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Pertussis surveillance in Sweden

Progress Report October 1997 - September 2005 with an executive summary

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AVDELNINGARNA FÖR EPIDEMIOLOGI OCH FÖR VIROLOGI, IMMUNOLOGI OCH VACCINOLOGI

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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, and infant vaccination with Pa vaccines was hence introduced in an endemic setting.

There is a well-established child health care system i 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. There is also a long-standing Swedish tradition of pertussis reporting, beginning with the "tjänsteläkarrapporten" by county health officers early in the 20th century, and continuing with voluntary laboratory reporting of culture-confirmed cases in the 1980s. Since 1997, both clinical and laboratory reporting of pertussis cases has been mandatory according to the revised national communicable disease act.

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 pertussis surveillance project in October 1997, including collection of clinical data as well as *Bordetella pertussis* isolates. We used the regular passive surveillance system to identify cases confirmed by culture (later also PCR) in children born from January 1996, with ascertainment of vaccination status and information on clinical course, and we also embedded follow-up of previous trial cohorts [2,3] in this enhanced follow-up. The Gothenburg area was excluded from the follow-up until January 2003 because of an ongoing mass vaccination project, studying the effects of free catch-up vaccination to children under 10 years of age [6]. In the laboratory part, run in parallel until September 2004, there was an agreement with all Swedish laboratories for clinical bacteriology to send isolates of *Bordetella pertussis* from the same birth cohorts.

The changes over time in age-specific rates have been considered the main outcome of the clinical part of the surveillance project, and we have also related clinical outcome to vaccination status. In the laboratory part, the primary aim was to establish reference methods for epidemiological typing of B. pertussis and to compare isolates over time and with other countries. A secondary aim was to relate the obtained patterns to vaccination policy and vaccine effectiveness.

We have specifically refrained from estimating vaccine effectiveness by percent reduction of disease rates among vaccinated compared to unvaccinated children to avoid inflated levels of protection due to ascertainment bias [7] and lack of a computerised vaccination register for proper denominators. 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. Therefore, 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 Gothenburg area). As for Gothenburg, we have refrained from inclusion of these data in the yearly 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, and also because of different vaccination regimen until spring 2000.

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 years and seven years of enhanced clinical follow-up in Sweden (except Gothenburg) has been published previously [8,9,10,11] and also reported in the technical progress reports [12,13,14,15,16,17]. Section 2 of this report covers continued follow-up of the same areas for eight years. In Section 3 we report general information on laboratory-confirmed pertussis in the whole country and all ages before and after introduction of Pa vaccines. Also the experience from the laboratory surveillance has been published [18,19] or submitted [20,21] separately, and also reported in the technical progress reports [12,13,14,15,16,17]. Section 4 of the present report updates the analyses made on strains collected until September 2004.

1.2 Materials and methods

A detailed description of the enhanced surveillance program, ongoing since October 1997 in all of Sweden except Gothenburg, 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 1996, and in children participating in the nation-wide trials 1993-96 [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 [22].

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 Gothenburg 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 summarized the database information for all episodes, except those occurring in the Gothenburg area, up to end of the previous project year, with the present 8 y report updating the information from October 1997 until September 30, 2005.

1.2.2 General information on pertussis in Sweden

General information on pertussis in Sweden have been included in the progress reports, including the number of reports of laboratory-verified pertussis per month from 1986 and onwards, as well as the annual age-specific incidence rates of culture- or PCR-confirmed cases in the whole population and in all ages for the years 1986-1995, when there was no general vaccination against pertussis, and from 1998 and onwards. The progress reports have summarized the general information up to the previous calendar year, with the present 8 y report updating this general information until December 2005.

1.2.3 Person time and incidence calculations

Age-specific incidence rates of pertussis for children born 1 January 1996 until 30 September 2005 and for children in the 1993-96 trial were based on the number of notified pertussis cases during the study period 1 October 1997 to 30 September 2005 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 Strain characterization methods

During the 8-year period 1 October 1997 to 30 September 2005 altogether approx. 5400 clinical isolates of *Bordetella pertussis* were collected from children born 1992 or later. Funding from the EU-Commission financed a 39-month period August 2001 through September 2004.

1.2.5 Vaccines used from 1996

The vaccines used 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 Gothenburg 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. The corresponding hexavalent vaccines are sometimes used to infants at risk for hepatitis B, but most of these are vaccinated with monovalent hepatitis B vaccine administered separately or concomitantly with the pentavalent vaccine.

1.3 Results

1.3.1 Pertussis incidence for children born 1996 through September 2005

During the eight-year period of this study there were 1572 followed cases of laboratory confirmed pertussis outside the Gothenburg area among 1570 children born 1996 or later, with detailed vaccination history available for all 1572 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 of DTPa-containing vaccine) below 2 years of age (13 per 100,000 including unvaccinated children of this age). Between 2-<6 years of age the age-specific incidences were 16-20 per 100,000 person years, with an increase at ages 6-<8 years to 31-28 per 100,000 person years, and further increasing to 59 per 100,000 among the oldest age groups from 8 years of age, Table A.

Table A Total person-time of follow-up, number of observed culture- or PCR-confirmed cases and incidence per 100,000 person years in the different age-groups for children born from January 1996 until September 2005, followed from 1 October 1997 until 30 September 2005. Age-specific incidences per 100,000 person-years in vaccinees but irrespective of vaccine are given for the period before Dose 1 (< 3 months of age), the period after Dose 1 before Dose 2 (3 - <5 months of age, the period after Dose 2 before Dose 3 (5 - <12 months of age) and periods after Dose 3 (from 12 months of age). In parenthesis are given figures including the unimmunised children of respective age group (intent to treat). *In italics, in the second row, are the corresponding figures for children who fulfilled WHO case definition of 21 or more days of spasmodic cough.*

	Follow-up in person years	**No. of laboratory confirmed cases**	**Incidence per 100 000 person years**	**95% confidence interval for incidence per 100 000 person years**
<3 months	169 760	n.a. (396)	n.a. (233)	n.a. (211 – 254)
of which ≥21d		*n.a. (351)*	*n.a. (207)*	*n.a. (186 – 229)*
3- <5 months 1 dose	112 920	237 (310)	210 (281)	184 – 238 (244 – 306)
of which ≥21d		*204 (268)*	*181 (237)*	*157 – 206 (209 – 267)*
5- <12 months 2 doses	393 995	124 (151)	31 (38)	26 – 37 (32 – 45)
of which ≥21d		*89 (114)*	*23 (29)*	*18 – 28 (24 – 35)*
12- <24 months 3 doses	692 040	60 (90)	9 (13)	7 – 11 (10 – 16)
of which ≥21d		*44 (73)*	*6 (11)*	*5 – 9 (8 – 13)*
24- <36 months 3 doses	602 040	95 (116)	16 (19)	13 –19 (16 – 23)
of which ≥21d		*75 (96)*	*12 (16)*	*10 – 16 (13 – 19)*
36- <48 months 3 doses	514 400	91 (111)	18 (22)	14 – 22 (18 – 26)
of which ≥21d		*70 (89)*	*14 (17)*	*11 – 17 (14 – 21)*
48- <60 months 3 doses	432 540	81 (101)	19 (23)	15 – 23 (19 – 28)
of which ≥21d		*62 (82)*	*14 (19)*	*11 – 18 (15 – 24)*
60- <72 months 3 doses	350 940	70 (83)	20 (25)	16 – 25 (19 – 29)
of which ≥21d		*52 (63)*	*15 (18)*	*11 – 19 (14 – 23)*
72- <84 months 3 doses	269 340	84 (86)	31 (32)	25 – 39 (26 – 39)
of which ≥21d		*65 (67)*	*24 (25)*	*19 – 31 (19 – 32)*
84- <96 months 3 doses	190 290	53 (60)	28 (32)	21 – 36 (24 – 41)
of which ≥21d		*41 (47)*	*22 (25)*	*15 – 29 (18 – 33)*
96- months 3 doses	102 815	61 (68)	59 (66)	45 – 76 (51 – 84)
of which ≥21d		*48 (54)*	*47 (53)*	*34 – 62 (39 – 68)*
All 12- months 3 doses	3 154 405	595 (715)	19 (23)	17 – 20 (21 – 24)
of which ≥21d		*457 (571)*	*14 (18)*	*13 – 16 (17 – 20)*

1.3.2 Clinical outcome of pertussis disease

Data on duration of cough and presence of spasmodic cough were available for all 1572 episodes, whereas data on presence of any complication were available for 1559/1572 episodes and data on hospitalisation admission for 1566/1572 episodes.

All episodes but 5 (0.3%) included coughing. Spasmodic cough for 21 days or more was reported for 1304 (83.0%) and spasmodic cough for less than 21 days was reported for 115 (7.3%) of the episodes. The remaining 148 episodes (9.4%) presented cough of non-spasmodic type of varying duration (Table 12).

It is well known that infants with pertussis may present without typical clinical picture. In our material 73 of the 115 children with spasmodic cough of shorter duration than 21 days were <1 year of age, whereof 36 infants were unimmunised, 20 had received one dose and 17 had received 2 doses of vaccine. 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 1532/1572 would fulfil this definition. Among the 40 cases that would not fulfil the EU definition, 22 were infants and 18 were aged 1-6 years. All but three infants had received erythromycin or trimetoprim-sulfametoxazol, whereas only three of the children aged 1-6 years were treated with antibiotics. In all, 7 of the infants were unvaccinated, 5 had received one dose and 10 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. The fatal case occurred in a non-treated and non-vaccinated infant.

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 avoidning exposure and by the use of erythromycin to those who were accidently 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 months23. Infants treated with antibiotics within one week after start of pertussis episode had significantly shorter duration of cough, Section 2.19, Table 13.

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 274 episodes with respiratory complications, whereof 132 with apnea and 142 without. Neurological or other serious complications were only reported for 9 and 4 children respectively. 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 (Section 2.17).

Among the 1,566 cases of pertussis in children born 1996 until 30 September 2005 or later for whom we have data on hospitalisation, there were 409 children with a hospital admission due to pertussis disease, whereof 324 (79.2%) occurred in unimmunised children. Most of these were below three months of age at start of the pertussis episode. The hospitalisation rate among unimmunised children was 53%. The duration of hospital stay was shorter in the vaccinated children compared to the unvaccinated children. There were 20 hospitalised children, who had received two or more doses of DTPa, but only 2 (10%) were hospitalised for 7 days or more.

The overall age-specific incidence rates for a hospital admission was 164, 76, 8 and 0,5 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 a strong association between hospitalisation and a complication due to the pertussis disease. Seventy-one percent of the children with at least one reported complication also had a hospital admission compared to 13% admissions among children without any complication during the episode (p<0,001). In all, there were 348 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 eight-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 between 3 and 11 years of age during the follow-up period, October 1997 to September 2005.

1.3.4 Strain characterisation

Epidemiological typing was performed on approximately 3,000 out of 5,400 isolates collected from 1970 to 2005. Methods included serotyping of fimbriae, gene typing of pertactin and the pertussis toxin subunit S1, and chromosomal fingerprinting by means of Pulsed Field Gel Electrophoresis, PFGE.

By use of a modified (one-enzyme) PFGE a total of 1,810 Swedish isolates from 1970 to 2003 were analysed and totally 176 separate PFGE-profiles were identified. Thirty-five profiles were represented by 85% of all isolates, with a minimum similarity of 70% by dendrogram analysis. This reference material was deposited at CCUG [1]. There was a 100% correlation between PFGE profile and pertactin type [18]. When a collection of isolates from other European countries were analysed, a majority of them could be assigned a known profile code using the Swedish reference system

Circulating Swedish strains constantly have differed from vaccine strains. The Swedish population of *Bordetella pertussis* strains was characterized from 1,247 isolates covering a wholecell vaccine program up to 1979, a 17-year period without vaccination (1979 to 1996), and a period after the introduction of general vaccination among newborns with acellular pertussis vaccines (1997 to 2003). There were shifts of serotype connected with shifts of vaccination program. Serotype Fim3 was most frequent during the periods with general vaccination schedules, whereas serotype Fim2 was predominant during the 17-year vaccine-free period. Pertactin 1 was predominant during the pertussis wholecell (Pw) vaccine period but was thereafter replaced by prn2 and has not reappeared after the introduction of acellular pertussis (Pa) vaccines. ptxA was predominant over all three decades. The profiles seen in Sweden have come in waves, disappeared and been replaced by new profiles. A few PFGE profiles were predominant over the years: BpSR25 (serotype Fim3 prn1/7) and BpSR18 (serotype Fim3 prn2) during the Pw period, BpSR1 (serotype Fim2 prn2) during the 17 years without general vaccination, and BpSR11 (serotype Fim3 prn2) after the reintroduction of general vaccination in 1996 [19]. Interestingly BpSR11 was first described from France in 1994. In Sweden it appeared in 1997 and two years later in Finland [24].

We also investigated changes in the B. pertussis population between three noted incidence peaks, in 1999-2000, 2002 and 2004. 158 available "peak" isolates from fully vaccinated individuals representing whole Sweden except the Gothenburg area were analysed together with 361 isolates from unvaccinated or partially vaccinated children representing 6 Swedish counties. The isolates showed changing profile composition in and between the peaks. The PFGE-profile BpSR11 appearing in the first peak 1999 dominated during the entire period but others with BpSR11-related profiles appeared with an increasing trend, BpSR5 in peak 2, BpSR12 and BpSR13 in peak 3 and BpSR10 between peak 2 and 3 [20]. Sequence analysis showed statistically significant trends toward increasing specific alleles in 3 out of 5 studied genes ptxC, prn and tcfA. Although vaccination with acellular pertussis vaccine has been effective and reduced disease, new variants have emerged representing clones surviving in the immunized population.

It is shown under 2.15 Table 9c that the earlier advantage of the DTPa5 over the DTPa3 vaccine disappeared in the long run. The mechanism are not clear but the shift from serotype Fim2 to serotype Fim3 strains during this period may have contributed. Trial I results also indicated that DTPa5 was significantly more efficious against Fim2 than Fim3 strains [19]. In conclusion, we find a possible impact of strain variation on vaccine effectiveness.

Impact on vaccine effectiveness is further supported by by clinical outcome results. We analysed the association of Pulsed-Field Gel Electrophoresis (PFGE)-profile and serotype to severity of disease for all children followed during the first seven years of the project. There were in all 927 children born 1996 and later with both clinical information and strain characterisation data available. When clinical outcomes were compared between two groups of strains, characterised by PFGE-profile or serotype, there were significantly more children with a long duration of hospital stay in the most frequent PFGE-profile group (BpSR11) compared to the PFGE-group of all other profiles (p=0,041). There was no statistically significant association between serotype and hospitalisation, nor were there any statistically significant association between serotype or PFGE-profile and duration of spasmodic cough or complications. Continued monitoring of strains seems important.

1. The Culture Collection of the University of Gothenburg, Gothenburg, Sweden

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

The number of 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 – 2005, Figure A. The annual incidence of laboratory confirmed B. pertussis was 89-150 per 100,000 before introduction of acellular pertussis vaccines, Section 3 Table 15. After a rapid drop in 1996-1997 the overall annual incidence reached 7 to 26 per 100,000 person years. The age specific incidence rates before and after introduction of DTPa-containing vaccines are shown in Figure B based on Table 15.

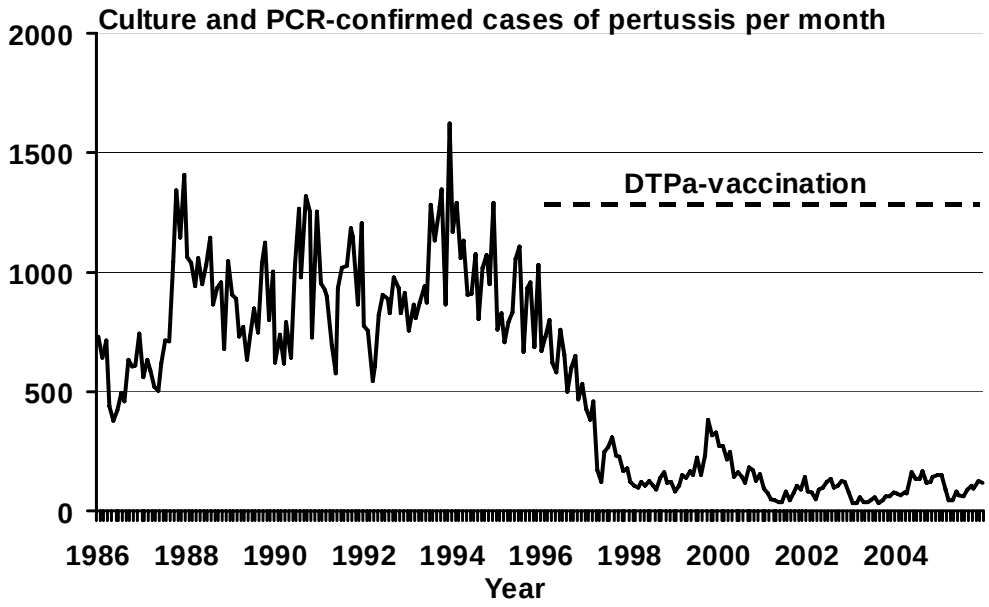


Figure A Number of culture- and PCR-confirmed pertussis cases in Sweden per month from January 1986 to December 2005.

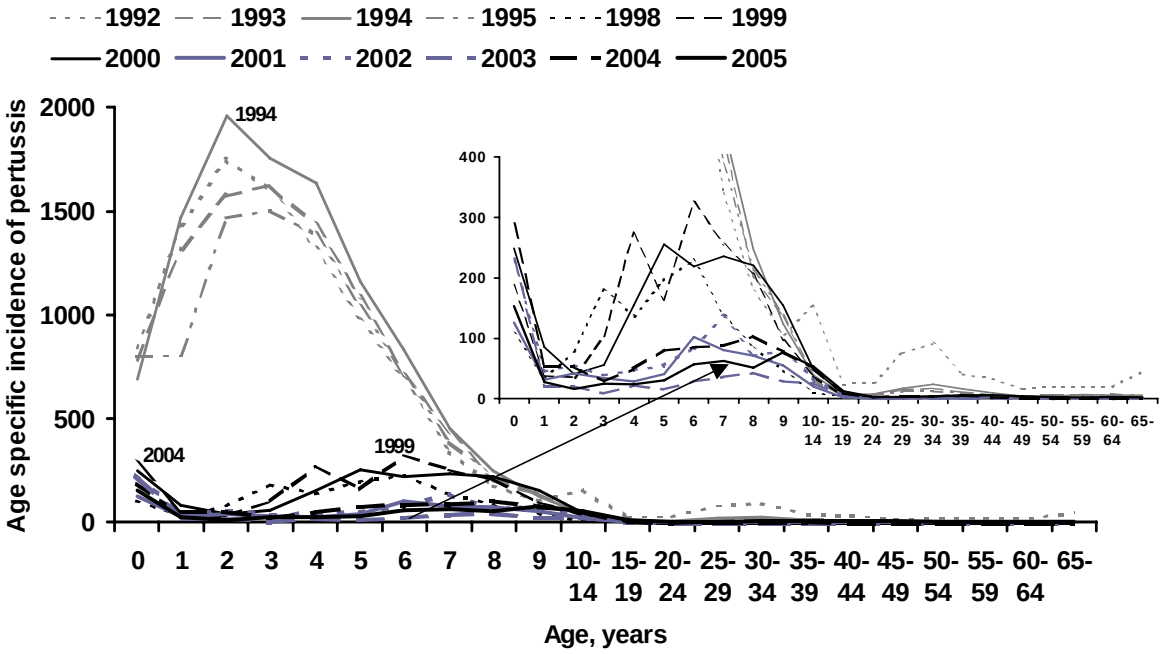


Figure B Age specific incidence of laboratory confirmed pertussis in 1992-5 and culture or PCR in 1998-2004, from Section 3, Table 12. Enlarged curves are shown in the insertion. The arrow highlights the incidence curve for year 2005

After the introduction of these vaccines in 1996 the incidence rates are markedly lower as compared to before 1996. 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. However, the reduction of age specific incidence was least marked below one year of age.

Cross-sectional population data suggests a shift in pertussis incidence peaks moving from 2-4 years during the non-vaccination period to 3 and 5-6 year olds in 1998, 4 and 6-7 year olds in 1999, 5 and 6-8 year olds in 2000, corresponding to the youngest unvaccinated or partially vaccinated birth cohorts. This shift was not continued in the same way during the low incidence years 2001 and 2002. The trend was interrupted in 2004-2005 when the first cohort of vaccinated born in 1996 reached 8-9 years. This cohort had the highest incidence after infancy during these two calendar periods. We interpret this observation as a possible first sign of waning immunity 6-7 years after completed primary vaccinations with DTPa.

1.4 Discussion

In the eight-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 80 to 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 reduced pertussis among unvaccinated and partially vaccinated infants.

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 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.

In accordance with the experience of other countries, most cases in Sweden are reported 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 [25,26,27], but the sensitivity of passive surveillance based on culture- and PCR confirmation is too low to permit accurate estimates of pertussis among adults and adolescents.

Previously reported randomised studies have shown that acellular vaccines were efficacious in clinical trial settings in young children [11,12] but there are little data on the effectiveness of the vaccines when given to school age children, nor of the long-term effectiveness of 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 4-5years following the completion of the full vaccination schedule, Section 2.12, table 8b. These findings are in accord with Italian and German experiences [14,15]. 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 [28], and after four doses of a four-component vaccine [29]. The incidence of confirmed pertussis is increasing from 6 years of age and the concomitant incidence among infants suggests that a booster dose is warranted at 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 [4].

The Swedish National board of health and Welfare has recently initiated a major revision of 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. The incidence in infants and the first signs of waning immunity in previously vaccinated cohorts have contributed to an interim measure. Until the final proposal, which is likely to include a pre-school booster, the Board in August 2005 recommended a booster dose at 10 years of age in order not to miss the opportunity to boost pertussis immunity in children who will have passed pre-school age at time of implementation of the new program. The new proposal will be presented during 2006 [30].

Analysis of age-specific incidence showed substantially lower rates for children born in the years after the introduction of acellular pertussis vaccines, Figure A and Section 3, Table 12. The reduction of pertussis incidence at 4-8 years of age already observed during the first 3 surveillance years can be explained by a combination of different factors such as the participation in a vaccine trial ([3], 40-45% of birth cohorts 1993 to 1994), a catch-up programme during the first years after reintroduction of general pertussis vaccination (59 percent of birth cohort 1995 have been immunised), and indirect immunity through a decrease in circulation of B. pertussis as suggested by the 38%-reduction of the incidence among 0 to 2-month old children and a 68% reduction of the incidence among 3 to 5 month old infants from 1986-1995 to 1998-2002 [6]. As for the latest three project years, it is to be noted that all pre-school cohorts are vaccinated in infancy, with a coverage of about 98%, and furthermore that the first vaccinated birth cohorts (born 1996 - 1998) have in fact by now entered school age.

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. A problem with culture confirmation is the differential sensitivity of culture-confirmation in vaccinated compared to unvaccinated individuals. Furthermore the sampling rates may vary over time and according to the awareness of pertussis, local clinical practice, level of suspicion and laboratory experience in different parts of the country.

The Swedish surveillance system remained essentially unchanged from 1986 until 2002, but thereafter confirmation by PCR has increasingly replaced culture-confirmation, Figure 7. The switch from culture-confirmation to PCR-confirmation at an increasing number of laboratories during the last few years will erroneously decrease observed differences between pre and post vaccination periods, but may also confound comparisons over time regarding waning protection.

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

Potential differences of effectiveness between vaccines may remain unidentified for a number of years. Another possibility is the opposite, i.e. that protection differences demonstrated in efficacy trials wane over the years, with little or no difference at all in the long run. Such late effects may only be detected by sustained disease surveillance combined with detailed national vaccination registry data [31]. Yet, the validity of comparing effectiveness of different vaccines will be limited by local differences in completeness of case ascertainment.

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 [32], and provide a better understanding of who has exposed the infant. Studies of neonatal vaccination would be useful to evaluate the possibility to initiate a vaccination response already at birth, and/or studies of maternal vaccination for induction of protection already before birth.

Additional clinical studies to understand the pathogenesis of the severe pulmonary complications in infantile pertussis are also warranted [33,34]. Furthermore, 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 epidemiologic changes in other groups, including changes in maternal antibodies over time.

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 11-16/100 000 in 2001-2005 (including PCR-confirmed)
- The highest incidence occurs in infants who are unvaccinated or have received only one dose of DTPa. Most hospitalisations and complications occur in infants who are unvaccinated. Early antibiotic treatment in this age group reduces the duration of pertussis episode.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 may now be suggested in 2004-2005 by
  - highest age specific incidence among 8-9-year olds born in 1996, the first DTPa cohort
  - increasing age specific incidence from 6 years of age
- A concomitant increase in incidence among infants suggests that a booster dose is warranted at 5-6 years of age
- 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 8-year clinical pertussis surveillance Oct 1997 – Sept 2005

2.1 Background

2.1.1 Routine reporting system

During 1980 to1995 laboratory confirmed pertussis was voluntarily reported from all bacteriological laboratories with full personal identifiers. Pertussis was included in the new Communicable Disease Act in 1997. Since Fall 1997 all cases of pertussis, either clinically suspected or/and laboratory confirmed by culture and by polymerase chain reaction (PCR) were reported to the Swedish Institute for Infectious Disease Control through a computer-linked reporting system.

2.1.2 Intensified surveillance program

The enhanced pertussis surveillance started in October 1997 in Sweden, 1¾ year after the introduction of acellular pertussis vaccines at 3, 5 and 12 months in the general vaccination program. All routine reports of culture- and PCR-positive samples from children born since 1996, the year when Pa vaccines were included in the national vaccination program, and also in children born 1993-94 who participated in the nation-wide trial 1993-96, Trial II [3], have since then been identified through the national register. All episodes of pertussis, except those occurring 971001-021231 in the Gothenburg area, were further followed-up in detail by study nurses who documented the clinical course and vaccination history by telephone 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 sulfamethoxazol was collected. Detailed vaccination history for children born since 1996 was obtained form the medical records of the Child Health Care Centres by telephone to the nurse attending the individual child. Parental permission was obtained to request medical records as needed.

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 [22]. In the discussion part, comparisons were made with the current clinical case reporting definitions of EU [35] and WHO [36].

2.1.4 Vaccines used

In the beginning of 1996, when a pertussis vaccine was reintroduced in the vaccination program, only one DTPa (Infanrix®, GlaxoSmithKline, GSK) was used in all parts of Sweden except Gothenburg 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 Gothenburg and surrounding communities, an area with at about 9% of the Swedish population, another DTPa (Di-Te-Kik®, SSI) was used until spring 2000, whereafter these communities switched to Pentavac®, already used in the rest of the county of Västra Götaland. 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 have lately started to use hexavalent combinations for vaccination of infants at risk for hepatitis B, whereas other use 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 (see Figure 2).

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 with a five-component DTPa vaccine (Connaught Laboratories Limited, CLL), a two-component DTPa vaccine (SmithKline Beecham, SB) or a DTPw (CLL) [2].

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

2.1.5 Vaccination schedules

Children born in Sweden from 1996 are recommended three doses of acellular pertussis vaccine according to the 3-5-12 month schedule. Unvaccinated immigrants or children delayed for some other reason are normally vaccinated according to the same principle, i.e. two doses with a two month interval, followed by a third dose after six months (or more).

The Gothenburg mass vaccination project offered free catch-up vaccination 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. Catch-up to children aged 2 years of more were in most cases administered according to a two-dose schedule.

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. Children vaccinated with a two-component DTPa or the US DTPw 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 1996 or later and residing outside the Gothenburg area at time of pertussis, and children born 1993-1994 who participated in Trial II [3], are followed continuously from 1 October 1997. Children born 1996 or later and residing in the Gothenburg area at time of pertussis are followed continuously from 1 January 2003.

Originally the pertussis surveillance project covered all children born 1992 or later. In preparing a previous report, presented in March 2000, 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. 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. However, earlier data for laboratory confirmed pertussis episodes for children in dropped cohorts are still maintained in the surveillance database. Detailed clinical follow-up was then 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.

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.

1999-04 Children born 1999 - 2004. Part of the 2004 cohort still not fully immunised. Vaccine coverage for three doses Pa at 2 years of age was above 98%, according to the statistics form the Child Health Centres.

2005:1-9 Children born January to September 2005, still not fully vaccinated.

Results are first summarised for each annual birth cohort. Available data are then presented for three cohorts of children 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.
- The 1996-1997.6 cohort, children vaccinated with Infanrix.
- The 1997.7-2005.9 cohort, children vaccinated with either Infanrix, Pentavac, Infanrix-Polio-Hib or vaccinated in a mixed Infanrix/Pentavac schedule in some of the counties.

In all presentations in this eight year document children from the Gothenburg area are excluded. During the first years of the enhanced surveillance the Gothenburg children were followed by other investigators within a clinical trial in that area of Sweden [6]. From January 2003 we started to collect clinical and immunisation information also for the Gothenburg children, but, the previous two progress reports, covering respectively ¾ and 1 ¾ year of surveillance in the Gothenburg area, did not include any analyses of these data. The main reason was the relatively short time of enhanced surveillance in this area, and also that we wanted to not hamper comparisons with previous yearly surveillance reports. In accordance with a project epidemiology meeting in January 2005, we will present results for the Gothenburg area in a separate document, also including a list of plausible explanations to the differences in reported incidences in this area as compared to in the rest of the country.

2.3 Surveillance database in January 2005

There were 5 746 episodes of laboratory confirmed pertussis reported and entered in the surveillance database from the start of the enhanced follow-up on 1 October 1997 until the beginning of January 2006. Since the seven-year report 414 new cases of laboratory confirmed pertussis cases have been entered in the database for still followed birth cohorts.

From the Gothenburg area (area 14.2 in Fig 1) there were 1 290 reports from the routine reporting system entered in the surveillance database. Of remaining 4,456 episodes, 278 have not been possible to follow-up for clinical or immunisation data due to e.g. confidential phone numbers, language "problems" etc. Forty-five episodes with an onset of cough earlier than 1 October 1997 were excluded from this report and so were also 29 episodes with an onset of cough later than 30 September 2005. Finally, there were 83 episodes, with a date for the culture after October, 2005, for which the household not yet has been contacted. All those reports were withdrawn before the statistical analysis.

2.4 Laboratory confirmed pertussis cases used for this report

After the above exclusions episodes for 4,021 children remain in the database. Those children were born between 1 January 1992 and 30 September 2005 and they had an onset of cough during a laboratory positive pertussis episode which occurred between 1 October 1997 and 30 September 2005. They were living in households, outside the Gothenburg area, which have been possible to contact for data on both vaccinations and clinical follow-up.

Sections that follow were based on a subset of the 4,021 children. All episodes (1,873) for cohorts not under surveillance any longer, see Section 2.2, were also excluded. In sections 2.5 – 2.13 we present results for the remaining 2,148 episodes of laboratory confirmed pertussis. Compared to the seven year report 318 new cases of laboratory confirmed pertussis were entered in the database during the last 12-months period for these cohorts. Vaccine failures among participants in Trial I and II are reported separately in Section 2.15.

In section 2.16, we present results on hospitalisation for children born January 1996 until September 2005 for whom we have data on length of hospitalisation. The corresponding results for complications due to the pertussis illness during the pertussis episode and the duration of spasmodic cough are found in sections 2.17 and 2.18.

2.5 Laboratory confirmed pertussis per calendar period & birth cohort

All 2,148 laboratory confirmed cases of pertussis were divided on the still followed birth-cohorts and calendar periods for onset of cough at the episode. Table 1a report cases among children born 1996 or

later, the DTPa vaccination period (n=1,572) and Table1b cases among children born during enrolment period of Trial II (n=576).

Table 1a Reported laboratory confirmed cases of pertussis from 1 October 1997 until 30 September 2005 per birth-cohort and period of onset of cough.

	Calendar period for laboratory confirmed cases of pertussis									
Birth-cohort	**1997 Q4**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005 Q1-Q3**	**Total**
1996	**5**	**18**	**40**	**42**	**20**	**39**	**14**	**61**	**20**	**259**
1997	**23**	**29**	**19**	**25**	**17**	**30**	**9**	**27**	**12**	**191**
1998	**-**	**61**	**36**	**14**	**7**	**17**	**12**	**34**	**17**	**198**
1999	**-**	**-**	**96**	**66**	**9**	**19**	**8**	**18**	**11**	**227**
2000	**-**	**-**	**-**	**88**	**31**	**16**	**7**	**20**	**10**	**172**
2001	**-**	**-**	**-**	**-**	**33**	**21**	**9**	**17**	**7**	**87**
2002	**-**	**-**	**-**	**-**	**-**	**99**	**15**	**15**	**7**	**136**
2003	**-**	**-**	**-**	**-**	**-**	**-**	**53**	**41**	**10**	**104**
2004	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**115**	**37**	**152**
2005 Q1-Q3	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**46**	**46**
Total	**28**	**108**	**191**	**235**	**117**	**241**	**127**	**348**	**177**	**1 572**

Table 1b Reported laboratory confirmed cases of pertussis from 1 October 1997 until 30 September 2005 for the birth-cohort covering the Trial II recruitment period, per period of onset of cough.

	Calendar period for laboratory confirmed cases of pertussis									
Birth-cohort	**1997 Q4**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005 Q1-Q3**	**Total**
1993. 6 - 1994. 5	**21**	**79**	**167**	**138**	**51**	**43**	**18**	**36**	**23**	**576**

2.6 Laboratory confirmed pertussis among unimmunised children

Among 2,148 followed children with laboratory confirmed pertussis, 957 (44,6%) 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 1 October 1997 until 30 September 2005, 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 laboratory confirmed cases of pertussis									
Birth-cohort	**1997 Q4**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005 Q1-Q3**	**Total**
1996	**2**	**3**	**5**	**6**	**3**	**0**	**0**	**5**	**2**	**26**
1997	**12**	**8**	**0**	**3**	**3**	**3**	**3**	**6**	**1**	**39**
1998	**-**	**38**	**7**	**2**	**3**	**1**	**1**	**1**	**0**	**53**
1999	**-**	**-**	**61**	**26**	**3**	**5**	**4**	**5**	**1**	**105**
2000	**-**	**-**	**-**	**58**	**19**	**7**	**1**	**6**	**2**	**93**
2001	**-**	**-**	**-**	**-**	**22**	**5**	**1**	**5**	**3**	**36**
2002	**-**	**-**	**-**	**-**	**-**	**67**	**5**	**5**	**1**	**78**
2003	**-**	**-**	**-**	**-**	**-**	**-**	**42**	**17**	**1**	**60**
2004	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**77**	**12**	**89**
2005 Q1-Q3	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**37**	**37**
Total	**14**	**49**	**73**	**95**	**53**	**88**	**57**	**127**	**60**	**616**

Table 2b Number of reported laboratory confirmed cases of pertussis from 1 October 1997 until 30 September 2005, for the birth-cohort corresponding to the recruitment period of Trial II, 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 laboratory confirmed cases of pertussis									
Birth-cohort	**1997 Q4**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005 Q1-Q3**	**Total**
1993. 6 - 1994. 5	**12**	**50**	**101**	**80**	**31**	**32**	**9**	**13**	**13**	**341**

In birth cohort 1993.6 - 1994.5, a majority (59%) 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 (10%) due to the very high vaccine coverage (Table 2a and Table 1a). Most children in the cohort had received three vaccine doses before the present follow-up started in October 1997. The rising rate of cases among unimmunised in the later (1997-) birth cohorts depend on the overlap between the vaccination period and the calendar period for collection of laboratory confirmed pertussis cases (Table 2a and Table 1a). All episodes, but two, among the unimmunised children were symptomatic according to the clinical follow-up. The minimum duration of cough, if cough, was 9 days - the median duration was 47 days. Spasmodic cough for 21 days or more (episodes according to the WHO-definition) was reported for 91% of the episodes - the median duration was 37 days. For 38 (4,0%) of the episodes there were no spasmodic cough.

Table 3 shows for 561 unimmunised children born from October 1997 or later the age distribution of the laboratory confirmed cases at onset of cough. Most of the pertussis cases (70%) in this subgroup ooccurred before three months of age, i.e. before the scheduled first dose of a DTPa-containing vaccine.

Table 3 Age at onset of cough for 561 laboratory confirmed cases of pertussis from 1 October 1997 until 30 September 2005, among unimmunised children born October 1997 or later.

Birth cohorts 1997 Q3 - 2005 Q3	
Age at onset of cough	**Number (%)**
0 – 30 days	**99 (18%)**
31 – 60 days	**152 (27%)**
61 – 90 days	**140 (25%)**
91 – 120 days	**54 (10%)**
121 – 150 days	**15 (3%)**
151 – 180 days	**6 (1%)**
181 – 360 days	**19 (4%)**
361 - days	**76 (14%)**
Total	**561 (100%)**

2.7 Laboratory confirmed pertussis among vaccinated children

Among 2,148 followed children 1,191 (55,4%) had received at least one dose of a pertussis vaccine prior to onset of the pertussis episode - 813 children had received 3-4 doses or 2 doses after two years of age (2 children), 131 had received 2 doses and 247 had received only one dose of pertussis vaccine. Figures for laboratory confirmed pertussis cases among vaccinated children for the different birth-cohorts and calendar periods are given in Tables 4a and b.

Nine hundred and fifty-six children born from 1996 and vaccinated with at least one dose of a pertussis vaccine had a laboratory confirmed pertussis between October 1997 and September 2005. Among those children 595 (62%) 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 twenty-four children (13%) had received two doses and 237 (25%) one dose before the pertussis episode.

In the birth cohort that corresponds to the recruitment phase of Trial II, 235 vaccinated children had a laboratory confirmed pertussis episode, 218 (93%) had received a full primary series before onset of the confirmed pertussis episode, 7 had received 2 doses and 10 one dose before onset of cough. Most of those children, two hundred and twenty-three of the 235, participated in vaccine Trial II. Detailed data for vaccine failures among Trial II children with three or four doses (for 211 of the 223 children) are given in section 2.15.

Table 4a Laboratory confirmed cases of pertussis with onset of cough from 1 October 1997 until 30 September 2005, per birth-cohort and period, among children with at least one dose of DTPa or monovalent P prior to onset of cough. In parenthesis are given the number of children with 1dose/2 doses under 2 years of age /3,4 doses or 2 doses from 2 years of age prior to onset.

	Calendar period for onset of cough of laboratory confirmed cases of pertussis								
Birth-cohort	**1997 Q4**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005 Q1-Q3**
1996	**3 (0, 2, 1)**	**15 (0, 1, 14)**	**35 (0, 0, 35)**	**36 (0, 2, 34)**	**17 (1, 0, 16)**	**39 (0, 0, 39)**	**14 (0, 0, 14)**	**56 (0, 0, 56)**	**18 (0, 0, 18)**
1997	**11 (5, 6, 0)**	**21 (6, 12, 3)**	**19 (0, 1, 18)**	**22 (0, 0, 22)**	**14 (0, 0, 14)**	**27 (0, 0, 27)**	**6 (0, 0, 6)**	**21 (0, 0, 21)**	**11 (0, 0, 11)**
1998	**-**	**23 (16 ,7 ,0)**	**29 (9, 14, 6)**	**12 (0, 0, 12)**	**4 (0, 0, 4)**	**16 (1, 0, 15)**	**11 (0, 0, 11)**	**33 (0, 0, 33)**	**17 (0, 0, 17)**
1999	**-**	**-**	**35 (29, 6, 0)**	**40 (16, 19, 5**	**6 (0, 0, 6)**	**14 (2, 0, 12)**	**4 (0, 0, 4)**	**13 (0, 0, 13)**	**10 (0, 0, 10)**
2000	**-**	**-**	**-**	**30 (25, 5, 0)**	**12 (6, 4, 2)**	**9 (0 ,0, 9)**	**6 (0, 0, 6)**	**14 (1, 0, 13)**	**8 (0, 0, 8)**
2001	**-**	**-**	**-**	**-**	**11 (8, 3, 0)**	**16 (6, 8, 2)**	**8 (0, 0, 8)**	**12 (0, 0, 12)**	**4 (0, 0, 4)**
2002	**-**	**-**	**-**	**-**	**-**	**32 (29, 3, 0)**	**10 (7, 1, 2)**	**10 (0, 0, 10)**	**6 (0, 0, 6)**
2003	**-**	**-**	**-**	**-**	**-**	**-**	**11 (9, 2, 0)**	**24 (7, 12, 5)**	**9 (0, 0, 9)**
2004	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**38 (34, 4, 0)**	**25 (11, 12, 2**
2005 Q1-Q3	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**9 (9, 0, 0)**
Total	**14 5, 8 , 1**	**59 22,20,17**	**118 38,21,59**	**140 41,26,73**	**64 15,7,42**	**153 38,11,104**	**70 16,3,51**	**221 42,16,163**	**117 20,12,85**

Table 4b Laboratory confirmed cases of pertussis with onset of cough from 1 October 1997 until 30 September 2005, per birth-cohort and period among children with at least one dose of DTPa or monovalent P prior to onset of cough. In parenthesis are given the number of children with 1dose/2 doses under 2 years of age /3,4 doses or 2 doses from 2 years of age prior to onset

	Calendar period for onset of cough of laboratory confirmed cases of pertussis								
Birth-cohort	**1997 Q4**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005 Q1-Q3**
1993. 6 – 1994. 5	**9 (1 , 0 , 8)**	**29 (1, 2 ,26)**	**66 (3, 0 , 63)**	**58 (3 ,2, 53)**	**20 (0, 0, 20)**	**11 (0, 1, 10)**	**9 (1 ,0, 8)**	**23 (1, 0, 22)**	**10 (0, 2, 8)**

All children but five of the vaccinated, with known clinical follow-up, were coughing during the pertussis episode. The minimum duration of cough, if cough, was 3 days – the median duration was 44 days.

Spasmodic cough for 21 days or more (WHO-definition) was reported for 78% of the episodes (compared to 91% for the unimmunised children) – the median duration was 33 days. For 13% of the episodes there was no spasmodic cough compared to 4% 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 Laboratory confirmed pertussis in children born 1996 or later

In sections 2.10 - 2.13 data for laboratory confirmed episodes observed from 1 October 1997 until 30 September 2005 among children born 1996 until 30 September 2005 are summarised.

Children were divided in two sub-cohorts; children born 1996 until 30 June 1997, and children born 1 July 1997 until 30 September 2005. We regard the first 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 cohort has been more complex to analyse since the procurement of vaccines has varied considerably among the counties for children born after June 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®); 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.

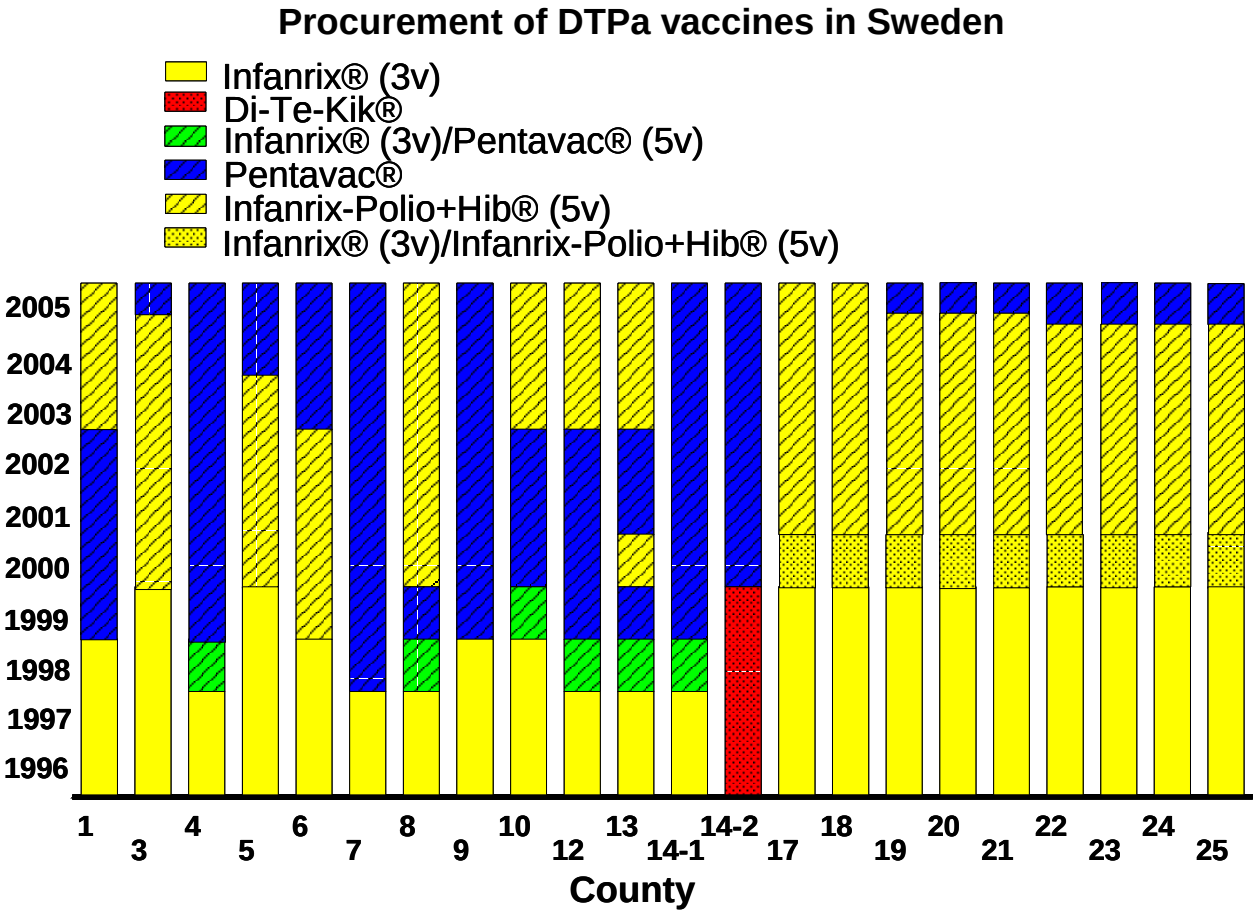


Figure 1 Procurement of vaccines by county 1996 –2005. County number on the X-axis and on the map are given on next page (p 23), together with county name name and population figure are given below 2

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).

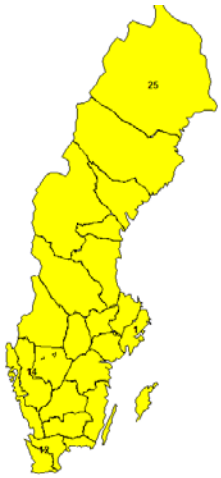
Sub-cohort analysis for the vaccine specific cohorts for children born 1 July 1997 until 30 September 2005 are presented in Appendix 2. Carefully, observe that figures in table 7 are modified before the calculations presented in Appendix 2. The reclassification mainly concerns children in table 7 who 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 switched from Infanrix®/Infanrix-Polio+Hib® to Pentavac®, there is a possibility that a later dose should have been from the other vaccine, then the child instead is 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 Laboratory confirmed pertussis in children born 1996 - 30 June 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 Gothenburg area. Available figures show vaccine coverage at about 98% for children born 1996. Nearly all children born 1996 until June 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 351 reports of laboratory confirmed pertussis in the database from 1 October 1997 until 30 September 2005. Forty of these reports concern children without any pertussis



No.	County	2004 Mid year population	No.	County	2004 Mid year population
1	Stockholm	1 866 886	14	V Götaland	1 518 444
3	Uppsala	301 530	17	Värmland	273 555
4	Södermanland	260 725	18	Örebro	273 928
5	Östergötland	415 444	19	Västmanland	260 570
6	Jönköping	328 323	20	Dalarna	276 281
7	Kronoberg	177 867	21	Gävleborg	276 731
8	Kalmar	234 691	22	Västernorrland	244 150
9	Gotland	57 598	23	Jämtland	127 535
10	Blekinge	150 112	24	Västerbotten	256 416
12	Skåne	1 156 808	25	Norrbotten	252 730
13	Halland	282 555		**Sweden**	**8 993 531**

vaccination prior to onset of the pertussis episode. Four children had received one dose, 15 children two doses and 292 children were fully vaccinated before the episode, Table 5.

One of the unimmunised children was between 5 and 12 months and 39 were older than 12 months of age at onset of cough. All, but four, of the unimmunised children had spasmodic cough for at least 21 days. One child vaccinated with an "other vaccine" at the third dose prior to onset of cough had earlier received two doses of Infanrix®, and 7 children had only received "Other vaccine". Three children had received three doses of Di-Te-Kik. The remaining vaccinated children had only received Infanrix®. Ninety 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 1 October 1997 until 30 September 2005, among children born 1996 until 30 June 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	26	-	-	26 (23)
	1	-	1	0	1 (1)
	2	-	5	0	5 (4)
	3-4	-	219	8	227 (176)
1997.1 - 6	0	14	-	-	14 (13)
	1	-	3	0	3 (2)
	2	-	10	0	10 (5)
	3	-	62	3	65 (56)
Total	0	40 (36)	-	-	40 (36)
	1	-	4 (3)	0	4 (3)
	2	-	15 (9)	0	15 (9)
	3-4	-	281 (223)	11 (9)	292 (232)
Total	-	40 (36)	300 (235)	11 (9)	351 (280)

2.11 Person-time & incidence in children born 1996 - 30 June 1997

According to Statistics Sweden 95 158 children were born 1996 and 90 383 children were born during 1997. County specific figures show that 9,1% of the children were born in the Gothenburg and surrounding areas, not under our surveillance for this report, and we end up with an estimate of about 126 540 children who were born in our follow-up areas between 1996 and 30 June 1997.

To simplify person-time calculations we assume an equal number of new-born during each of the 18 birth months – i.e. 7 030 children per month. We also assume that all children were born in the middle of the month and that vaccination according to the regular schedule took place in the middle of the third, fifth and twelfth month after the day of birth. With these simplifications we estimated the number of person-months for each monthly cohort of new-borns in the following intervals and according to the rules above:

- Person-months from birth to the first of 30 September 2005 or dose 1.
- Person-months between Dose 1 and the first of 30 September 2005 or dose 2.
- Person-months between Dose 2 and the first of 30 September 2005 or dose 3.
- Person-months after dose 3 until 30 September 2005.

Person-time before 1 October 1997 will not be included since the collection of laboratory confirmed cases of pertussis started from that date.

Children born 1996 until 30 June 1997 were followed from 1 October 1997 until 30 September 2005. Altogether approximately 126 540 children have been followed for approximately 1,012,320 person-years of follow-up. During follow-up 351 cases of laboratory confirmed pertussis have been reported to the surveillance system - 311 cases among vaccinated and 40 among unimmunised children (Table 5).

Table 6a presents the 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 eight one-year intervals.

Table 6a Person-time of follow-up for children born 1996 until 30 June 1997 and followed from 1 October 1997 until 30 September 2005 divided by period before Dose 1 (before 3 months of age), period after Dose 1 before Dose 2, period after Dose 2 before Dose 3 and period after Dose 3. Number of observed cases in the different periods and incidence per 100 000 person-years of follow-up irrespective of vaccine are also given. In parenthesis are given figures including the unimmunised children of respective age group (intent to treat). *In Italics, in the second row, are the corresponding figures for children with 21 or more days of spasmodic cough.*

Period or (Age)[3]	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 (<3 months of age)	-	-	-	-
Between Dose 1 and 2 (3-<5 months of age)	**1 170**	**4** ***3***	**342** ***256***	**(93-875)** ***(53-749)***
Between Dose2 and 3 (5-<12 months of age)	**22 555**	**15 (16)** ***9 (10)***	**67 (71)** ***40 (44)***	**(37-110) (40-115)** ***(18-76) (21-82)***
After Dose 3 (>=12 months of age)	**988 595**	**292 (331)** ***232 (267)***	**30 (33)** ***23 (27)***	**(26-33) (30-37)** ***(21-27) (24-30)***

Table 6b Person-time of follow-up after Dose 3, or from 12 months of age for children born 1996 until 30 June 1997, and followed from 1 October 1997 until 30 September 2005. Follow-up is divided in eight age intervals. (see also legend Table 6a)

Period[4]	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 between 12 and <24 months of age	**126 540**	**10 (15)** ***7 (12)***	**8 (12)** ***6 (9)***	**(4-15) (7-20)** ***(2-11) (5-16)***
After Dose 3 and/or between 24 and <36 months of age	**126 540**	**33 (36)** ***28 (31)***	**26 (28)** ***22 (24)***	**(18-37) (20-39)** ***(15-32) (17-35)***
After Dose 3 and/or between 36 and <48 months of age	**126 540**	**49 (56)** ***38 (44)***	**39 (44)** ***30 (35)***	**(29-51) (33-57)** ***(21-41) (25-47)***
After Dose 3 and/or between 48 and<60 month of age	**126 540**	**33 (39)** ***28 (34)***	**26 (31)** **22 (27)**	**(18-37) (22-42)** ***(15-32) (19-38)***
After Dose 3 and/or between 60 and<72 month of age	**126 540**	**33 (38)** **25 (29)**	**26 (30)** **20 (23)**	**(18-37) (21-41)** ***(13-29) (15-33)***

[3] Age intervals in the heading classifies the unimmunised children
[4] For both children with three doses prior to onset of cough and for the unimmunised children

After Dose 3 and/or between 72 and<84 month of age	**126 540**	**39 (40)** ***32 (33)***	**31 (32)** ***25 (26)***	**(22-42) (23-43)** ***(17-36) (18-37)***
After Dose 3 and/or between 84 and<96 month of age	**126 540**	**34 (39)** ***26 (30)***	**27 (31)** ***21 (24)***	**(19-38) (22-42)** ***(13-30) (16-34)***
After Dose 3 and/or from 96 months of age	**102 815**	**61 (68)** ***48 (54)***	**59 (66)** ***47 (53)***	**(45-76) (51-84)** ***(34-61) (39-69)***

We know from earlier studies that the risk of being exposed to pertussis illness rises with age during pre-school years. In Table 6b follow-up from 12 months of age is divided in eight age intervals - 12-<24 months, 24 -<36 months, 36-<48 months, 48-<60 months, 60 - <72 months, 72 - <84 months, 84-<96 months and older than 96 months of age.

One must bear in mind that children in this cohort lack follow-up in the surveillance program for the period before October 1997. Results in Table 6b might suggest a waning immunity among fully vaccinated children.

2.12 Laboratory confirmed pertussis in children born 1 July 1997 or later

Since the vaccination period for children born 1 July 1997 or later coincides with the period of collecting laboratory confirmed cases of pertussis all laboratory confirmed pertussis cases.

For children in this cohort there were 1 221 reports of laboratory confirmed pertussis in the database for episodes between 1 October 1997 and 30 September 2005, whereof 576 reports concern children without any pertussis vaccination prior to onset of the pertussis episode and 645 children 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" (67 children) were first vaccinated with Infanrix®, then with Pentavac®. The other 345 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 1 October 1997 until 30 September 2005, among children born 1 July 1997 until 30 September 2005 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)
1997.7 – 12	**0**	**25**	**-**	**-**	**-**	**25 (21)**
	1	**-**	**8**	**-**	**0**	**8 (7)**
	2	**-**	**9**	**-**	**0**	**9 (6)**
	3	**-**	**53**	**-**	**4**	**57 (45)**
1998	**0**	**53**	**-**	**-**	**-**	**53 (46)**
	1	**-**	**19**	**7**	**0**	**26 (20)**
	2	**-**	**14**	**1**	**6**	**21 (15)**
	3	**-**	**39**	**19**	**40**	**98 (74)**
1999	**0**	**105**	**-**	**-**	**-**	**105 (95)**
	1	**-**	**14**	**30**	**3**	**47 (44)**
	2	**-**	**11**	**14**	**0**	**25 (18)**
	3	**-**	**21**	**24**	**5**	**50 (36)**
2000	**0**	**93**				**93 (88)**
	1	**-**	**15**	**17**	**0**	**32 (26)**

	2	**-**	**3**	**6**	**0**	**9**	**(7)**
	3	**-**	**13**	**18**	**7**	**38**	**(26)**
2001	**0**	**36**				**36**	**(34)**
	1	**-**	**1**	**13**	**0**	**14**	**(12)**
	2	**-**	**5**	**6**	**0**	**11**	**(7)**
	3	**-**	**5**	**21**	**0**	**26**	**(19)**
2002	**0**	**78**				**78**	**(72)**
	1	**-**	**12**	**24**	**0**	**36**	**(30)**
	2	**-**	**0**	**4**	**0**	**4**	**(4)**
	3	**-**	**3**	**12**	**3**	**18**	**(14)**
2003	**0**	**60**	**-**	**-**	**-**	**60**	**(49)**
	1	**-**	**9**	**7**	**0**	**16**	**(13)**
	2	**-**	**6**	**8**	**0**	**14**	**(11)**
	3	**-**	**9**	**4**	**1**	**14**	**(11)**
2004	**0**	**89**				**89**	**(79)**
	1		**30**	**15**	**0**	**45**	**(40)**
	2		**10**	**6**	**0**	**16**	**(12)**
	3		**1**	**0**	**1**	**2**	**(0)**
2005.1-9	**0**	**37**	**-**	**-**	**-**	**37**	**(34)**
	1		**4**	**5**	**0**	**9**	**(9)**
	2		**0**	**0**	**0**	**0**	**(0)**
	3		**-**	**-**	**-**		
Total	**0**	**576**	**-**	**-**	**-**	**576**	**(518)**
Total	**1**	**-**	**112 (99)**	**118 (99)**	**3 (3)**	**233**	**(201)**
Total	**2**	**-**	**58 (43)**	**45 (32)**	**6 (5)**	**109**	**(80)**
Total	**3**	**-**	**144 (109)**	**98 (73)**	**61 (43)**	**303**	**(225)**
Total	**0 – 3**	**576 (518)**	**314 (251)**	**261 (204)**	**70 (51)**	**1221**	**(1024)**

Among the 576 unimmunised children 396 (69%) 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. Seventy-three were between 3 and 5 months of age, 26 between 5 and 12 months of age and 81 were older than 12 months at the onset.

Ninety 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 80%, and 78%, respectively.

2.13 Person-time & incidence in children born 1 July 1997 - 30 Sept. 2005

According to data from Statistics Sweden (http://www.scb.se) there were 90,383 children born during 1997, 89,028 during 1998, 88,176 during 1999, 90,441 during year 2000, 91,466 during 2001 , 95,815 during 2002 and 99,230 during 2003. In 2004, 101,090 children were born and according to preliminary figures for 2005 there were at about 102,000 children born that year. Thus, there were considerably more newborns during 2002 until 2005 compared to 1997 until 2001.

To simplify person-time calculations we assume an equal number of new-born children during each of the 60 calendar months of birth's for the period 1 July 1997 until 30 June 2002 - 6 800 children per month. For the period 1 July 2002 until 30 September 2005 we take into account the larger birth cohorts of 2002 until 2005. For each of the 39 calendar months in this period we calculate person time of follow-up with 7500 children per month. Altogether approximately 712,000 children have been followed for approximately 2,818 million years of follow-up.

Table 8a gives the total number of person-months and laboratory confirmed pertussis cases divided in age/vaccination intervals described in section 2.11.

Table 8a Person-time of follow-up for children born from 1 July 1997 until 30 September 2005 and followed from 1 October 1997 until 30 September 2005 divided by period before Dose 1 (< 3 months of age), period after Dose 1 before Dose 2, period after Dose 3 before Dose 3 and period after Dose 3. Number of observed cases in the different periods and incidence per 100,000 person-years irrespective of vaccine is also given. In parenthesis are given figures including the unimmunised children of respective age group (intent to treat). *In Italics are the corresponding figures for children with 21 or more days of spasmodic cough.*

Period or (Age)[5]	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 (<3 months of age)	**169 760**	**396** ***351***	**233** ***207***	**(211-257)** ***(186-229)***
Between Dose 1 and 2 (3- <5 months of age)	**111 750**	**233 (306)** ***201 (265)***	**208 (274)** ***180 (237)***	**(183-236) (244-395)** ***(156-209) (209-266)***
Between Dose2 and 3 (5- <12 months of age)	**371 440**	**109 (135)** ***80 (104)***	**29 (36)** ***22 (28)***	**(24-36) (30-43)** ***(17-27) (23-34)***
After Dose 3 (>=12 months of age)	**2 165 810**	**303 (384)** ***225 (304)***	**14 (18)** ***10 (14)***	**(12-16) (16-20)** ***(9-12) (13-16)***

In Table 8b the interval after 12 months of age was divided in seven age-intervals 12-<24, 24-<36, 36-<48, 48-<60, 60-<72, 72-<84 and above 84 months of age.

Table 8b Person-time of follow-up after Dose 3, or from 12 months of age for children born from 1 July 1997 until 30 September 2005, and followed from 1 October 1997 until 30 September 2005. Follow-up is divided in seven age intervals. (see also legend Table 8a)

Period	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 between 12 and <24 months of age	**565 500**	**50 (75)** ***37 (61)***	**9 (13)** ***7 (11)***	**(7-12) (10-17)** ***(5-9) (8-14)***
After Dose 3 and/or between 24 and <36 months of age	**475 500**	**62 (80)** ***47 (65)***	**13 (17)** ***10 (14)***	**(10-17) (13-21)** ***(7-13) (11-17)***
After Dose 3 and/or between 36 and <48 months of age	**387 860**	**42 (55)** ***32 (45)***	**11 (14)** ***8 (12)***	**(8-15) (11-18)** ***(6-12) (8-16)***
After Dose 3 and/or between 48 and <60 months of age	**306 000**	**48 (62)** ***34 (48)***	**16 (20)** **11 (16)**	**(12-21) (16-26)** ***(8-16) (12-21)***
After Dose 3 and/or between 60 and <72 months of age	**224 400**	**37 (45)** ***27 (34)***	**16 (20)** ***12 (15)***	**(12-22) (15-27)** ***(8-17) (10-21)***
After Dose 3 and/or between 72 and <84 months of age	**142 800**	**45 (46)** ***33 (34)***	**32 (32)** ***23 (24)***	**(23-42) (24-43)** ***(16-32) (16-33)***
After Dose 3 and/or from 84 months of age	**63 750**	**19 (21)** ***15 (17)***	**30 (33)** ***24 (27)***	**(18-47) (20-50)** ***(13-39) (16-43)***

[5] Age intervals in the heading classifies only the unimmunised children

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 that has been observed in Sweden during follow-up from 1997 to 2005 as described in Section 3, Figure 6b

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 this type of open and non-randomised study based on 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. Late effects may only be detected by sustained disease surveillance combined with national vaccination registers containing lot specific information on which vaccines have been administered to each individual.

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 1 October 1997 until 30 September 2005 among children with 3 or 4 doses before onset of cough. During eight-year of follow-up there were 16 more cases in the Trial II cohort compared to the seven-year report. In all there were 230 cases of laboratory confirmed pertussis participants in Trial I and Trial II who had received 3 trial doses.

The overall incidence was 33 per 100,000 person years of follow-up (Table 9b). The trial participants were between 4 and 13 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 1, 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 1996 until September 2005, Tables 6 and 8. Interestingly, the estimated incidence after four doses in the DTPa2 trial arm (25/100 000 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 (40/100 000 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 Q1–Q3	Total
Trial I										
3d CLI DTPw	0	0	0	1	0	1	0	0	0	2
3d CLI DTPw + 1 d. CLL Pa5	0	1	0	0	0	0	0	0	0	1
3d SB DTPa2	0	0	1	0	0	0	0	0	0	1
3d SB DTPa2 + 1 d. SB Pa3	0	1	1	0	1	0	0	1	0	4
3d CLL DTPa5	1	1	1	4	2	1	0	1	0	11
Sum	1	3	3	5	3	2	0	2	0	19
Trial II										
3d Evans DTPw	0	4	18	4	3	3	3	6	1	42
3d SB DTPa2	0	6	5	5	1	1	0	6	3	27
3d SB DTPa2 + 1 d. SB Pa3	3	4	8	8	4	0	0	0	0	27
3d Chiron DTPa3	1	5	11	18	6	2	1	5	1	50
3d CLL DTPa5	4	6	18	18	6	4	3	4	2	65
Sum	8	25	60	53	20	10	7	21	7	211
Total Trials I & II	9	28	63	58	23	12	7	23	7	230

Table 9b No. of laboratory confirmed cases among participants in Trial I and Trial II from 1 October 1997 until 30 September 2005 (see Table 9a), no. of fully vaccinated children, estimated person years of follow up, and incidence per 100 000 person years of follow up during the eight 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	16 008	3	19	4 – 55
3d SB DTPa2 +/-1 d. SB Pa3	2 538	20 304	5	25	8 – 57
3d CLL DTPa5,	2 551	20 408	11	54	27 - 96
Trial II					
3d Evans DTPw	19 971	159 768	42	26	19 – 36
3d SB DTPa2	6 444	51 552	27	52	35 – 76
3d SB DTPa2 + 1 d. SB Pa3	13 731	109 848	27	25	16 – 36
3d Chiron DTPa3	20 239	161 912	50	31	23 – 41
3d CLL DTPa5	20 230	161 840	65	40	31 – 51
Total Trials I & II	87 705	701 640	230	33	29 - 37

Table 9c shows the incidence figures during the eight-year follow up for children immunized at 3, 5 and 12 months of age in Trial II. The overall rate varies from 21/100 000 in the DTPw group compared to 33-47 /100 000 in the DTPa groups. 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=1.65 (1.09 – 2.50).

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 1 October 1997 until 30 September 2005 at 3 to 12 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**	**139 960**	**29**	**21** **14-30**	**1.00**
3d SB DTPa2	**5 542**	**44 336**	**21**	**47** **29-72**	*2.29* **1.30 – 4.01**
3d SB DTPa2 + 1 d. SB Pa3	**12 122**	**96 976**	**20**	**21** **13-32**	*1.00* **0.56 – 1.76**
3d Chiron DTPa3	**17 739**	**141 912**	**47**	**33** **24-44**	*1.60* **1.01 – 2.54**
3d CLL DTPa5	**17 728**	**141 824**	**50**	**35** **26-46**	*1.70* **1.08 – 2.69**
Total Trial II	**70 626**	**565 008**	**167**	**30** **25-34**	

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 1 566 of 1 572 children born 1996 until September 2005 (see section 2.4). Four hundred and nine (26%) of the children had a hospital admission during the pertussis episode and 1 157 had none.

2.16.1 Hospital admission and age at the pertussis episode

In all 278 of 397 infants (71%), 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 245 children in age-group 3-<5 months, for 192 children in age-group 5-<12 months and for 732 children aged 12-months at the beginning of the pertussis episode were respectively 35%, 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.

Table 10 Duration of hospital stay due to the pertussis disease among children born 1996 until September 2005, during October 1, 1997 until September 30, 2005, 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 number of children
			0-30 days	31-60 days	61-90 days	91-150 days	151-360 days	361- days	
Unimmunised children	**Duration of hospital stay**	**0 days**	16	42	60	42	16	115	**291**
		1-7 days	33	60	53	19	7	3	**175**
		8- days	51	51	29	12	4	2	**149**
	Total number of children		**100**	**153**	**142**	**73**	**27**	**120**	**615**
	Total no. and rate of children with a hospital stay		***84*** ***84%***	***111*** ***73%***	***82*** ***58%***	***31*** ***42%***	***11*** ***41%***	***5*** ***4%***	***324*** ***53%***
Children vaccinated with one dose	**Duration of hospital stay**	**0 days**	-	-	1	117	48	6	**172**
		1-7 days	-	-	1	39	9	0	**49**
		8- days	-	-	0	16	0	0	**16**
	Total number of children		-	-	**2**	**172**	**57**	**6**	**237**
	Total no. and rate of children with a hospital stay		-	-	***1*** ***50%***	***55*** ***32%***	***9*** ***16%***	***0*** ***0%***	***65*** ***27%***
Children vaccinated with two or more doses	**Duration of hospital stay**	**0 days**	-	-	-	-	98	596	**694**
		1-7 days	-	-	-	-	9	9	**18**
		8- days	-	-	-	-	1	1	**2**
	Total number of children		-	-	-	-	**108**	**606**	**714**
	Total no. and rate of children with a hospital stay		-	-	-	-	***10*** ***9%***	***10*** ***2%***	***20*** ***3%***
All children regardless of vaccination status	**Duration of hospital stay**	**0 days**	16	42	61	159	162	717	**1 157**
		1-7 days	33	60	54	58	25	12	**242**
		8- days	51	51	29	28	5	3	**167**
	Total number of children		**100**	**153**	**144**	**245**	**192**	**732**	**1 566**
	Total no. and rate of children with a hospital stay		***84*** ***84%***	***111*** ***73%***	***83*** ***58%***	***86*** ***35%***	***30*** ***16%***	***15*** ***2%***	***409*** ***26%***

The age specific incidence rate of hospitalisation due to pertussis is highest, 164 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. Age specific incidence of hospitalisation was highest among children below three months of age at beginning of the pertussis

episode and decreases rapidly thereafter by increasing age, suggesting that circulating pertussis in the country has not decreased to a level that offers sufficient protection for the youngest, nearly always, unimmunised infant.

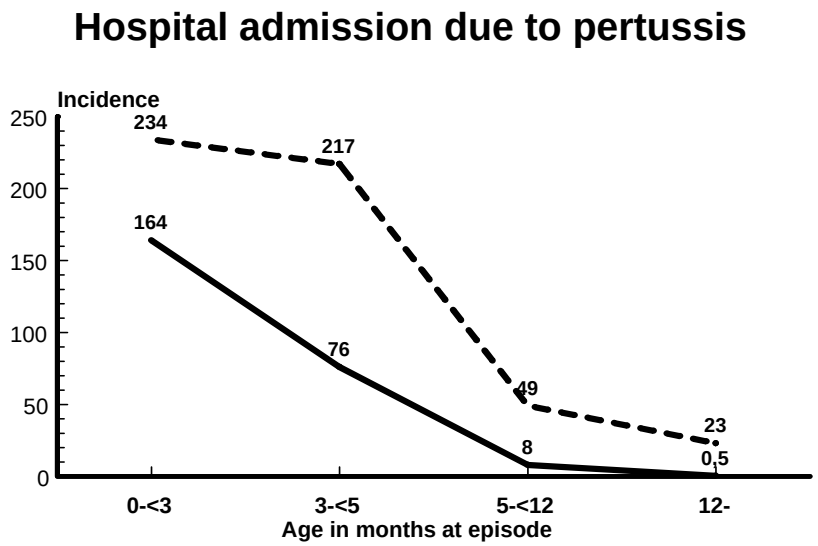


Figure 2 Age specific incidence of hospital admission due to the pertussis disease, below, and age specific incidence of all pertussis per 100 000 years of follow-up regardless of vaccination status for children born 1996 to September 2005 with a laboratory confirmed *B. pertussis* reported from October 1, 1997 until September 30, 2005.

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 84%, 73% and 58% respectively, and drops to only 4% for unimmunised children above one year of age. For children between 3-<5 and 5-<12 months of age the rate of hospital admission was still 42% respectively 41%. 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 levels for these trends are lower when compared to that for the unvaccinated children.

The overall rate of hospital admission for unimmunised children was 53%. For those children at about 45% 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 27%, with at about 25% of the admissions longer than a week, respectively 3%, with 10% of the admissions longer than a week, for children vaccinated with 2 or more doses before the pertussis episode ($p<0{,}001$).

However, this "striking" association between rate of hospital admission and vaccination status before the episode is confounded by age. For children >=12- months of age, the rate of hospital admission was low and "independent" of the vaccination status of the child. In the age interval 5-<12 months the hospitalisation rates were 41%, 16% and 9% for unimmunised, and for children vaccinated with one and with two or more doses (for most children two doses) respectively. This downward "trend" in rate of hospitalisation by number of doses of a pertussis vaccine before the episode was statistically significant, $p<0{,}001$.

Comparing the same age groups for unimmunised and those children who had been given one dose of a pertussis vaccine before the episode we receive the following results:

1. Forty-two percent of unimmunised and 32% of one-dose vaccinated children were hospitalised during a pertussis episode which occurred between 3 and less than 5 months of age of the child.

This difference was not statistically significant, 0,10<p<0,20. The median age at start of episode was 101 days for the 73 unvaccinated and 122 days for the 172 vaccinated.

2. Forty-one percent of unimmunised and 16% of one-dose vaccinated children were hospitalised during a pertussis episode between 5 and less the 12 months of age. This difference was statistically significant, p<0,025. The median age at start of episode was 251 days for the 27 unvaccinated and 169 days for the 57 vaccinated children.
3. Combining the two age groups we have 42% and 28% of the children with a hospital admission for unimmunised respectively for vaccinated with one dose during a pertussis episode which occurred in the age interval 3-<12 months of age. This difference was statistically significant, p<0,025. The median age at start of episode was 109 days and 128 days for the 100 unvaccinated respectively for the 229 children vaccinated with one dose before the episode.
4. Given a hospital admission, 38% and 25% of the admissions have a duration longer than a week for unimmunised and vaccinated with one dose respectively. This difference was not statistically significant, 0,10<p<0,20.

These results together might indicate that, if the child has received a pertussis disease, there might 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 also 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 1,560 of the 1,572 children born 1996 until September 2005.

A respiratory complication (with apnea, n=132, or without apnea, n=142) was reported for 274 (17%) and a dehydration for 138 (9%) of the children. Uncommon complications, i.e. neurological and other serious complications, were reported for 9 (0,6%) and 4 (0,2%) of the children respectively. Two of the latter represent deaths. (In addition there are three more deaths among infants and and one death in a 3 y old child, buth these 4 were not followed within the project.)

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. Three hundred and forty-six children (22.2%) had at least one complication due to the pertussis disease during their pertussis episode and 1,214 (77,8) had no complication at all.

2.17.1 Any complication and age at the pertussis episode

In all 185 of 395 children (47%), who were below 3 months of age at beginning of the episode, had at least one complication. The corresponding rates for 245 children in age-group 3-<5 months, for 190 children in age-group 5-<12 months and for 730 children aged 12- months at the beginning of the pertussis episode were 19%, 15% and 12% (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).

The age specific incidence rate of any complication due to pertussis is highest, 109 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.

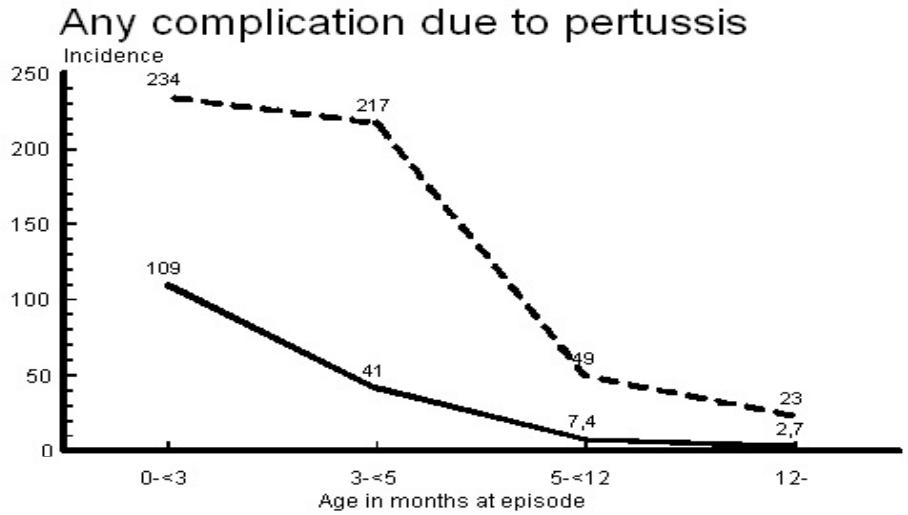


Figure 3 Age specific incidence of any complication due to the pertussis disease, below, and age specific incidence of all pertussis per 100,000 years of follow-up regardless of vaccination status for children born 1996 to September 2005 with a laboratory confirmed *B. pertussis* reported from October 1, 1997 until September 30, 2005.

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

The events "any complication" were also 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 rate was 62%, 46% and 37% respectively, and drops to 12% for children above one year of age. For children between 3-<5 and 5-<12 months of age the rate of any complication was 26% and 38% - for the combined age group it was 29%. 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 of complication rate by increasing age are not observed for the vaccinated children, neither for children vaccinated with only one dose nor for children who have received two or more doses of a pertussis vaccine before the pertussis episode. 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 37%. Regardless of age the rate of any complication for children vaccinated with one dose was 17%, and 11% 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 12% 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 38% 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, $p<0.001$.

Comparing the same age groups for unimmunised children and children vaccinated with one dose of a pertussis vaccine before the episode we receive the following results:

1. Twenty-six percent of the unimmunised and 16% of children vaccinated with one dose before the episode had at least one complication during a pertussis episode occurring between 3 and less than 5 months of age. This difference was not statistically significant, $0.10<p<0.20$.
2. Thirty-eight percent of the unimmunised and 14% of children vaccinated with one dose before the episode had at least one complication during a pertussis episode occurring between 5 and less the 12 months of age. This difference was statistically significant, $p<0.025$.

3. Combining the two age groups we have 29% and 16% of the children with a complication during the pertussis episode for unimmunised respectively for vaccinated with one dose. This difference was statistically significant, p<0,001.

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

Table 11 Any complication due to the pertussis disease among children born 1996 until September 2005, from October 1, 1997 until September 30, 2005, 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 number of children**
			0-30 days	**31-60 days**	**61-90 days**	**91-150 days**	**151-360 days**	**361- days**	
Unimmunised children	**Any complication**	**No**	38	82	90	54	16	106	**386**
		Yes	61	70	52	19	10	13	**225**
	Total number of children		**99**	**152**	**142**	**73**	**26**	**119**	**611**
	Rate of children with any complication		***62%***	***46%***	***37%***	***26%***	***38%***	***11%***	***37%***
Children vaccinated with one dose	**Any complication**	**No**	-	-	0	144	49	4	**1975**
		Yes	-	-	2	28	8	2	**40**
	Total number of children		-	-	**2**	**172**	**57**	**6**	**237**
	Rate of children with any complication		-	-	***100%***	***16%***	***14%***	***33%***	***17%***
Children vaccinated with two or more doses	**Any complication**	**No**	-	-	-	-	96	535	**631**
		Yes	-	-	-	-	11	70	**81**
	Total number of children		-	-	-	-	**107**	**605**	**712**
	Rate of children with any complication		-	-	-	-	***10%***	***12%***	***11%***
All children regardless of vaccination status	**Any complication**	**No**	38	82	90	198	161	645	**1 214**
		Yes	61	70	54	47	29	85	**348**
	Total number of children		**99**	**152**	**144**	**245**	**190**	**730**	**1 560**
	Rate of children with any complication		***62%***	***46%***	***38%***	***19%***	***15%***	***12%***	***22%***

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-one percent, 245 of 346, of children with at least one

complication also had a hospital admission due to the disease during the episode. For 1214 children without any complication the hospitalisation rate was 13% (p<0.001). For children with any complication at about 50% of the hospital admissions had a duration 8 days or longer. For children without any complication 25% of the hospital admissions were longer than 8 days (p<0.001)

2.18 Spasmodic cough during the pertussis episode

Data on cough and spasmodic cough were available for all 1 572 children born 1996 until September 2005. All children but 5 were coughing during their pertussis episode. One thousand four hundred and nineteen (90,2%) of the children had spasmodic cough during the pertussis episode and 153 (9,8%) reported no spasmodic cough. Spasmodic cough for 21 or more days during the pertussis episode was reported for 82,9% of the children.

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

In all 353 of 398 infants (89%), 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 245 children in age-group 3-<5 months, for 193 children in age-group 5-<12 months and for 736 children aged 12- months at the beginning of the pertussis episode were 86%, 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).

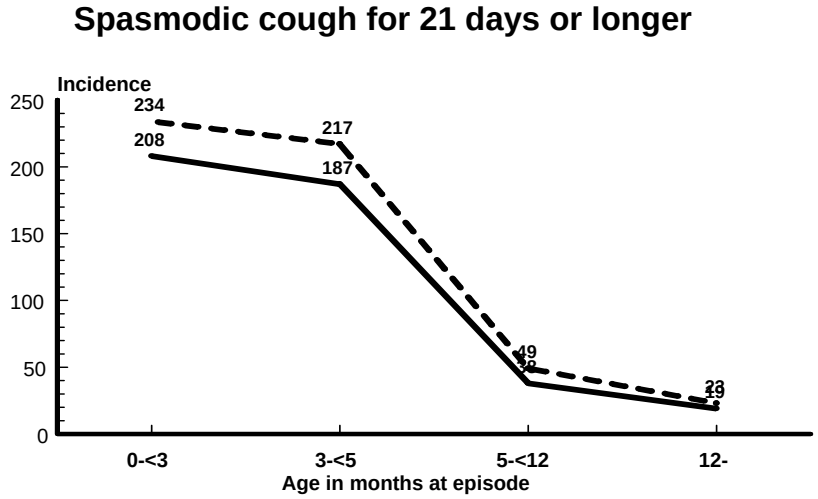


Figure 4 Age specific incidence of spasmodic cough for 21 or more days due to the pertussis disease, below, and age specific incidence of all pertussis per 100,000 years of follow-up regardless of vaccination status for children born 1996 to September 2005 with a laboratory confirmed *B. pertussis* reported from October 1, 1997 until September 30, 2005.

The age specific incidence rate of pertussis with 21 or more days of spasmodic cough was highest, 208 per 100,000 years of follow-up, for children 0 to <3 months of age and decreases to19 per 100,000 years for children above one year of age at the pertussis episode. Thus, there was a weak association between age of child at beginning of the pertussis episode and, if a pertussis disease, the risk of also suffering a long duration of spasmodic cough during the pertussis disease. The risk for a long duration of spasmodic cough was even high for the elderly children.

2.18.2 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.

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 *90%*. 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 *76%*. 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, $p<0.001$.

Table 12 Duration of spasmodic cough due to the pertussis disease among children born 1996 until September 2005, during October 1, 1997 until September 30, 2005, 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 number of children
			0-30 days	31-60 days	61-90 days	91-150 days	151-360 days	361- days	
Unimmunised children	**Duration of spasmodic cough**	**0 days**	4	6	8	2	0	4	**24**
		1-20 days	3	18	6	7	2	2	**38**
		21- days	93	130	128	64	25	114	**554**
	Total number of children		**100**	**154**	**142**	**73**	**27**	**120**	**616**
	Rate of children with spasmodic cough for 21 days or longer		***93%***	***84%***	***90%***	***88%***	***93%***	***95%***	***90%***
Children vaccinated with one dose	**Duration of spasmodic cough**	**0 days**	-	-	0	9	4	0	**13**
		1-20 days	-	-	0	16	4	0	**20**
		21- days	-	-	2	147	49	6	**204**
	Total number of children		-	-	**2**	**172**	**57**	**6**	**237**
	Rate of children with spasmodic cough for 21 days or longer		-	-	***100%***	***85%***	***86%***	***100%***	***86%***
Children vaccinated with two or more doses	**Duration of spasmodic cough**	**0 days**	-	-	-	-	15	101	**116**
		1-20 days	-	-	-	-	17	40	**57**
		21- days	-	-	-	-	77	469	**546**
	Total number of children		-	-	-	-	**109**	**610**	**719**
	Rate of children with spasmodic cough for 21 days or longer		-	-	-	-	***71%***	***77%***	***76%***
All children regardless of vaccination status	**Duration of spasmodic cough**	**0 days**	4	6	8	11	19	105	**153**
		1-20 days	3	18	6	23	23	42	**115**
		21- days	93	130	130	211	151	589	**1 304**
	Total number of children		**100**	**154**	**144**	**245**	**193**	**736**	**1 572**
	Rate of children with spasmodic cough for 21 days or longer		***93%***	***85%***	***90%***	***86%***	***78%***	***80%***	***83%***

In summary: There was a weak association between vaccination status of the child before the episode and the risk of a duration of spasmodic cough for 21 days or longer during the disease.

2.19 Duration of cough in infants and antibiotic treatment

As stated in section 2.18, data on cough and spasmodic cough were available for all 1,572 children born 1996 until September 2005, whereof 841 were infants. All children but 5 were coughing during their pertussis episode, including 4 infants.

Applying the EU clinical case definition of pertussis with 2 weeks of more of coughing (any type) in conjunction with positive laboratory sample, in all 1532/1572 would fulfil this definition. Among the 40 cases that would not fulfil the EU definition, 22 were infants and 18 were aged 1-6 years. All but three infants had received erythromycin or trimetoprim-sulfametoxazol, whereas only three of the children aged 1-6 years were treated with antibiotics. In all, 7 of the infants were unvaccinated, 5 had received one dose and 10 had received both doses. One child aged one year had received only two doses and the remaining children aged 1-6 years had received three doses. The fatal case occurred in a non-treated and non-vaccinated infant.

2.19.1 Duration of cough in infants and antibiotic treatment

There was information on antibiotic treatment, or not, including date at start of treatment for 1,563/1,572 chilren, including 838/841 infants. In this latter subgroup an early start, within the first week after onset of cough, of the antibiotic treatment significantly ($p<0.001$) reduced duration of cough compared to both "no antibiotic treatment" and a late start, later than 2 weeks after onset (Table 13).

Table 13 Duration of cough due to the pertussis disease among infants born 1996 until September 2005, during October 1, 1997 until September 30, 2005, by age at onset of cough and start of antibiotic treatment in relation to start of pertussis episode

Age at beginning of episode	Treated with erothromycin	N	Mean	Std. Deviation	Median
0-90 days	No	28	52,89	18,011	48,0
	Yes, with start before or within first week after onset of cough	46	41,28	21,391	34,0
	Yes, with start within second week after onset of cough	130	47,99	19,871	45,0
	Yes, with later start of treatment	193	52,71	18,415	49,0
	Total	397	49,85	19,531	47,0
91-150 days	No	49	45,39	18,892	45,0
	Yes, with start before or within first week after onset of cough	23	37,83	12,748	38,0
	Yes, with start within second week after onset of cough	73	43,19	15,236	40,0
	Yes, with later start of treatment	99	48,88	18,704	45,0
	Total	244	45,43	17,519	44,0
151-365 days	No	50	48,14	16,463	44,0
	Yes, before or within first week after onset of cough	33	32,61	20,149	31,0
	Yes, with start within second week after onset of cough	41	37,37	15,288	37,0
	Yes, with later start of treatment	73	48,34	17,873	48,0
	Total	197	43,37	18,470	42,0
Total	No	127	48,13	17,856	46,0
	Yes, with start before or within first week after onset of cough	102	37,70	19,551	33,0
	Yes, with start within second week after onset of cough	244	44,77	18,232	42,0
	Yes, with later start of treatment	365	50,80	18,450	48,0
	Total	838	47,04	18,898	44,0

3 Overall rates of laboratory confirmed 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 laboratory confirmed pertussis incidence in the Swedish population, Figure 5. The incidence in 2001- 2005, 5-9 years after the introduction of DTPa-containing vaccines, was at a level of the 60:s and early 1970:s , when the Swedish whole-cell vaccine programme 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 raising, 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 9a.

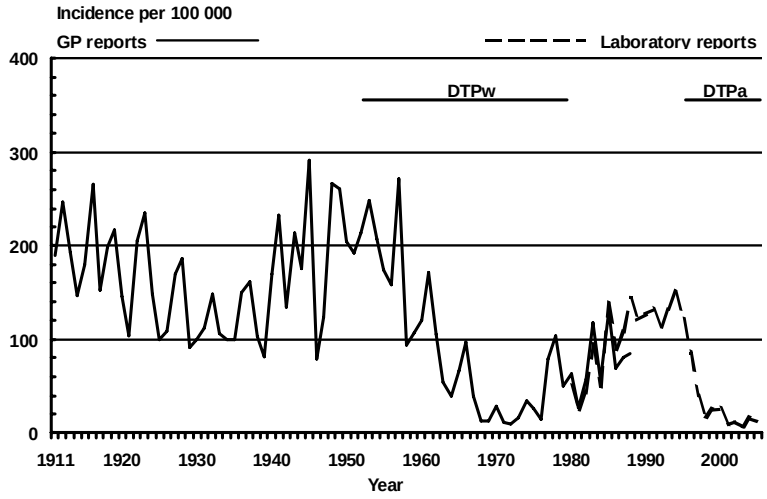


Figure 5 Pertussis incidence in Sweden. Sources: reports from general practitioners (GP) and laboratories

Figure A, Section 1, gives a close-up on the monthly reporting of culture or PRC-confirmed cases during the last 17 years. The overall incidence in the peak epidemic year1994 was 150/100.000 population years, and dropped steadily to 17/ 100.000 in 1998. In the winter of 1999 and 2000 there was an aborted peak to about 25 per 100,000, but thereafter there has been no major national peaks The overall incidence is now 7-16 per 100,000 population years, Table 15A.

3.2 Changes in age-specific incidences

The overall age specific incidences in different age groups during the years before and after 1996 is illustrated in Figure 7, with incidences in age-groups from 10 years and above enlarged in figure 8B. Note that the mean incidences in the age groups 0-9 years include both vaccinated and unvaccinated children during the years 1998-2005. For details about vaccinated cohorts, see Figure B and Table15A, giving the age-specific incidences during the years 1986-95 and 1998-2005, with the corresponding numbers of culture or PCR-confirmed pertussis in each age-group in Table 15B.

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 ages than had the corresponding age-groups before implementation of the Pa vaccination in infancy in 1996, and also in early school age. The age specific incidence for pre-school children dropped from >1000 per 100,000 to approximately 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 the mainly 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.

When the first cohort of immunized born in 1996 reached 8-9 years in 2004-05, these age-groups have the peak incidence after infancy (Figure B, Table 15A). The age-incidence peaks at 8 and 9 years during

2004-2005 implies that we may now have observed the first signs of waning immunity 6-7 years after completed primary vaccinations with DTPa.

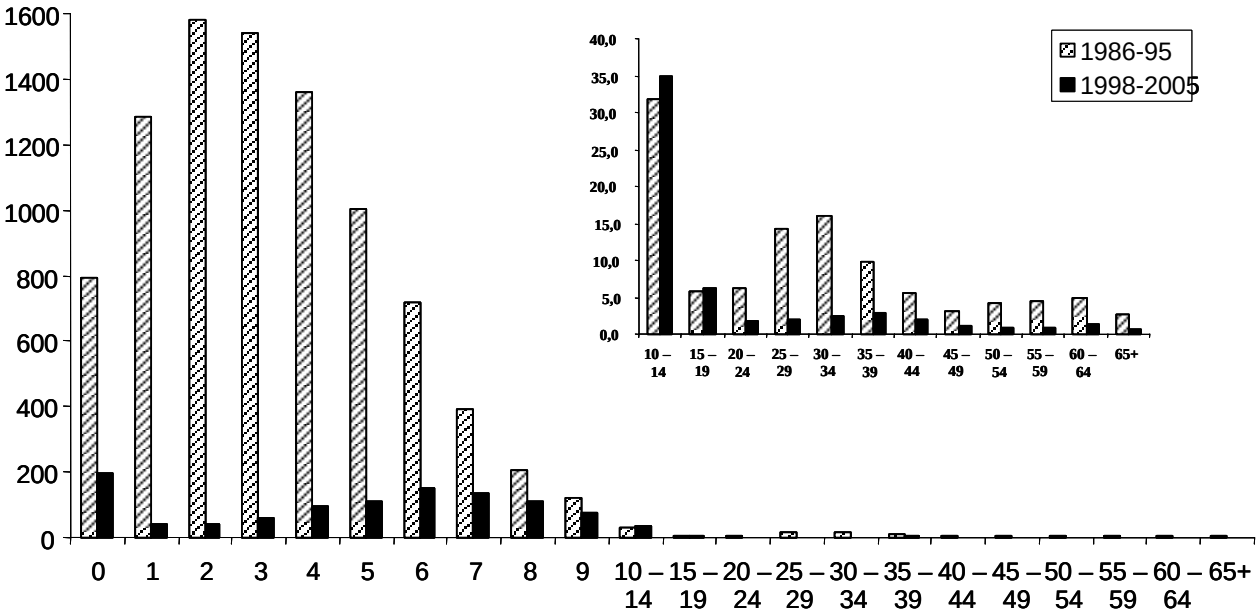


Figure 7 Mean incidence in defined age groups during 11 calendar years (1986-95) before and during 8 years after (1998-2005) introduction of DTPa in 1996. Data from the year 1997 are excluded because of change in reporting system during that year. Enlarged curves for the age groups 10 years and above are shown in the insertion.

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, is still well above 100/100,000 person years with a peak of 289/100,000 in 2005 (Table A). All seven deaths in infancy during the years 1997-2005 were in unvaccinated infants. The number of culture-confirmed pertussis per month of age in infancy before and after 1996 is illustrated in Figure 8.

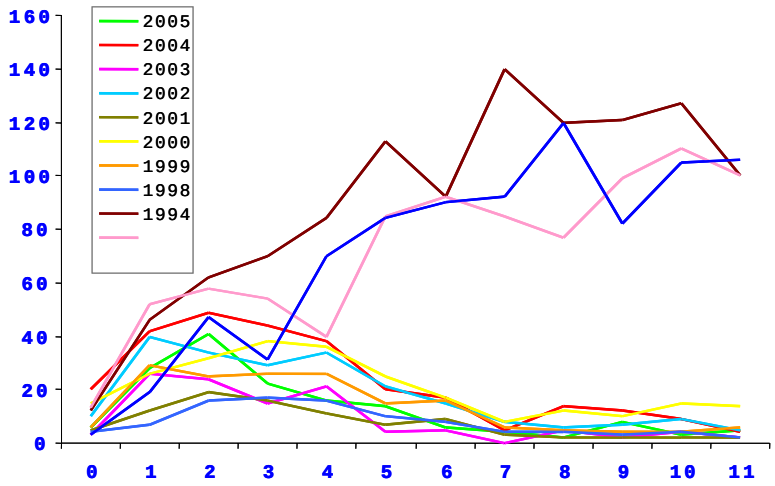


Figure 8 The reported number of culture- or PCR-verified pertussis cases in infants during 3 calendar years (1992-94) before and during 8 years after (1998-2005) introduction of DTPa in 1996.

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 6 illustrates the geographic variations in reported pertussis (clinical and laboratory reported) cases during the years 1997-2005.

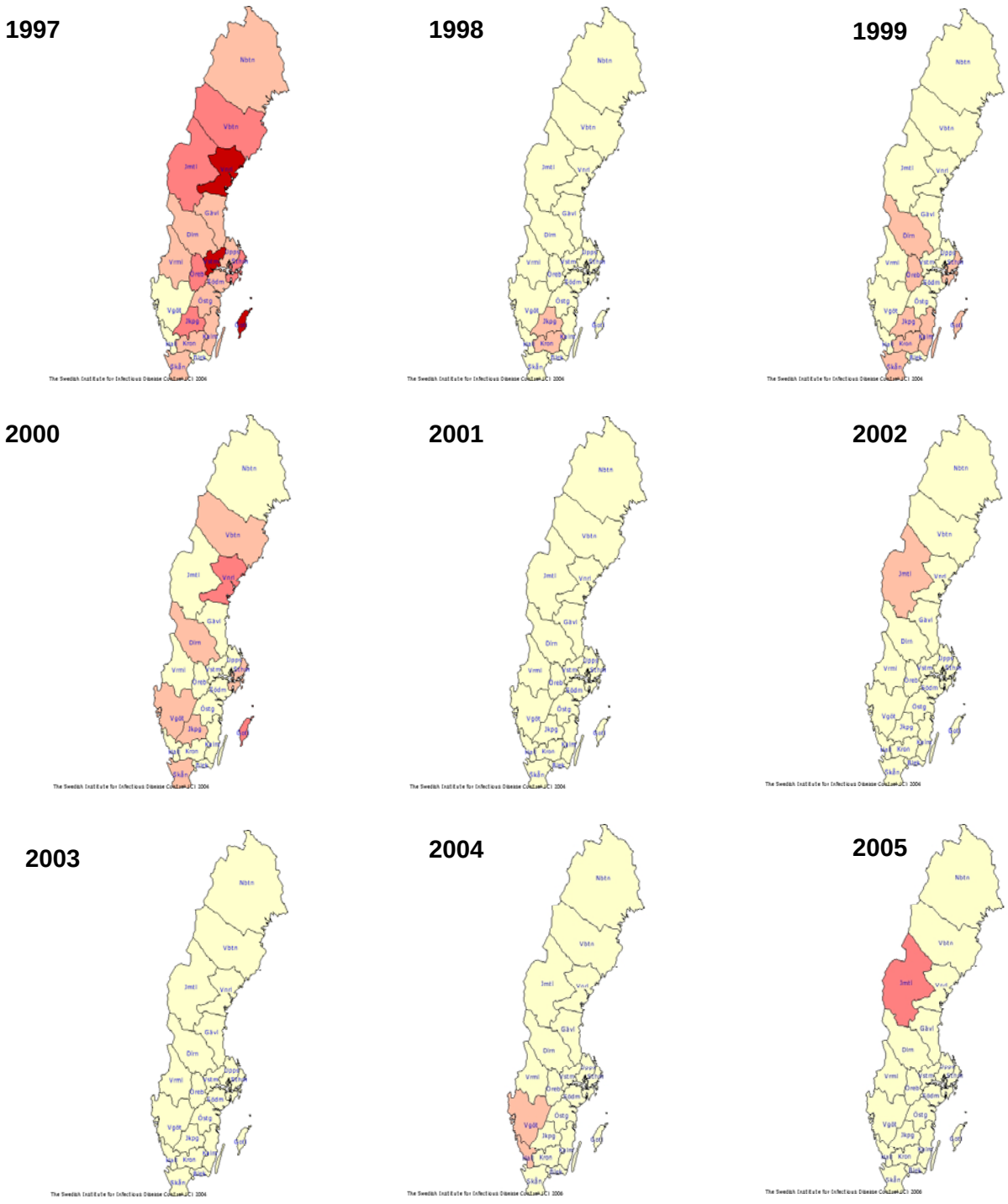


Figure 6 Incidence of reported pertussis (clinical and laboratory reports) in different areas of Sweden from 1997-2005. Source: Smi-Net

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 9, and has remained at this level since then. With one exception the coverage at county level has been 97% or above in all acounties and all cohorts born from 1996. The exception ws 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.

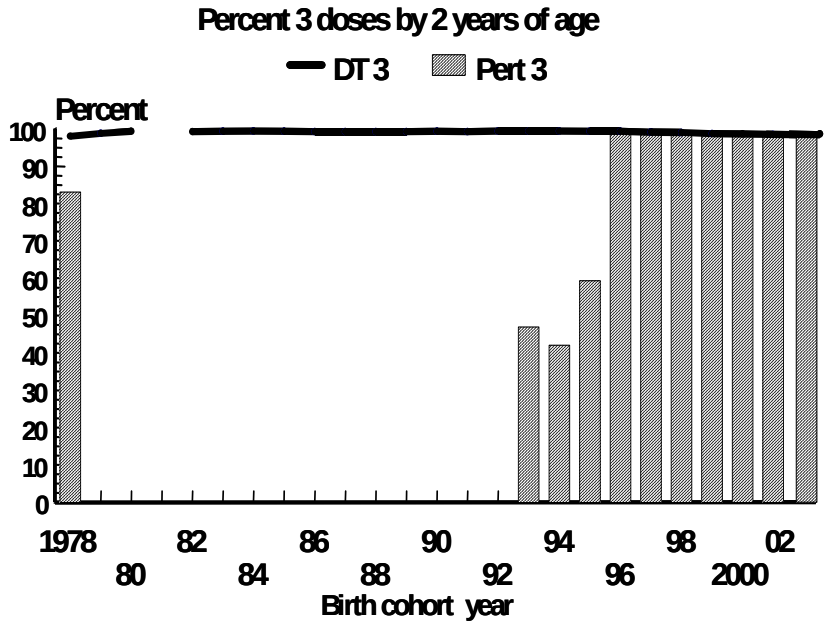


Figure 9 Vaccine coverage 1978-2003 for 3 doses DT P (source SMI Annual Reports).

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 10, demonstrating the deviation from schedule day (D0) for the first three doses of Pa vaccination in all children followed within the enhanced surveillance.

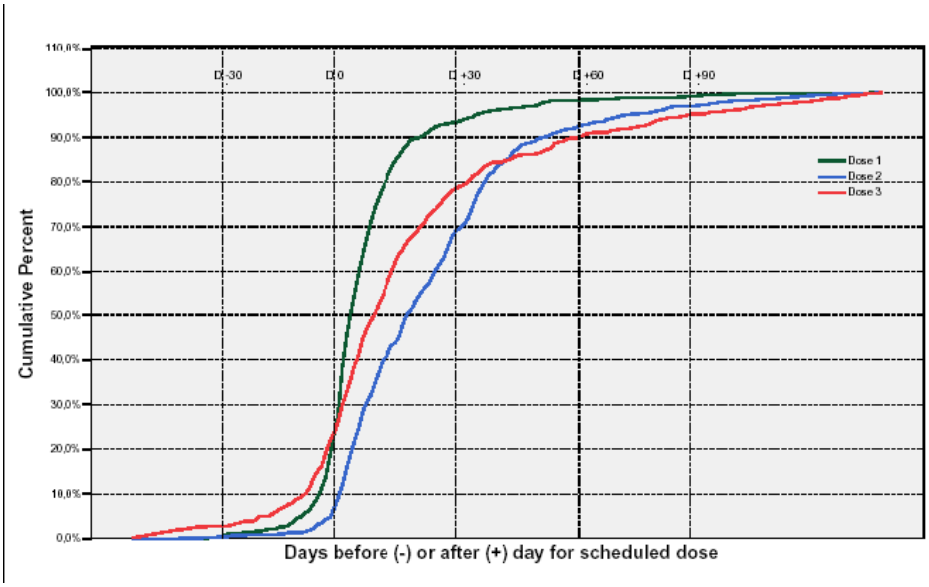


Figure 10 Cumulative proportion of children vaccinated in relation to scheduled day (DO) for the scheduled doses at 90 days, 150 days and 365 days, in children born from 1996 and until September 2005, with a pertussis episode between October 1, 1997 and September 30, 2005

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

Table 14 Mean age at dose 1-3 in Trial II (1993-94) and during the 1997-2005 enhanced surveillance period. The scheduled ages are 3-5-12 months, corresponding to 90-150-365 days.

Mean 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 1997-2005 (n = 1,572 children)	98	176	383

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 59%.

Free catch-up vaccinations to more than 65,000 children born in the 1990:s were offered in the Gothenburg area from 1997 to 1999. In all, about 60% of children aged 1-10 years were vaccinated with three doses of Pa-containing vaccine [6]. Toddlers and school children were vaccinated to some degree also in the rest of the country, but at the expense of the parents. Monovalent vaccines were withdrawn from the Swedish market in spring 2000.

Within studies, minor groups of children were boosted during the 1990:s, and most of the 10,194 children included in the 2-4-6 mo schedule in Trial II [3]. There was no general Pa-containing boosters were included in the Swedish schedule until autmn 2005, when a fourth dose of DTPa was recommended at 10 years of age [28].

3.6 Case ascertainment

Until 1997 there was no clinical reporting but a voluntary laboratory reporting system. During this year the Communicable Disease Act was changed to include pertussis, and since then cases may be reported either by clinicians, by microbiological laboratories or both ways. Figure 11 illustrates the number of pertussis cases reported on clinical basis only, the number reported both ways and the number reported on laboratory basis only. From 1998 about 90% of the pertussis cases are either reported both ways or on laboratory basis only, which means that the enhanced surveillance is based on 90% of the reported pertussis cases.

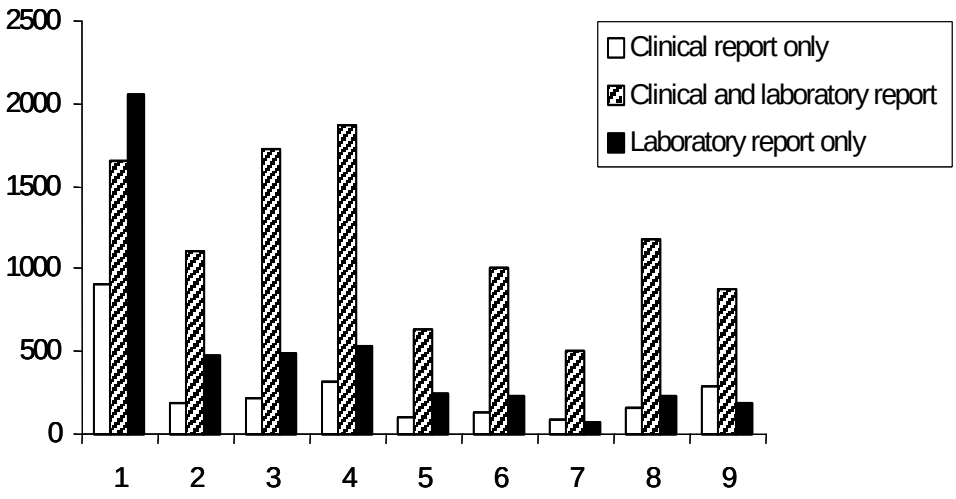


Figure 11 The number of reported pertussis cases 1997-2005; clinical reports only, combined clinical and laboratory reports, and laboratory reports only.

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 by slowly becoming replaced by PCR, although many laboratories have continued to perform cultures on PCR-positive samples. In 1997 the proportion of PCR-verified cases was 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 ocurred 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, Figure 12.

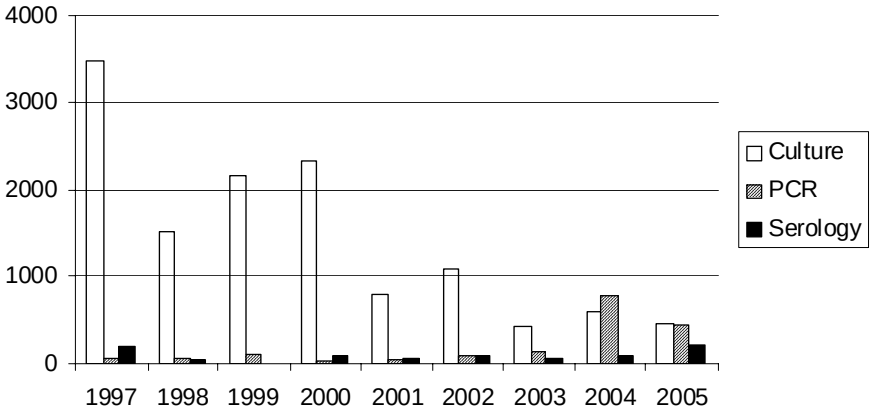


Fig 12 Laboratory methods used for verification of cases reported according to the Communicable Disease Act.

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 have with a timely association to media attention or to medical information campaigns drawing attention to pertussis. At both national level the increased reporting of pertussis among teenagers and young adults in 1992 may indicate increase awareness due to Trial I, Figure 13A, and in one region there was a 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 13 B

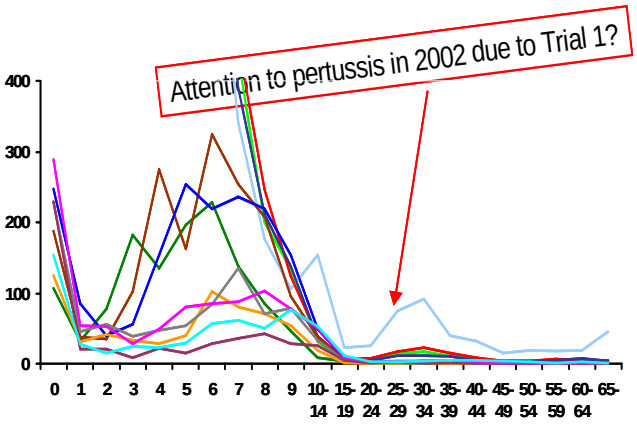


Figure 13A Age-specific incidence of pertussis at time of Trial I (1992 = blue line)

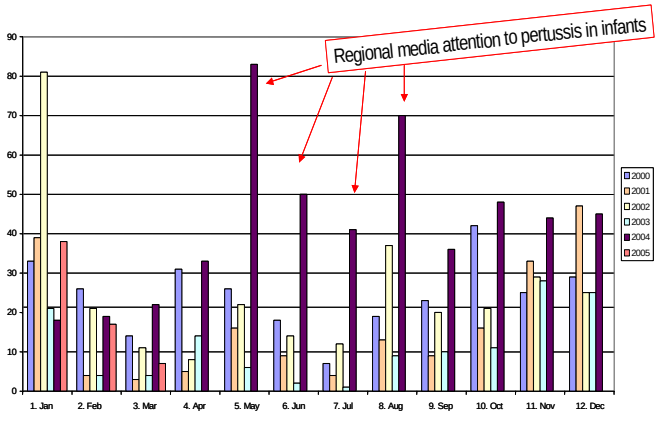


Figure 13 B Number of pertussis reports in a county of during the years 2000-04, with arrows indicating local attention to pertussis in media

.

Table 15A Overall and age-specific incidence of notified culture- or PCR-confirmed pertussis per 100,000 from 1986 to 1995. before introduction, and 1998 to 2005 after introduction of acellular pertussis vaccine in Sweden. (n.a. not available: age-specific incidences cannot be reported for 1996 and 1997 due to changes in the Communicable Disease Act, which temporarily prohibited laboratory reports of pertussis with personal identifiers).

Age, years	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
All ages	**89**	**108**	**142**	**120**	**128**	**132**	**113**	**132**	**150**	**121**	**86**	**40**	**17**	**25**	**26**	**11**	**12,9**	**6,7**	**15,5**	**12,0**
0	779,5	773,3	1084,4	843,1	633,7	902,3	682,3	777,6	688,9	797,9	**n.a.**	**n.a.**	**107**	**188,1**	**247,9**	**125,1**	**234,5**	**229,8**	**288,5**	**153,0**
1	1117,8	1288,4	1834,9	1428	1052	1381,7	1154	1317,4	1465,9	807,4	n.a.	**n.a.**	**32,3**	**37,7**	**84,9**	**31,3**	**45,4**	**20,7**	**53,7**	**26,7**
2	1244,3	1496,9	1953,7	1676,3	1223,5	1695,3	1441,7	1571,4	1959,3	1468,5	n.a.	n.a.	**77,4**	**35,4**	**39,7**	**41,9**	**55,3**	**20,4**	**53,5**	**15,1**
3	1201	1458,2	1953,6	1603,2	1157,4	1712,2	1384,1	1625,8	1751,2	1500,4	n.a.	n.a.	181,7	**102,4**	**55,5**	**33,1**	**38,8**	**8,7**	**27,9**	**24,0**
4	1042,7	1308	1597,4	1446,6	1028,6	1444,5	1188,5	1436,2	1633,4	1387,7	n.a.	n.a.	135,8	274,9	**154,1**	**29**	**48,2**	**22,1**	**49,0**	**23,5**
5	804,8	975,3	1239,2	1003,2	739,5	1055	913,9	1081,5	1165,5	1036,3	n.a.	n.a.	195,9	162,5	254,7	**40,6**	**54,1**	**15,3**	**79,8**	**29,3**
6	624,2	753,5	854	709,7	531,2	782,1	662,2	705,6	829,7	708,8	n.a.	n.a.	228,5	324,9	219,4	102,3	**83,5**	**28,1**	**85,4**	**56,7**
7	228,7	462	498,3	396,6	297,3	419,1	340,4	433	451,8	389,6	n.a.	n.a.	137,5	254,5	235,7	80,2	135,3	**36,0**	**88,1**	**62,5**
8	130	201,9	296,9	237,4	157,5	194,6	182,3	199,5	246,7	211,5	n.a.	n.a.	84,9	207,4	219,6	71,1	71,2	42,8	**103,4**	**50,2**
9	123,1	88,9	109,5	152,2	87,4	119,5	109,8	134,2	123,9	138,6	n.a.	n.a.	46,3	95,2	153,4	54,3	79	28,9	77,3	**76,5**
10 – 14	29,6	26,1	33,8	30,3	25,6	34,7	31,3	31,6	38,4	36	n.a.	n.a.	8,8	38	48,5	19,3	33,3	26,0	50,4	53,1
15 – 19	4,2	5,8	9,6	5,5	3,7	6,6	4,2	5,3	6,8	6,1	n.a.	n.a.	3,6	5,2	8,1	1,4	4,9	5,1	8,7	11,6
20 – 24	6,9	7,2	7,7	7,3	4,1	6,7	4,4	5,5	8,2	5,1	n.a.	n.a.	1,1	1,3	2,7	0,6	1,2	1,7	2,3	2,5
25 – 29	14,3	15,6	19,5	12,1	12,1	15	11,7	14,2	16,8	11,8	n.a.	n.a.	0,8	2,7	2	0,5	0,9	2,2	3,4	2,8
30 – 34	15,1	15,4	17,2	13	13,9	19,1	15,8	16,8	23	11,8	n.a.	n.a.	1,4	2,5	3,9	1,4	1,6	1,0	3,9	3,4
35 – 39	6,8	9,6	11,8	10,9	8	9,2	6,8	10,1	15	9,7	n.a.	n.a.	1,5	3	3,9	0,6	2,4	1,5	5,3	4,7
40 – 44	3,2	4,9	5,2	6,1	5,1	6	5,1	5,9	8,5	4,7	n.a.	n.a.	0,7	1,4	1,9	1,4	1,4	1,3	2,5	5,3
45 – 49	1,5	2,2	3,6	3,8	4	3,2	2,3	3,4	3,7	4	n.a.	n.a.	0,3	1,3	1,2	0,2	1,4	0,5	1,4	3,4
50 – 54	3,3	3,7	4,6	3,3	5,2	5,5	4,1	5,4	3,6	3,9	n.a.	n.a.	0,9	0,3	0,6	0,3	1,2	0,5	1,2	2,2
55 – 59	3	4,6	3,3	3,1	3,6	5,3	4,3	5,6	6,1	4,9	n.a.	n.a.	1,2	1,1	1,4	0,3	0,6	1,2	0,8	0,8
60 – 64	1,9	6,2	5,2	2,3	3,5	7,6	4,6	4,4	5,7	7,4	n.a.	n.a.	0,2	1,9	2,1	0,5	1,7	0,4	1,0	3,1
65+	1,1	1,7	2,3	2	2,6	2,6	2,9	2,4	4,7	4	n.a.	n.a.	0	0,6	0,8	0,1	0,5	0,9	0,8	1,6

Note! All age specific incidence figures in table 15 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 8.

Table 15B Number of culture- or PCR confirmed cases of pertussis in defined age-groups from 1986 to 1995. before introduction, and 1998 to 2005 after introduction of acellular pertussis vaccine in Sweden. (n.a. not available for 1996 and 1997 due to changes in the Communicable Disease Act, which temporarily prohibited laboratory reports of pertussis with personal identifiers).

Age, years	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
	7449	9069	11980	10191	10955	11375	9795	11508	13171	10680	7591	3538	1505	2215	2307	979	1151	600	1394	1084
0	779	797	1173	960	760	1116	839	933	790	858	**n.a.**	**n.a.**	**96**	**167**	**222**	**114**	**220**	**224**	**289**	**155**
1	1081	1299	1908	1558	1208	1668	1435	1627	1763	928	n.a.	**n.a.**	**30**	**34**	**76**	**28**	**42**	**20**	**53**	**27**
2	1166	1455	1980	1754	1344	1957	1745	1959	2430	1770	n.a.	n.a.	**77**	**33**	**36**	**38**	**50**	**19**	**51**	**15**
3	1120	1372	1908	1636	1220	1891	1604	1976	2200	1871	n.a.	n.a.	196	**102**	**52**	**30**	**35**	**8**	**26**	**23**
4	984	1225	1511	1423	1058	1532	1318	1672	2002	1753	n.a.	n.a.	156	297	**154**	**27**	**44**	**20**	**45**	**22**
5	776	924	1167	956	733	1091	973	1205	1369	1278	n.a.	n.a.	236	187	276	**41**	**51**	**14**	**73**	**27**
6	608	729	813	673	510	780	688	755	933	838	n.a.	n.a.	285	392	253	111	**84**	**27**	**79**	**52**
7	218	451	484	380	284	405	341	452	488	441	n.a.	n.a.	174	318	285	93	148	**36**	**84**	**58**
8	124	193	291	232	152	187	177	201	260	230	n.a.	n.a.	105	263	275	86	83	47	**105**	**48**
9	121	85	105	150	86	116	106	131	126	147	n.a.	n.a.	55	118	195	68	96	34	85	**78**
10 – 14	162	139	175	153	127	171	154	156	191	180	n.a.	n.a.	47	210	279	115	205	162	313	322
15 – 19	24	33	54	31	21	37	23	28	35	31	n.a.	n.a.	18	26	41	7	26	28	49	68
20 – 24	41	44	48	45	25	40	26	32	48	30	n.a.	n.a.	6	7	14	3	6	9	12	13
25 – 29	80	87	110	70	73	94	75	92	108	74	n.a.	n.a.	5	16	12	3	5	12	19	15
30 – 34	87	89	99	75	80	110	91	98	138	73	n.a.	n.a.	9	16	25	9	10	6	24	21
35 – 39	44	60	72	65	47	54	40	59	88	57	n.a.	n.a.	9	18	24	4	16	10	35	30
40 – 44	20	32	35	41	34	39	32	36	51	28	n.a.	n.a.	4	8	11	8	8	8	15	33
45 – 49	7	11	19	21	24	20	15	23	25	26	n.a.	n.a.	2	8	7	1	8	3	8	20
50 – 54	14	16	20	15	24	26	20	28	20	23	n.a.	n.a.	6	2	4	2	7	3	7	13
55 – 59	13	20	14	13	15	22	18	24	27	22	n.a.	n.a.	6	6	8	2	4	8	5	5
60 – 64	9	28	23	10	15	32	19	18	23	30	n.a.	n.a.	1	8	9	2	8	2	5	17
65+	16	25	34	30	40	40	44	37	72	62	n.a.	n.a.	0	9	12	2	8	14	12	25

Note! All age specific incidence figures in table 15 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 8.

4 *Bordetella pertussis* strain characterisation

This will be a summary of the laboratory work with strain characterisation during the 8-year period 1 October 1997 to 30 September 2005. Altogether approx. 5400 clinical isolates of *Bordetella pertussis* were collected from children born 1992 or later, and frozen. Funding from the EU-Commission financed a 39-month period August 2001 through September 2004.

4.1 Aims

The primary aim of the study was to establish reference methods for epidemiological typing of *B. pertussis* and compare isolates over time. A secondary aim was to relate the obtained patterns to vaccination policy and vaccine effectiveness.

The specific aims were:

I. To develop a PFGE-profile based reference sytem, i.e. reference methods and reference materials, using the Swedish clinical material
II. collect information about circulating strains related to effect of different vaccination programs with focus on comparing:
    a. isolates over time based on components included in acellular vaccines
    b. circulating strains with strains used for production of vaccines
    c. isolates from vaccinated and unvaccinated children when possible
III. To identify incidence peaks of notified cases and to investigate if such peaks followed the appearance of novel PFGE-profiles of pertussis bacteria.
IV. To investigate the transmission of *B. pertussis* strains between Sweden and Finland.
V. To study if there is any association between strain characteristics and clinical outcome of a pertussis episode.

Results are covered by the **references 18-21 and 24, summarized below:**

4.2 Reference systems

4.2.1 A reference system for PFGE typing [18]

Pulsed-Field Gel Electrophoresis (PFGE) has been used as an epidemiological tool for surveillance studies of *B. pertussis* since the early 1990s. To date however there is no standardised procedure for comparison of results, and therefore it has been difficult to directly compare PFGE results between laboratories. We propose a profile based reference system for PFGE-characterisation of *B. pertussis* strain variation and to establish traceability of *B. pertussis* PFGE-results. We initially suggest 35 Swedish reference strains as reference material for PFGE traceability. This reference material is deposited at Culture Collection of the University of Gothenburg, Gothenburg, Sweden (CCUG). Altogether 1,810 Swedish clinical isolates from between 1970 and 2003 were studied together with the Swedish Pw-vaccine strain, six reference strains and two US isolates. Our system provides evidence that profiles obtained using only one enzyme i.e. XbaI, give enough data to analyse the epidemiological relationship between them. Characterization with one enzyme is far less labour intensive, yielding results in half the time than when a two-enzyme procedure is used. Also, we can see there is a correlation between PFGE-profile and pertactin type. One common PFGE-profile, BpSR11 (n=455) showed 100 % prn2 and 100 % Fim3 when analyzed for pertactin type and serotype. On the other hand strains with the same profile may express varying serotypes when isolated over longer periods of time. Subculturing of the same isolate eight times or lyophilization caused no change in PFGE profile.

4.3 Epidemiology of B. pertussis

4.3.1 Shifts during three periods with different vaccination program [19]

The Swedish population of *Bordetella pertussis* strains was characterised from 1,247 isolates covering a whole-cell vaccine programme up to 1979, a 17-year period without vaccination (1979 to 1996) and a period after the introduction of general vaccination of newborns with acellular pertussis vaccines (1997 to

2003). Strains were characterised by serotyping and genotyping of pertactin and ptxA and by means of pulsed-field gel electrophoresis (PFGE).

With emphasis on vaccine-related markers, the vast majority of circulating strains were of nonvaccine type. There were shifts of serotype connected with shifts of vaccination program. Serotype Fim3 was most frequent during the periods with general vaccination schedules, whereas serotype Fim2 was predominant during the 17-year vaccine-free period. Pertactin 1 was predominant during the pertussis wholecell (Pw) vaccine period but was thereafter replaced by prn2 and has not reappeared after the introduction of acellular pertussis (Pa) vaccines. ptxA was predominant over all three decades. There was a significant difference in the distribution of serotypes between vaccinated and unvaccinated individuals, but not for pertactin. A few PFGE profiles were predominant over the years: BpSR25 (serotype Fim3 prn1/7) and BpSR18 (serotype Fim3 prn2) during the Pw period, BpSR1 (serotype Fim2 prn2) during the 17 years without general vaccination, and BpSR11 (serotype Fim3 prn2) after the reintroduction of general vaccination in 1996. Despite differences between the pertactin and toxin types of Pa vaccines and circulating strains, there is no evidence that there is a threat, i.e., the vaccination program so far has been effective against whooping cough, and there seems to be no impact on the effectiveness of the vaccination program from the bacterial polymorphism.

4.3.2 Changes during three incidence peaks [20]

In the 7 y period of the enhanced surveillance program, covering 1 October 1997 through 2004, isolates and clinical information were collected after introduction of vaccination with acellular pertussis vaccines in 1996. We investigated changes in the B. pertussis population within three noted incidence peaks, in 1999-2000, 2002 and 2004The data were used to identify strains of interest for further study. 158 available "peak" isolates from vaccinated individuals representing whole Sweden except the Gothenburg area were analysed by PFGE, serotyping and sequencing of the virulence factor genes ptxA, ptxC, prn, tcfA and fim3. As a control of PFGE- profile trends 361 isolates from unvaccinated or partially vaccinated children representing 6 Swedish counties were used.

Seven of 76 PFGE-profiles represented 63 % (283 out of 447 fully vaccinated) and showed changing profile composition in and between the peaks. The PFGE-profile BpSR11 appearing in the first peak 1999 dominated during the entire period but others with BpSR11-related profiles appeared with an increasing trend, BpSR5 in peak 2 and BpSR10, BpSR12 and BpSR13 in peak 3. Each PFGE-profile showed a typical combination of certain genetic markers. This relationship was further supported by the dendrogram analyses. Sequence analysis showed statistically significant trends toward increasing specific alleles in 3 out of 5 studied genes *ptxC, prn* and *tcfA*. Only four allele-combinations were noted among 97 % (154/158) of the isolates. BpSR11 represented the most dominant allele-combination 2/2/2/B (*ptxC2/prn2/tcfA2/fim3B*). Although vaccination with acellular pertussis vaccine has been effective and reduced disease, new variants have emerged representing clones surviving in the immunized population.

4.3.3 A comparison with Finnish isolates [24]

In Finland, a whole-cell pertussis vaccine has been used since 1952 with high coverage. In Sweden, whole-cell vaccinations were introduced in 1953 but ceased in 1979, and pertussis vaccinations with acellular vaccines were introduced in 1996. Two epidemic peaks occurred in Sweden in 1999 and 2002 and in Finland in 1999 and 2003. In this study, we compared Finnish (N=193) and Swedish (N=455) *B. pertussis* isolates circulating in 1998-2003 together with vaccine strains used in these neighbouring countries with different vaccination histories. The isolates were analysed by serotyping, genotyping of pertussis toxin S1 subunit and pertactin, and pulsed-field gel electrophoresis.

The results suggest that the sequential epidemics were caused by clonal expansion of a certain *B. pertussis* strain transmitted from Sweden to Finland. The roles of *B. pertussis* antigenic variation in immunity-driven evolution in both countries are discussed.

4.4 Clinical outcome

4.4.1 Clinical outcome in relation to PFGE-profile and serotype [21].

We analysed the association of Pulsed-Field Gel Electrophoresis (PFGE)-profile and serotype to severity of disease for all children followed during the first seven years of the project. There were in all 927 children with both clinical information and strain characterisation data available. Two hundred and sixty of these children were hospitalised during the pertussis episode. When clinical outcomes were compared between two groups of strains, characterised by PFGE-profile or serotype, there were significantly more children with a long duration of hospital stay in the most frequent PFGE-profile group (BpSR11) compared to the PFGE-group of all other profiles (p=0.041). There was no statistically significant association between serotype and hospitalisation, nor were there any statistically significant associations between serotype or PFGE-profile and duration of spasmodic cough or complications.

5 Plan for continued work

The plans for project year nine include

- Further analyses of Gothenburg data in collaboration with the investigators responsible for surveillance in that area during the first years after introduction of DTPa in the national program. The aim is to present results for the Gothenburg area in a separate document, also including a list of plausible explanations to the differences in reported incidences in this area as compared to in the rest of the country.
- The clinical information in the eight-year database will be further evaluated, included analyses of antibiotic use. A scientific publication on clinical course is planned.
- A comment on case definitions in infancy will be forwarded to ECDC
- The project database will be transferred to a database in communication with the national disease reporting system, allowing access for the county medical officers in communicable disease control to enhanced data from their respective counties.

6 Administration

Contracts for the project Pertussis surveillance in Sweden have been agreed for continued follow-up of clinical epidemiology during year 2004 to 2005 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 transparence, it has been agreed that annual progress report is posted on www.smittskyddsinstitutet.se. The two vaccine specific Appendix 2 should also be posted, with a clear note of caution that comparisons between vaccines should not be performed.

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

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