITTSKYDDSINSTITUTET

SMITTSKYDDSINSTITUTET
Swedish Institute for Infectious Disease Control

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Författare: CARLSSON RM, GUSTAFSSON L

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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1 Executive Summary

1.1 Introduction

In January 1996, seventeen years after the withdrawal of the whole-cell pertussis (Pw) vaccine due to concerns about safety and efficacy [1], the results of the major acellular pertussis vaccine trials [2, 3, 4, 5] allowed licensure of diphtheria-tetanus-acellular pertussis (DTPa) vaccines and vaccination against pertussis was again included in the Swedish vaccination program. The overall incidence during the vaccine-free period had reached more than 100 cases /100,000 person years, and up to 1,000 cases/ 100,000 infant years. Infant vaccination with Pa vaccines was hence introduced in an endemic setting.

There is a well-established child health care system in Sweden with a 98-99% vaccination coverage in infancy. The three-dose coverage for pertussis vaccination at 3, 5 and 12 months of age rapidly reached this average, since the introduction of DTPa only meant a switch from DT vaccine to DTPa, and this coverage has remained unchanged during the subsequent switch to multivalent combinations including Pa.

There is also a long-standing Swedish tradition of pertussis reporting, beginning with the "tjänsteläkar-rapporten" by county health officers early in the 20th century, and continuing with voluntary laboratory reporting of culture-confirmed cases 1980 to 1996 with full personal identifiers. Because of reintroduction of pertussis vaccination in 1996, pertussis was included in the Communicable Disease Act in 1997.

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

Recognising the unique situation in Sweden, a modern western country with endemic pertussis, a well implemented vaccination program and a long-standing tradition of quality reporting (laboratory-confirmed cases), we started a long-term enhanced pertussis surveillance project October 1, 1997. We used the obligatory case-based reporting system to identify cases confirmed by culture (later also PCR) in children born from January 1, 1996, and collected detailed data on vaccination status and clinical course by structured telephone interview, and we also embedded follow-up of previous trial cohorts [2, 3] in this enhanced follow-up. In the clinical part of the surveillance project, the changes over time in age-specific rates have been considered the main outcome, and we have also related clinical outcome to vaccination status. Initially there was laboratory part of the surveillance project, run in parallel until 2004.

One area of Sweden, called the Göteborg study area, was originally excluded from the enhanced follow-up until January 1, 2003, because pertussis surveillance in this area was already done within a clinical trial setting [4, 6], including a mass vaccination project during a 3-4 year period, with free catch-up vaccination to children under 10 years of age [7].

We have specifically refrained from estimating vaccine effectiveness by percent reduction of disease rates among vaccinated compared to unvaccinated children because of the passive reporting system with inherent ascertainment bias, which will inflate levels of protection [8], and because there is no computerised vaccination register for calculation of proper incidence denominators. Furthermore there is a selection bias since the very small proportion (1-2%) of unvaccinated children is likely to differ from Swedish children in general, with some of the unvaccinated children living in institutions or in other "households" that are not a representative sample of Swedish households. We have also refrained from long-term comparisons of vaccines and geographic areas, since the use of the different Pa vaccines has varied with and within calendar periods and areas. Also, to avoid potentially biased comparisons between vaccines, the yearly progress report analyses are limited to the aggregate data on all Pa vaccinations in Sweden (except Göteborg area).

The main aims of the project were to follow the long-term protection after vaccinations with DTPa-containing vaccines and to document possible strain changes. The experience from one, three, four, five, six, seven, eight and nine years of enhanced clinical follow-up in Sweden (except Göteborg) has been published previously [9, 10, 11,] and also reported in the technical progress reports [12, 13, 14, 15, 16, 17, 18, 19]. Section 2 of this report covers continued follow-up of the same areas October 1, 1997 until December 31, 2007, i.e. for ten years and three months – for short in the rest of the report called ten years. In Section 3 of the main ten-year report we report general information on laboratory-confirmed pertussis in the whole country and all ages before and after introduction of Pa vaccines. The experience from the laboratory surveillance has been published [20, 21, 22, 23, 24] separately, and also reported in former technical progress reports

As for children from the Göteborg area, we have until last year refrained from inclusion of these data in the yearly main progress report because the enhanced surveillance started 5 ¼ year later in this area than in the rest of Sweden, hampering the long-term aggregation of data.

In 2007, a separate first technical report from the Göteborg area - with the enhanced surveillance information collected from this area during the period January 1, 2003 until September 30, 2006 (3 ¾ year), together with an update on culture-confirmed cases reported from this area in comparison with the rest of Sweden during the period October 1, 1997 and until September 30, 2006 (9 years) was presented as a complement to the main nine-year report [25]. This Göteborg nine year report included analyses of culture-confirmed cases in relation to age at time of laboratory sampling, and we also provided retrospectively collected individual vaccination data from children with reported pertussis for the period October 1, 1997 and until December 31, 2002 (5 ¼ year), together with regional information on laboratory-confirmed pertussis in all ages before and after introduction of Pa vaccines [25].

The Göteborg report is now updated and covers enhanced surveillance in this area from January 1, 2003 until December 31, 2007 (5 years) as well as the other (non-enhanced) comparisons between this area and the rest of Sweden for the whole ten-year period October 1, 1997 until December 31, 2007. The section 1.4 of Göteborg report includes an updated list and discussion of plausible explanations to the differences in reported incidence in the Västra Götaland region as compared to the rest of the country.

1.2 Materials and methods

A detailed description of the enhanced surveillance program, ongoing since October 1, 1997 in all of Sweden (except Göteborg until January 2003), and the routine reporting system of pertussis in place in Sweden, has been published [9] and is also described in Section 2. Briefly, the materials and methods for the enhanced surveillance are given here:

All episodes of pertussis occurring in children born since January 1, 1996, and also in children participating in the nation-wide trials 1992-96 [2, 3], were identified via the national register of reports according to the Communicable Disease Act. 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 [26]. Additional analyses according to the EU and WHO surveillance case definitions of 2002-2003 [27, 28], i.e. prolonged coughing of at least fourteen days, have been added as appropriate.

1.2.1 Clinical part of enhanced surveillance

In the clinical part of the enhanced surveillance project, these episodes of pertussis (except those occurring 971001-021231 in the Göteborg area) were followed-up in detail. Vaccination data, as well as detailed clinical data (including data on hospitalisation, complications and antibiotic treatment) was collected by telephone interviews. All clinical data and the unique Swedish personal identifier were entered in a "clinical" database. Progress reports have summarised the database information for all episodes (except those occurring in the Göteborg area) up to end of the previous project year, with the present ten-year report updating the information from October 1, 1997 until December 31, 2007.

1.2.2 General information on pertussis in Sweden

General information on pertussis in Sweden have been included in the progress reports. This information includes a time-trend illustration of the number of laboratory-reported cases of pertussis per month from 1986 and onwards, as reported according to the Communicable Disease Act. These laboratory reports are based on culture, PCR or serology. The general information also include annual incidence rates of culture- or PCR-confirmed cases in the whole population and by age-groups for the years 1986-1995 (no general vaccination against pertussis), and from 1998 and onwards (after introduction of Pa). The progress reports have summarised the general information up to the previous calendar year, with Section 3 of the present ten-year report updating this general information until December 31, 2007.

1.2.3 Person time and incidence calculations

Age-specific incidence rates of pertussis for children born January 1, 1996 until December 31, 2007 and for children in the 1993-96 trial were based on the number of notified pertussis cases during the study period October 1, 1997 to December 31, 2007 as described in Sections 2.9, 2.11, 2.13 & 2.15. In addition, annual overall incidences and age-specific incidences of pertussis in Sweden were based on the number of notified culture- or PCR-confirmed pertussis in the whole population and in all age groups, based on age at notification, and on the corresponding mid-year populations derived from the mean of population figures at two consecutive new years divided by two (data from Statistics Sweden, http://www.scb.se).

1.2.4 Vaccines used from 1996

The vaccines used in infancy differed in time and geographic regions during the surveillance period. During 1996 and 1997 a trivalent three-component DTPa containing pertussistoxoid (PT), filamentous haemagglutinin (FHA) and pertactin (Infanrix®, GlaxoSmithKline, GSK) was used in the whole country, except in Göteborg area where a trivalent one-component DTPa with only PT (DiTeKik®, SSI) was used. From the end of 1998 Infanrix® was replaced in a number of counties by a pentavalent two-component DTPa-IPV-Hib with PT and FHA (Pentavac®, Sanofi Pasteur MSD). In 2000, the corresponding pentavalent three-component vaccine (Infanrix®-Polio-Hib) came into use. Since then pentavalent vaccines are purchased and used by all counties for the primary vaccination series. In some counties a hexavalent vaccine is used to infants at risk for hepatitis B, whereas others use monovalent hepatitis B vaccine administered separately or concomitantly with the pentavalent vaccine.

From 2007 the Swedish vaccination program includes a pre-school and a school-leaving booster against diptheria-tetanus-pertussis to children born from 2002. Full dose vaccine is recommended at school entry and reduced antigen vaccine at school leaving. A catch-up at 10 years of age in form of one full-dose vaccination against the three diseases is recommended since the autumn of 2005, i.e. all children born from implementation in 1996 of primary acellular pertussis vaccination will receive at least one pertussis booster in school [29].Hitherto no child in the study database has reported any booster dose according to the revised schedule prior to the pertussis episode.

1.3 Results

1.3.1 Pertussis incidence for children born January 1, 1996 through December31, 2007

During the ten-year period of this study there were 2 042 followed cases of laboratory confirmed pertussis outside the Göteborg area among 2 041 children born January 1, 1996 until December 31, 2007, with detailed vaccination and clinical history available for all episodes of pertussis.

Most cases were reported in the youngest birth-cohort in each calendar period, with a marked decline after the second dose at 5 months of age, Table A. The lowest age-specific incidence was seen in fully vaccinated children (3 doses of DTPa-containing vaccine) below 2 years of age (12 per 100 000 including unvaccinated children of this age). Between 2-<6 years of age the age-specific incidences were 16-21 per 100,000 person years, with a further increase at ages 6-<9 years to 29-33 per 100,000 person years. However, there was a decrease to 8 per 100 000 among the oldest age groups from 10 years of age, Table A.

Table A Children born from **January 1, 1996 until December 31, 2007** and followed from **October 1, 1997 until December 31, 2007** with reported Culture- or PCR-confirmed *B. pertussis*. We present person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person years and 95% confidence interval in the following age-/vaccine-groups at onset of the pertussis episode; 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 or after Dose 4) in one-year age intervals[1]. In parenthesis figures including the unimmunised children of respective age group (intent to treat) are given. *In italics the corresponding figures for children who fulfilled the WHO case definition of 21 or more days of spasmodic cough (typical pertussis) are given*[2].

Onset of pertussis episode[3] occurred (in Vaccine-/Age-group[4])	**Person-years of follow-up**	**Number of laboratory confirmed cases**	**Incidence per 100 000 person-years**	**95% confidence interval for incidence per 100 000 person-years**
Before Dose 1				
During 0 - <3 months of age	223 435	n.a. (496)	n.a. (222)	n.a. (202 – 242)
of which ≥21d		*n.a. (445)*	*n.a. 199*	*n.a. (181 – 218)*
Between Dose 1 and 2 or				
During 3 - <5 months of age	148 460	278 (362)	187 (244)	166 – 211 (219 – 270)
of which ≥21d		*240 (315)*	*162 (212)*	*141 – 183 (189 – 236)*
Between Dose 2 and 3 or				
During 5 - <12 months of age	516 635	138 (169)	27 (33)	22 – 32 (28 – 38)
of which ≥21d		*97 (126)*	*19 (24)*	*15 – 23 (20 – 29)*
After Dose 3 or 4 and/or				
During 1 year of age	875 275	73 (106)	8 (12)	7 – 11 (10 - 15)
of which ≥21d		*53 (85)*	*6 (10)*	*5 – 8 (8 – 12)*
During 2 years of age	806 285	109 (131)	14 (16)	11 –16 (14 – 19)
of which ≥21d		*89 (111)*	*11 (14)*	*9 – 14 (11 – 16)*
During 3 years of age	715 130	106 (125)	15 (17)	12 – 18 (15 – 21)
of which ≥21d		*80 (97)*	*11 (14)*	*9 – 14 (11 – 17)*
During 4 years of age	624 815	103 (126)	16 (20)	13 – 20 (17 – 24)
of which ≥21d		*74 (97)*	*12 (16)*	*9 – 15 (13 – 19)*
During 5 years of age	536 690	99 (115)	18 (21)	15 – 23 (18 – 26)
of which ≥21d		*73 (87)*	*14 (16)*	*11 – 17 (13 – 20)*
During 6 years of age	452 115	116 (125)	27 (29)	23 – 32 (24 – 35)
of which ≥21d		*95 (104)*	*22 (24)*	*18 – 27 (20 – 29)*
During 7 years of age	369 930	111 (121)	30 (33)	25 – 36 (27 – 39)
of which ≥21d		*85 (94)*	*23 (25)*	*18 – 28 (21 – 31)*
During 8 years of age	289 120	86 (94)	30 (33)	24 – 37 (26 – 40)
of which ≥21d		*70 (77)*	*24 (27)*	*19 – 30 (21 – 33)*
During 9 years of age	208 930	55 (58)	26 (28)	20 - 34 (21 – 36)
of which ≥21d		*44 (47)*	*21 (22)*	*15 – 28 (17 – 30)*
During 10 - 11 years of age	170 885	14 (14)	8 (8)	5 - 14 (5 – 14)
of which ≥21d		*13 (13)*	*8 (8)*	*4 – 13 (4 – 13)*
After Dose 3 or 4 and/ or from 1 year of age	5 049 175	872 (1015)	17 (20)	16 – 18 (19 – 21)
of which ≥21d		*676 (812)*	*13 (16)*	*12 – 14 (15 – 17)*

[1] Part of the 5-year group and part of the group of children older than 9 to10 years of age has received Dose 4 as a booster dose according to the revised national vaccination program – see section 2.1.6 for details.
[2] We have used typical pertussis as an end-point, since the alternative 14 or more days of cough includes 98% of all 2042 reported pertussis episodes in Table A – meaning that a row for a 14 days alternative should have been nearly identical to the (upper) row for all age intervals.
[3] At date for onset of cough, or if no cough at date for the positive sample, during the pertussis episode.
[4] Age interval in the heading classifies the unimmunised children.

1.3.2 Clinical outcome of pertussis disease

Data on duration of cough and presence of spasmodic cough were available for all 2 042 episodes, whereas data on presence of any complication were available for 2 035/2 042 episodes and data on hospitalisation admission for 2 036/2 042 episodes.

All episodes but 3 (0.15%) included coughing. Applying the EU clinical case definition of pertussis with 2 weeks of more of coughing (any type) in conjunction with positive laboratory sample, in all 1 999/2 042 (97.9%) would fulfill this definition. The remaining 40 episodes (1.95%) presented cough of shorter duration than 14 days. Typical pertussis, i.e. spasmodic cough for 21 days or more was reported for 1 698 (83,2%). Fifty-five of 2 042 cases (2,7%) had a duration of cough (spasmodic or non-spasmodic) between 14 and 21 days.

Among the 43 cases that would not fulfill the EU definition, 21 were infants and 22 were aged 1-6 years. All but two of these infants had received erythromycin or trimetoprim-sulfametoxazol, whereas 14/22 of the children aged 1-6 years were treated with antibiotics. Seven of the infants were unvaccinated, 3 had received one dose and 11 had received both doses. One child aged one year had received two doses and the remaining children aged 1-6 years had received three doses. Infants treated with antibiotics within one week after start of pertussis episode had significantly shorter duration of cough compared to untreated in the same age-group(s), Section 2.19, Table 13. Since most of the 21 infants with a short duration of cough also had an early start of treatment it is likely that most of the cases that did not fulfill the EU definition would have had a longer duration of cough (fulfilling the EU definition or even the definition of typical pertussis) if left untreated.

The fact that most infants with short duration of cough were treated with antibiotics reflects a Swedish tradition implemented during the seventeen-year period without general vaccination against pertussis. In 1983 the National Board of Health and Welfare recommended protection of infants by avoiding exposure and by the use of erythromycin to those who were accidentally exposed. Post-exposure prophylaxis was recommended if the infant was below 6 months of age, and early treatment at first symptoms to infants 6-12 months [30].

The solicited complications asked for in the interview were respiratory complications, neurological complications, dehydration with >5% loss of weight or other serious complication. There were 320 episodes with respiratory complications, whereof 155 with apnea and 165 without. Neurological or other serious complications were only reported for 10 and 2 children respectively. There was a strong inverse association between age at the beginning of the pertussis episode and the risk of a complication due to the disease for an unimmunised child. There was also an inverse association between vaccination status before the episode and the risk of any complication (Section 2.17).

Among the 2 042 cases of pertussis in children born January 1, 1996 until December 31, 2007 for whom we have data on hospitalisation, there were 524 children (25.7%) with a hospital admission due to pertussis disease, whereof 410 (78.2%) occurred in 759 unimmunised children, which means that 54% of unvaccinated children as in contrast to 9% of vaccinated (114/1283) were hospitalized. Most of the unvaccinated children were below three months of age at start of the pertussis episode.

The duration of hospital stay was shorter in the older and vaccinated children compared to the younger and unvaccinated children. There were 28 hospitalised children, who had received two or more doses of DTPa, but only 3 (10.7%) were hospitalised for 8 days or more. The overall age-specific incidence rates for a hospital admission was 160, 75, 7 and 0.4 per 100,000 person years of follow-up for children in age groups 0-<3, 3-<5, 5-<12 and ≥12 months respectively, Section 2.16 Table 10 and Figure 3.

There was also a strong association between hospitalisation and a complication due to the pertussis disease. Seventy-two percent of the children with at least one reported complication also had a hospital admission compared to 14% admissions among children without any complication during the episode (p<0,001). In all, there were 418 (20.5%) children with at least one complication due to the pertussis disease during the episode. Detailed information in relation to vaccinations and age is found in section 2.17.

1.3.3 Pertussis incidence in the trial cohorts born 1992 and in 1993-1994

Cases of pertussis during the ten-year follow-up period among children who had received three doses in the nation-wide pertussis vaccine trials [2, 3] are shown in Section 2.15 Tables 9 a-c. These children were born in 1992 or between June 1993 and May/June 1994 and were vaccinated within the trials at 2-4-6 months (Trial I; all children, Trial II; 10,194 children) or at 3-5-12 months (Trial II, 72,698 children). Due to study results, an extra dose of Pa was offered in early childhood to children vaccinated with DTPa2. Interestingly, the estimated incidence in children vaccinated with DTPa2 (completed with a booster dose at the end of Trial II) was lower than in cohorts vaccinated with three doses of DTPa3, DTPa5 and DTPwc, all shown to be efficacious in the trial. Among children vaccinated according to the 3-5-12 schedule, i.e. including an early booster, the incidence was higher in the five-component than in the whole-cell group – in contrary to what was estimated in the trial, section 2.15, table 9c.

1.3.4 Pertussis incidence in the whole country before and after1996 (introduction of acellular pertussis vaccines)

The number of reported laboratory confirmed cases per month shows peaks every third winter: 1987-88, 1990-91 (continuing into 1992) and 1993-94 in the pre-vaccination period and a small peak in 1999-2000, thereafter small undulations at low levels during 2001 – 2007, Figure A.

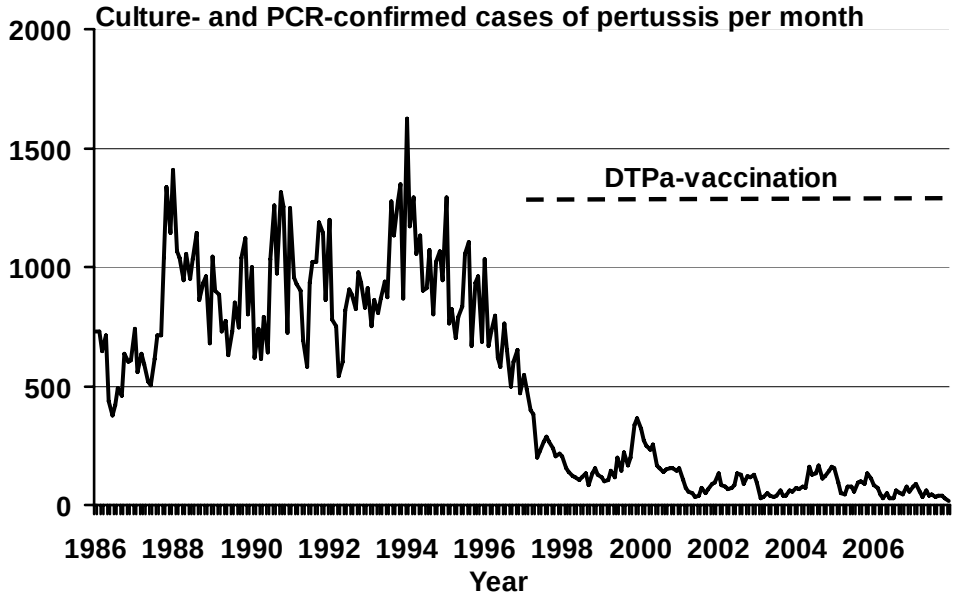

Figure A Number of culture- and PCR-confirmed pertussis cases in Sweden per month from January 1986 to December 2007.

The annual incidence of laboratory confirmed *B. pertussis* was 89-150 per 100,000 before introduction of acellular pertussis vaccines, Section 3 Table 15A. After a rapid drop in 1996-1997 the overall annual incidence reached 10 to 27 per 100,000 person years in 1999-2001, with a further reduction to between 6 and 16 per 100,000 person years in 2002-2007.

The peak incidence in the pre-1996 era was approximately 1600 cases per 100,000 and occurred in 2-4 year old children. Pertussis incidence in the fully vaccinated cohorts born after 1996 was below 90 cases per 100,000 person years, Section 3 Figure 6. However, the reduction of age specific incidence was least marked below one year of age, Section 3 Figure 7. In this age-group incidence was between 107 and 290 per 100,000 until 2006, when the age-specific incidence in infancy for the first time was below 100 per 100,000. The age specific incidence for pre-school children dropped from >1000 per 100,000 to approx. 100/100,000 in 1998-2000, to 50/100,000 in 2001 and further to approximately 20/100,000 in 2003. The rate has also dropped to below 100/100,000 among vaccinated children during the first years in school. In unvaccinated 10-14 year-olds the age-specific incidence remained about the same before and after introduction of acellular pertussis vaccine until 2005, with a slight drop thereafter to 22-15/100,000 in 2006-2007.

1.4 Discussion

In the ten-year period after the introduction of DTPa-containing vaccines in Sweden, we report a widespread decline in pertussis incidence throughout the country. The reported incidence of laboratory confirmed pertussis is more than 90 % lower than it was before these vaccines were introduced. The reported incidence is similar to that observed in the late 1960's and early 1970's when a Swedish-produced whole-cell pertussis vaccine was used with a high coverage [1].

Our observations indicate that the acellular pertussis vaccines used in the Swedish national vaccination programme have markedly reduced the reported incidence of pertussis in immunised cohorts, and also to some extent reduced pertussis among unvaccinated and partially vaccinated infants as well as among parental generation of adults, section 3.2, figures 6 and 8, indicating some level of herd immunity

In spite of the dramatic decrease, the disease is however still endemic with peaks every 3-5 years, and the reduction of incidence in the unvaccinated infants is not as marked as in older age-groups. The incidence also remains high during the age period 3-5 months, i.e. after the first dose, Section 2.12, table 8a, although hospitalisation due to pertussis was significantly reduced at that age.

The lowest age-specific incidences were found from 1-<6 years of age, with a slight increase at ages 6-<8 years and during 2004-2005 also a marked increase at 8-<9 years. Already in 2004 we observed for the first time the highest reported specific incidence in the first birth cohort who received acellular pertussis vaccine within the new immunisation programme. These data, together with the increase in incidence from 6 years of age, with age-specific incidence at about or higher than that for 5-12 month-old infants (after the second dose of pertussis vaccine), is suggesting waning protection by 6-8 years of age [11].

In accordance with the experience of other countries, most cases in Sweden are reported in infants and among older children. So far we have, however, not observed an emergence of pertussis among adolescents and young adults such as that reported in other settings [31, 32, 33], but the sensitivity of passive surveillance may be too low to permit accurate estimates of pertussis in these age-groups.

Previously reported randomised studies have shown that acellular vaccines were efficacious in clinical trial settings in young children [2, 3, 4, 5] but there is little data on the effectiveness of the vaccines when given to school age children, and no data outside this project of the long-term effectiveness of acellular vaccines administered in infancy without later vaccine boosters. Our data indicate that the vaccines appear to be effective from the second dose administered at 5 months of age, and the third dose of vaccine was associated with a further reduction in disease incidence, Section 2.12, table 8a. The reduction in disease was more pronounced during the first year following vaccination, but seemed to remain fairly stable for 4-5 years following the completion of the full vaccination schedule, Section 2.12, table 8b. These findings are in accordance with Italian and German experiences [34, 35]. Open long-term follow-up studies suggest sustained efficacy during the first six years of life after only three doses of three-component acellular pertussis vaccines in infancy [34], and after four doses of a four-component vaccine [35]. The incidence of laboratory-confirmed pertussis is increasing from 6 years of age and the concomitant incidence among infants suggests that a booster dose is warranted before 6-7 years of age [11]. However, the very high efficacy estimates presented in the post-trial studies should be regarded with caution since such studies are open to biases that predictably will over-estimate efficacy [8].

The Swedish National board of health and Welfare has recently revised the schedule of the national vaccination program, including an evaluation of the pertussis schedule in order to achieve better control of the spread of *B. pertussis*. From 2007 a preschool and also a school leaving booster is recommended to children born from 2002 (DTPa at age 5-6 years, reduced antigen vaccines at age 14-16 years), and children born 1995-2001 are recommended a catch-up (DTPa at age 10 years) [29]. Noteworthy, only one of the children born 1995-1997 with a pertussis episode had received his/her booster at age 10 years before this episode, and no child born 2002-2003 with an episode of pertussis had received their 5-6 year booster before the episode.

Noteworthy is the high rate of erythromycin prescription to infants, which is in accordance with a recommendation from the Swedish National Board [30]. This regulation was issued during the vaccine-

free period to reduce the morbidity and mortality among infants, since these were at particular high risk of exposure in an endemic setting. It is well known that erythromycin may reduce the severity and duration of disases if prescribed early during the course of pertussis. However, there is no consensus about the definition of early. In fact, it is generally believed that there is little or no reduction of severity from erythromycin if prescribed after the catarrhal phase. Interestingly, we found that erythromycin prescribed up to one week after onset of cough significantly reduces the length of the coughing period and especially the period with paroxysmal cough, section 2.19, table 13. A beneficial effect of erythromycin, even when started during the paroxysmal phase, has previously been published [36].

Our analysis is subject to important limitations. The study design is open and, with exception of clinical trial participants, non-randomized. Case ascertainment is based on routine surveillance of culture- and PCR-confirmed pertussis. The sampling rates may vary geographically and over time, according to the awareness of pertussis, local clinical practice, level of suspicion and laboratory experience in different parts of the country. The problems with laboratory confirmation are mainly the lower sensitivity of culture-confirmation in vaccinated compared to unvaccinated individuals, and also the higher sensitivity of PCR-confirmation compared to culture-confirmation. PCR has replaced culture at an increasing number of laboratories during the last few years, Section 3.6, Figure 14, which may erroneously decrease observed differences between pre and post vaccination periods and may also confound comparisons over time regarding waning protection.

On the other hand, the Swedish experience provide a reporting system that is stable over time, providing an unique opportunity to conduct a phase IV follow-up after introduction of acellular vaccines in an endemic setting. What we can learn from this long-term surveillance is the overall impact of an acellular vaccination program, including estimates of duration of vaccine-induced protection after vaccination in infancy, and – provided continuation of the project – after introduction of pre-school booster. What we can not learn from this type of follow-up is the vaccine effectiveness by percent reduction of disease rates among vaccinated compared to unvaccinated children, nor can we perform long-term comparisons of vaccines and geographic areas. However, taking these limitations into account, the results of this study provide valuable evidence on the "effectiveness" of the pertussis vaccination programme and may serve as the basis for decisions on future vaccination strategies.

1.4.1 Future priorities

Protection differences demonstrated between vaccines in efficacy trials may wane over the years, with little or no difference at all in the long run. Additional boosters may further decrease differences observed after priming (or priming + early booster). Another possibility could be the opposite, i.e. that differences of effectiveness between vaccines may remain unidentified for a number of years. Such late effects may only be detected by sustained disease surveillance combined with detailed national vaccination registry data [37]. Yet, the validity of comparing effectiveness of different vaccines will be limited by local and time differences in completeness of case ascertainment.

Infants are especially vulnerable to pertussis and recent studies indicate that *B. pertussis* pneumonia triggers a cascade of events that includes acute pulmonary vasoconstriction and pertussis toxin-mediated increases in circulating leukocyte mass. Ultimately, these responses compromise pulmonary blood flow, exacerbate hypoxemia, and create a vicious cycle of refractory pulmonary hypertension in the infant [38].

Studies of neonatal vaccination are now on their way [39, 40, 41], evaluating the possibility to initiate a vaccination response already at birth. Also studies of maternal vaccination would be useful to evaluate induction of protection already before birth. In general, there is a need for better understanding of the epidemiology of pertussis in infancy, including studies relating changes over time in infant age-specific incidence to epidemiological changes in other groups, especially studies relating vaccination of older age-groups to changes in infant epidemiology. Furthermore, changes in maternal antibodies over time may relate to changes in age-specific incidence in infancy.

While waiting for different immunisation strategies to be evaluated, such as neonatal vaccination, vaccination of the family of the new-born, pre-school/school booster doses and/or adult vaccination, contact tracing around young infants should draw attention to the need for a stricter implementation of

antibiotic chemoprophylaxis around the exposed infant [42], and provide a better understanding of who has exposed the infant.

As for routine surveillance of pertussis, the case definitions currently used may lead to an underestimation of the circulation of pertussis in infants. Serious manifestations of pertussis including deaths may occur in this age-group in spite of duration of cough shorter than 2 weeks. Also cases with a milder clinical course because of antibiotic treatment may fall outside the reporting.

1.5 Summary in brief

- The overall incidence of laboratory confirmed pertussis dropped From 121-150/100 000 in 1993-1995 to 6-16/100 000 in 2001-2007 (including PCR-confirmed pertussis)
- The highest incidence occurs in infants who are unvaccinated or have received only one dose of Pa. The incidence declines from the second dose and remains low for about 5 years after the third dose without a later booster dose.Waning protection was suggested in 2004-2005 by
  - highest age specific incidence in 2004-2005 among 8-9-year olds born in 1996, the first DTPa cohort
  - increasing age specific incidence from 6 years of age
- These suggestions of waning protection together with a concomitant increase in incidence among infants suggests that a booster dose was warranted at 5-6 years of age, and such a booster is since 2007 implemented in Sweden.
- Most hospitalisations and complications occur in infants who are unvaccinated.
- There was an association between vaccination status of the child before the episode and the risk of a hospitalisation or a complication, indicating that in children with pertussis there might be some protection against "severe" disease, expressed as a hospitalisation or a complication, already by the first vaccine dose.
- An early start of the antibiotic treatment, within the first week (≤6 days) after onset of cough during the episode was, in all age groups, associated with a shorter duration of cough compared to both "no antibiotic treatment" and start of the antibiotic treatment later than two weeks after onset. The same was true for spasmodic cough.
- Noteworthy, the Swedish National Board of Health and Welfare has since 1982 recommended post-exposure prophylaxis with antibiotics to infants below 6 months of age, and early treatment at first symptoms to infants 6-12 months. The rates of antibiotic treatment in the age-groups <3 months, 3-<5 months and 5-<12 months during the ten years of surveillance were respectively 92%, 79% and 70%.
- The relatively small difference between the proportion of cases meeting the WHO case definition in vaccinated and unimmunised children is not in accordance with data in the randomised controlled trials in 1992-5 and 1993-96, and suggests an underreporting of mild cases among vaccinated children.
- Clinical case definitions used for routine reporting of pertussis in infancy need revision, because pertussis in this age-group may be serious and even cause death in spite of coughing period shorter than 2 weeks. Also successfully implemented post-exposure prophylaxis in this age-group may lead to shorter coughing period.

2 10-year clinical pertussis surveillance Oct 1997 – Dec 2007

2.1 Background

2.1.1 Routine reporting system

During 1980 to1996 laboratory confirmed pertussis was voluntarily reported from all bacteriological laboratories with full personal identifiers. Pertussis was included in the new Communicable Disease Act in 1997. Since Fall 1997 all cases of pertussis, either clinically suspected or/and laboratory confirmed by culture, polymerase chain reaction (PCR) or serology were reported to the Swedish Institute for Infectious Disease Control through a computer-linked reporting system.

2.1.2 Enhanced surveillance program

The enhanced pertussis surveillance started in October 1, 1997 in Sweden, 1¾ year after the introduction of acellular pertussis vaccines at 3, 5 and 12 months in the general vaccination program. All reports according to the Communicable Disease Act of culture- and PCR-positive cases of pertussis in children born since January 1, 1996, the year when Pa vaccines were included in the national vaccination program, and also in children born 1992 and 1993-94 who participated in the two nation-wide trials of 1992-1993 and 1993-96, Trial I and Trial II [2, 3], have since then been identified through the national register of communicable disease reports, and entered in a separate study database. Almost all of these cases of pertussis have also been followed-up in detail by study nurses who documented the vaccination history and clinical course by structured telephone interview according to the same procedures carried out during Trial II [3]. Parameters reflecting severity of disease were duration of spasmodic cough and total duration of cough, presence of complications, and hospital admissions including length of hospital stay. Also information on antibiotic treatment with erythromycin or other relevant antibiotics was collected. Detailed vaccination history for children born since 1996 was obtained from the medical records of the Child Health Care or School Health Care Centres by telephone to the nurse attending the individual child. Parental permission was obtained to request medical records as needed.

Reports of culture- or PCR-confirmed pertussis occurring 971001-021231 in the Göteborg area were also identified and entered in the study database but without any clinical follow-up. Vaccination history for most of these episodes was in 2006-07 retrospectively collected by telephone to the Child or School Health Care nurses. Episodes occurring from January 1, 2003 in the Göteborg area were followed by the same routines as in the rest of Sweden for children born since January 1, 1996.

Reports based on serology or clinical reports without laboratory confirmation were not at all included in the enhanced follow-up from October 1997 through December 2007.

2.1.3 Pertussis case definitions

An episode of pertussis was defined by (primary case definition) detection of *Bordetella 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 established for use in clinical trials [26]. In the discussion part, comparisons were made with the current clinical case reporting definitions of EU [27] and WHO [28].

2.1.4 Vaccines used

In the beginning of 1996, when a pertussis vaccine was reintroduced in the vaccination program, only one DTPa vaccine (Infanrix®, GlaxoSmithKline, GSK) was used in all parts of Sweden except Göteborg area. From at about September 1998 and during 1999 some counties in Sweden switched to the first licensed combined DTPa-Hib-IPV vaccine (Pentavac®, Sanofi Pasteur MSD), and from the year 2000 another pentavalent combination vaccine (Infanrix-Polio+Hib®, GSK) was licensed and came into use. In

Göteborg and surrounding communities, an area with at about 9,5-10,0% of Swedish new-borns during the follow-up period, another DTPa (Di-Te-Kik®, SSI) was used until spring 2000, whereafter these communities switched to Pentavac®. From 2000-2001 all counties in Sweden administer the five vaccinations recommended to all infants by use of the pentavalent combination vaccines. Vaccination against hepatitis B is not included in the general part of the Swedish vaccination program but recommended to children at risk. A few counties use the one available hexavalent combination for vaccination of infants at risk for hepatitis B (Infanrix Hexa®, GlaxoSmithKline), whereas others use a monovalent hepatitis B vaccine together with DTPa-IPV-Hib vaccine.

In short, the use of Pa vaccines within the national vaccination program have varied by time and county, ranging from the initial use of trivalent one or three-component vaccines to the later use of multivalent two or three-component vaccines. Several counties have reconsidered their procurement more than once during the project years for the first three doses of Pa-containing vaccine (see Figure 1).

Children vaccinated within the two vaccine efficacy trials in Sweden performed 1992-1995, were vaccinated according to the following:

I. The Stockholm Trial I included 9,829 infants in 1992. They were vaccinated at 2-4-6 months of age with a five-component DTPa vaccine (Connaught Laboratories Limited, CLL), a two-component DTPa vaccine (GlaxoSmithKline, GSK) or a DTPwc (CLL) [2].

II. The Stockholm Trial II included 82,892 infants in 1993/94. They were vaccinated with the five-component vaccine (CLL), the two-component vaccine (GSK), a three-component vaccine (Chiron) or a DTPwc vaccine (Evans) [3].

2.1.5 Vaccination schedules, primary immunisation and early booster

2.1.5.1 Children born from 1995

Children born in Sweden from 1996 are recommended three doses of acellular pertussis vaccine according to the 3-5-12 month schedule.

Many children born in 1995 were vaccinated against pertussis during their second year of life, either by delaying start of the ordinary vaccinations until spring 1996, or by catch-up vaccination with monovalelnt pertussis vaccine. In all, 59% of the birth cohort 1995 was vaccinated by two years of age.

Unvaccinated immigrants born from 1996, or children delayed for some other reason, were until spring 2002 normally vaccinated according to the same principle during second year of life, i.e. two doses with a two month interval, followed by a third dose after six months, and from age 2 years according to a two dose schedule (except in Göteborg, where a three-dose schedule was used regardless of age). However, since monovalent Pa vaccine was withdrawn in 2000, children can only receive Pa if they are also unvaccinated against diphtheria and tetanus. If so, pre-teen children are normally vaccinated with two doses of DTPa with a two month interval, followed by a third dose after six months (or more). From age 13 years primary immunisation against pertussis is not done.

2.1.5.2 Children born before 1995

The Göteborg mass vaccination project offered free catch-up vaccination with 3 doses to all children born in the 1990:s during the years 1996-1999. There was no free catch-up in the rest of the country, but monovalent Pa vaccine was available until the year 2000, and many children were vaccinated at the expense of the parents during these years.

Within the Trial I a 2-4-6 month schedule was used (9,829 infants) and in Trial II either a 3-5-12 month (72,698 infants) or a 2-4-6 month schedule (10,194 infants) was used.

2.1.6 Vaccination schedules, booster vaccinations after the first three doses

2.1.6.1 Children born from 1995

In 2005 a revision of the national schedule was initiated. As a first step, a booster was recommended to children in school year 4 (age approx. 10 years) from autumn 2005. The first cohort recommended this 4th dose of Pa were children born 1995, i.e. the year before formal introduction of DTPa in infancy, because this

cohort was to a large extent (59%) catch-up-vaccinated before two years of age.[5] The schedule revision was completed December 2006, and will include a 4th dose already at 5-6 years and a 5th dose at 14-16 years to children born from 2002.[6]

2.1.6.2 Children born before 1996

Children vaccinated with a two-component DTPa or the US DTPwc according to the non-boosted schedule (Trial I) and also children vaccinated with the two-component DTPa according to either schedule (Trial II) were later offered a booster. See Section 2.15, Tables 9a-c.

2.2 Presently followed birth cohorts

Children born January 1, 1996 or later and residing outside the Göteborg area at time of pertussis, and children born 1992 and who participated in Trial I [2], as well as children born 1993.06-1994.05 the recruitment cohort for Trial II [3], are followed continuously from October 1, 1997 within the surveillance project. Children born January 1, 1996 or later and residing in the Göteborg area at time of pertussis are followed continuously from January 1, 2003 in the same way as children from other parts of the country.

Originally the pertussis surveillance project covered all children born 1992 or later. In preparing a previous report, presented in March 2001 [13], it was realised that accurate vaccination coverage data would not be available for some of the birth cohorts followed from the start of the project, except for during the first two calendar year after birth, since this is the time period covered by the present yearly Swedish coverage survey. It was then decided that cohorts that were subjected to catch up vaccination of unknown rates should be dropped from the surveillance project.

Children no longer under surveillance are those born 1992, except for children taking part of pertussis Trial I, and children born 1993.1-5 or 1994.6-1995.12. Earlier data for laboratory confirmed pertussis episodes for children in dropped cohorts are still maintained in the surveillance database but these episodes are not included in the yearly progress reports.

Detailed clinical follow-up, summarised in the yearly progress reports from 2001, is hence restricted to children with a laboratory confirmed pertussis in the cohorts listed below. To each cohort there is a short description and an estimate of the vaccination rate.

1992	Children participating in Trial I.
1993.6-94.5	Children born June 1993 to May 1994 (in the county of Malmö also June 1994). This was the enrolment period for Stockholm Trial II a vaccine trial in which nearly 83,000 children were vaccinated. Rate of vaccination was just above 83%.
1996-97	Children born 1996. First cohort after the introduction of DTPa vaccination. Vaccine coverage for three doses Pa at 2 years of age is above 98%, according to the statistics from the Child Health Centres from 1999. Follow-up data is lacking for the period 1996-97.09.
1998	Children born 1998. Vaccine coverage for three doses Pa at 2 years of age was above 98%, according to the statistics from the Child Health Centres from 2001. This is the first one-year birth-cohort completely covered by this surveillance project.
1999-06	Children born 1999 - 2006. For children born 1999-2005 the vaccine coverage for three doses Pa at 2 years of age was above 98%, according to the statistics from the Child Health Centres from 2002-2008.
2007	Children born 2007, still not fully immunized

Results are first summarised for each annual birth cohort. Available data are then presented for three child cohorts which can be characterised as follows:

- The 1993.6-94.5 cohort, a cohort which also includes all children enrolled in the Stockholm vaccine Trial II. For children in Trial II we have access to all pertussis vaccination data.

[5] One child born 1996 with a pertussis episode in October 2007 had received this booster dose in December 2006, i.e. during the present follow/up period.
[6] No child born in 2002-2003 with a pertussis episode during the follow-up period had received the pre-school booster.

- The 1996-1997.9 cohort, nearly all children vaccinated with Infanrix.
- The 1997.10-2007 cohort, children vaccinated with either Infanrix, Pentavac, Infanrix-Polio-Hib, Infanrix Hexa or vaccinated in a mixed Infanrix/Pentavac schedule in some of the counties.

In all presentations in this ten-year main surveillance report, children from the Göteborg area are excluded.

2.3 Ten year surveillance database

There were 6 278 episodes of laboratory confirmed pertussis reported and entered in the surveillance database from the start of the enhanced follow-up on October 1, 1997 until the end of February 2008 and representing pertussis episodes starting no later than December 31, 2007. Since the nine-year report 286 new cases of laboratory confirmed pertussis cases have been entered in the database for still followed birth cohorts.

From the Göteborg area (area 14.2 in Fig 1) there were 1 382 reports from the routine reporting system entered in the surveillance database. These are analysed in a separate Göteborg report. Of remaining 4 896 episodes, 319 (6.5%) have not been possible to follow-up for clinical data due to e.g. confidential phone numbers, language "problems" etc. Forty-five episodes with an onset of cough earlier than October 1, 1997 were also excluded from the statistical analysis. After the above exclusions 4 532 episodes remain in the database.

Nine of those episodes concern children who have died due to the pertussis disease. For ethical reasons those households were not contacted for clinical information, but data on the vaccinations status before the fatal pertussis episode was collected from the CHC also for those children.

For 4 523 children living in households outside the Göteborg area - born between January 1, 1992 and December 31, 2007, and with an onset of cough during a laboratory positive pertussis episode which occurred between October, 1 1997 and December 31, 2007 - we have access to data on both vaccinations and clinical follow-up.

Before the statistical analysis, also episodes (1 839) for cohorts not under surveillance any longer, see Section 2.2, were excluded from the remaining 4 532 before the statistical analysis in this main report.

2.4 Laboratory confirmed pertussis cases analysed in this 10 y report

In sections 2.5 – 2.19 we present results for the remaining 2 693[7] episodes of laboratory confirmed pertussis – 2 042 episodes occurred among children born between January 1, 1996 and December 31, 2007, 28 and 614 episodes concerned children from Trial I respectively children who were born according to the recruitment period for Trial II.

Finally, there are laboratory reports in the database for 9 children born 1996 - 2007 who died due to the pertussis disease (data for those children are only used in section 2.17).

Compared to the nine year report 232 new cases of laboratory confirmed pertussis were used in this main ten-year report. Vaccine failures among participants in Trial II are reported separately in Section 2.15, also including vaccine failures in Trial I participants.

In section 2.16, we present results on hospitalisation for children born January 1, 1996 until December 31, 2007 for whom we have data on length of hospitalisation (2 036). Results for complications (2 035) due to the pertussis illness during the pertussis episode and the duration of spasmodic cough (2 042) are found in sections 2.17 and 2.18. Treatment with antibiotics is covered in section 2.19.

[7] There was one child with two episodes of pertussis. His/her first episode was at 14 months of age, and the second at 5 years.

2.5 Laboratory confirmed pertussis per calendar period & birth cohort

All "remaining" 2 684 laboratory confirmed cases of pertussis were divided on the still followed birth-cohorts and calendar periods for onset of cough (or, if no cough – 5 children, whereof 3 born 1996-2007 – during the episode, at date of the positive sample) at the episode. Table 1a report cases among children born January 1, 1996 until December 31, 2007, the DTPa vaccination period (2 042) and Table 1b cases (28) among children in the Trial I cohort and cases (614) among children born during the enrolment period of Trial II, June 1, 1993 until May 31, 1994.

Table 1a Reported laboratory confirmed cases of pertussis from October 1, 1997 until December 31, 2007 per birth-cohort and period of onset of cough. In italics, below, number of children with two or more doses of a pertussis vaccine prior to the positive episode is given.

	Calendar period, for onset of cough, for laboratory confirmed cases of pertussis											
Birth-cohort	**1997 Q4**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**Total**
1996	**5** ***3***	**18** ***15***	**40** ***35***	**41** ***35***	**20** ***16***	**39** ***39***	**14** ***14***	**60** ***55***	**41** ***38***	**14** ***13***	**3** ***3***	**295** ***266***
1997	**23** ***6***	**29** ***15***	**19** ***19***	**25** ***22***	**17** ***14***	**32** ***29***	**7** ***4***	**25** ***20***	**26** ***25***	**16** ***14***	**13** ***12***	**232** ***180***
1998	**-**	**61** ***7***	**36** ***20***	**14** ***12***	**7** ***4***	**17** ***15***	**12** ***11***	**34** ***33***	**40** ***40***	**21** ***19***	**13** ***12***	**255** ***173***
1999	**-**	**-**	**96** ***6***	**65** ***23***	**9** ***6***	**19** ***14***	**8** ***4***	**18** ***13***	**25** ***24***	**12** ***11***	**18** ***18***	**270** ***119***
2000	**-**	**-**	**-**	**88** ***5***	**31** ***6***	**16** ***9***	**7** ***6***	**21** ***14***	**14** ***11***	**24** ***17***	**17** ***16***	**218** ***84***
2001	**-**	**-**	**-**	**-**	**33** ***3***	**21** ***10***	**8** ***7***	**16** ***11***	**13** ***10***	**10** ***8***	**8** ***7***	**109** ***56***
2002	**-**	**-**	**-**	**-**	**-**	**98** ***3***	**15** ***3***	**15** ***10***	**10** ***9***	**8** ***7***	**3** ***3***	**149** ***35***
2003	**-**	**-**	**-**	**-**	**-**	**-**	**52** ***2***	**40** ***17***	**11** ***10***	**6** ***6***	**7** ***7***	**116** ***42***
2004	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**116** ***4***	**40** ***16***	**12** ***11***	**7** ***6***	**175** ***37***
2005	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**74** ***0***	**14** ***5***	**4** ***4***	**92** ***9***
2006	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**63** ***3***	**22** ***6***	**85** ***9***
2007	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**46** ***0***	**46** ***0***
Total	**28** ***9***	**108** ***37***	**191** ***80***	**233** ***97***	**117** ***49***	**242** ***119***	**123** ***51***	**345** ***177***	**294** ***183***	**200** ***114***	**161** ***94***	**2 042** **1 010**

Table 1b Reported laboratory confirmed cases of pertussis from October 1, 1997 until December 31, 2007 for children in the Trial I cohort and for the birth-cohort covering the Trial II recruitment period, per period of onset of cough. In italics, below, number of children with two or more doses of a pertussis vaccine prior to the positive episode is given.

	Calendar period, for onset of cough, for laboratory confirmed cases of pertussis											
Birth-cohort	**1997 Q4**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**Total**
Trial I	**2** ***1***	**4** ***3***	**5** ***3***	**6** ***5***	**5** ***3***	**2** ***2***	**0** ***0***	**2** ***2***	**0** ***0***	**2** **1**	**0** ***0***	**28** ***20***
1993.6-1994.5	**21** ***8***	**79** ***28***	**167** ***63***	**138** ***55***	**51** ***20***	**43** ***11***	**18** ***8***	**36** ***23***	**37** ***21***	**17** ***13***	**7** ***4***	**614** ***254***

2.6 Laboratory confirmed pertussis among unimmunised children

Among 2 684 followed children with laboratory confirmed pertussis, 1 111 (41.4%) had not received a pertussis vaccine prior to the illness. Figures for unimmunised children are given in Tables 2a and 2b.

Table 2a Number of reported laboratory confirmed cases of pertussis from October 1, 1997 until December 31, 2007 per birth-cohort and per period of onset of cough for unimmunised children (i.e. children who have not received any pertussis vaccine before onset of cough).

	Calendar period, for onset of cough, for laboratory confirmed cases of pertussis											
Birth-cohort	**1997 Q4**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**Total**
1996	**2**	**3**	**5**	**6**	**3**	**0**	**0**	**5**	**2**	**1**	**0**	**27**
1997	**12**	**8**	**0**	**3**	**3**	**3**	**3**	**5**	**1**	**2**	**1**	**41**
1998	**-**	**38**	**7**	**2**	**3**	**1**	**1**	**1**	**0**	**2**	**1**	**56**
1999	**-**	**-**	**61**	**26**	**3**	**5**	**4**	**5**	**1**	**1**	**0**	**106**
2000	**-**	**-**	**-**	**58**	**19**	**7**	**1**	**6**	**3**	**7**	**1**	**102**
2001	**-**	**-**	**-**	**-**	**22**	**5**	**1**	**4**	**3**	**2**	**1**	**38**
2002	**-**	**-**	**-**	**-**	**-**	**66**	**5**	**5**	**1**	**1**	**0**	**78**
2003	**-**	**-**	**-**	**-**	**-**	**-**	**41**	**16**	**1**	**0**	**0**	**58**
2004	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**77**	**13**	**1**	**1**	**92**
2005	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**60**	**5**	**0**	**65**
2006	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**44**	**12**	**56**
2007											**35**	**35**
Total	**14**	**49**	**73**	**95**	**53**	**87**	**56**	**124**	**85**	**66**	**52**	**754**

Table 2b Number of reported laboratory confirmed cases of pertussis from October 1, 1997 until December 31, 2007 for the birth-cohort corresponding to the recruitment period of Trial II and per period of onset of cough for unimmunised children (i.e. children who have not received any pertussis vaccine before onset of cough).

	Calendar period, for onset of cough, for laboratory confirmed cases of pertussis											
Birth-cohort	**1997 Q4**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**Total**
Trial I	**1**	**1**	**2**	**1**	**2**	**0**	**0**	**0**	**0**	**1**	**0**	**8**
1993.6-1994.5	**12**	**50**	**101**	**80**	**31**	**32**	**9**	**12**	**16**	**3**	**3**	**349**

In birth cohort 1993.6 - 1994.5, a majority, 349 of 614 (56,8%), of the followed children with laboratory confirmed pertussis had not been vaccinated, and were (thus) not participants in Trial II.

In the 1996 birth cohort there were few laboratory confirmed cases among the unimmunised (9,2%) due to the very high vaccine coverage. Most children in the cohort had in fact received three vaccine doses before the present follow-up started October 1, 1997. (Table 2a and Table 1a). In all, 754 of 2 042 episodes (36,9%), among children born 1996 or later, occurred among the unimmunised.

All 1 103 episodes, but one, 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 47 days. Spasmodic cough for 21 days or more (episodes according to the WHO-definition) was reported for 91,0% of the episodes - the median duration was 37 days. For 45 (4,1%) of the episodes there were no spasmodic cough at all.

Table 3 shows for 697 unimmunised children born from October 1, 1997 or later (i.e. children born during the period for the pertussis surveillance) the age distribution of the laboratory confirmed cases at onset of cough. Most of the pertussis cases (70%) in this subgroup of unimmunised children occurred before three months of age, i.e. before the scheduled first dose of a DTPa-containing vaccine, 16% occurred between 3 and 12 months of age, i.e. during the "normal" period for pertussis vaccinations and 14% occurred after one year of age.

Table 3 Age at onset of cough for 697 laboratory confirmed cases of pertussis from October 1, 1997 until December 31, 2007 among unimmunised children born from October 1, 1997 or later.

Birth cohorts 1997 Q3 - 2006 Q3		
Age at onset of cough	**Number**	**%**
0 – 30 days	**127**	**18**
31 – 60 days	**190**	**27**
61 – 90 days	**174**	**25**
91 – 120 days	**62**	**9**
121 – 150 days	**18**	**3**
151 – 180 days	**8**	**1**
181 – 365 days	**21**	**3**
≥366 days	**97**	**14**
Total	**697**	**100**

2.7 Laboratory confirmed pertussis among vaccinated children

Among 2 684 reported children 1 573 (58,6%) had received at least one dose of a pertussis vaccine prior to onset of the pertussis episode – 1 138 children had received 3-4 doses or 2 doses after two years of age (2 children), 146 had received 2 doses and 289 had received only one dose of pertussis vaccine.

One thousand two hundred and eighty-eight children born from 1996 until 2007 and vaccinated with at least one dose of a pertussis vaccine had a laboratory confirmed pertussis between October 1, 1997 and December 31, 2007. Among those children 872 (67,7%) had received a full primary series (i.e. they are vaccinated according to the Swedish schedule in infancy, with 3 doses of DTPa within the first two years of life, or with 2 doses of a monovalent Pa vaccine after two years of age) before onset of cough in the pertussis episode. One hundred and thirty-eight children (10,7%) had received two doses and 278 (21,6%) one dose before the pertussis episode.

In the birth cohort that corresponds to the recruitment phase of Trial II, 265 vaccinated children had a laboratory confirmed pertussis episode, 247 (93,2%) had received a full primary series before onset of the confirmed pertussis episode, 7 had received 2 doses and 11 one dose before onset of cough. Most of those children, two hundred and fifty-two of the 265, participated in vaccine Trial II. Detailed data for vaccine failures among Trial II children with three or four doses (for 239 of the 252 children) are given in section 2.15.

In the Trial I cohort of 9 829 children, 20 children vaccinated with at least two doses of a pertussis vaccine had a laboratory confirmed pertussis during the period of intensified follow-up – 19 of those children were vaccinated with at least three doses (section 2.15).

All children but four of the vaccinated were coughing during the pertussis episode. The minimum duration of cough, if cough, was 3 days – the median duration was 45 days. Spasmodic cough for 21 days or more (WHO-definition) was reported for 78,1% of the episodes (compared to 91,0% for the unimmunised children) – the median duration was 33 days. For 14,2% of the episodes there was no spasmodic cough compared to 4,0% for the unimmunised children. The relatively small difference

between the proportion of cases meeting the WHO case definition in vaccinated and unimmunised children is not in accordance with data in the randomised controlled trials in 1992-5 and 1993-96, and suggests an underreporting of mild cases among vaccinated children.

2.8 Lab. confirmed pertussis in children born Jan 1,1996 until Dec 31, 2007

In sections 2.10 - 2.13 data for laboratory confirmed episodes observed from October 1, 1997 until December 31, 2007 among children born from January 1, 1996 until December 31, 2007 are summarised.

Children were divided in two sub-cohorts; children born from January 1, 1996 until September 30, 1997, and children born from October 1, 1997 until December 31, 2007. We regard the first 21 month cohort a "pure" Infanrix cohort, since that vaccine was the solely used pertussis vaccine for this birth-cohort in the areas in Sweden for the present surveillance. The second 123 month cohort (10 years 3 months) has been more complex to analyse since the procurement of vaccines has varied considerably among the counties for children born after September 1997 (Figure 1). The calendar time for the switch of vaccines has varied between counties, and replacement may take place immediately or be phased in by time. Thus, there are many children who received a mixed schedule of vaccines. However, with some minor approximations, we have been able to split the second cohort of children in three geographically/calendar time sub-cohorts; children with a "pure" three-component schedule (Infanrix®/Infanrix-Polio+Hib®/Infanrix hexa®); children with a "pure" two-component schedule (Pentavac®); or children with a "mixed" two/three-component schedule (Infanrix®/Pentavac® or Infanrix®-Polio+Hib/Pentavac®). Laboratory confirmed cases of pertussis as well as person time of follow up could be split between the three sub-cohorts. This sub-cohort analysis is presented in a separate Appendix 2 for each vaccine.

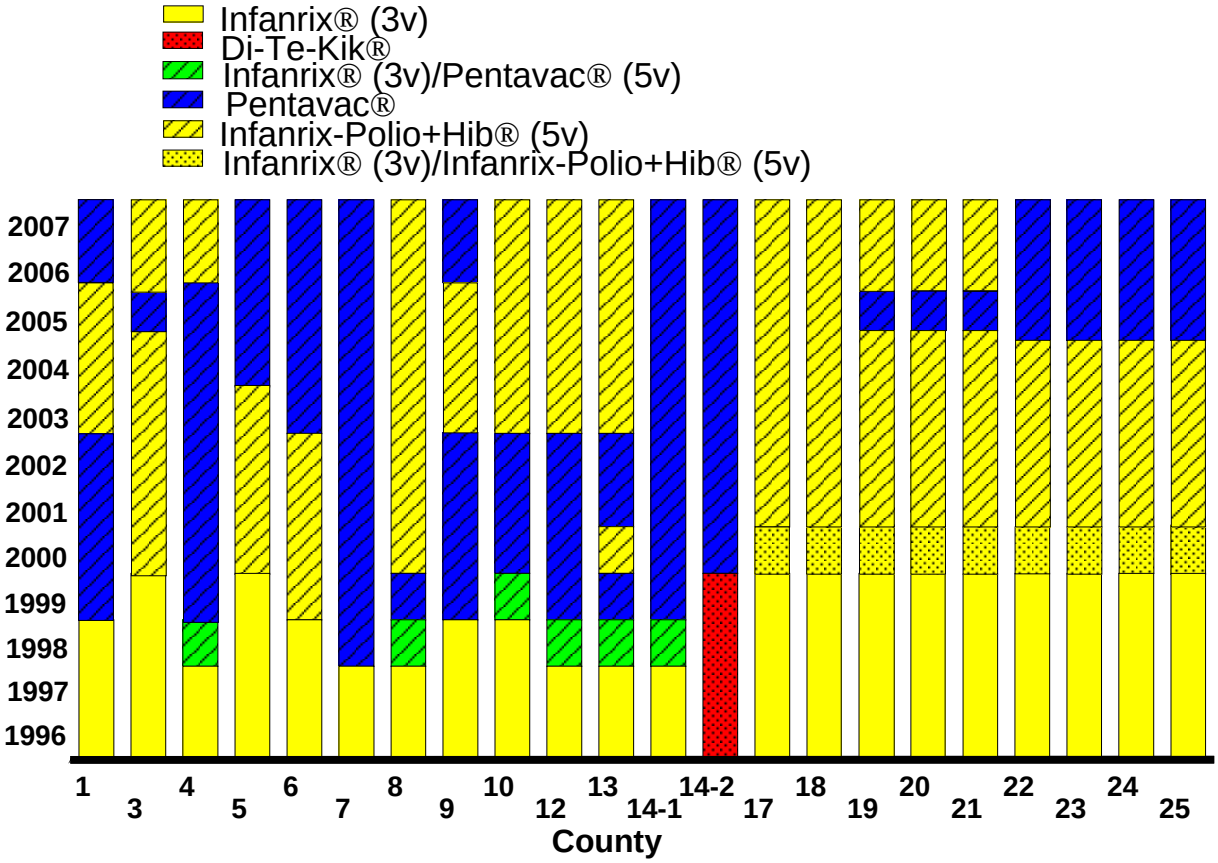

Figure 1 Procurement of vaccines by county 1996 –2007. County number on the X-axis and on the map are given below (p 23), and county name and population figure are given below.

Table 4 Population in Sweden 2007 by county.

No.	County	2007 Mid year population	No.	County	2007 Mid year population
1	Stockholm	1 933 810	14	V Götaland	1 542 791
3	Uppsala	321 598	17	Värmland	273 658
4	Södermanland	264 145	18	Örebro	275 549
5	Östergötland	419 388	19	Västmanland	248 841
6	Jönköping	332 575	20	Dalarna	275 665
7	Kronoberg	180 211	21	Gävleborg	275 605
8	Kalmar	233 805	22	Västernorrland	243 714
9	Gotland	57 210	23	Jämtland	126 979
10	Blekinge	151 668	24	Västerbotten	257 587
12	Skåne	1 191 929	25	Norrbotten	251 244
13	Halland	290 126		**Sweden**	**9 148 092**

2.9 Person-time of follow-up & incidence calculations

Tables 5 and 7 (rightmost column) respectively give the number of laboratory confirmed pertussis cases used in the incidence calculations that follow in sections 2.11 (Table 6a and b) and 2.13 (Table 8a and b).

Sub-cohort analyses for the vaccine specific cohorts for children born from October 1, 1997 until December 31, 2007 are presented in Appendix 2. Carefully, observe that figures in table 7 are slightly modified before the calculations presented in Appendix 2. The reclassification mainly concerns children in table 7 who have received one or two doses of Infanrix® (or Infanrix-Polio+Hib®) before onset of cough. If one of those children is living in a county that later, during the vaccination period of the child, switched from e.g. Infanrix®/Infanrix-Polio+Hib® to Pentavac®, a next dose should have been with the Pentavac® vaccine. The child is therefore reclassified to the mixed cohort

To some extent the reclassification of cases of table 7, for the vaccine specific analysis, also concerns children with only Pentavac® vaccination(s). It might be e.g., that the vaccination with Pentavac® started earlier in some counties (or part of the county) compared to the information we use for splitting the cohort in three parts - see discussion in section 2.8. However only a few of the laboratory confirmed pertussis cases with only Pentavac® vaccination(s) are "misclassified" according to the information on the time for the switch we have got from the counties. We take this as an evidence that it is meaningful to use this county-specific information for person-time and incidence calculations in two sub-cohorts. Table I in Appendix 2 reports the number of laboratory confirmed cases and Tables II a and b the incidence figures for the "pure" Infanrix®/Infanrix-Polio+Hib® respectively the "pure" Pentavac® schedule.

2.10 Lab. confirmed pertussis in children born Jan. 1, 1996 - Sept. 30, 1997

This cohort of children was the first one in the regular vaccination program that included a Pa vaccine in the 3, 5 and 12-month schedule. Infanrix (DTPa) was licensed in the beginning of 1996 and was then the only used DTPa vaccine outside Göteborg area. Available figures show vaccine coverage at about 98% for children born 1996. Nearly all children born 1996 until September 30, 1997 have received three doses of Infanrix®. We regard this birth cohort a "pure" Infanrix® cohort. Results are presented in Table 5.

For this cohort of children there were 479 reports of laboratory confirmed pertussis in the database from October 1, 1997 until December 31, 2007. Fifty-seven of these reports concern children without any pertussis vaccination prior to onset of the pertussis episode. Nine children had received one dose, 19 children two doses and 394 children were fully vaccinated before the episode. Five of the unimmunised children were younger than 3 months, four between 3 and 5 months, two between 5 and 12 months and 46 were older than 12 months of age at onset of cough. All, but seven, of the unimmunised children had spasmodic cough for at least 21 days, Table 5.

Eighty-eight percent of the unimmunised and 78% of the vaccinated children had spasmodic cough for 21 days or more.

Table 5 Laboratory confirmed cases of pertussis from October 1, 1997 until December 31, 2007, among children born from 1996 until September 30, 1997 divided per birth-cohort, number of vaccine doses before episode and pertussis vaccine prior to the episode. (The number of cases with 21 or more days of spasmodic cough is given in parenthesis).

Birth-cohort	Number of doses of a pertussis vaccine	Not immunised before onset of episode No. (>=21)	Only Infanrix vaccine No. (>=21)	Other vaccine/ Mixed vaccines No. (>=21)	Total No. (>=21)
1996	0	27	-	-	27 (24)
	1	-	1	1	2 (2)
	2	-	5	0	5 (4)
	3-4	-	255	6	261 (202)
1997.1 - 9	0	30	-	-	30 (26)
	1	-	7	0	7 (5)
	2	-	14	0	14 (7)
	3	-	127	6	133 (110)
Total	0	57 (50)	-	-	57 (50)
	1	-	8 (6)	1 (1)	9 (7)
	2	-	19 (11)	0	19 (11)
	3-4	-	382 (301)	12 (11)	394 (312)
Total	-	57 (50)	409 (318)	13 (12)	479 (380)

2.11 Incidence in children born January 1, 1996 - September 30, 1997

According to Statistics Sweden 95 297 children were born 1996 and 90 502 children were born during 1997. County specific figures show that 86 548 respectively 82 100 of these children were born outside Göteborg and surrounding municipalities (an area not included in the main ten-year report) - and we end up with an estimate of about 148 123 children born in main follow-up areas between January 1, 1996 and September 30, 1997.

To simplify calculations of person-time of follow-up we assume an equal number of new-born infants during each month during a calendar year – i.e. 7 212 children per month during 1996 and 6 842 children during 1997. We also assume that all children were born in the middle of the month and that vaccination took place according to the regular schedule, i.e. at three, five and twelve month of age. Person-time before October 1, 1997 will not be included since the collection of laboratory confirmed cases of pertussis started from that date. With these simplifications we calculated the number of person-months for each monthly cohort of new-borns in the following age/vaccination-intervals:

- Person-months from birth to three months of age (before Dose 1).
- Person-months between three and five month of age (between Dose 1 and Dose 2).
- Person-months between five and twelve month of age (between Dose 2 and Dose 3).
- Person-months after twelve month of age (after Dose 3) until December 31, 2007.

Children born January 1, 1996 until September 30, 1997 were followed from October 1, 1997 until December 31, 2007 for approximately 1 518 250 person-years. During follow-up 479 cases of laboratory confirmed pertussis have been reported to the surveillance system - 422 cases among vaccinated and 57 among unimmunised children (Table 5). Table 6a presents total number of person-years and laboratory confirmed pertussis cases divided in age/vaccination intervals described above. In Table 6b the interval after 1 year of age is divided in ten one-year intervals.

Table 6a Children born from **January 1, 1996 until September 30, 1997** and followed from **October 1, 1997 until December 31, 2007** with observed Culture- or PCR-confirmed *B.pertussis*. We present Person-years of follow-up, Number of laboratory confirmed cases, Incidence per 100,000 person years and 95% confidence interval in the following age-/vaccine-groups at onset of the pertussis episode; 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 after12 months of age (after Dose 3). In parenthesis figures including the unimmunised children of respective age group (intent to treat) are given. *In italics the corresponding figures for children who fulfilled the WHO case definition of 21 or more days of spasmodic cough (typical pertussis) are given.*

Onset of pertussis episode[8] occurred (in Vaccine-/Age-group[9])	**Person-years of follow-up**	**Number of laboratory confirmed cases**	**Incidence per 100 000 person-years**	**95% confidence interval for incidence per 100 000 person-years**
Before Dose 1 **During 0-<3 months of age**	**2 565**	**(5)** ***(4)***	**(195)** ***(156)***	**(62-443)** ***(41-389)***
Between Dose 1 and 2 or **During 3 - <5 months of age**	**4 560**	**9 (13)** ***7 (10)***	**197 (285)** ***154 (219)***	**88-365 (148-474)** ***60-308 (102-393)***
Between Dose2 and 3 or **During 5-<12 months of age**	**34 065**	**19 (21)** ***11 (12)***	**56 (62)** ***32 (35)***	**32-85 (37-92)** ***16-56 (18-60)***
After Dose 3 and/or **After 1 year of age**	**1 477 060**	**394 (440)** ***312 (354)***	**27 (30)** ***21 (24)***	**24-29 (27-33)** ***19-24 (22-27)***

Table 6b Children born from **January 1, 1996 until September 30, 1997** and followed from **October 1, 1997 until December 31,2007** - Person-years of follow-up etc. after Dose 3, or from 1 year of age for the unimmunised children, is divided in ten age intervals (see also legend to Table 6a).

Onset of pertussis episode occurred (in Vaccine-/Age-group)	**Person-years of follow-up**	**Number of laboratory confirmed cases**	**Incidence per 100 000 person-years**	**95% confidence interval for incidence per 100 000 person-years**
After Dose 3 and/or **During 1 year of age**	**123 780**	**13 (18)** ***9 (14)***	**11 (15)** ***7 (11)***	**6-18 (9-23)** ***3-14 (6-19)***
After Dose 3 and/or **During 2 years of age**	**148 120**	**41 (45)** ***36 (40)***	**28 (30)** ***24 (27)***	**20-38 (22-41)** ***17-34 (19-37)***
After Dose 3 and/or **During 3 years of age**	**148 120**	**51 (58)** ***40 (46)***	**34 (39)** ***27 (31)***	**26-45 (29-51)** ***19-37 (23-42)***
After Dose 3 and/or **During 4 years of age**	**148 120**	**44 (52)** ***34 (42)***	**30 (35)** ***23 (28)***	**22-40 (26-46)** ***16-32 (21-38)***
After Dose 3 and/or **During 5 years of age**	**148 120**	**37 (43)** **28 (33)**	**25 (29)** **19 (22)**	**18-35 (21-39)** ***13-27 (15-31)***
After Dose 3 and/or **During 6 years of age**	**148 120**	**42 (43)** ***34 (35)***	**28 (29)** ***23 (24)***	**21-38 (21-39)** ***16-32 (17-33)***
After Dose 3 and/or **During 7 years of age**	**148 120**	**45 (51)** ***33 (38)***	**30 (34)** ***22 (26)***	**22-41 (26-45)** ***15-31 (18-35)***
After Dose 3 and/or **During 8 years of age**	**148 120**	**62 (68)** ***50 (55)***	**42 (46)** ***34 (37)***	**32-54 (36-58)** ***25-45 (28-48)***
After Dose 3 and/or **During 9 years of age**	**148 120**	**45 (48)** ***35 (38)***	**30 (32)** ***24 (27)***	**22-41 (24-43)** ***16-33 (18-35)***
After Dose 3 and/or **During 10-11 years of age**	**168 320**	**14 (14)** ***13 (13)***	**8 (8)** ***8 (8)***	**5-14 (5-14)** ***4-13 (4-13)***

[8] At date for onset of cough, or if no cough at date for the positive sample, during the pertussis episode
[9] Age interval in the heading classifies the unimmunised children.

2.12 Lab. confirmed pertussis in children born Oct. 1, 1997 –Dec. 31, 2007

For children in this cohort there were 1 563 reports of laboratory confirmed pertussis in the database for episodes between October 1, 1997 and December 31, 2007, whereof 697 reports concern children without any pertussis vaccination prior to onset of the pertussis episode and 866 reports concerns children who had received at least one dose before the episode, Table 7.

Most children vaccinated with two or three doses and classified to the group named "Other vaccine /Mixed schedule" (106 children) were first vaccinated with Infanrix®, then with Pentavac®. The other 491 children with two or three doses prior to the episode were vaccinated with the same vaccine, Infanrix®/Infanrix-Polio+Hib® or Pentavac®, at all vaccinations.

Table 7 Laboratory confirmed cases of pertussis from October 1, 1997 until December 31, 2007, among children born October 1, 1997 until December 31, 2007 divided per birth-cohort, number of vaccine doses before episode and pertussis vaccine prior to the episode. (No. of cases with 21 or more days of spasmodic cough in parenthesis).

Birth-cohort	Number of doses of a pertussis vaccine	Not immunised No. (>=21)	Only Infanrix vaccine No. (>=21)	Only Pentavac vaccine No. (>=21)	Other vaccine/ Mixed vaccines No. (>=21)	Total No. (>=21)
1997.10 – 12	0	11	-	-	-	10 (10)
	1	-	4	-	0	4 (4)
	2	-	5	-	0	5 (4)
	3	-	27	-	1	28 (24)
1998	0	56	-	-	-	56 (49)
	1	-	19	7	0	26 (20)
	2	-	14	1	6	21 (15)
	3	-	62	28	62	152 (117)
1999	0	106	-	-	-	106 (96)
	1	-	14	30	1	45 (42)
	2	-	11	14	0	25 (18)
	3	-	36	48	10	94 (71)
2000	0	102				102 (97)
	1	-	15	17	0	32 (26)
	2	-	3	6	0	9 (7)
	3	-	31	36	8	75 (55)
2001	0	38				38 (36)
	1	-	1	13	1	15 (13)
	2	-	5	6	0	11 (7)
	3	-	11	30	4	45 (36)
2002	0	78				78 (73)
	1	-	12	24	0	36 (30)
	2	-	0	4	0	4 (4)
	3	-	8	20	3	31 (23)
2003	0	58	-	-	-	58 (49)
	1	-	9	7	0	16 (13)
	2	-	6	8	0	14 (11)
	3	-	18	5	5	28 (22)
2004	0	92				92 (81)
	1	-	31	14	1	46 (41)
	2	-	10	8	0	18 (14)
	3	-	8	6	5	19 (12)

2005	**0**	**65**	**-**	**-**	**-**	**65 (57)**
	1	**-**	**7**	**9**	**2**	**18 (16)**
	2	**-**	**1**	**3**	**0**	**4 (2)**
	3	**-**	**2**	**2**	**1**	**5 (4)**
2006	**0**	**56**	**-**	**-**	**-**	**56 (53)**
	1	**-**	**11**	**8**	**1**	**20 (18)**
	2	**-**	**2**	**5**	**1**	**8 (4)**
	3	**-**	**0**	**1**	**0**	**1 (0)**
2007	**0**	**35**	**-**	**-**	**-**	**35 (34)**
	1	**-**	**4**	**7**	**-**	**11 (10)**
	2	**-**	**0**	**0**	**0**	**0**
	3	**-**	**0**	**0**	**0**	**0**
Total	**0**	**697**	**-**	**-**	**-**	**697 (635)**
Total	**1**	**-**	**127 (113)**	**136 (114)**	**6 (6)**	**269 (233)**
Total	**2**	**-**	**57 (44)**	**55 (37)**	**7 (5)**	**119 (86)**
Total	**3**	**-**	**203 (161)**	**176 (130)**	**99 (73)**	**478 (364)**
Total	**0 – 3**	**697 (635)**	**387 (318)**	**367 (281)**	**112 (84)**	**1563 (1318)**

Among the 697 unimmunised children 491 (70%) were younger than 3 months at the onset of the episode, i.e. they started to cough before the scheduled first dose of acellular pertussis vaccine. Eighty were between 3 and 5 months of age, 29 between 5 and 12 months of age and 97 were older than 12 months at the onset.

Ninety-one percent of the unimmunised children had spasmodic cough for 21 or more days during the episode. For Infanrix®/Infanrix-Polio+Hib® and Pentavac® recipients the corresponding figures were 82%, and 77%, respectively.

2.13 Incidence in children born October 1, 1997 – December 31, 2007

Data on number of new-borns during 1997 until 2007, from Statistics Sweden (http://www.scb.se), have been used for person time of follow-up calculations. Detailed figures are presented in Appendix 1.

Altogether approximately 895 000 children have been followed for approximately 4 420 million years of follow-up from October, 1 1997 until December 31, 2007.

Table 8a and 8b gives the total number of person-months and laboratory confirmed pertussis cases divided in age/vaccination intervals.

Table 8a Children born from **October 1, 1997 until December 31, 2007** and followed from **October 1, 1997 until December 31, 2007** with observed Culture- or PCR-confirmed *B.pertussis*. We present - Person-years of follow-up, Number of laboratory confirmed cases, Incidence per 100,000 person years and 95% confidence interval in the following age-/vaccine-groups at onset of the pertussis episode; 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 after12 months of age (after Dose 3). In parenthesis figures including the unimmunised children of respective age group (intent to treat) are given. *In italics the corresponding figures for children who fulfilled the WHO case definition of 21 or more days of spasmodic cough (typical pertussis) are given.*

Onset of pertussis episode[10] occurred (in Vaccine-/Age-group[11])	Person-years of follow-up	Number of observed laboratory confirmed cases	Incidence per 100 000 person-years	95% confidence interval for incidence per 100 000 person-years
Before Dose 1 **During 0-<3 months of age**	**220 870**	**(491)** ***(441)***	**(222)** ***(200)***	**(203-243)** ***(182-219)***
Between Dose 1 and 2 or **During 3-<5 months of age**	**143 900**	**269 (349)** ***233 (305)***	**187 (243)** ***162 (212)***	**165-211 (218-270)** ***142-183 (189-236)***
Between Dose2 and 3 or **During 5-<12 months of age**	**482 570**	**119 (148)** ***86 (114)***	**25 (31)** ***18 (24)***	**20-29 (26-36)** ***14-22 (19-28)***
After Dose 3 and/or **After 1 year of age**	**3 572 115**	**478 (575)** ***364 (458)***	**13 (16)** ***10 (13)***	**12-15 (15-19)** ***9-11 (12-14)***

Table 8b Children born from **October 1, 1997 until December 31, 2007** and followed from **October 1, 1997 until December 31, 2007** - Person-years of follow-up etc. after Dose 3, or from 1 year of age for the unimmunised children, is divided in eight age intervals (see also legend to Table 8a).

Onset of pertussis episode occurred (in Vaccine-/Age-group)	Person-years of follow-up	Number of observed laboratory confirmed cases	Incidence per 100 000 person-years	95% confidence interval for incidence per 100 000 person-years
After Dose 3 and/or **During 1 year of age**	**751 495**	**60 (88)** ***44 (71)***	**8 (12)** ***6 (9)***	**6-10 (9-14)** ***4-8 (7-12)***
After Dose 3 and/or **During 2 years of age**	**658 165**	**68 (86)** ***53 (71)***	**10 (13)** ***8 (11)***	**8-13 (10-16)** ***6-11 (8-14)***
After Dose 3 and/or **During 3 years of age**	**567 010**	**55 (67)** ***40 (51)***	**10 (12)** ***7 (9)***	**7-13 (9-15)** ***5-10 (7-12)***
After Dose 3 and/or **During 4 years of age**	**476 695**	**59 (74)** ***40 (55)***	**12 (16)** **8 (12)**	**9-16 (12-19)** ***6-11 (9-15)***
After Dose 3 and/or **During 5 years of age**	**388 570**	**62 (72)** ***45 (54)***	**16 (19)** ***12 (14)***	**12-20 (14-23)** ***8-15 (10-18)***
After Dose 3 and/or **During 6 years of age**	**303 995**	**74 (82)** ***61 (69)***	**24 (27)** ***20 (23)***	**19-31 (21-33)** ***15-26 (18-29)***
After Dose 3 and/or **During 7 years of age**	**221 810**	**66 (70)** ***52 (56)***	**30 (32)** ***23 (25)***	**23-38 (25-40)** ***17-31 (19-33)***
After Dose 3 and/or **During 8-9 years of age**	**204 375**	**34 (36)** ***29 (31)***	**17 (18)** ***14 (15)***	**11-23 (12-24)** ***9-20 (10-22)***

Compared to Table 6b the incidence was at about the same for the first age-interval but lower for the others. The observed differences between the two cohorts might depend on variations of the general exposure to pertussis in Sweden during follow-up from 1997 to 2007 as described in Section 3, Figure 6b.

[10] At date for onset of cough, or if no cough at date for the positive sample, during the pertussis episode
[11] Age interval in the heading classifies the unimmunised children.

2.14 Caveats in estimating vaccine specific effectiveness

There are a number of caveats that need to be considered before any attempts are made to perform any vaccine specific estimates of effectiveness, some of them discussed in the study protocol, from 8 September 1997, page 8:

- *"The study is explorative, aiming at estimating the effectiveness of individual vaccines and the detection of potential changes in circulating* Bordetella *strains.*
- *The design is open and non-randomised, and case ascertainment based on routine surveillance of laboratory confirmed pertussis. Exposure to different pertussis vaccines varies with birth cohort and geographic areas. Therefore, comparisons between vaccines should be avoided and analyses of vaccine effectiveness should be limited to well defined age groups and locations.*
- *Statistical analysis should be carried out according to written plans approved by the advisory group."*

Data so far accumulated illustrate the difficulties inherent in routine surveillance. We have no control over the rate of ascertained cases in unimmunised versus vaccinated, nor in infants by age in months, or infants by number of received doses.

Data suggest progressive underreporting of cases with increasing age and number of doses rendering any estimates of effectiveness inflated as compared to vaccine efficacy estimates obtained in randomised placebo controlled trials. In fact, the underreporting of cases among vaccinated children may well obscure any true differences between vaccines.

Therefore, data from the present surveillance scheme should only be used for an overall assessment of changes in pertussis incidence after reintroduction of pertussis vaccine, and do not permit comparisons between vaccines. To avoid undue comparisons between vaccines the advisory group agreed at a meeting in Stockholm 12 April 2002 that a separate Appendix 2 should be prepared for vaccine specific data for each manufacturer to be used for internal distribution and submissions to regulatory bodies.

There are other constraints secondary to the underreporting of cases among vaccinated children. The counties are free to change vaccines when a new tender is due, the possibility to accumulate sufficient person months of follow up may thus be hampered. We should also expect the pertussis incidence to decline further as more birth cohorts are vaccinated. Finally, the recently implemented school booster will add complexity to the analysis.

2.15 Laboratory confirmed pertussis in previous trial cohorts

The following tables, 9a-c, summarises the number of cases reported among Trial I children born 1992, and among children born 1993.6-1994.5 who participated in Trial II.

Table 9a reports laboratory confirmed cases of pertussis during follow-up period from October 1, 1997 until December 31, 2007 among children with 3 or 4 doses before onset of cough. During ten-year of follow-up there were 9 more cases in the Trial II cohort compared to the nine-year report. In all there were 258 cases of laboratory confirmed pertussis participants in Trial I and Trial II who had received 3 trial doses. Tables 9a and 9b include children vaccinated in either a 2, 4 and 6 or a 3, 5 and 12 months schedule

The overall incidence was 29 per 100,000 person years of follow-up (Table 9b). The trial participants were between 4 and 14 years old during the follow-up period and received the primary series of pertussis vaccine before 1 year of age. Due to poor efficacy shown in Trial I, US DTPw, and in both trials, DTPa2, the recipients of these vaccines were offered a fourth dose of acellular pertussis vaccines. The overall pertussis incidence for the trial children was similar to the incidence observed between dose 2 and 3, but higher than that measured after dose 3, among children born from 1996 until December 31,2007, Table A. Interestingly, the estimated incidence after four doses in the DTPa2 trial arm (19/100 000 person years) in Trial II was in the lower range of the three vaccines, DTPa3, DTPa5 and DTPw, all shown to be efficacious in Trial II. Among the three, the five-component vaccine had the highest incidence (36/100 000 person years)

Table 9a Laboratory confirmed cases among participants in Trial I and Trial II

Trial vaccines	1997 Q4	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	Total
Trial I												
3d CLI DTPw	0	0	0	1	0	1	0	0	0	0	0	2
3d CLI DTPw + 1 d. CLL Pa5	0	0	0	0	0	0	0	0	0	0	0	0
3d GSK DTPa2	0	0	1	0	0	0	0	0	0	1	0	2
3d GSK DTPa2 + 1 d. GSK Pa3	0	1	1	0	1	0	0	1	0	0	0	4
3d CLL DTPa5	1	1	1	4	2	1	0	1	0	0	0	11
Sum	1	2	3	5	3	2	0	2	0	1	0	19
Trial II												
3d Evans DTPw	0	4	18	4	3	3	4	6	2	3	2	49
3d GSK DTPa2	0	6	5	5	1	1	0	6	7	3	0	34
3d GSK DTPa2 + 1 d. GSK Pa3	3	4	8	8	4	0	0	0	0	0	0	27
3d Chiron DTPa3	1	5	11	18	6	2	1	5	3	2	0	54
3d CLL DTPa5	4	6	18	18	6	4	3	4	6	4	2	75
Sum	8	25	60	53	20	10	8	21	18	7	4	239
Total Trials I & II	9	27	63	58	23	12	8	23	18	13	4	258

Table 9b No. of laboratory confirmed cases among participants in Trial I and Trial II from October 1, 1997 until December 31, 2007 (see Table 9a), no. of fully vaccinated children (3 doses at either 2-4-6 or 3-5-12 months), estimated person years of follow up, and incidence per 100 000 person years of follow up during the ten year period.

Trial vaccines	Enrolled children	Person years of follow-up	No. of laboratory confirmed cases	Incidence/ 100 000 person years	95% c.i.
Trial I					
3d CLI DTPw +/-1 d. CLL Pa5	2 001	20 510	2	10	1 - 35
3d GSK DTPa2 +/-1 d. GSK Pa3	2 538	26 015	6	23	8 - 50
3d CLL DTPa5,	2 551	26 150	11	42	21 - 75
Trial II					
3d Evans DTPw	19 971	204 705	49	24	18 - 32
3d GSK DTPa2	6 444	66 050	34	51	36 - 72
3d GSK DTPa2 + 1 d. GSK Pa3	13 731	140 745	27	19	13 - 28
3d Chiron DTPa3	20 239	207 450	54	26	20 - 34
3d CLL DTPa5	20 230	207 360	75	36	28 - 45
Total Trials I & II	87 705	898 985	258	29	25 - 32

Table 9c shows the incidence figures during the ten-year follow up for children immunized at 3, 5 and 12 months of age in Trial II. The overall rate varies from 20/100 000 in the DTPw group compared to 27-49 /100 000 in the DTPa groups who had received three doses of a pertussis vaccine. It also demonstrates the relative risk of pertussis for acellular vaccine recipients compared to recipients of the British whole cell vaccine Evans DTPw.

Comparing recipients of 3doses CLL DTPa5 or 3doses Chiron DTPa3 with recipients of 3doses Evans DTPw gave the following result, RR=1.47 (1.01 – 2.14).

Table 9c Number of culture- or PCR-confirmed pertussis cases and incidence per 100 000 person years of follow up among participants who had followed the 3, 5, 12 months schedule in the 1993-96 randomised controlled pertussis vaccine trial [3] reported from October 1, 1997 until December 31, 2007 at 3 to 14 years of age. Relative risks are given for acellular vaccine recipients compared to recipients of the British whole cell vaccine Evans DTPw.

Trial cohort (vaccines)	No of children	Person years of follow-up	No. of laboratory confirmed cases	Incidence/ 100 000 PY 95% confidence intervals	RR 95% confidence intervals
3d Evans DTPw	**17 495**	**179 325**	**36**	**20** **14 - 28**	**1.00**
3d GSK DTPa2	**5 542**	**56 805**	**28**	**49** **32 - 71**	*2.46* **1.50 –4.02**
3d GSK DTPa2 + 1 d. GSK Pa3	**12 122**	**124 250**	**20**	**16** **10- 25**	*0.80* **0.46 – 1.39**
3d Chiron DTPa3	**17 739**	**181 825**	**49**	**27** **20 - 36**	*1.34* **0.87 – 2.06**
3d CLL DTPa5	**17 728**	**181 710**	**58**	**32** **24 - 41**	*1.59* **1.05 – 2.41**
Total Trial II	**70 626**	**723 915**	**191**	**26** **23 - 30**	

2.16 Hospital admission for pertussis

Data on hospitalisation, defined as at least one night at hospital due to the pertussis disease during the episode, was available for 2 036 of 2 042 children born from 1996 until December 31, 2007 (see section 2.4). Five hundred and twenty-four (26%) of the children had a hospital admission during the pertussis episode and 1 512 had none.

2.16.1 Hospital admission and age at the pertussis episode

In all 357 of 497 infants (72%), who were below 3 months of age at start of the pertussis episode, were hospitalised. The corresponding rates, regardless of vaccination status at the episode, for 291 children in age-group 3-<5 months, for 221 children in age-group 5-<12 months and for 1 027 children from 12 months of age at the beginning of the pertussis episode were respectively 38%, 16% and 2% (Table 10).

Age specific incidence rates of hospitalisation due to pertussis per 100 000 years of follow up in the four age groups are shown in Figure 2 (lower curve). For comparison the figure also gives the age specific incidence rates for all pertussis (upper curve). Person time of follow up for incidence calculations for the four age groups was taken from Table A in the execute summary.

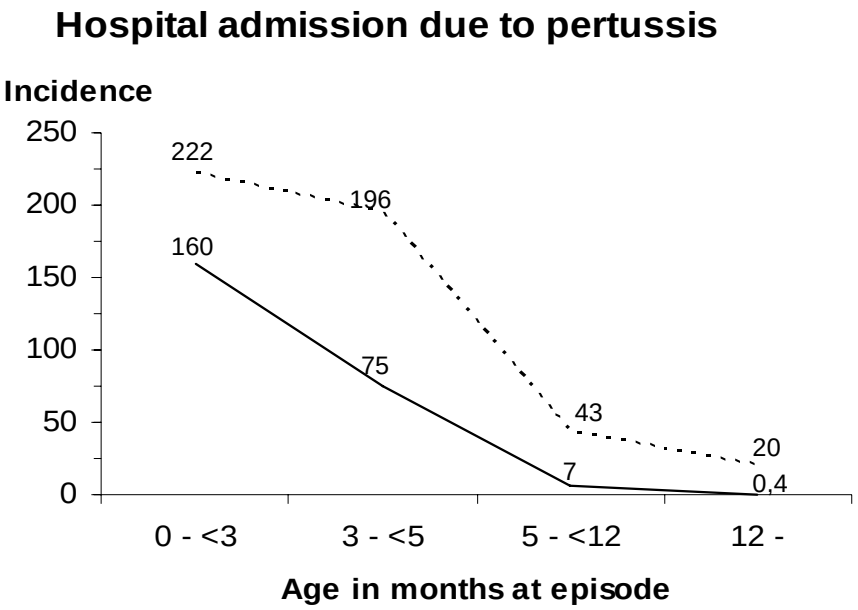

Figure 2 Age specific incidence of hospital admission due to the pertussis disease, below, and age specific incidence of all pertussis per 100 000 years of follow-up regardless of vaccination status for children born from 1996 to December 31, 2007 with a laboratory confirmed *B. pertussis* reported during g surveillance from October 1, 1997 until December 31, 2007.

The age specific incidence rate of hospitalisation due to pertussis is highest, 160 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.

Thus, there is a strong association between age of child at beginning of the pertussis episode and, if a pertussis disease, the risk of also suffering a hospital admission due to the disease, suggesting that circulating pertussis in the country has not decreased to a level that offers sufficient protection for the youngest, nearly always, unimmunised infant.

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

Hospital admissions were also studied in relation to age, duration of hospital stay as well as vaccination status at start of the pertussis episode. Detailed data are given in Table 10.

The rate of hospital admission among unimmunised children aged 0-30, 31-60 and 61-90 days at beginning of the pertussis episode was 86%, 72% and 61% respectively, and drops to only 3% for unimmunised children above one year of age. For unimmunised children between 3-<5 and 5-<12 months of age the rate of hospital admission was still 45% respectively 39%. This downward trend by age in hospitalisation rate was also observed for vaccinated children, both for children vaccinated with only one dose and for children who have received two or more doses of a pertussis vaccine before the pertussis episode, but the hospitalisation rates are lower when compared to those for the unvaccinated children.

The overall rate of hospital admission for unimmunised children was 54%. For those children at about 47% of the hospital admissions had a duration longer than one week - this proportion was even higher among the very young. Regardless of age the rate of hospitalisation for children vaccinated with one dose was 31%, with at about 25% of the admissions longer than a week, , and for children vaccinated with 2 or more doses before the pertussis episode 3%, with 11% of these admissions longer than a week. However, this "striking" association between rate of hospital admission and vaccination status before the episode was confounded by age. For, e.g., children >=12- months of age, the rate of hospital admission was low and "independent" of the vaccination status of the child.

Table 10 Duration of hospital stay due to the pertussis disease among children born from 1996 until December 31 2007, during surveillance from October 1, 1997 until December 31, 2007, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

Number of doses of a pertussis vaccine prior to the episode			Age of child at beginning of the pertussis episode							Total no. of children
			0-30 days	31-60 days	61-90 days	91-150 days	151-180 days	181-365 days	366- days	
Unimmunised children	**Duration of hospital stay**	**0 days**	18	53	68	46	3	16	139	**343**
		1-7 days	44	73	70	22	4	4	2	**219**
		8- days	66	65	38	16	2	2	2	**191**
	Total number of children		**128**	**191**	**176**	**84**	**9**	**22**	**143**	**753**
	Total no. and rate of children with a hospital stay		***110*** ***86%***	***138*** ***72%***	***108*** ***61%***	***38*** ***45%***	***6*** ***67%***	***6*** ***27%***	***4*** ***3%***	***410*** ***54%***
Children vaccinated with one dose	**Duration of hospital stay**	**0 days**	-	-	1	133	39	14	5	**192**
		1-7 days	-	-	1	54	7	2	1	**65**
		8- days	-	-	0	20	1	0	0	**21**
	Total number of children		-	-	**2**	**207**	**47**	**16**	**6**	**278**
	Total no. and rate of children with a hospital stay		-	-	***1*** ***50%***	***74*** ***36%***	***8*** ***17%***	***2*** ***13%***	***1*** ***17%***	***86*** ***31%***
Children vaccinated with two or more doses	**Duration of hospital stay**	**0 days**	-	-	-	-	14	99	864	**977**
		1-7 days	-	-	-	-	1	11	13	**25**
		8- days	-	-	-	-	0	2	1	**3**
	Total number of children		-	-	-	-	**15**	**112**	**878**	**1 005**
	Total no. and rate of children with a hospital stay		-	-	-	-	***1*** ***7%***	***13*** ***12%***	***14*** ***2%***	***28*** ***3%***
All children regardless of vaccination status	**Duration of hospital stay**	**0 days**	18	53	69	179	56	129	1 008	**1 512**
		1-7 days	44	73	71	76	12	17	16	**309**
		8- days	66	65	38	36	3	4	3	**215**
	Total number of children		**128**	**191**	**178**	**291**	**71**	**150**	**1 027**	**2 036**
	Total no. and rate of children with a hospital stay		***110*** ***86%***	***138*** ***72%***	***109*** ***61%***	***112*** ***38%***	***15*** ***21%***	***21*** ***14%***	***19*** ***2%***	***524*** ***26%***

Finally: Comparing hospitalisations among unimmunised children with those who had been given one dose of a pertussis vaccine before the episode in a comparable age group - the age interval between 3 and 12 months of age at beginning of the pertussis episode - we like to make attention to the following results:

1. The median (mean) age at start of episode was 109 (145) days and 127 (132) days for 115 unvaccinated respectively for 270 children vaccinated with one dose before the episode. Thus the two groups are "comparable" in age.

2. We have 43% and 31% of the children with a hospital admission for unimmunised respectively for vaccinated with one dose during the pertussis episode which occurred in the age interval. This difference was statistically significant (p<0,025).
3. Given a hospital admission due to a pertussis disease at 3-<12 months of age, 40% and 25% of the admissions have a duration longer than a week for unimmunised and vaccinated children with one dose respectively. This difference was not statistically significant (0,05<p<0,10).

These results together might indicate that, if the child has received a pertussis disease, there may be some protection against "severe" pertussis, expressed as a hospitalisation due to the disease, already after one dose of a pertussis vaccine.

In summary: There was a strong association between age of child at beginning of the pertussis episode and also an association between vaccination status of the child before the episode and the risk of a hospitalisation due to the disease. The same conclusion holds for the duration of the hospital stay and age.

2.17 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 2 035 of the 2 042 children born January 1, 1996 until December 31, 2007 with vaccination and follow-up information. A respiratory complication (with apnea, n=155, or without apnea, n=165) was reported for 320 (16%) and a dehydration for 180 (9%) of the children. Uncommon complications, i.e. neurological and other serious complications, were reported for 10 (0,5%) and 2 (0,1%) of the children respectively.

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. Four hundred and eighteen children (20,5%) had at least one complication due to the pertussis disease during their pertussis episode and 1 617 (79,5%) had no complication at all.

2.17.1 Any complication and age at the pertussis episode

In all 221 of 497 children (45%), who were below 3 months of age at beginning of the episode, had at least one complication. The corresponding rates for 291 children in age-group 3-<5 months, for 221 children in age-group 5-<12 months and for 1 026 children aged 12- months at the beginning of the pertussis episode were 21%, 15% and 10% (Table 11).

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 3 (lower curve). For comparison the figure also gives the age specific incidence rates for all pertussis (upper curve).

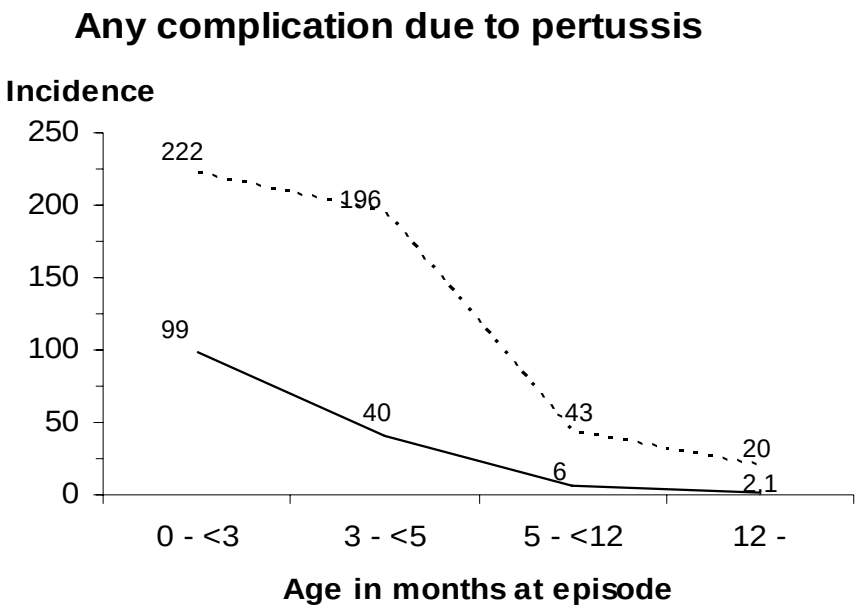

Figure 3 Age specific incidence of any complication due to the pertussis disease, below, and age specific incidence of all pertussis per 100,000 years of follow-up regardless of vaccination status for children born from January 1, 1996 to December 31, 2007 with a laboratory confirmed *B. pertussis* reported during surveillance from October 1, 1997 until December 31, 2007.

The age specific incidence rate of any complication due to pertussis is highest, 99 per 100,000 years of follow-up, for children 0-<3 months of age and decreases, by increasing age, to less than 3 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.

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

The events "any complication" were studied in relation to age as well as vaccination status at beginning of the pertussis episode. Detailed data are given in Table 11.

For unimmunised children aged 0-30, 31-60 and 61-90 days at the beginning of the pertussis episode the complication rates was 57%, 45% and 37% respectively, and drops to 11% for children above one year of age. For children between 3-<5 and 5-<12 months of age the rate of any complication was 25% and 35% - for the combined age group it was 28%. Thus, for the unimmunised children there was a strong association between rate of any complication due to the disease and age of child at beginning of the pertussis episode. This downward trend by increasing age is 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. Thus, the downward rate by age, noted regardless of vaccination status of the child in the preceding section, was due to the unimmunised children.

The overall rate of any complication for unimmunised children was 36%. Regardless of age the rate of any complication for children vaccinated with one dose was 19%, and 10% for children vaccinated with 2 or more doses before the pertussis episode ($p<0.001$). This significant difference was confounded by age. For the oldest children the rate of any complication was at about 10 to 11% both for unimmunised children and children vaccinated with two or more doses. In the age interval 5-<12 months at the episode, the complication rate was 35% for unimmunised children, 14% for vaccinated with one dose and 10% for children vaccinated with 2 or more doses prior to the episode. This downward "trend" in rate by number of doses prior to the pertussis episode was statistically significant, $p<0.001$.

Table 11 Any complication due to the pertussis disease among children born from January 1, 1996 until December 31, 2007, during surveillance from October 1, 1997 until December 31, 2007, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

Number of doses of a pertussis vaccine prior to the episode			Age of child at beginning of the pertussis episode							Total no. of children
			0-30 days	31-60 days	61-90 days	91-150 days	151-180 days	181-365 days	366- days	
Unimmunised children	**Any complication**	**No**	55	110	111	63	6	14	126	**485**
		Yes	73	81	65	21	3	8	16	**267**
	Total number of children		**128**	**191**	**176**	**84**	**9**	**22**	**142**	**752**
	Rate of children with any complication		***57%***	***42%***	***37%***	***25%***	***33%***	***36%***	***11%***	***36%***
Children vaccinated with one dose	**Any complication**	**No**	-	-	0	168	40	14	4	**226**
		Yes	-	-	2	39	7	2	2	**52**
	Total number of children		-	-	**2**	**207**	**47**	**16**	**6**	**278**
	Rate of children with any complication		-	-	***100%***	***19%***	***15%***	***13%***	***33%***	***19%***
Children vaccinated with two or more doses	**Any complication**	**No**	-	-	-	-	15	99	792	**906**
		Yes	-	-	-	-	0	13	86	**99**
	Total number of children		-	-	-	-	**15**	**112**	**878**	**1 005**
	Rate of children with any complication		-	-	-	-	***0%***	***12%***	***10%***	***10%***
All children regardless of vaccination status	**Any complication**	**No**	55	110	111	231	61	127	922	**1 617**
		Yes	73	81	67	60	10	23	104	**418**
	Total number of children		**128**	**191**	**178**	**291**	**71**	**150**	**1 026**	**2 035**
	Rate of children with any complication		***57%***	***42%***	***38%***	***21%***	***14%***	***15%***	***10%***	***21%***

Finally: Comparing any complication among unimmunised children with those who had been given one dose of a pertussis vaccine before the episode in a comparable age group - the age interval between 3 and 12 months of age at beginning of the pertussis episode - we will make attention to the following results:

1. The median (mean) age at start of episode was 109 (145) days and 127 (132) days for 115 unvaccinated respectively for 270 children vaccinated with one dose before the episode. Thus the two groups are "comparable" in age.
2. We have 28% and 18% of the children with a hospital admission for unimmunised respectively for vaccinated with one dose during the pertussis episode which occurred in the age interval. This difference was statistically significant ($p<0,05$).

These results together might indicate that, if the child has received a pertussis disease, there was some protection against "severe" pertussis, expressed as any complication due to the disease, already after one dose of a pertussis vaccine.

In summary: There was a strong association between age at the beginning of the pertussis episode and the risk of a complication due to the disease for an unimmunised child. There was also an association between vaccination status before the episode and the risk of any complication.

Finally (and for obvious reasons), there was also a strong association between any complication and a hospital stay during the pertussis episode. Seventy-two percent, 300 of 418, of children with at least one complication also had a hospital admission due to the disease during the episode. For 1 617 children without any complication the hospitalisation rate was 14% ($p<0.001$). For children with any complication at about 51% of the hospital admissions had a duration of 8 days or longer. For children without any complication 27% of the hospital admissions were longer than 8 days ($p<0.001$).

2.17.3 Deceased children

In addition there were eight deaths among unvaccinated infants and one death in a vaccinated 2 y old child with severe underlying disease. The parents of these children were not contacted within the project and only limited information, obtained from medical personnel, is available. Five infants were full term and 4 were born before gestational week 37. Ages at death among were from 1-3 months (full term) and from 3-6 months (premature). The one deceased at 6 months fell ill with pertussis at about 3-4 months).

2.18 Spasmodic cough during the pertussis episode

Data on cough and spasmodic cough were available for all 2 042 children born January 1, 1996 until December 31, 2007. All children but 3 were coughing during their pertussis episode. One thousand eight hundred and twenty-four (89,3%) of the children had spasmodic cough during the pertussis episode and 218 (10,7%) reported no spasmodic cough. Spasmodic cough for 21 or more days during the pertussis episode was reported for 83,2% of the children.

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

In all 447 of 498 infants (90%), who were below 3 months of age at start of the pertussis episode, had spasmodic cough for 21 days or longer. The corresponding rates for 291 children in age-group 3-<5 months, for 222 children in age-group 5-<12 months and for 1 031 children aged 12- months at the beginning of the pertussis episode were 87%, 78% and 80% (Table 12).

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 4 (lower curve), and age specific incidence rates for all pertussis (upper curve).

The age specific incidence rate of pertussis with 21 or more days of spasmodic cough was highest, 200 per 100,000 years of follow-up, for children 0 to <3 months of age and decreases to 16 per 100,000 years for children above one year of age at the pertussis episode.

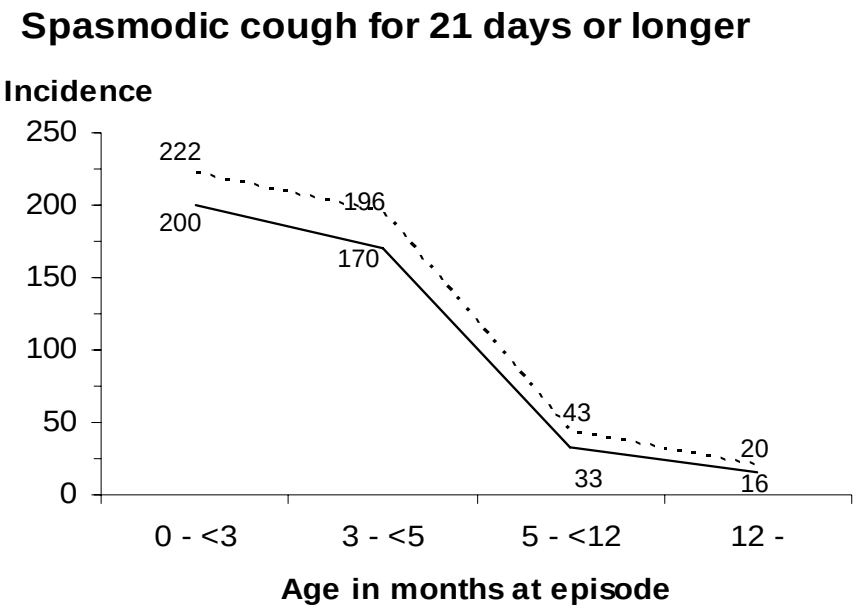

Figure 4 Age specific incidence of spasmodic cough for 21 or more days due to the pertussis disease, below, and age specific incidence of all pertussis per 100,000 years of follow-up regardless of vaccination status for children born from January 1, 1996 to December 31, 2007 with a laboratory confirmed *B. pertussis* reported from October 1, 1997 until December 31, 2007.

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

Duration of spasmodic cough for 21 days or longer was also studied in relation to age as well as vaccination status at start of the pertussis episode. Detailed data are given in Table 12.

Table 12 Duration of spasmodic cough due to the pertussis disease among children born from January 1, 1996 until December 31, 2007, during surveillance from October 1, 1997 until December 31, 2007, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

Number of doses of a pertussis vaccine prior to the episode			**Age of child at beginning of the pertussis episode**							**Total no. of children**
			0-30 days	**31-60 days**	**61-90 days**	**91-150 days**	**151-180 days**	**181-365 days**	**366- days**	
Unimmunised children	**Duration of spasmodic cough**	**0 days**	5	7	10	2	0	0	5	**29**
		1-20 days	4	18	7	7	0	2	2	**40**
		21- days	119	167	159	75	9	20	136	**685**
	Total number of children		**128**	**192**	**176**	**84**	**9**	**22**	**143**	**754**
	Rate of children with spasmodic cough for 21 days or longer		***93%***	***87%***	***90%***	***89%***	***100%***	***91%***	***95%***	***91%***
Children vaccinated with one dose	**Duration of spasmodic cough**	**0 days**	-	-	0	10	4	0	0	**14**
		1-20 days	-	-	0	20	2	2	0	**24**
		21- days	-	-	2	177	41	14	6	**240**
	Total number of children		-	-	**2**	**207**	**47**	**16**	**6**	**278**

	Rate of children with spasmodic cough for 21 days or longer		-	-	***100%***	***86%***	***87%***	***88%***	***100%***	***86%***
Children vaccinated with two or more doses	**Duration of spasmodic cough**	**0 days**	-	-	-	-	2	20	153	**175**
		1-20 days	-	-	-	-	0	17	45	**62**
		21- days	-	-	-	-	13	76	684	**773**
	Total number of children		-	-	-	-	**15**	**113**	**882**	**1 010**
	Rate of children with spasmodic cough for 21 days or longer		-	-	-	-	***87%***	***67%***	***78%***	***77%***
All children regardless of vaccination status	**Duration of spasmodic cough**	**0 days**	5	7	10	12	6	20	158	**218**
		1-20 days	4	18	7	27	2	21	47	**126**
		21- days	119	167	161	252	63	110	826	**1 698**
	Total number of children		**128**	**192**	**178**	**291**	**71**	**151**	**1 031**	**2 042**
	Rate of children with spasmodic cough for 21 days or longer		***93%***	***87%***	***90%***	***87%***	***89%***	***73%***	***80%***	***83%***

The rate of episodes with 21 or more days of spasmodic cough among unimmunised children varied slightly around 90% for the different age groups. The overall rate for unimmunised children was *91%*. Neither were there any downward trends by age in this rate for the vaccinated children. Regardless of age the rate of children with 21 or more days of spasmodic cough among vaccinated with one dose was 86% and among those vaccinated with 2 or more doses *77%*. This downward "trend" in rate of a long duration of spasmodic cough by number of doses of a pertussis vaccine before the episode was statistically significant, $p<0.001$.

2.19 Duration of cough, spasmodic cough and antibiotic treatment

As stated in section 2.18, data on cough and spasmodic cough were available for all 2 042 children born from January 1, 1996 until December 31, 2007, whereof 1 011 were infants. All children but 3 were coughing during their pertussis episode, including 2 infants.

Applying the EU and current WHO clinical case definition of pertussis with 2 weeks of more of coughing (any type) in conjunction with positive laboratory sample, in all 1 999/2 042 (97,9%) would fulfil this definition. Among the 43 cases that would not fulfil the EU or WHO definitions, 21 were infants and 22 children aged 1-6 years. All but two of those infants had received erythromycin or trimetoprim-sulfametoxazol, whereas fourteen of the 22 children aged 1-6 years were treated with antibiotics. Seven of those infants were unvaccinated, 3 had received one dose and 11 had received two doses. One child aged one year had received only two doses and the remaining children aged 1-6 years had received three doses.

2.19.1 Duration of cough, spasmodic cough and antibiotic treatment

There was information on antibiotic treatment, or not, including date at start of treatment for 2 034/2 042 children, including 1 008/1 011 infants. No treatment at all was reported for 700 children, whereof 147 were infants. Before further statistical analysis 28 treated cases with a short duration of treatment, 1 – 6 days with Erymax, were excluded. Most often the described treatment period was shortened due to diarrhoea etc.

In Table 13 result for; children aged 0-90 days at onset of the episode, without any pertussis vaccination prior to onset, 488 children; children aged 91-150 days at onset of the episode, with one dose of a pertussis vaccine prior to onset, 203 children; children aged 151-365 days at onset of the episode, with two

doses of a pertussis vaccine prior to onset, 123 children; and for children one year or older at onset of the episode, with three or more doses prior to onset, 843 children, in all 1 657 children was reported.

Table 13 Duration of cough and spasmodic cough due to the pertussis disease among infants born from January 1, 1996 until December 31, 2007 under surveillance from October 1, 1997 until December 31, 2007, by age at onset of cough and day for start of antibiotic treatment in relation to onset of pertussis episode.

Age at beginning of episode	Day after onset of cough for start of antibiotic treatment with Erytromycin etc. during the pertussis episode	Number of children	Duration, days of cough	Duration, days of spasmodic cough
			Median	Median
0-90 days	**No treatment**	**38**	**48**	**36,5**
	Early start, latest at day 6	***58***	***38***	***32,5***
	Start day 7 until day 13	163	45	38
	Late start, day 14 or later	229	49	38
	Total	**488**	**47**	**37**
91-150 days	**No treatment**	**39**	**47**	**35**
	Early start, latest at day 6	***17***	***40***	***25***
	Start day 7 until day 13	63	39	32
	Late start, day 14 or later	84	46	35,5
	Total	**203**	**44**	**34**
151-365 days	**No treatment**	**36**	**48**	**34,5**
	Early start, latest at day 6	***18***	***31***	***0***
	Start day 7 until day 13	27	35	25
	Late start, day 14 or later	42	40,5	31,5
	Total	**123**	**41**	**31**
1 year or older	**No treatment**	**448**	**46**	**33**
	Early start, latest at day 6	***41***	***32***	***19***
	Start day 7 until day 13	109	42	33
	Late start, day 14 or later	245	53	38
	Total	**843**	**46**	**34**
All ages	**No treatment**	**561**	**46**	**34**
	Early start, latest at day 6	***134***	***34***	***28,5***
	Start day 7 until day 13	362	43	35
	Late start, day 14 or later	600	49	37
	Total	**1 657**	**46**	**35**

An early start of the antibiotic treatment, within the first week (<=6 days) after onset of cough during the episode was, in all age groups, 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 for spasmodic cough.

Children below one year of age were in general treated with antibiotics, 701 (86%) of 814 children. The treatment rates in the age-groups 0-<3 months, 3-<5 months and 5-<12 months were respectively 92% (450/488), 81% (164/203) and 71% (87/123). Among those aged one year or more at onset of cough during the episode, 47% (395/843) children were treated.

3 Overall rates of pertussis in Sweden

3.1 Incidence changes over time

Since the introduction of acellular pertussis vaccination at 3, 5 and 12 months of age during 1996, there has been a decline in pertussis incidence in the Swedish population, Figure 5. The incidence in 2001- 2007, 5-11 years after the introduction of DTPa-containing vaccines, was at a level of the late 60:s and early 70:s, when the Swedish whole-cell vaccine program still was effective. The decline in incidence after 1996 seems to be more rapid than when DTPw was introduced during the 1950:s. One explanation might be that vaccination coverage in those days was only gradually rising, over decades, reaching 90 percent of the infants, whereas the coverage for DT in the 1990s already was more than 98% and the reintroduction of pertussis vaccination only meant a switch from DT to DTPa, Figure 10.

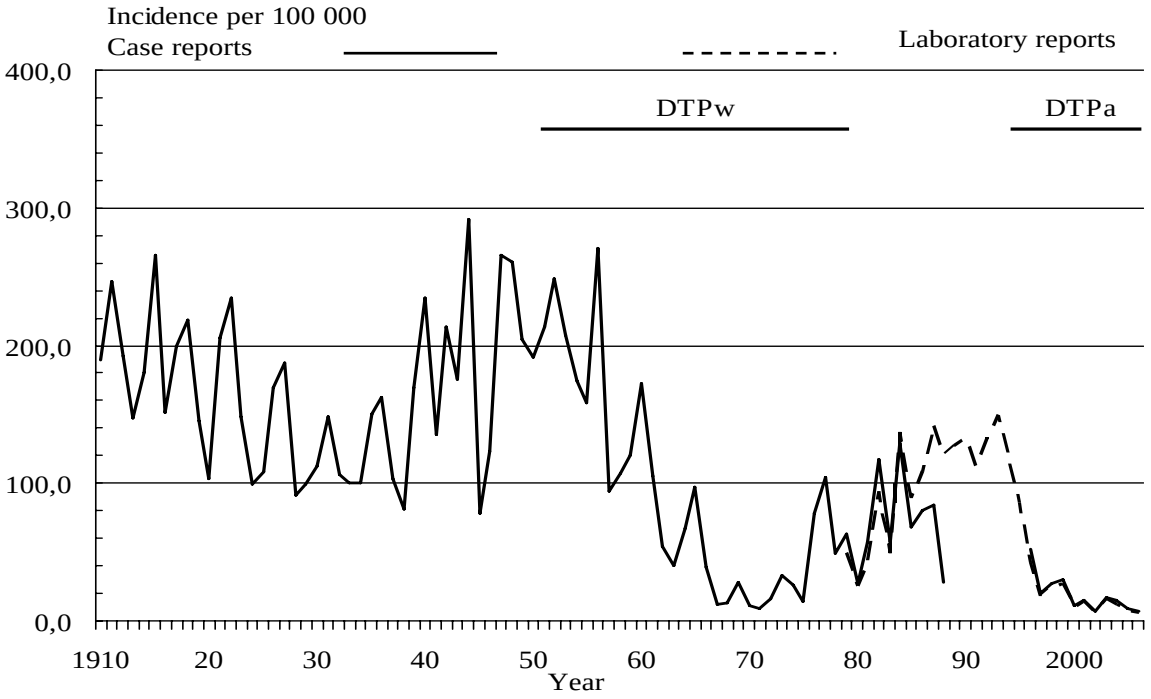

Figure 5 Pertussis incidence in Sweden. Sources: Case reports from general practitioners until mid 1980:s and according to the communicable disease act from 1997, lab-reports from 1980.

The overall incidence in the peak epidemic year 1994 was 150/100.000 population years, and dropped steadily to 17/100,000 in 1998. In the winter of 1999 and 2000 there was a minor peak to about 25 per 100,000, and thereafter there has been two additional minor national peaks, figure 5. Since 2001, the overall incidence is now 6-16 per 100,000 population years, Table 15A.

3.2 Changes in age-specific incidences of laboratory reported pertussis

The overall age specific incidences of laboratory reported pertussis in different age groups during the years before and after 1996 is illustrated in Figure 6 and 7,. Figure 6 represents mean age specific incidence during 10 years before and 11 years from 1996, with incidences in age-groups from 10 years and above enlarged in insertion, whereas figure 7 illustrates mean age-specific incidence during a three year-period (1992-94) before introduction of DTPa, during peak periods after 1996 (the calendar years 1999-2000, 2002 and 2004-2005) and during "ordinary" incidence periods after 1996 (1998, 2001+2003 and 2006-2007). Note that the mean incidences in the age groups 0-9 years include both vaccinated and unvaccinated children during the years 1998-2007.

For details about vaccinated cohorts, see Table15A, giving the age-specific incidences during the years 1986-95 and 1997-2007, with the corresponding numbers of laboratory reported pertussis in each age-group in Table 15B.

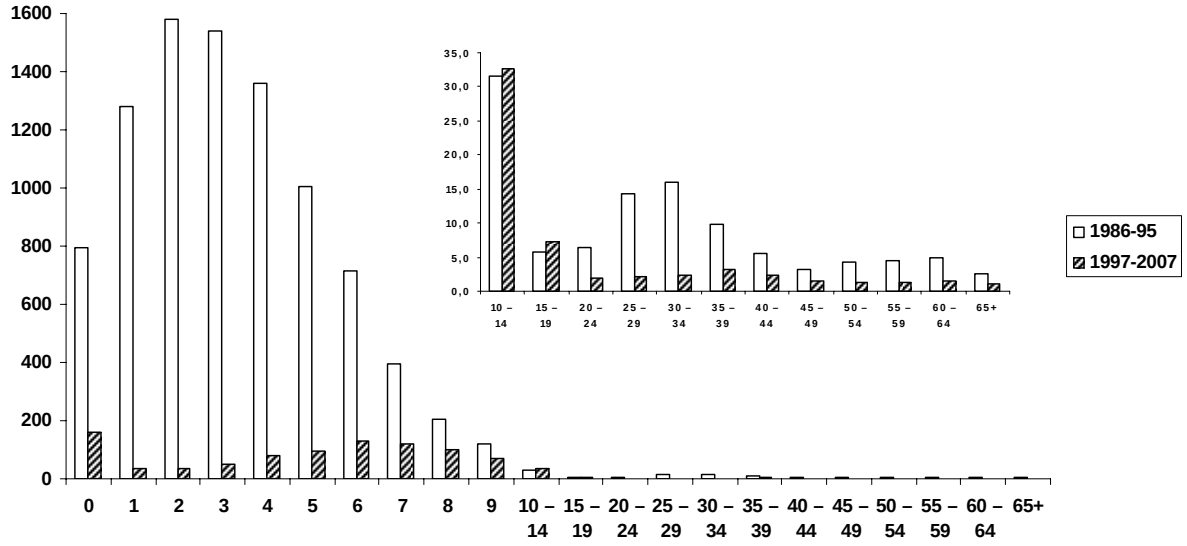

Figure 6 Mean incidence in defined age groups during 10 calendar years before (1986-95) before and 11 years after (1997-2007) introduction of DTPa in 1996. Enlarged curves for the age groups 10 years and above are shown in the insertion.

It is obvious that the vaccinated birth cohorts born 1996 or later had a much lower age specific incidence of laboratory confirmed cases of *B. pertussis* in pre-school and early school ages than had the corresponding age-groups before implementation of the Pa vaccination in infancy in 1996. The age specific incidence for pre-school children dropped from >1000 per 100,000 to approx. 100/100,000 in 1998-2000, to 50/100,000 in 2001 and further to approximately 20/100,000 in 2003, table 15A. During the latest years the rate has also dropped to below 100/100,000 among the nowadays vaccinated children during the first years in school. In unvaccinated 10-14 year-olds, however, the age-specific incidence remains about the same before and after introduction of acellular pertussis vaccine, whereas the incidence among young adults is reduced.

Also the reported incidence in unvaccinated age-groups is reduced after implementation, but less so in infancy. In fact, the age specific incidence below one year of age, for unvaccinated and not fully vaccinated infants, was above 100/100,000 person years until 2006, with a peak of 289/100,000 in 2005. In 2006-2007, the age-specific incidence in infancy for the first time was below 100/100,000 (Table 15A).

Interestingly, there are some differences after 1996 when comparing calendar years including "peak periods" with periods without increased incidence, Figure 7. The age-specific incidence among infants 0-11 months old was around 700/100,000 before 1996, decreasing to a mean of around 220/100,000 during peak periods after 1996, with lowest incidence of 90-120/100,000 during "non-peak periods" after 1996.

The decline in incidence among infants after 1996 is to a large extent explained by decreasing number of infant cases from 5-11 months, i.e. from the scheduled age of second dose of Pa. The mean number of infants with laboratory reported pertussis per age (in months) during infancy is illustrated in Figure 8, during three years before and during "peak" and "ordinary" incidence periods after introduction of acellular pertussis vaccination in infancy.

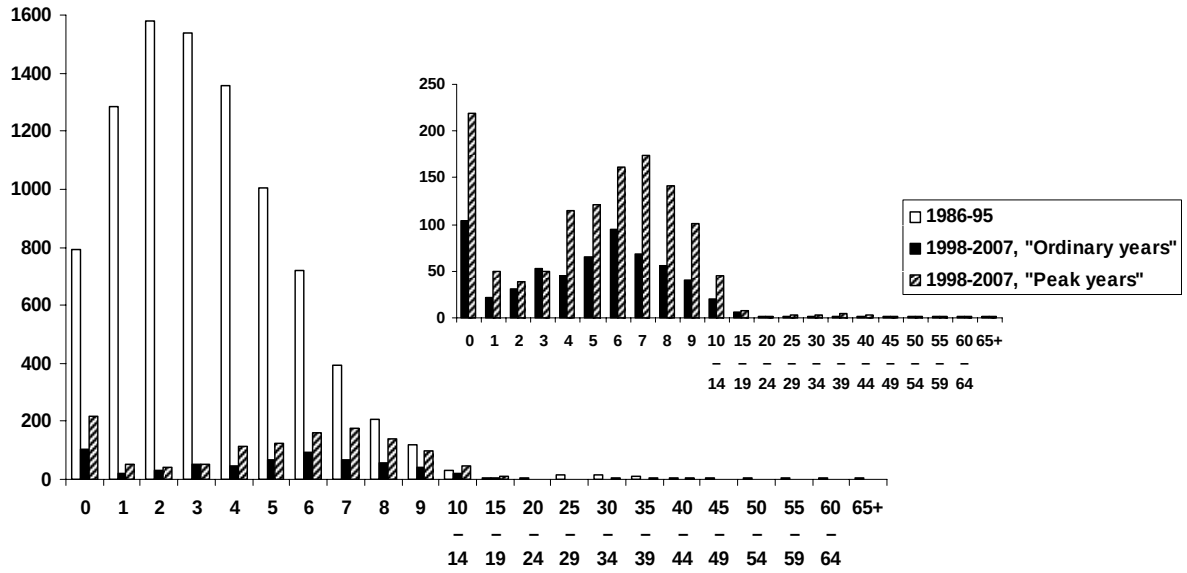

Figure 7 Mean incidence in defined age groups during three calendar years (1992-94) before introduction of DTPa, during "ordinary" incidence periods after 1996 (the calendar years 1998, 2001+2003 and 2006-2007) and during three peak periods after 1996 (the calendar years 1999-2000, 2002 and 2004-2005). Enlarged curves for the "ordinary" and "peak" periods are shown in the insertion.

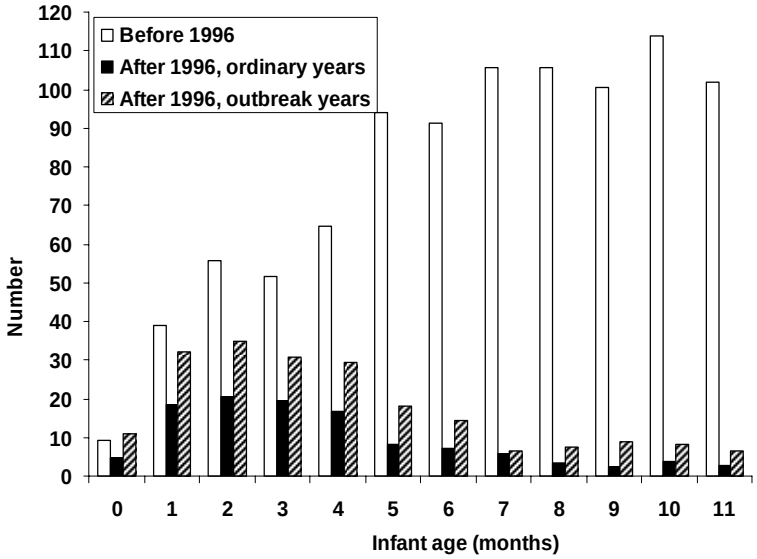

Figure 8 The mean number of infants with culture- or PCR-verified pertussis cases per month of age during 3 calendar years (1992-94) before and during 10 years after (1998-2007) introduction of DTPa in 1996. Mean incidence in defined age groups after 1996 is calculated for "ordinary" incidence periods after 1996 (the 5 calendar years 1998, 2001+2003 and 2006-2007) and during three peak periods after 1996 (the 5 calendar years 1999-2000, 2002 and 2004-2005).

3.3 Regional differences in incidence over time

At subnational (county) level there are undulations in the incidence, with variations in time between different areas. Figure 9 illustrates the geographic variations in reported pertussis (clinical and laboratory reported) cases during the years 1997-2006. There is no corresponding map from the year 2007 due to technical changes in the processing of data from the national register of communicable diseases.

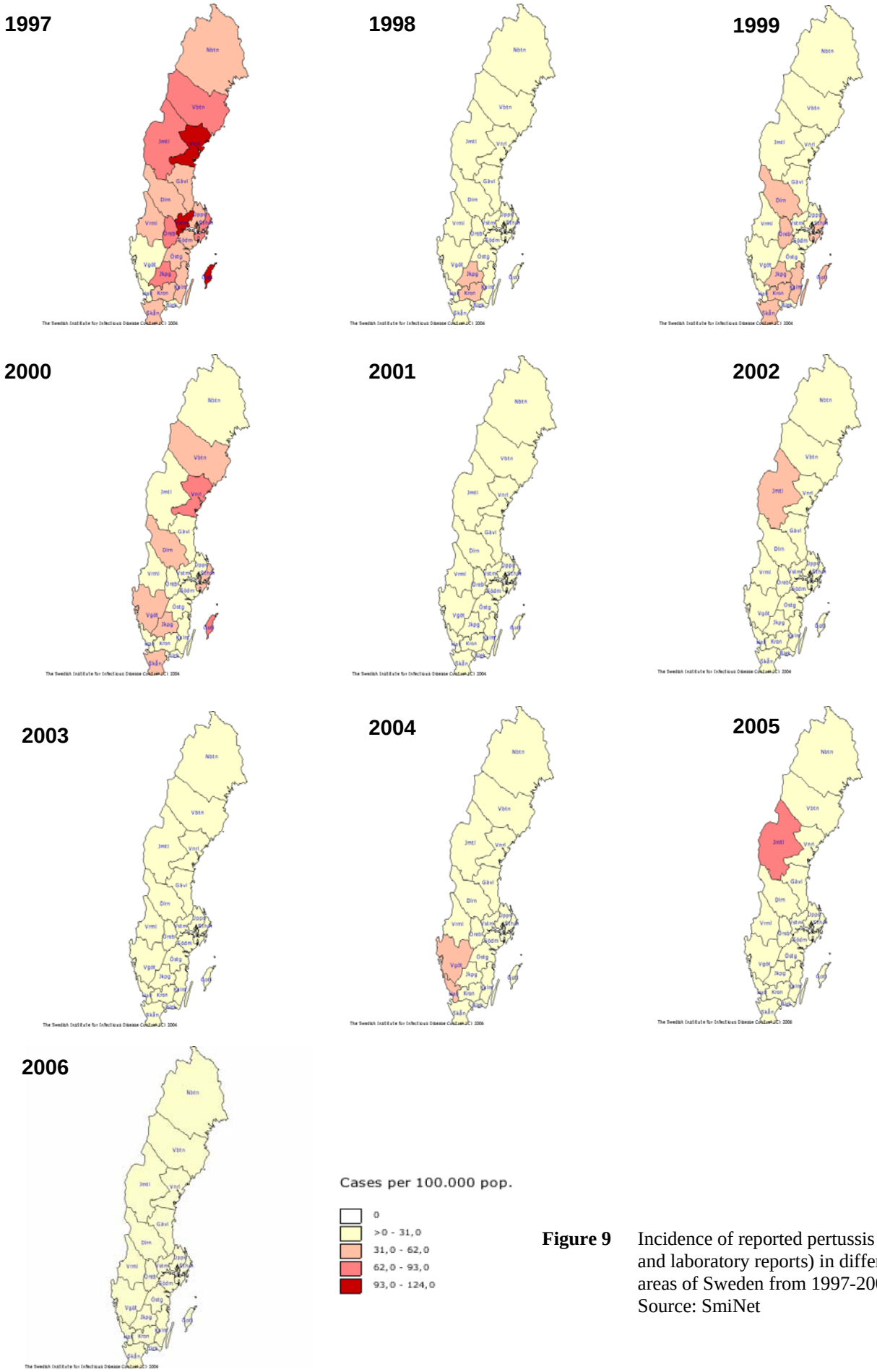

Figure 9 Incidence of reported pertussis (clinical and laboratory reports) in different areas of Sweden from 1997-2006. Source: SmiNet

3.4 Vaccination coverage and timing of doses

The large scale trials in children born 1991-1994 preceded the reintroduction of DTPa vaccines in 1996 and prepared the acceptance of pertussis vaccination.

The vaccination coverage rapidly reached more than 98.5%, Figure 10, and has remained at this level since then. With one exception the coverage at county level has been 97% or above in all counties and all cohorts born from 1996. The exception was a county in the north, where the overall coverage for the year 1996 was 93% because of a few months of delay in start of the DTPa program.

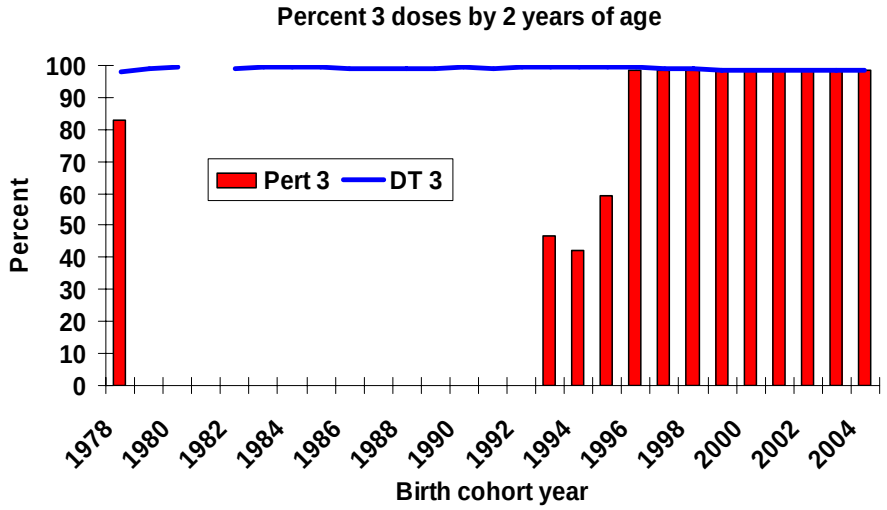

Figure 10 Vaccine coverage 1978-2004 for 3 doses DT P (source SMI Annual Reports).

The Swedish Child Health Care system evolved during the first half of last century, with at or above 99% of all children registered. The system is area-based and the nurses have statutory rights to handle the general part of the national vaccination program within their area. The consistency in adherence to the recommended schedule is illustrated in Figure 11, demonstrating the deviation from schedule day (Day 0) for the first three doses of Pa vaccination in all children followed within the enhanced surveillance.

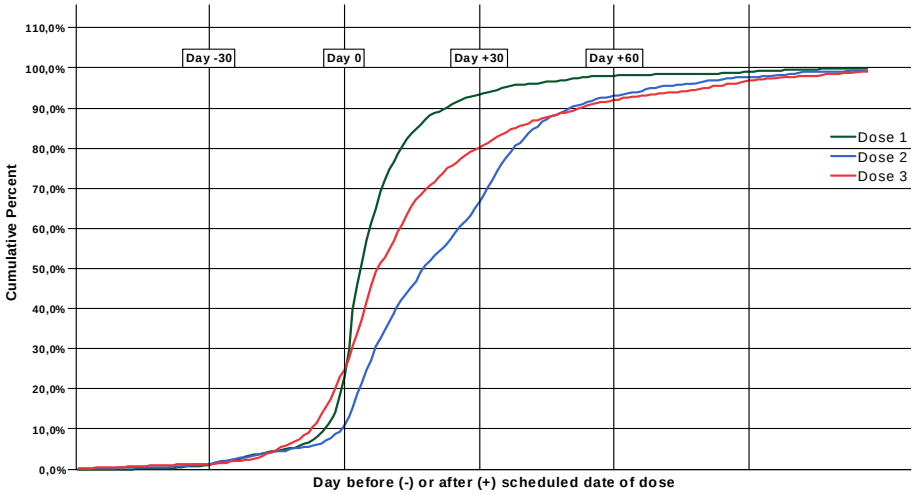

Figure 11 Cumulative proportion of children vaccinated in relation to scheduled day (Day 0) for the doses at 90 days, 150 days and 365 days, in children born from 1996 and until December 31, 2007, with a pertussis episode between October 1, 1997 and December 31, 2007.

The consistency over time is further illustrated in Table 14, comparing the median ages (in days) at dose 1-3 for children followed within the enhanced surveillance with the corresponding ages during the nation-wide Trial II in early 1990:s.

Table 14 Median age at dose 1-3 in Trial II (1993-94) and during the 1997-2006 enhanced surveillance period. The scheduled ages are 3-5-12 months, corresponding to 90, 150 and 365 days.

Median ages at vaccination (days)	Dose 1 (90 days)	Dose2 (150 days)	Dose 3 (365 days)
Trial 2 (n = 72,698 infants included in 3-5-12 mo schedule)	100	174	386
Surveillance project from 1997-2007 (children, exc.Göteborg, with vaccination data)	94	167	375

3.5 Catch-up and booster vaccinations

Infants born during the latter part of 1995 were vaccinated in most parts of the country, because the start of their vaccination program was delayed until the Pa vaccines were licensed in January 1996. At age 2 years, the overall 3-dose coverage for the 1995 cohort was 60%. Free catch-up vaccinations to more than 65,000 children born in the 1990:s were offered in the Göteborg area from 1997 to 1999 [6]. Children were vaccinated to some degree also in the rest of the country, but at the expense of the parents.

Some study children from Trial I-II [2, 3] were booster in early childhood (almost all children vaccinated with DTPw in Trial I, and almost all children vaccinated with DTPa2 in the two trials). Within other studies, minor groups of children were boosted at around 5-6 years during the 1990:s

The national vaccination calendar was changed in 2007 (cohorts born from 2002) to include a 4th dose of DT and Pa already at 5-6 years and furthermore to include a 5th dose at 14-16 years. Children born 1995-2001 receive a catch-up vaccination at 10 years of age since autumn 2005, when a fourth dose of DTPa was recommended at 10 years of age.

3.6 Case ascertainment

From 1997 cases may be reported either by clinicians, by microbiological laboratories or both ways. Figure 12 illustrates the number of pertussis cases reported per calendar year 1997-2007 on either clinical or laboratory basis, or both ways.

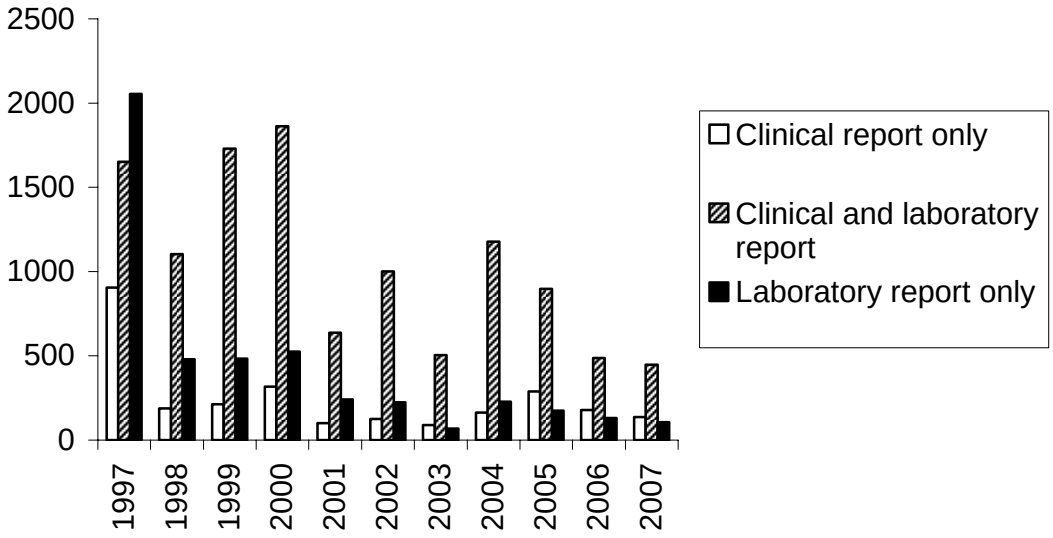

Figure 12 The number of reported pertussis cases 1997-2006; clinical reports only, combined clinical and laboratory reports, and laboratory reports only.

From 1998-2004 about 90% and from 2005 about 80% of the pertussis cases are reported from laboratories (either from both clinicians and laboratories, or from laboratories only). Figure 13 illustrate the number of cases reported per month (all cases and lab-reported cases).

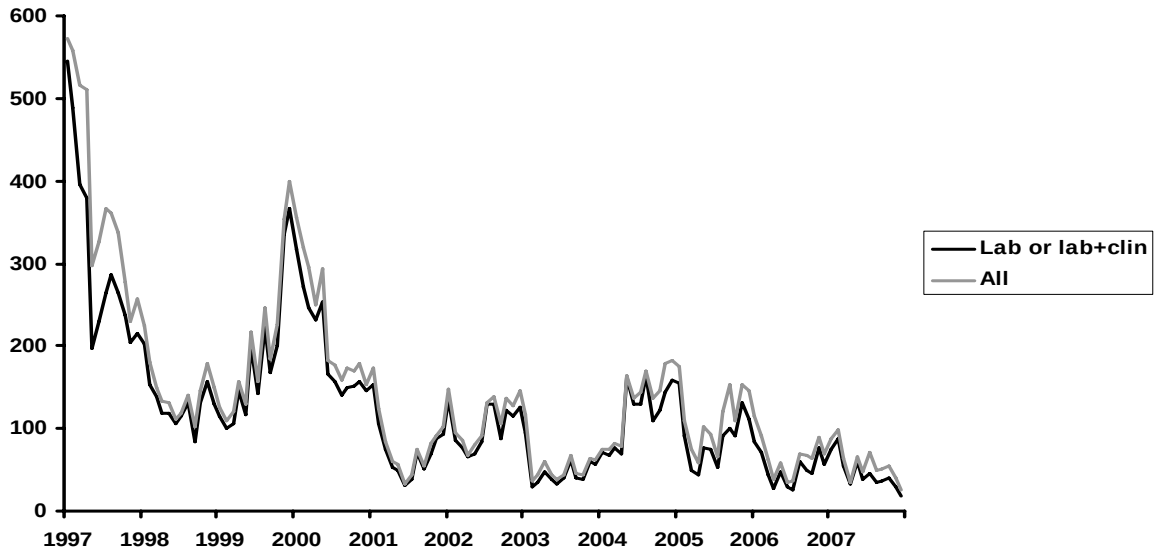

Figure 13 The number of reported pertussis cases reported per month 1997-2006; all cases (including cases reported only from clinicians) and laboratory reported cases. The difference between the two lines represents cases reported only from clinicians (without laboratory confirmation).

The laboratory reporting from the Swedish microbiological laboratories is based on culture, PCR or serology, Figure 12. Cases reported on the basis of culture or PCR are followed within the enhanced surveillance. Confirmation of *B. pertussis* by culture is 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 at about 5% or less. Since 2002 more laboratories use PCR and in 2003 around 20% of all laboratory reports were based on PCR. During the last two year a further increase in the use of PCR has occurred and nowadays at about 50% of the pertussis reports are based on PCR. Only few cases are reported on the basis of serologic results, with a slight increase during 2005-2007, Figure 14.

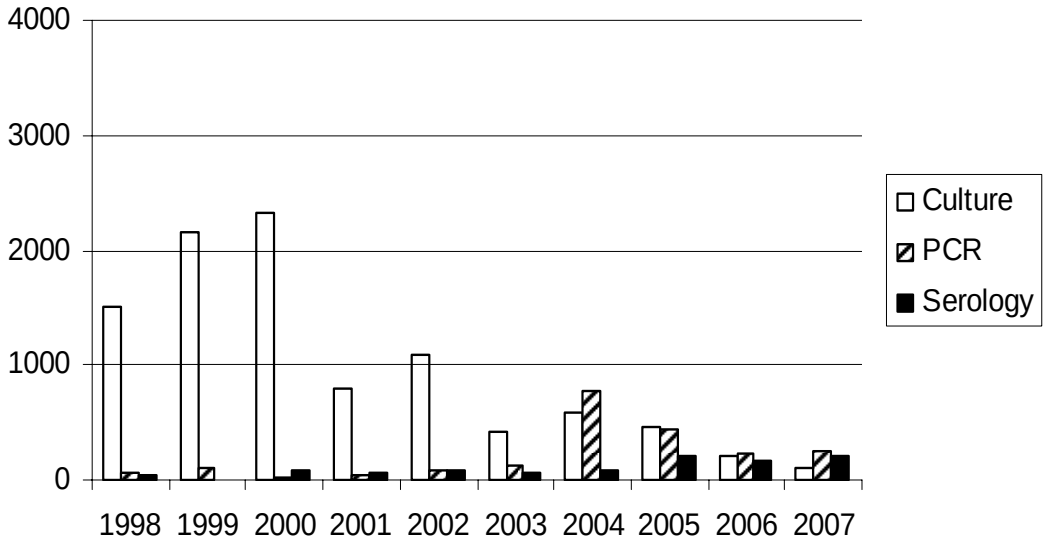

Fig 14 Laboratory methods used for verification of cases reported according to the Communicable Disease Act 1997-2007.

3.7 Potential differences in awareness

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 one region there was an increased reporting after an illustration of an infant case on the cover of the local newspaper (followed by media attention also at national level), Figure 15. Three years earlier, there was an increased reporting during one month after a letter from the regional dept of communicable disease control to all regional doctors, asking them to be aware of pertussis.

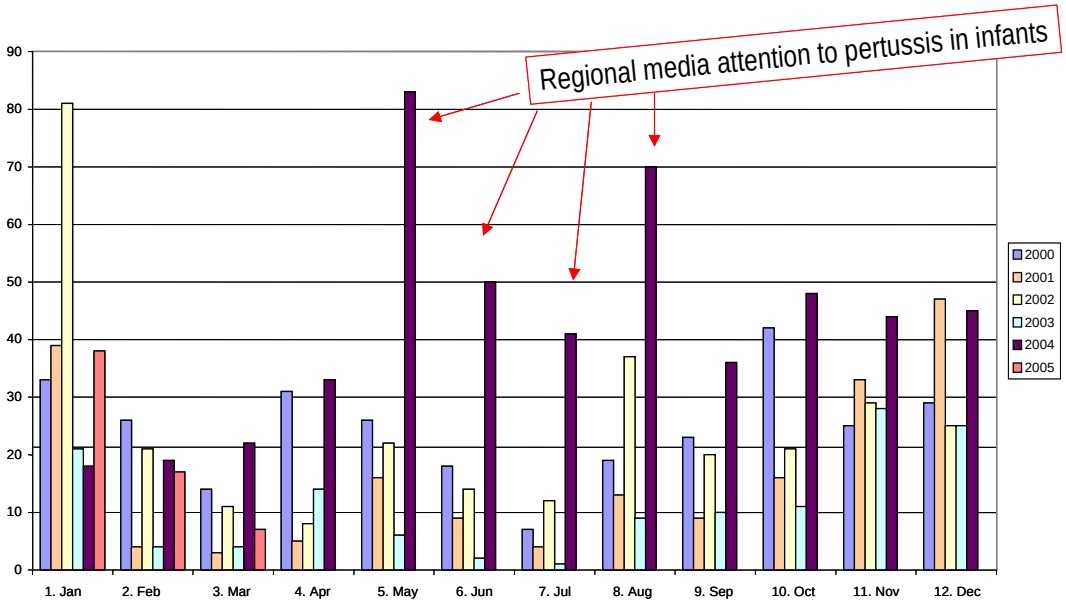

Fig 15 Number of pertussis reports in a county during the years 2000-04, with arrows indicating local attention to pertussis in media

Table 15A Overall and age-specific incidence of laboratory-reported pertussis per 100,000 from 1986 to 1995 before introduction, and 1996 to 2007 after introduction of acellular pertussis vaccine in Sweden.

	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
All ages	**89,5**	**108,5**	**142,7**	**121,2**	**92,0**	**132,6**	**112,8**	**132,4**	**150,2**	**121,7**	**95,8**	**41,9**	**17,9**	**25,0**	**26,9**	**9,9**	**13,7**	**6,4**	**15,6**	**11,9**	**6,8**	**6,0**
0	777,5	770,4	1082,5	840,4	632,1	900,7	665,2	772,6	677,5	779,3	**567,5**	**185,8**	**102,6**	**185,8**	**243,5**	**126,1**	**231,2**	**114,7**	**283,5**	**152,0**	**97,2**	**82,2**
1	1113,6	1290,4	1832,0	1427,1	1050,3	1375,9	1156,4	1305,2	1462,6	809,1	924,5	**164,1**	**25,8**	**37,7**	**86,0**	**36,5**	**45,6**	**20,0**	**54,7**	**27,7**	**15,6**	**16,2**
2	1249,6	1495,9	1957,6	1678,2	1224,4	1700,5	1437,6	1567,4	1943,9	1456,9	599,5	394,1	**74,4**	**34,3**	**39,7**	**41,1**	**58,3**	**19,4**	**52,4**	**14,1**	**13,7**	**8,7**
3	1196,7	1455,0	1951,5	1599,2	1153,6	1707,7	1384,1	1635,7	1760,8	1493,2	1126,3	316,0	190,0	**94,4**	**55,5**	**32,9**	**40,9**	**9,8**	**33,3**	**24,0**	**8,0**	**6,8**
4	1042,7	1308,0	1597,4	1443,5	1028,6	1445,5	1203,8	1419,0	1622,0	1396,5	1190,7	547,3	133,1	269,3	**153,1**	**30,8**	**50,2**	**22,0**	**54,4**	**21,4**	**10,4**	**9,9**
5	805,9	975,3	1232,8	1005,3	737,5	1048,2	904,5	1101,3	1187,7	1044,4	918,8	499,9	197,6	163,4	260,3	**46,8**	**52,9**	**15,2**	**73,3**	**26,0**	**22,4**	**10,3**
6	625,3	754,6	861,3	708,7	535,3	793,1	665,1	708,4	828,0	706,2	687,1	375,8	234,9	316,6	215,1	111,3	**86,3**	**26,3**	**83,3**	**55,6**	**23,7**	**26,4**
7	231,8	466,1	496,2	401,8	296,2	419,1	347,4	440,7	460,2	400,2	401,4	238,8	137,5	251,3	289,5	85,6	134,7	**30,6**	**86,0**	**59,3**	**28,2**	**30,0**
8	128,9	199,8	296,9	238,4	160,7	199,8	182,3	198,6	246,7	210,6	216,2	135,1	84,9	202,6	230,0	86,6	79,2	41,1	**105,3**	**53,3**	**32,2**	**19,4**
9	123,1	91,0	113,6	153,2	86,4	115,4	116,0	131,1	127,8	137,6	126,8	58,2	46,3	96,0	164,4	62,9	81,3	29,2	79,1	**72,6**	**25,0**	**29,8**
10	63,5	53,8	64,6	57,0	68,6	71,8	72,9	61,8	62,9	87,9	70,6	50,4	20,2	69,8	105,4	34,5	58,7	36,0	72,7	92,5	**22,5**	**13,4**
11	42,5	31,2	50,6	27,0	19,6	56,2	33,2	38,8	59,2	37,3	43,9	28,2	20,1	34,2	52,8	25,7	45,3	33,2	64,5	61,4	24,3	**9,7**
12	21,6	24,0	25,3	39,3	12,4	16,4	29,0	31,1	32,4	30,4	34,2	24,3	17,8	37,4	35,0	20,0	29,5	22,6	49,7	53,7	25,5	11,6
13	17,9	18,9	20,2	16,5	10,0	15,4	11,2	18,9	24,9	20,1	15,2	5,0	11,7	26,2	28,2	12,2	20,0	17,5	39,6	36,2	26,7	18,6
14	7,1	5,4	13,4	15,6	8,7	15,0	10,2	13,2	12,8	7,9	10,1	9,1	6,0	21,3	19,6	7,3	15,6	9,9	32,5	22,4	16,4	19,3
15	7,1	8,8	8,9	5,4	9,1	9,6	6,0	10,2	14,1	8,8	8,9	9,0	10,1	7,0	10,6	6,5	11,7	7,8	10,7	19,8	10,8	15,6
16	4,6	3,6	11,4	5,3	6,2	7,3	5,7	5,9	7,1	8,0	5,9	3,9	6,0	7,0	11,0	1,9	9,2	9,0	14,6	17,3	11,0	10,7
17	1,8	8,2	13,3	4,4	2,6	5,3	0,9	6,7	2,0	6,0	5,0	2,0	3,9	6,0	14,0	1,0	5,7	2,8	7,2	7,7	3,3	10,2
18	2,5	0,9	10,0	4,4	3,5	5,3	6,2	1,8	8,5	2,9	0,0	2,0	4,9	3,9	7,0	0,0	5,9	1,0	8,2	5,3	7,7	5,7
19	4,9	7,6	4,4	8,1	6,1	6,0	2,6	2,6	3,6	4,7	3,9	7,0	0,0	1,9	4,9	2,0	1,0	2,9	1,9	8,2	6,2	3,4
20-24	6,9	7,0	7,7	7,3	4,1	6,7	4,4	5,5	8,2	5,1	3,1	1,8	1,1	1,3	2,7	0,6	2,7	1,5	2,5	2,3	2,1	2,0
25-29	14,3	15,6	19,5	11,9	11,9	15,0	11,5	14,2	16,8	11,5	8,0	4,5	1,0	2,7	2,4	1,2	1,4	2,0	3,4	2,9	3,1	2,4
30-34	14,9	15,4	16,7	13,0	14,0	19,1	15,9	16,6	22,6	11,9	10,5	3,7	1,7	2,3	4,4	1,8	2,0	1,0	3,9	3,4	1,8	1,3
35-39	7,1	9,6	12,0	11,1	7,8	9,2	6,5	10,2	15,1	9,9	7,4	3,9	1,9	3,2	4,7	0,9	3,0	1,5	5,0	4,7	4,1	2,7
40-44	3,2	4,9	5,2	6,1	5,3	6,0	5,1	5,7	8,3	4,7	3,7	3,4	0,7	1,4	2,4	1,4	1,9	1,4	3,0	5,3	2,3	4,4
45-49	1,5	2,2	3,4	3,8	4,0	3,2	2,3	3,6	3,9	3,8	1,4	1,1	0,5	1,3	1,0	0,2	1,7	0,5	1,2	3,4	2,1	3,1
50-54	3,3	3,7	4,6	3,1	5,0	5,5	4,1	5,4	3,6	4,1	3,1	1,7	1,1	0,3	0,8	0,6	1,5	0,5	1,4	2,1	2,1	1,9
55-59	2,7	4,6	3,3	3,3	3,8	5,3	4,3	5,6	6,1	4,9	3,7	1,0	0,6	1,1	1,4	0,8	1,1	1,1	1,1	0,8	3,1	2,1
60-64	2,1	6,2	5,0	2,3	3,5	7,6	4,6	4,4	5,7	7,4	4,0	2,5	0,5	0,7	2,1	0,4	1,5	0,6	0,8	2,9	2,7	2,4
65+	1,0	1,7	2,3	2,0	2,5	2,6	2,9	2,4	4,7	4,0	3,5	1,4	0,6	0,9	0,9	0,1	0,7	0,8	0,9	1,7	1,5	2,4

Note! All age specific incidence figures in table 15A concern children from two yearly birth cohorts: Age specific incidence figures in black bold (upper right corner of table) concern children born 1996 or later, i.e. only children born after introduction of Pa vaccine in Sweden. 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 children from birth cohorts born before introduction of Pa vaccine in Sweden. For vaccine coverage per birth cohort, see figure 10.

Table 15B Number of laboratory reported cases of pertussis in defined age-groups from 1986 to 1995 before introduction and 1996 to 2007 after introduction of acellular pertussis vaccine in Sweden.

	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
All ages	**7494**	**9112**	**12040**	**10291**	**7875**	**11427**	**9781**	**11542**	**13185**	**10741**	**8473**	**3707**	**1582**	**2213**	**2388**	**878**	**1225**	**574**	**1404**	**1071**	**617**	**553**
0	777	794	1171	957	758	1114	818	927	777	838	**562**	**172**	**92**	**165**	**218**	**115**	**217**	**112**	**284**	**154**	**101**	**88**
1	1077	1301	1905	1557	1206	1661	1438	1612	1759	930	997	**163**	**24**	**34**	**77**	**33**	**42**	**19**	**54**	**28**	**16**	**17**
2	1171	1454	1984	1756	1345	1963	1740	1954	2411	1756	689	425	**74**	**32**	**36**	**37**	**53**	**18**	**50**	**14**	**14**	**9**
3	1116	1369	1906	1632	1216	1886	1604	1988	2212	1862	1357	363	205	**94**	**52**	**30**	**37**	**9**	**31**	**23**	**8**	**7**
4	984	1225	1511	1420	1058	1533	1335	1652	1988	1764	1484	659	153	291	**153**	**29**	**46**	**20**	**50**	**20**	**10**	**10**
5	777	924	1161	958	731	1084	963	1227	1395	1288	1161	623	238	188	282	**47**	**50**	**14**	**67**	**24**	**21**	**10**
6	609	730	820	672	514	791	691	758	931	835	848	475	293	382	248	121	**87**	**25**	**77**	**51**	**22**	**25**
7	221	455	482	385	283	405	348	460	497	453	475	295	174	314	350	99	147	**31**	**82**	**55**	**26**	**28**
8	123	191	291	233	155	192	177	200	260	229	245	160	105	257	288	105	92	45	**107**	**51**	**30**	**18**
9	121	87	109	151	85	112	112	128	130	146	138	66	55	119	209	79	99	34	87	**74**	**24**	**28**
10	65	53	62	55	68	71	71	60	62	90	75	55	23	83	131	44	74	44	85	102	**23**	**13**
11	46	32	50	26	19	56	33	38	58	37	45	30	22	39	63	32	58	42	79	72	27	**10**
12	24	26	26	39	12	16	29	31	32	30	34	25	19	41	40	24	37	29	63	66	30	13
13	20	21	22	17	10	15	11	19	25	20	15	5	12	28	31	14	24	22	51	46	33	22
14	8	6	15	17	9	15	10	13	13	8	10	9	6	22	21	8	18	12	41	29	21	24
15	8	10	10	6	10	10	6	10	14	9	9	9	10	7	11	7	13	9	13	25	14	20
16	5	4	13	6	7	8	6	6	7	8	6	4	6	7	11	2	10	10	17	21	14	14
17	2	9	15	5	3	6	1	7	2	6	5	2	4	6	14	1	6	3	8	9	4	13
18	3	1	11	5	4	6	7	2	9	3		2	5	4	7	0	6	1	9	6	9	7
19	6	9	5	9	7	7	3	3	4	5	4	7	0	2	5	2	1	3	2	9	7	4
20-24	41	43	48	45	25	40	26	32	48	30	18	10	6	7	14	3	14	8	13	12	11	11
25-29	80	87	110	69	72	94	74	92	108	72	49	27	6	16	14	7	8	11	19	16	17	13
30-34	86	89	96	75	81	110	92	97	136	74	67	24	11	15	28	11	12	6	24	21	11	8
35-39	46	60	73	66	46	54	38	60	89	58	43	23	11	19	29	6	20	10	33	30	26	17
40-44	20	32	35	41	35	39	32	35	50	28	22	20	4	8	14	8	11	8	18	33	15	29
45-49	7	11	18	21	24	20	15	24	26	25	9	7	3	8	6	1	10	3	7	20	12	18
50-54	14	16	20	14	23	26	20	28	20	24	19	11	7	2	5	4	9	3	8	12	12	11
55-59	12	20	14	14	16	22	18	24	27	22	17	5	3	6	8	5	7	7	7	5	19	13
60-64	10	28	22	10	15	32	19	18	23	30	16	10	2	3	9	2	7	3	4	16	16	15
65+	15	25	35	30	38	39	44	37	72	61	54	21	9	14	14	2	10	13	14	27	24	38

Note! All age specific incidence figures in table 15B concern children from two yearly birth cohorts: Age specific incidence figures in black bold (upper right corner of table) concern children born 1996 or later, i.e. only children born after introduction of Pa vaccine in Sweden. 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 children from birth cohorts born before introduction of Pa vaccine in Sweden. For vaccine coverage per birth cohort, see figure 10.

4 Plan for continued work

Study objectives from 2008:
- To study 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 for suitable interval until next booster

In addition, analyses will from 2008 focus on
- pertussis in infants and boosted 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 analyses 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 will be added for infants. Progress reports will be based on data collected per calendar year

Scientific publications and presentations:
- Manuscripts planned during project year 11 include a 10 year project summary, with 10 year data concerning Göteborg presented separately, and 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
- An international workshop on pertussis epidemiology will be organised in Stockholm November 19-21, 2008

5 Administration

Contracts for the project Pertussis surveillance in Sweden have been agreed for continued follow-up of clinical epidemiology during year 2004 to 2007 with the participating manufacturers, Sanofi-Pasteur-MSD, Lyon, Sanofi-Pasteur, Canada, and Glaxo SmithKline, Belgium.

The Advisory Group met annually. Progress reports are prepared as postmarketing follow-up for regulatory agencies. For transparency, it has been agreed that annual progress report is posted on www.smittskyddsinstitutet.se. The two vaccine specific 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.

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