Pertussis surveillance in Sweden

Fifteen year report

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Förord

Det svenska uppföljningsprogrammet för kikhosta (pertussis) är unikt och följs internationellt. Den övergripande och viktiga frågan är hur man ytterligare ska kunna minska spädbarnens kikhosta, särskilt hos de barn som inte fått något vaccin (mindre än 3 månaders ålder) eller som ännu inte uppnått ett optimalt skydd. Den här rapporten syftar till att bland annat belysa denna fråga.

I Sverige vaccinerade vi inte mot kikhosta under åren 1979-1995, till skillnad mot de flesta andra europeiska länder. Detta berodde på att det dåvarande vaccinet inte hade tillräcklig skyddseffekt och att biverkningsfrekvensen var något hög. Efter introduktion av nya vacciner, så kallade acellulära kikhostevaccin 1996 med god skyddseffekt och få biverkningar, har vaccination mot kikhosta ingått i det allmänna barnvaccinationsprogrammet.

Svenska data över insjuknande i kikhosta är populationsbaserade och håller god kvalitet. I Sverige är kikhosta en anmälningspliktig sjukdom och barn och vuxna med klinisk och laboratoriebekräftad kikhosta ska rapporteras till Smittskyddsinstitutet.

Utöver den obligatoriska rapporteringen av kikhostefall har vi i Sverige haft en noggrann uppföljning av barn som kikhostevaccinerats. Alla familjer med ett barn som fått kikhosta har kontaktats för intervju, diagnostiken har bedömts, anamnestiska data såsom svårighetsgraden av kikhostan, inklusive dess duration, antal givna vaccindoser, antibiotikainsättande etc har utvärderats. Resultaten från femton års uppföljning av denna utökade övervakning av kikhostefall hos barn beskrivs i denna rapport. Uppföljningen startade den 1 oktober 1997 för barn vaccinerade från 1 januari 1996 i Sverige.

Projektet med denna utökade övervakning som drivs av Smittskyddsinstitutet avrapporteras separat för två geografiska områden, uppföljningen i Göteborgs-området (ca 11% av Sveriges befolkning) och övriga Sverige. Dessa områden har skiljt sig åt med avseende på de vacciner som givits under de första åren när de nya kikhostevaccinerna introducerades. Denna rapport beskriver materialet från Sverige där Göteborgsområdet är exkluderat. Data från uppföljningen i Göteborg finns redovisat i en separat rapport.

Det har varit en dramatisk minskning av antalet kikhostefall från år 1996 hos barn som fått kikhostevaccin, jämfört med perioden 1979-1995, då kikehostevaccination inte ingick i det allmänna barnvaccinationsprogrammet. Vi ser även denna kraftiga minskning för spädbarn – den grupp som det är allra viktigast att skydda eftersom de kan bli allvarligt sjuka i kikhosta.

En viktig fråga idag är om den ökning av kikhosta som sågs under senare delen av 2012 var tillfällig. De första 7 månaderna 2013 har dock visat betydligt lägre antal fall. Under 2012 har vi haft 19 barn med rapporterad kikhosta som varit mindre än 3 månader gamla och som haft minst 2 veckors hosta och ingår i uppföljnings-studien. Av dessa 19 barn blev 17 inlagda på sjukhus.

Andelen sjukhusinläggningar och komplikationer beror både på barnets ålder och om de fått kikhostevaccin. Dessutom visar detta material att vaccinerade barn som ändå fått kikhosta har en betydligt lindrigare sjukdom.

Uppföljningen av vaccinationsprogrammet har visat att vi har kvarstående kikhosta bland ungdomar och vuxna i Sverige. År 2005 infördes en boosterdos vid 10 års ålder som från 2007 ersatts med en 5-6-årsbooster för barn födda från 2002. För att bibehålla skyddseffekten rekommenderas även en påfyllnadsdos vid 14-16 års ålder som kommer att introduceras från och med 2016. En minskning av incidensen kikhosta för berörda åldersgrupper har setts efter att boostervaccinationerna har införts.

Det är fortfarande viktigt att följa kikhosteutvecklingen i Sverige eftersom det på senare år har förekommit epidemier i flera andra länder. Exempelvis var det under 2010 en mycket svår kikhosteepidemi i Kalifornien med 10 dödsfall. Det finns också stora utbrott i England, Australien och Nederländerna. Det finns dock andra länder där kikhoste-incidensen är i sjunkande.

De tre viktigaste skälen till fortsatt uppföljning är

- den kvarstående svåra kikhostan hos spädbarn, framförallt hos de som ännu inte fått något kikhostevaccin, där även smittvägar kartläggs.

- utvärderingen av effekten av vaccinationsschemat med förnyelsedoser som beslutats under de senaste åren

- den ökade incidensen av kikhosta i flera andra länder trots vaccination och den ökning som sågs i Sverige under senare delen av 2012.

Delar av rapporterna beskrivs också i detalj i svenska och utländska vetenskapliga artiklar.

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Content

Executive summary

Review

The acellular pertussis vaccination programme in Sweden was introduced in January 1996 after 17 years without pertussis vaccination (1). Summary of the results with acellular pertussis vaccines are shown below.

After the executive summary and the Material and Methods sections there are three chapters concerning the epidemiology of pertussis. The first chapter describes the laboratory reporting of pertussis with PCR, culture and serology according to the Communicable Disease Act. The 2nd and 3rd chapters define the enhanced surveillance study in Sweden between October 1, 1997 and December 31, 2012 as well as the two trials in Sweden with children born during 1992, and mid 1993 to mid 1994, respectively (2, 3). Thereafter, case contacts of pertussis are described, information that is available since Jan 1, 2009.

As 2012 has been a year with low pertussis incidence during the first 6 months and then an increase in the incidence during the rest of the year.

In 2012 there were equal number of subjects with laboratory verified pertussis in children 0-19 years of age as in adults, 134 persons in each group. In 2011, the cases of pertussis was lower, 97 children 0-19 years of age and 71 adults had whooping cough. About 3 infants per month had pertussis in 2011 and in the first six months of 2012 two infants per month suffered from pertussis. However, during the last six months of 2012 about seven infants had pertussis disease each month. This increase does not seem to continue during the first seven months of 2013.

Laboratory reported incidence
of pertussis in Sweden. Chapter 1 results

The number of reported laboratory confirmed cases per month shows a significant decrease after onset of regular pertussis vaccination in 1996. It also 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 peaks during 2001 – 2011, and another peak in the incidence of pertussis during the autumn 2012, Figure 1 (Exec sum):
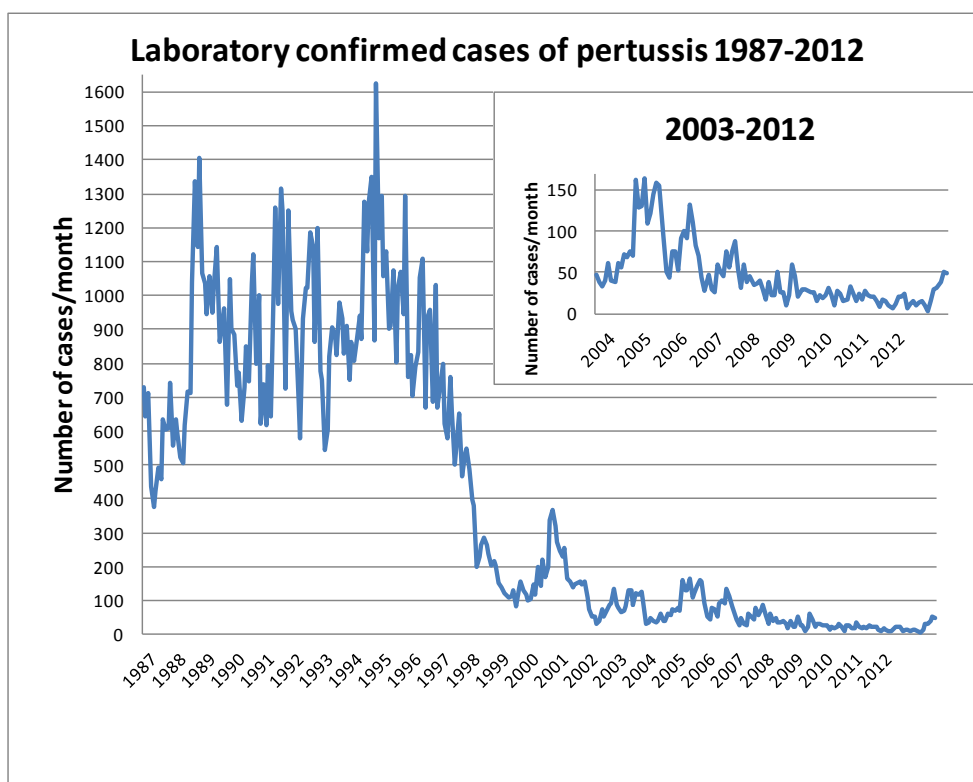
Figure 1 (Exec sum): Number of laboratory-confirmed pertussis cases in Sweden per month from January 1986 to December 31, 2012. See also text above and chapter 1.

The annual incidence of laboratory confirmed Bordetella pertussis was around 120-150 per 100,000 before introduction of acellular pertussis vaccines, Chapter 1, Table 1.2.for the years 1989-1995. After a rapid drop in 1996-1997 the overall annual incidence reached 10 to 27 per 100,000 person years in 1999-2001, with a further reduction to 6.8 and 1.8 per 100,000 person years in 2006 and 2011. However, the incidence was higher in 2012; 2.8 per 100,000 person years.

The peak age specific 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 vaccinated cohorts born from 2009 is below 10 cases per 100,000 person years see Table 1.2. However, the reduction of age specific incidence was least marked below one year of age, see chapter 1, figure 1.2 and 1.3. In this age-group incidence was between 103 and 284 per 100,000 until 2006, when the age-specific incidence in infancy for the first time was below 100 per 100,000. From 2008 the incidence in infants has been stable, below 50/100,000. The age specific incidence for pre-school children dropped from >1000 per 100,000 to approx. 100/100,000 in 1998-2000, to 50/100,000 in 2001 and further to approximately 20/100,000 in 2003. The rate has also dropped to below 10/100,000 among vaccinated children during the first years in school. In unboosted 10-14 year-olds the age-specific incidence remained about the same before and after introduction of acellular pertussis vaccine until 2005. The booster effect was described in the Pertussis Surveillance report for 2010 (4), and has also been described on a poster at the European Society for Paediatric Infectious Diseases (ESPID) meeting in 2010 (5).

The presence of a booster was shown to have a strong effect, with an estimated RR of 0.34 (95% CI 0.14 - 0.71).

Enhanced surveillance of pertussis for children, outside the Gothenburg study area, born January 1, 1996 through December 31, 2012.

Chapter 2A results (2A1 - 2A7).

During the fifteen-year period of the enhanced surveillance study of pertussis there were a total of 2553 cases in followed cohorts of laboratory confirmed pertussis outside the Gothenburg study area. These 2553 cases of pertussis have been described from 1 717 177 children born January 1, 1996 until December 31, 2012 with detailed vaccination and clinical history available for the episodes of pertussis. In the present fifteen-year report, 113 new cases of laboratory confirmed pertussis with vaccination and clinical data were included in the main analysis.

Most cases were reported in the youngest birth-cohort in each calendar period, with a marked decline at about 5 months of age, Table 1 (Exec sum). The lowest age-specific incidence of laboratory confirmed pertussis was seen in fully vaccinated children (3 doses of DTPa-containing vaccine) t 1-2 years of age (<10 per 100,000 including unvaccinated children of this age, Table 1 (Exec sum)). Between 2-5 years of age, the age-specific incidences were between 12 and 14 per 100,000 person years with an increase to 17-19/100,000 person years among children 6 - 8 years of age, Figure 3 (Exec sum) and Table 1 (Exec sum).
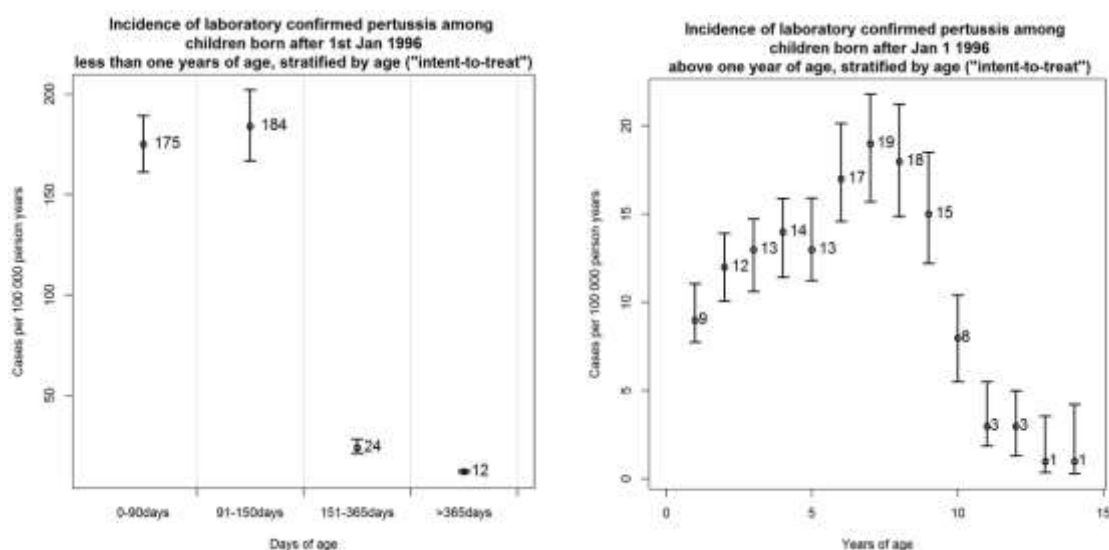
Figure 2 & 3 (Exec sum): Incidence of reported culture- or PCR-confirmed B. pertussis and from 2008 also serology-diagnosed cases of pertussis and 95% confidence intervals among children born 1, January 1996 to 31, December 2012 in children followed from 1, Oct 1997 to 31, Dec 2012. Figure 2 (exec sum) describes infants less than one year of age and figure 3 (exec sum) children above one year. The number of cases per 100,000 are stratified by age ("intent to treat") indicated in figure 2. In figure 3 the age intervals are 1-2,

14

2-3 years etc. See also case definition in the Material and Method part, section C. (For children outside the Gothenburg study area).

Onset of pertussis episode[1] occurred (in vaccine/age group[2])	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 (0-90 days)	348,009	608 (608)	175 (175)	161-189 (161-189)
Between 1 and 2 doses (91-150 days)	231,321	329 (425)	142 (184)	127-158 (167-202)
Between 2 and 3 doses (151-365days)	805,452	162 (197)	20 (24)	17-23 (21-28)
After dose 3 and/or during 1 year of age	1,366,168	85 (127)	6 (9)	5-8 (8-11)
During 2 years of age	1,288,608	121 (153)	9 (12)	8-11 (10-14)
During 3 years of age	1,186,992	121 (149)	10 (13)	8-12 (11-15)
During 4 years of age	1,088,064	115 (147)	11 (14)	9-13 (11-16)
During 5 years of age	990,972	108 (133)	11 (13)	9-13 (11-16)
During 6 years of age	895,416	131 (154)	15 (17)	12-17 (15-20)
During 7 years of age	802,53	127 (149)	16 (19)	13-19 (16-22)
During 8 years of age	711,804	110 (127)	15 (18)	13-19 (15-21)
During 9 years of age	621,912	87 (94)	14 (15)	11-17 (12-18)
During 10 years of age	534,198	38 (41)	7 (8)	5-10 (6-10)
During 11 years of age	450,006	12 (15)	3 (3)	1-5 (2-5)
During 12 years of age	368,184	10 (10)	3 (3)	1-5 (1-5)
During 13 years of age	287,742	3 (4)	1 (1)	0-3 (0-4)
During 14 years of age	207,93	3 (3)	1 (1)	0-4 (0-4)
During 15 years of age	127,002	15 (17)	12 (13)	7-19 (8-21)

Table 1 (Exec sum): From the enhanced surveillance study. Incidence of reported culture- or PCR-confirmed *B. pertussis* is described and from 2008 also serology-diagnosed cases of pertussis[1] among children outside the Gothenburg study area born from January 1, 1996 until December 31, 2012 and followed from October 1, 1997 until December 31, 2012. We present person years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person years and 95% confidence interval in the following age-/vaccine-groups at onset of the pertussis episode; 0-<3 months of age (before Dose 1)[2]; 3-<5 months of age (between Dose 1 and 2); 5-<12 months of age (between Dose 2 and 3); and after 12 months of age (after Dose 3) in one-year age intervals[3] in vaccinated children. In brackets figures including the unimmunised children of respective age group are given.

1. *At date for onset of cough, or, if no cough, at date for the positive sample, during the pertussis episode.*

2. *Age interval in the headings is chosen in relation to the first 3 doses recommended in the national vaccination program.*

3. *Part of the 5-6-year groups, most of the 6-9 year-olds, part of the 9-10 year olds and most of the groups of children older than 10 years of age have received Dose 4 as a booster dose according to the revised national vaccination program – see Material & Method part, section A for details.*

Enhanced surveillance of pertussis and complications in Sweden between Oct 1, 1997 and Dec 31, 2012.

Chapter 2B results (2B1-2B4).

This chapter in the enhanced surveillance pertussis study deals with data considering for the pertussis cases:

1a, cough and spasmodic cough

1b, complications

1c, hospitalisations, and

1d, antibiotic treatment

2, Incidence of reported pertussis and the severity of the disease in relation to the number of administered doses. This requires a detailed surveillance study.

Available cases for the results:

Data on duration of cough and presence of spasmodic cough were available for 2526/2553 episodes. Information about cough were available for all but 27 subjects, absence of coughing was reported for 3 subject.

Approximately 98% of the cases had 14 days or more of cough, and 83% had 21 or more days of spasmodic coughing (fulfilling the WHO case definition that was established to use in efficacy trials (11)). See also figure 4 (exec sum) that shows a flow chart of registered enhanced surveillance study cases.

Data on presence of any complication or hospitalisation were available for 2525 cases and missing for 28 of the cases. Figure 5 (exec sum) shows a flow chart of registered surveillance cases in regard to hospitalisations.

Among the 51 cases that did not fulfill the EU and WHO surveillance definitions of 14 or more days of any cough, 21 were infants and 30 were aged 1-10 years. All but two of these infants had received erythromycin or trimetoprim-sulfametoxazol, whereas 16/30 of the children aged 1-10 years were treated with antibiotics. Looking at all cases, infants treated with antibiotics within one week after start of pertussis episode had significantly shorter duration of cough compared to untreated in the same age-group(s), Chapter 2B, Figure 2.B.5. Since most of the infants with a short duration of cough also had an early start of treatment it is likely that most of the cases that did not fulfill the EU definition would have had a longer duration of cough (fulfilling the EU definition or even the definition of typical pertussis) if left untreated.

The fact that most infants with short duration of cough were treated with antibiotics reflects a Swedish tradition implemented during the seventeen-year period without general vaccination against pertussis. In 1982 the National Board of Health and Welfare recommended protective measures for infants such as avoiding exposure of pertussis and the use of erythromycin to those who were accidentally exposed.

Post-exposure prophylaxis was recommended if the infant was below 6 months of age, and early treatment at first symptoms to infants 6-12 months (6).
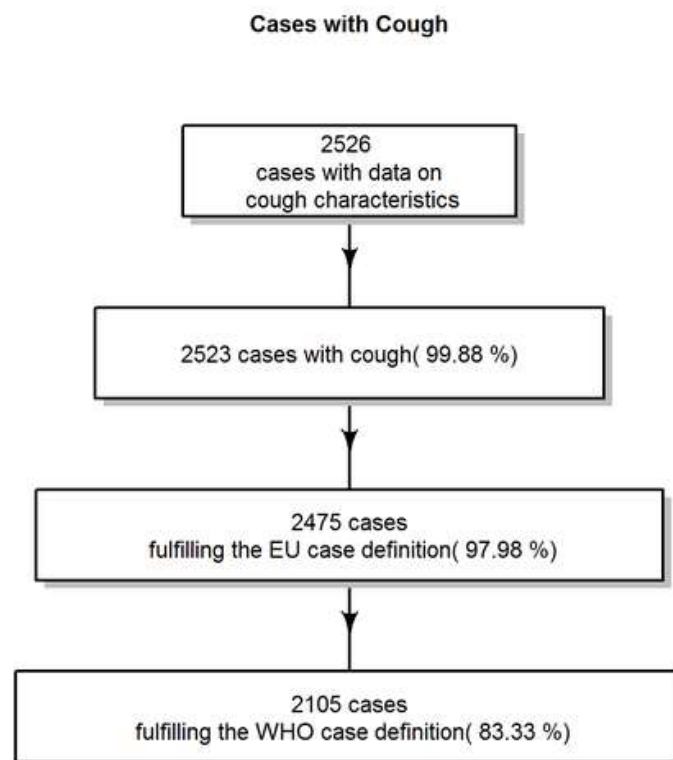
Cases with Cough

Figure 4 (Exec sum): Cough characteristics in a flow chart of 2526 cases of pertussis in the enhanced surveillance study of pertussis with children born January 1, 1996 to December 31, 2012 and followed from October 1, 1997 to December 31, 2012. The pertussis cases were diagnosed with culture or PCR and from 2008 also with serology.

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 380 episodes with respiratory complications, whereof 185 with apnea and 195 without, and 104 children with a dehydration event.. The six cases with other serious complications, there were 3 with seizures, with or without fever, one with swollen lymph nodes and arthralgia and one with neutropenia and lethargy. There was a strong inverse association between age at the beginning of the pertussis episode and the risk of a complication due to the disease for an unimmunised child. There was also an inverse association between vaccination status before the episode and the risk of any complication (Chapter 2B, Section 2.B.2).

Figure 5 (Exec sum) shows that a much higher proportion of unvaccinated (and often younger) children were hospitalized than vaccinated children. Most of the

unvaccinated children were below three months of age at start of the pertussis episode.

Hospitalization data


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                    ┌─────────────────────┐
                    │       2526          │
                    │  cases with data on │
                    │ cough characteristics│
                    └─────────────────────┘
                              │
                              ▼
                    ┌─────────────────────┐
                    │ 2525 cases with data on│
                    │complications and hospitalizations│
                    └─────────────────────┘
                      ╱                 ╲
                     ▼                   ▼
          ┌──────────────────┐  ┌──────────────────┐
          │ 960 Unimmunized  │  │ 1565 Immunized   │
          │     cases        │  │     cases        │
          └──────────────────┘  └──────────────────┘
                  │                      │
                  ▼                      ▼
          ┌──────────────────┐  ┌──────────────────┐
          │ 501 Hospitalized │  │ 141 Hospitalized │
          │  cases( 52.19 %) │  │  cases( 9.01 %)  │
          └──────────────────┘  └──────────────────┘
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Figure 5 (exec sum): Hospitalised cases in a flow chart of 2526 cases of pertussis in Sweden outside the Gothenburg study area in the enhanced surveillance study of pertussis with children born January 1, 1996 to December 31, 2012 and followed from October 1, 1997 to December 31, 2012. The pertussis cases were diagnosed with culture or PCR and from 2008 also with serology.

The duration of hospital stay was shorter in the older and vaccinated children compared to the younger and unvaccinated children. There were 36 hospitalised children, who had received two or more doses of DTPa, but only 5 (14%) were hospitalised for 8 days or more. The overall age-specific incidence rates for a hospital admission was 126, 58.4, 5.1 and 0.2 per 100,000 person years of follow-up for children in age groups 0-<3, 3-<5, 5-<12 and ≥12 months respectively, Chapter 2B; Figures 2.B.1 and 2.B.2.

As could be expected there was also a strong association between hospitalisation and a complication due to the pertussis disease. 72% (352/492) of the children with at least one reported complication also had a hospital admission compared to 14% (290/2033) admissions among children without any complication during the

episode (p<0.001). In all, there were 492 (19.5%) children with at least one complication due to the pertussis disease during the episode. Detailed information in relation to vaccinations and age is found in chapter 2.B, section 2.B.1, 2.B.2, and table 2 (exec sum) below.

Complication type	Hospitalized	Not Hospitalized	Sum
Respiratory, with apnoea	167(90%)	18(10%)	185
Respiratory, without apnoea	112 (57%)	85 (43%)	197
Dehydration	70 (67%)	34 (33%)	104
Other severe events	3 (50%)	3 (50%)	6
No complication	290(14%)	1743(86%)	2033
Sum	642(25%)	1883(75%)	2525

Table 2 (Exec sum): Type of complications in children with laboratory confirmed pertussis in the enhanced surveillance study and hospitalisation rates.

Pertussis incidence in the trial cohorts born 1992 and in 1993-1994 *Chapter 3 results.*

Cases of pertussis during the fifteen-year follow-up period among children who had received three doses DTP vaccines in the nation-wide pertussis vaccine trials [2-3] are shown in Chapter 3; Tables 3:1 – 3:4. These children were born in 1992 or between June 1993 and May/June 1994 and were vaccinated within the trials at 2-4-6 months (Trial I; all children, Trial II; 10,194 children) or at 3-5-12 months (Trial II, 72,698 children). Due to study results an extra dose of Pa was offered in early childhood to children vaccinated with DTPa2 (unregistered vaccine). The estimated incidence in children vaccinated with DTPa2 completed with a booster dose at the end of Trial II was lower than in cohorts vaccinated with three doses of DTPa3, DTPa5 or DTPw, all shown to be more efficacious in the trial. Among children vaccinated according to the 3-5-12 months schedule, i.e. including an early booster at twelve months of age, the long term incidence was higher in the five-component than in the high efficacy whole-cell group – in contrary to what was estimated in the trial.

Pertussis incidence after booster vaccination.

This has been evaluated in an abstract at the European Society of Pediatric infectious Diseases (ESPID) meeting in 2010. The results were shortly presented in chapter 4 of the 13-year surveillance report. The presence of a booster was shown to have a strong effect, with an estimated RR of 0.34 (95% CI 0.14 - 0.71) after booster vaccination.

Case contacts of pertussis in infants. *Chapter 4 results.*

This has been described in an abstract at the European Society of Pediatric Infectious Diseases meeting in 2012, see chapter 4. For short, 80% of the case-contacts were from the nuclear family, 30% from the mother, close to 30% from the father and 20% from siblings. Among siblings, 0-3 years of age was the most common age of a sibling to be a case contact.

Summary in brief

  - The overall incidence of laboratory confirmed pertussis dropped from 121-150/100,000 in 1993-1995 to 10-16-2.8/100,000 in 2001-2012 (including PCR-confirmed pertussis and from 2008 also with positive serology).

  - Among infants, the incidence of pertussis has steadily decreased until the last four years when the incidences have been similar. However, the incidences were higher during the last months of 2012 in comparison with the last four years but considering the whole year of 2012, still at a rather low level.

  - The highest incidence occurs in infants who are unvaccinated or have received only one dose of acellular pertussis vaccine.

  - Since the data have suggested waning protection, a booster dose at 5-6 years age was implemented in Sweden in 2007. A clear 5-year effect of the booster dose was observed with declining incidences of pertussis in the relevant age groups, as discussed in detail in the 13-year surveillance report. (5).

  - Most hospitalisations and complications occur in unvaccinated infants.

  - There was an association between vaccination status of the child before the episode and the risk of a hospitalisation or a complication, indicating that in children with pertussis there might be some protection against "severe" disease, expressed as a hospitalisation or a complication, already by the first vaccine dose.

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

  - Of note is that the Swedish National Board of Health and Welfare has since 1982 recommended post-exposure prophylaxis with antibiotics to infants below 6 months of age, a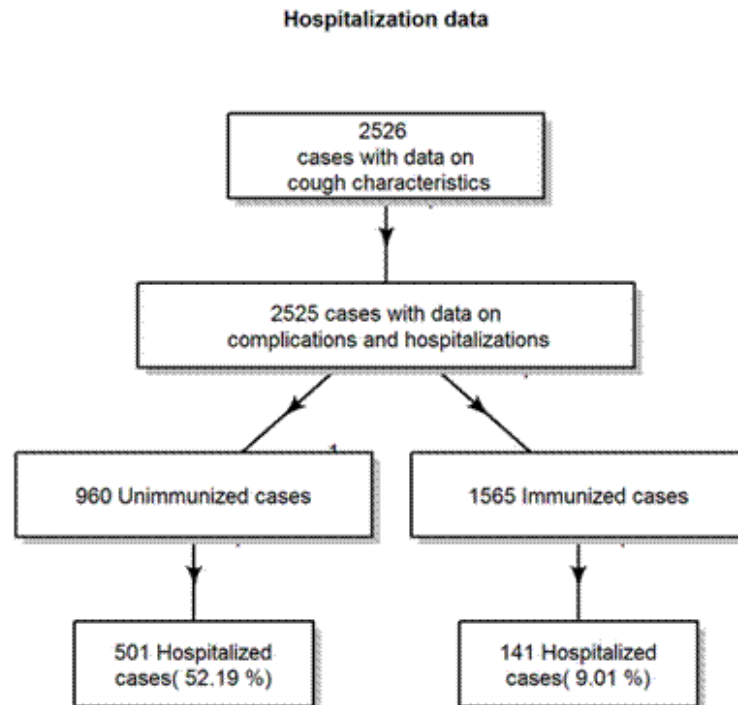nd early treatment at first symptoms to infants 6-12 months. The rates of antibiotic treatment in the age-groups <3 months, 3-<5 months and 5-<12 months during the twelve years of surveillance were 90.5%, 80.4% and 70.6% respectively.

  - 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.A.3).

- Clinical case definitions used for routine reporting of pertussis in infancy should include children with cough duration less than 14 days, since pertussis in this age-group may be serious and even fatal in spite of coughing period shorter than 2 weeks.

- Successfully implemented post-exposure prophylaxis in this age-group may lead to shorter coughing period.

Material and Methods.

A. Pertussis vaccination in Sweden

Vaccination schedules, primary immunisation

Vaccination with diphtheria-tetanus-acellular pertussis (DTPa) vaccines had its onset in January 1996 after a 17-year vaccine-free period following the withdrawal of the whole-cell pertussis (Pw) vaccine due to concerns about safety and efficacy [1]. The DTPa vaccine was registered in 1995 based on the results of several large acellular pertussis vaccine trials conducted in Sweden [2-3, 7-8] . The overall incidence of pertussis during the vaccine-free period had reached more than 100 cases /100,000 person years, and up to 1,000 cases/100,000 infant years. Infant vaccination with Pa vaccines was hence introduced in an endemic setting.

Before universal vaccination with DTPa started in 1996, pertussis Trial I with a 2-4-6 month schedule was performed in 9,829 infants born 1992. In Trial II with either a 3-5-12 month (72,698 infants) or a 2-4-6 month schedule (10,194 infants), the pertussis vaccine was administered in children born June 1993 to May/June 1994 (2-3) (see also Material and Method, section B about vaccines).

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

Children with delayed vaccination for some reason, were until spring 2002 normally vaccinated according to the same principle during second year of life, i.e. two doses with a two month interval, followed by a third dose after six months, and from age 2 years according to a two dose schedule (except in Gothenburg, where a three-dose schedule was used regardless of age). From age 13 years primary immunisation against pertussis is not generally recommended.

The Gothenburg mass vaccination project offered free catch-up vaccination with 3 doses to all children born in the 1990:s during the years 1996-1999 (9). There was no free catch-up offered 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.

Vaccination schedules, booster vaccination

In 2005 a revision of the national immunisation schedule was initiated. As a first step, a booster dose was recommended to children in school year 4 (age 10 years) from autumn 2005. The first cohort recommended this 4th dose of Pa were children born 1995, i.e. the year before formal introduction of DTPa in infancy, because this cohort was to a large extent (59%) catch-up-vaccinated below two years of age. A second step was taken in January 2007, when the schedule was changed to include

a 4th dose already at 5-6 years and a 5th dose at 14-16 years to children born from 2002. This means that from 2007, the Swedish vaccination programme has included a pre-school and a "school-leaving" booster against diphtheria-tetanus-pertussis to children born from 2002 (10). Full dose vaccine is recommended at school entry and a reduced antigen vaccine at school leaving.

B. Vaccines, and vaccine distribution

Vaccines used

In the beginning of 1996, when a pertussis vaccine was reintroduced in the vaccination program, only one Diphtheria-Tetanus-acellular Pertussis (DTPa) vaccine (Infanrix®, GlaxoSmithKline, GSK) was used in all parts of Sweden except in the Gothenburg area. This was a three-component acellular pertussis vaccine containing 25 □g Pertussis Toxoid (PT), 25 □g Filamentous Haemagglutinin (FHA) and 8 □g Pertactin (PRN). It was used in the whole country, except in the Gothenburg study area, where a one-component DTPa vaccine only containing PT, (40 □g) (DiTeKik, SSI) was used.

From September 1998 and during 1999 some counties in Sweden switched to the first licensed combined DTPa-Hib-IPV vaccine (Pentavac®, Sanofi Pasteur MSD), a two-component acellular pertussis vaccine containing 25 □g PT and 25 □g FHA. 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 covering 11.4% of Swedish newborns during the follow-up period, the Di-Te-Kik®, SSI vaccine was used. In 2000 these communities switched to Pentavac®. From 2000-2001 all counties in Sweden administer the five vaccinations recommended to all infants by use of the pentavalent combination vaccines.

Vaccination against hepatitis B is not included in the Swedish vaccination program, but recommended to infants and children at risk. However, in 10 counties the coverage of the hexavalent combination vaccine for infants with hepatitis B vaccine (Infanrix-Hexa®, GlaxoSmithKline) is 70% or more (Dec 2012). For 6 counties hexavalent vaccine is free of charge, 3 of them since January 1, 2013. Nine counties have not changed their policy and administer the hexavalent vaccine only to infants at risk. However, in these counties the coverage is between 27 and 67% (December 2012).

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

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

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

2. The Stockholm Trial II included 82,892 infants in 1993/94. They were vaccinated with the five-component vaccine (CLL), the two-component vaccine (GSK), a three-component vaccine (Chiron) or a DTPw vaccine (Evans) [3].
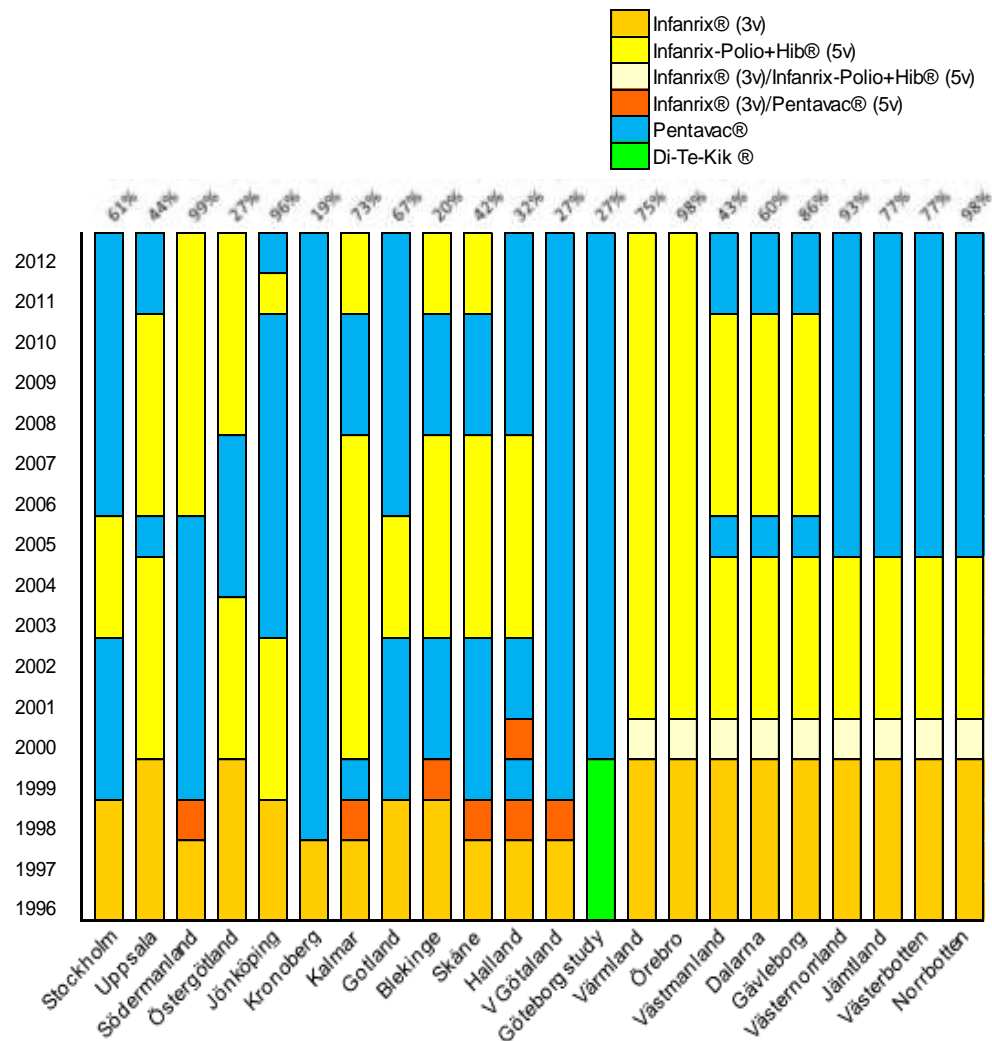
Figure 1 (M&M): Procurement of vaccines by county 1996 –2012. Population figures are given on top of the columns, respectively. "3v" indicates DTPa-vaccine, "5v" indicates DTPa-vaccine, polio and Haemophilus type b-vaccine. For six counties hexavalent vaccine is free of charge, 3 of them since January 1, 2013. In 10 counties the coverage rate of the hexavalent combination (Dec 2012) vaccine for infants with hepatitis B vaccine (Infanrix-Hexa®, GlaxoSmithKline) is 70% or more. For the remaining counties the coverage rate is between 27 and 67%.

Laboratory confirmed pertussis in children born Jan 1, 1996 until Dec 31, 2012 in regard to vaccine used.

In chapter 2A we summarize data for laboratory confirmed episodes observed outside the Gothenburg study area from October 1, 1997 until December 31, 2012 among children born from January 1, 1996 until December 31, 2012.

Children were divided in two sub-cohorts; children born from January 1, 1996 until September 30, 1997, and children born from October 1, 1997 until December 31, 2012. The first 21 month cohort is regarded as a "pure" Infanrix cohort, since that vaccine was the solely used pertussis vaccine for this birth-cohort in Sweden where Gothenburg study area is excluded. The second 183 month cohort (15 years 3 months) has been more complex to analyse since the procurement of vaccines has varied considerably among the counties for children born after September 1997 (Figure 1 M&M). 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 pertussis schedule (Infanrix®/Infanrix-Polio+Hib®/Infanrix hexa®); children with a "pure" two-component schedule (Pentavac®); or children with a "mixed" two/three-component pertussis 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.

C. Pertussis case definition

An episode of pertussis was defined by detection of B. pertussis by culture or PCR in a sample obtained >6 months after a previous positive sample, and regardless of symptoms (primary case definition). Typical pertussis was defined as culture- or PCR-confirmed pertussis with twenty-one days or more of spasmodic cough, corresponding to the WHO pertussis case definition of 1991, established for use in the efficacy trials [11]. From 2008 also positive serology episodes have been included. Additional analyses according to the EU and WHO surveillance case definitions of 2002-2003 [12-13], i.e. prolonged coughing of any type of at least fourteen days, have been added as appropriate.

D. Pertussis reporting

There is a long-standing Swedish tradition of pertussis reporting, beginning with the reports by county health officers early in the 20th century, continued by voluntary laboratory reporting of culture-confirmed cases 1980 to 1996 with full term personal identifiers, see Material and Method, section F. For chapter 2-3 – see also Material and Method, section I. At the time of reintroduction of pertussis vaccination in 1996, pertussis was included in the Communicable Disease Act in 1997.

E. Pertussis vaccine coverage

Vaccination coverage

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

There is a well-established child health care system in Sweden with a 98-99% coverage of the vaccinations recommended in the national vaccination program in infancy. The three-dose coverage for pertussis vaccination at 3, 5 and 12 months of age rapidly reached this level in 1996, since the introduction of a DTPa vaccine in 1996, only meant a switch from a DT vaccine to DTPa. The vaccination coverage has remained on the same level during the subsequent switch to multivalent combination vaccines including Pa.

The vaccination coverage after the reintroduction of pertussis vaccination in 1996, was already from the start higher than 98.5%, Table 1 (M&M); and has remained at this level since then. With one exception, the coverage at county level has been 97% or above in all counties and all cohorts born from 1996.

Birth year	3 DT	3 Pa
1993	99.4	46.9
1994	99.4	42.0
1995	99.3	59.3
1996	99.3	98.7
1997	99.1	98.6
1998	99.0	98.7
1999	98.8	98.5
2000	98.6	98.3
2001	98.6	98.4
2002	98.6	98.6
2003	98.7	98.7
2004	98.7	98.6
2005	98.4	98.3
2006	98.5	98.4
2007	98.0	98.0
2008	98.3	98.3
2009	98.3	98.3

Table 1 (M&M): Vaccine coverage of three doses of diphtheria and tetanus (DT), and acellular pertussis (DTPa) vaccination for children born from 1993 to 2009. The children

should have had their 2nd birthday before the evaluation in January each year (source SMI Annual Reports).

F. National register data of pertussis, Chapter 1.

Routine reporting system

During 1980 to 1996 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 and/or laboratory confirmed by culture, polymerase chain reaction (PCR) or serology were reported to the Swedish Institute for Communicable Disease Control through a computer-linked reporting system (SmiNet).

There were a few subjects in the Surveillance reports in 2011 and 2012 diagnosed only by cough and serology. These children were carefully evaluated and had obvious symptoms of whooping cough. Diagnosis based on serology is more common in the adult population.

Since 1997, the epidemiology of pertussis in the Swedish population including all age-groups is studied annually by analysing the obligatory reporting. Basic data in this routine reporting system include, for example, the national registration numbers (NRN), but there are only limited or no clinical or vaccination data available from the routine reports. The NRN are individually unique Swedish person identifiers that provide information on date of birth, sex and up to 1990 registered place of residence including county. Laboratory reports include laboratory method and (normally) date of sampling and/or date of positive result.

All episodes of pertussis occurring in children participating in the enhanced pertussis surveillance i.e. children born since January 1, 1996, and also in children participating in the nation-wide trials 1992-96 [2-3], were identified via the national register of reports according to the Communicable Disease Act.

General information on pertussis in Sweden

General results of all laboratory confirmed and reported pertussis in Sweden have also been included in the annual progress reports. This information includes a time-trend illustration of the number of laboratory-reported cases of pertussis per month from 1986 and onwards, as reported according to the Communicable Disease Act (Executive summary, figure 1). These laboratory reports are based on culture, PCR or serology. The general information also include annual incidence rates of culture-and/or PCR-confirmed cases in the whole population and by age-groups for the years 1986-1995 (no universal vaccination against pertussis), and from 1996 and onwards (after introduction of Pa). The annual progress reports have summarised the general information up to the previous calendar year, with Chapter 1 of the present fifteen-year report updating this general information until December 31, 2012.

G. Enhanced surveillance study Oct 1 1997- Dec 31. 2012. Methodology, Chapter 2

Enhanced surveillance program

The enhanced pertussis surveillance had its onset in October 1, 1997 in Sweden, 1¾ year after the introduction of acellular pertussis vaccines at 3, 5 and 12 months in the national vaccination program. All reports, according to the Communicable Disease Act of culture- and PCR-positive cases of pertussis in children born since January 1, 1996, have been entered in a database.

Recognising the unique situation in Sweden, a European country with endemic pertussis, a well-implemented vaccination program and a long-standing tradition of quality in the reporting (laboratory-confirmed cases), a long-term enhanced pertussis surveillance project was started in October 1, 1997. The obligatory case-based reporting system was used to identify cases confirmed by culture (later also PCR in children born from January 1, 1996 and from 2008 serology), and detailed data on vaccination status and clinical course were collected by structured telephone interviews. Also, previous trial cohorts [2-3] were followed-up. The changes over time in age-specific rates have been considered the main outcome, and we have also related clinical outcome to vaccination status. Initially, there was a laboratory part of the surveillance project, which ran in parallel until 2004.

Clinical part of enhanced surveillance

In the clinical part of the enhanced surveillance project, all episodes of pertussis (except those occurring October 1, 1997 to December 31, 2002 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) were collected by telephone interviews. All clinical data and the unique Swedish personal identifier were entered into a "clinical" database. Progress reports have summarised the database information for all episodes (except those occurring in the Gothenburg area) up to end of the previous project year, with the present fifteen-year report updating the information from October 1, 1997 until December 31, 2012.

Parameters reflecting severity of disease were duration of spasmodic cough and total duration of cough, presence of complications, and hospital admissions including length of hospital stay. Also, information on antibiotic treatment with erythromycin or other relevant antibiotics were collected. Detailed vaccination history for children born since 1996 was obtained from the medical records of the Child Health Care or School Health Care Centres by telephone to the nurse attending the individual child. Parental permission was obtained to request medical records as needed.

Birth cohorts followed

Children born January 1, 1996 or later and residing outside the Gothenburg area at time of pertussis, and children born 1992 and who participated in Trial I [2], as well as children born 1993.06-1994.05 the recruitment cohort for Trial II [3], are

followed continuously from October 1, 1997 within the surveillance project. Children born January 1, 1996 or later and residing in the Gothenburg area at time of pertussis are followed continuously from January 1, 2003 in the same way as children from other parts of the country. They are described in a separate pertussis surveillance report.

Results are first summarised for each annual birth cohort. Available data are also presented for three cohorts of children, i.e. Trial I, Trial II and the enhanced surveillance study, see below. Detailed clinical follow-up is hence restricted to children with a laboratory confirmed pertussis in the cohorts listed below.

- Children born 1992: Children participating in Trial I. Around 9,829 infants were enrolled in the study.

- Children born 1993.6-94.5 (in the county of Malmö also June 1994): This was the enrolment period for Stockholm Trial II; a vaccine trial in which 82,892 children were vaccinated. We have access to all vaccination data. Rate of vaccination was just above 83%.

- Children born January 1, 1996 to September 30, 1997: First cohort after the introduction of DTPa vaccination. Vaccine coverage for three doses Pa at 2 years of age was above 98%, according to the statistics from the Child Health Centres from 1999. Follow-up data for pertussis cases are lacking for the period January 1996-September 1997.

- Children born October 1, 1997 to December 31, 2010: 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.

- Children born in 2012: Still not fully immunized.

In all presentations in this fifteen-year main surveillance report, children from the Gothenburg study area are excluded.

Fifteen year surveillance database, flow schedule

There were a total of 6971 episodes of laboratory confirmed pertussis reported and added to the surveillance database from the start of the enhanced follow-up on October 1, 1997 until the end of April 2013 and representing pertussis episodes starting no later than December 31, 2012. Overall, 145 new cases occurred in 2012.

From the Gothenburg study area there were 1452 reports from the routine reporting system entered into the surveillance database. These are analysed yearly in a separate Gothenburg study report. Of the remaining 5519 episodes, 339 (6.1%) have not been possible to follow-up for clinical data due to e.g. confidential phone numbers, language "problems" etc. Forty-five episodes with an onset of cough earlier than October 1, 1997 were also excluded from the statistical analysis as well as 6 children without a date for onset of cough. After the above exclusions 4985 episodes remain in the database for children outside the Gothenburg study area.

For 5129 (one child had two episodes) children living in households outside the Gothenburg study area - born between January 1. 1992 and December 31, 2012, and with an onset of cough during a laboratory positive pertussis episode which

occurred between October 1, 1997 and December 31, 2012- we have access to data on both vaccinations and clinical follow-up.

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

Episodes for cohorts not under surveillance any longer (n=1874), i.e children born January 1992 until December 31, 1995 but not participating in the studies Trial I or Trial II were excluded from the study population before the statistical analysis was performed. The remaining children are then 3255, see Birth cohorts followed, Figure 2, below.
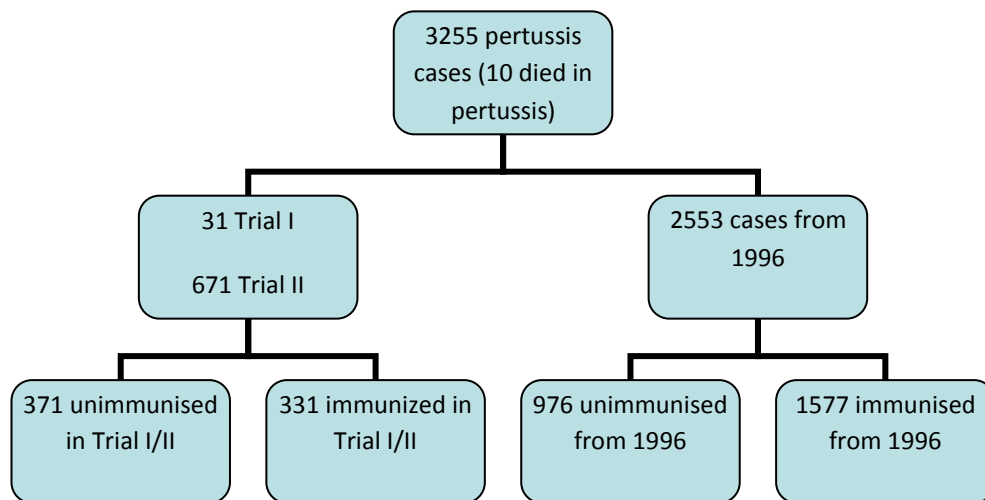
Figure 2 (M&M): Flowchart for children followed from Trial I (born 1992), Trial II (born June 1993 to May 1994) and all children outside the Gothenburg study area from 1996. The flow chart shows the contribution of unimmunised children from each group. The pertussis cases are defined in Material and Method section C. The number of pertussis cases are 3255 including the 10 children that died in pertussis. These children are not included in the other analyses in the report.

H. Enhanced surveillance study, trial I and II. Methodology Chapter 3

Children born 1992 and 1993-94 who participated in the two nation-wide trials of 1992-1993 and 1993-96, Trial I and Trial II [2, 3], have also since then been identified through the national register of communicable disease reports, and entered into a separate study database. Almost all of these cases of pertussis have also been followed-up in detail by study nurses, who documented the vaccination history and clinical course by structured telephone interview according to the same procedures carried out during Trial II [3].

I. Enhanced surveillance study. Calculations of cases and incidences. Chapter 2 and 3

Laboratory confirmed pertussis cases analysed in this 15 year report

In the chapters 2 and 3 results for the remaining 3255 episodes of laboratory confirmed pertussis are presented. Of these 2553 episodes occurred among children born between January 1, 1996 and December 31, 2012; 31 episodes concerned children from Trial I and 671 episodes concerned children who were born according to the recruitment period for Trial II.

In section 2.B.1, we present results on hospitalisation for children born January 1, 1996 until December 31, 2012 for whom we have data on length of hospitalisation (n=2553). Results for complications (n=2525) due to the pertussis illness during the pertussis episode and the duration of spasmodic cough (n=2553) are found in sections 2.B.2 and 2.B.3. Treatment with antibiotics is covered in section 2.B.4.

In the present fifteen-year report, 109 new cases of laboratory confirmed pertussis with vaccination and clinical data were included in the main surveillance analyses. Vaccine failures among participants in Trial II are reported separately in Chapter 3, also including vaccine failures in Trial I participants.

Finally, there are laboratory reports in the database for 10 children born 1996 - 2012 who died due to the pertussis disease (data for those children are only used in section 2.B.2 (complications during the pertussis episode)).

Person time and incidence calculations, definitions

Age-specific incidence rates of pertussis for children born January 1, 1996 until December 31, 2012 and for children in the 1993-96 trial were based on the number of notified pertussis cases during the study period October 1, 1997 to December 31, 2012 as described in Chapters 2 and 3. 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. This was based on age at notification, and on the corresponding mid-year populations derived from the mean of population numbers at two consecutive years divided by two (data from Statistics Sweden, *http://www.scb.se*). From 2008 serology-diagnosed patients were added.

Person-time of follow-up & incidence calculations

Table 2.A.6 and 2.A.9 (rightmost column) respectively give the number of laboratory confirmed pertussis cases used in the incidence calculations that follow in section 2.A.7.

J. Calculation of vaccine effectiveness

We have specifically refrained from estimating vaccine effectiveness by percent reduction of disease rates among vaccinated compared to unvaccinated children because of the passive reporting system with inherent ascertainment bias, which

will inflate levels of protection [14], and because there is no computerised vaccination register for calculation of proper incidence denominators. Furthermore there is a selection bias since the very small proportion (1-2%) of unvaccinated children is likely to differ from Swedish children in general, with some of the unvaccinated children living in institutions or in other "households" that are not a representative sample of Swedish households. We have also refrained from long-term comparisons by vaccines and geographic areas, since the use of the different Pa vaccines has varied with and within calendar periods and areas. In addition, 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 the Gothenburg study area).

The main aims of the surveillance study were to evaluate the impact of the vaccination program against pertussis, to follow the long-term protection after vaccinations with DTPa-containing vaccines and to document possible strain changes. The experience from one, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen and fourteen years of enhanced clinical follow-up in Sweden (except Gothenburg) has been published previously [15-17] and also reported in the progress reports [4, 18-29].

In Chapter 1 general information on laboratory-confirmed pertussis is reported from the whole country and all ages before and after introduction of Pa vaccines. The experience from the laboratory surveillance has been published separately [30-35], and also reported in former technical progress reports.

As for children from the Gothenburg area, we have until last year refrained from inclusion of these data in the yearly main progress surveillance 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.

Chapter 1. Incidence data from the SMI net data base

1.1 Overall incidence of laboratory reported pertussis 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 the overall pertussis incidence in the Swedish population, Figure 1.1 and 1.2 and figure 1 in the executive summary. The overall incidence during the last five years are 4.0, 3.0, 2.7, 1.8 and 2.8 per 100,000, respectively (Table 1.2). These incidences are lower compared to when the Swedish whole cell vaccine still was effective during the late 60'ies and early 70'ies (9.4-12.2/100,000).

The decline in incidence after 1996 has been more rapid than when DTPw was introduced during the 1950:s. One explanation might be that vaccination coverage in those days was only gradually rising over decades until reaching 90 percent of the infants, whereas the coverage for DT in the 1990s already was more than 98% since the reintroduction of pertussis vaccination only meant a switch from DT to DTPa, see Material and Method, section E, "Pertussis vaccine coverage".
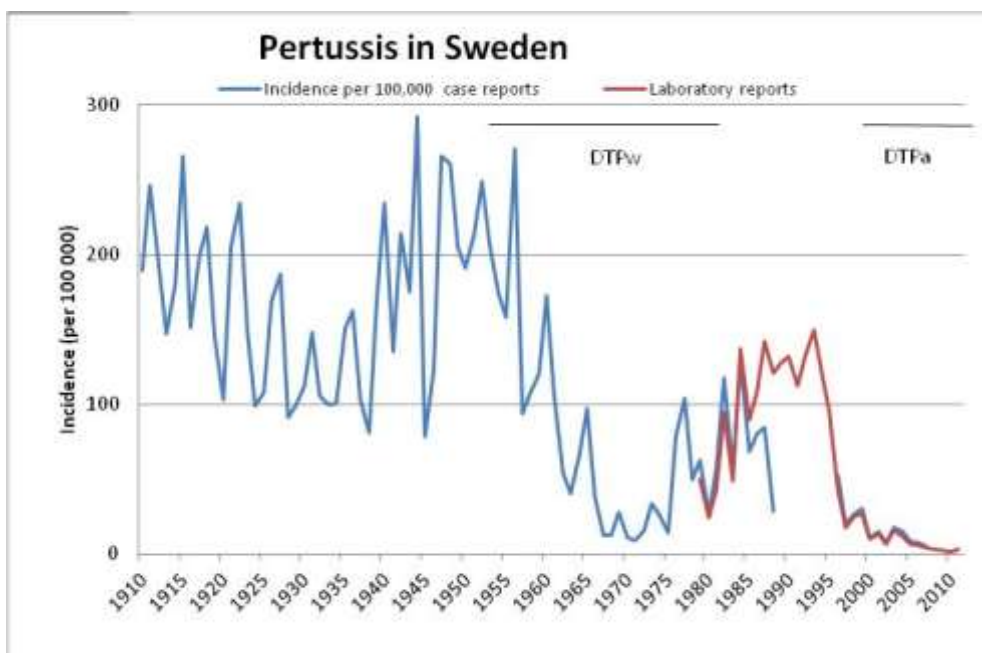
Figure 1.1 Overall pertussis incidence in Sweden. Sources: Case reports from general practitioners until mid 1980ies and according to the communicable disease act from 1997, lab-reports from 1980.

The overall incidence in the peak epidemic year 1994 was 150/100,000 populaton years, and dropped to 18/100,000 in 1998 (Table 1.2). In the winter of 1999 and 2000 there was a minor peak to about 25 per 100,000, thereafter there has been additional minor peaks in 2002 and 2004-2005, see Figure 1.1 and Figure 1 in the executive summary.

1.2 Age-specific incidences of laboratory reported pertussis over time

The age specific incidences of laboratory reported pertussis in different age groups during the years before and after 1996 is illustrated in Figure 1.2. This figure represents mean age specific incidence during 10 years before and 15 years after 1996, with incidences in age-groups from 10 years and above enlarged in insertion. Figure 1.3 illustrates mean age-specific incidence during "ordinary" (i.e. non-peak years) incidence periods after 1996 (1998, 2001-2003 and 2006-2012 and during peak periods after 1996 (the calendar years 1999-2000, 2002 and 2004-2005.

Note that the mean incidences in the age groups 0-15 years include both fully and partly vaccinated and unvaccinated children during the years 1998-2012 and that we from this source of information don't know the vaccination status of the pertussis cases.
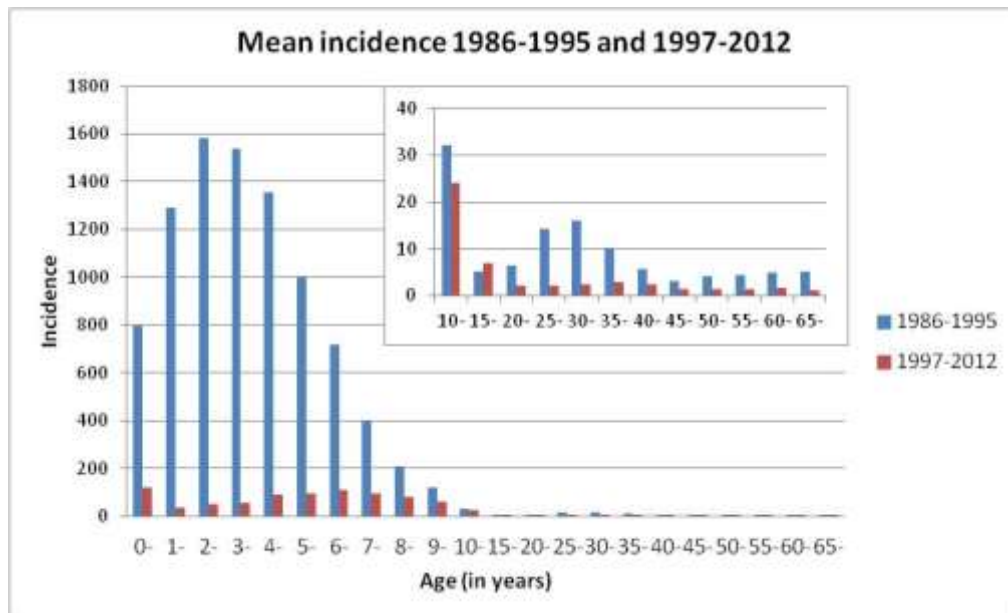
Figure 1.2 Mean incidence of pertussis in defined age groups during 10 calendar years before (1986-95) and 15 years after (1997-2012) introduction of DTPa in 1996. Enlarged curves for the age groups 10 years and above are shown in the insertion. Age in years at date for the positive sample.
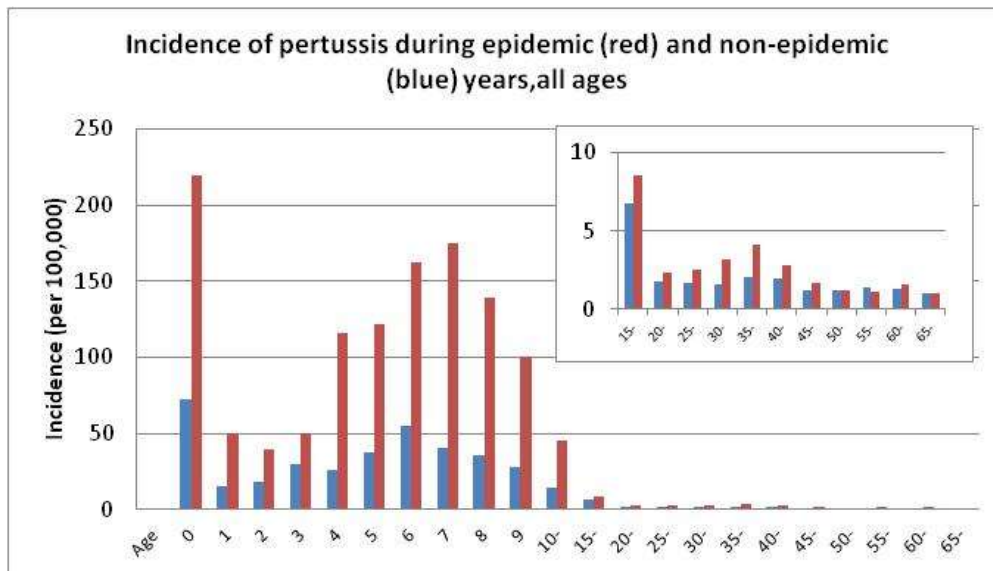
Figure 1:3: Mean incidence in defined age groups during "ordinary" incidence periods after 1996 (the calendar years 1998, 2001, 2003 and 2006-2012 combined) and during three peak periods after 1996 (the calendar years 1999-2000, 2002 and 2004-2005 combined). Age in years at date for the positive sample.

It is obvious that the vaccinated birth cohorts born from 1996 both had a lower age specific incidence of laboratory confirmed cases of B. pertussis in pre-school and early school age than the corresponding age-groups before implementation of the Pa vaccination in infancy in 1996. The age specific incidence for pre-school children dropped from >1000 per 100,000 to approx. 100-200/100,000 in 1998-2000, to 50/100,000 in 2001 and further to approximately 20/100,000 in 2003 and less than 4/100,000 in 2012 (Table 1.2). During the latest years the rate has also dropped to around 5/100,000 among children during the first years in school.

During the years after 1996 there are some differences when comparing calendar years including "peak periods" with periods without increased overall incidence (Figure 1.3). The age-specific incidence among infants 0-11 months old (Figure 1.4) was around 700/100,000 the 10-year period before 1996, decreasing to a mean of around 200/100,000 during peak periods after 1996, with lowest incidence of 41.5-126/100,000 during "non-peak periods" (Table 1.2).

The decline in the incidence among infants after 1996 is to a large extent explained by decreasing number of infant cases from the age of 5-12 months, i.e. from the scheduled age of second dose of DTPa. The mean number of infants with laboratory reported pertussis per age (in months) during infancy is illustrated in Figure 1.5a, during three years before and during "peak" and "ordinary" incidence periods after introduction of acellular pertussis vaccination in infancy. Pertussis cases in infants during years with acellular pertussis vaccinations is illustrated in Figure 1.5b where infant cases during 6 earlier years without outbreaks are compared with the last four years (2009-2012). "Relative number of pertussis cases" in pertussis in infancy is shown in Figure 1.6.
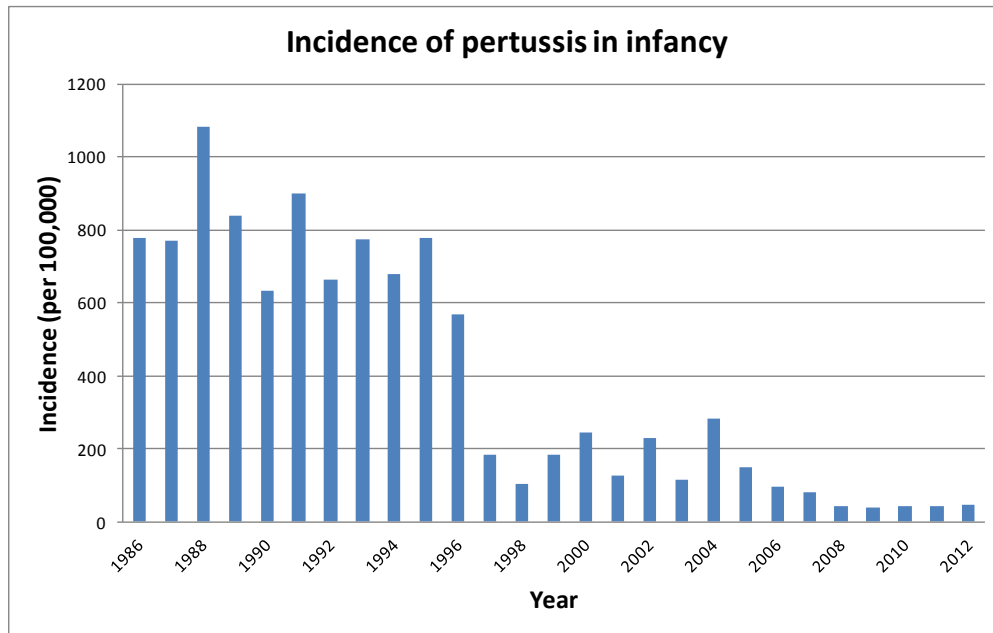
Figure 1.4 Incidence of pertussis in infancy 1986-2012, below one year of age with laboratory verified diagnoses. One of the main issues with pertussis vaccination is to lower the incidence of pertussis in the youngest infants as these have the highest morbidity and mortality. The incidence decreased fast after introduction of pertussis vaccination but kept oscillating around 200 per 100,000 from 1996 to 2005 when the slope went further downwards. This could be due to a higher frequency of vaccinated children in the population and to the pre-school booster vaccinations (the new schedule) and, the booster vaccination at 10 years of age (until 2011-2012).
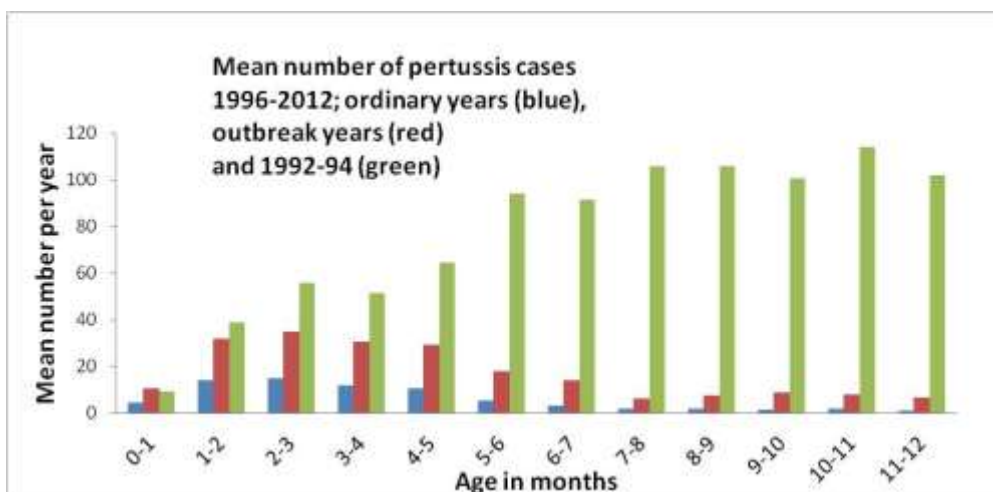
Figure 1.5a: The mean number of infants with laboratory-verified pertussis cases per month of age during 3 calendar years (1992-94) before and during 12 years after (1998-2012) introduction of DTPa in 1996. Mean incidence in defined age groups after 1996 is calculated for "ordinary" incidence periods (the 10 calendar years 1998, 2001+2003 and 2006-2012) and during three peak periods (the 5 calendar years 1999-2000, 2002 and 2004-2005). Age in months at date for the positive sample.
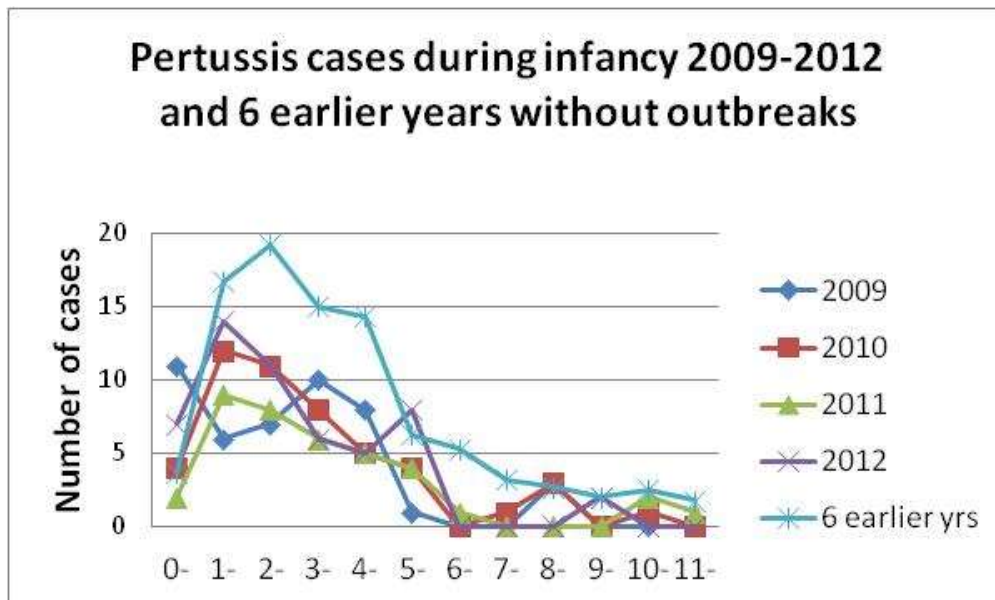
Figure 1.5b: The mean number of diagnosed pertussis during the first 12 months of age for the 6 years 1998, 2001+2003 and 2006-2008 are compared with pertussis disease during the first 12 months for the last four years, 2009-2012.
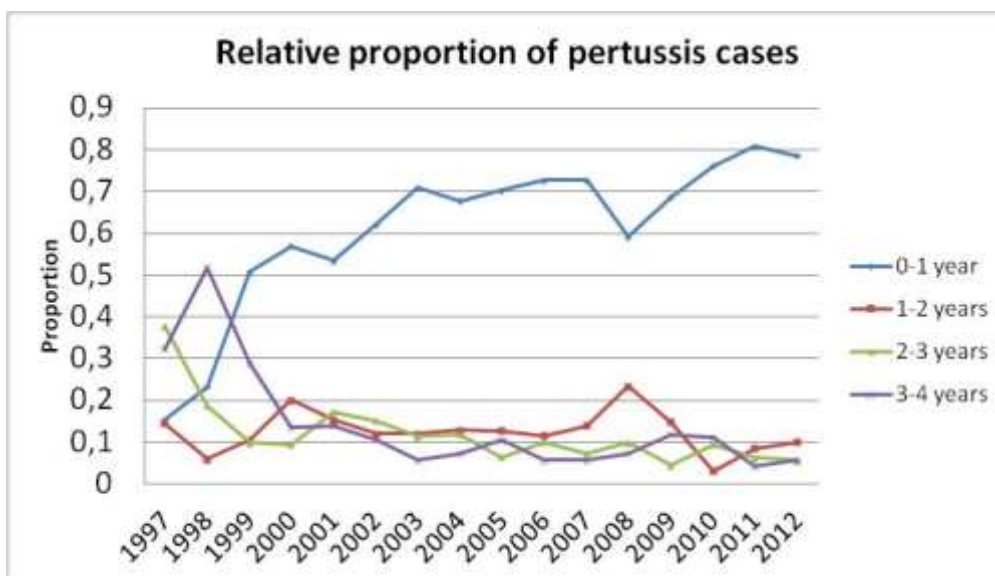
Figur 1.6: Relative proportion of pertussis cases per year for children 0-4 years of age. The first year (blue line), second year (red line), third year (green line) and fourth year (violet line) of life. The incidences of pertussis in 1995 were high for all ages; 779, 809, 1456 and 1493/100,000 for the 0-1, 1-2, 2-3 and 3-4 years of age cohorts, respectively. The incidences in 2012 were much lower, however relatively high for the infants, 45.2/100,000; and for the other age intervals 1-2, 2-3 and 3-4 years were 4.3, 3.4 and 3.5/100,000, respectively.

1.3 Regional differences in overall incidence over time

At subnational (county) level there are undulations in the incidence, with variations in time between different areas. Figure 1.7 illustrates the geographic variations in reported pertussis cases (clinical and laboratory reported) during the years 1997-2012.
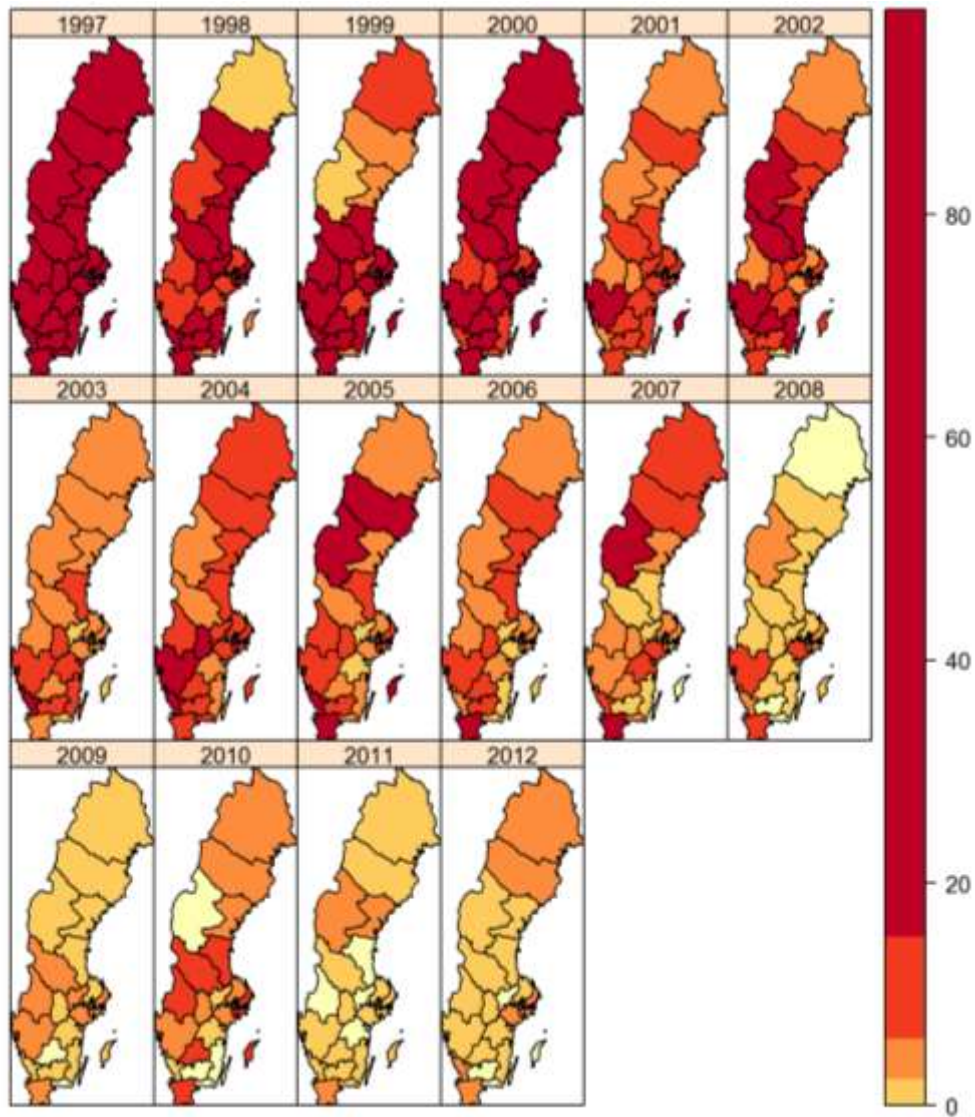
Figure 1.7 Incidence of reported pertussis (laboratory reports) in different areas of Sweden from 1997-2012. Colour breaks at 25%, 50% and 75% quantiles. Source: SmiNet.

1.4 Timing of doses

The Swedish Child Health Care system will register at or above 99% of all children. The system is area-based and the nurses have statutory rights to handle the practical part of the national vaccination program within their area. The consistency in adherence to the recommended schedule is illustrated in Figure 1.8, demonstrating the small deviation from scheduled day (Day 0) for the first three doses of Pa vaccination in all children. This is however data in children there pertussis has been reported within the enhanced surveillance until December 31, 2012.
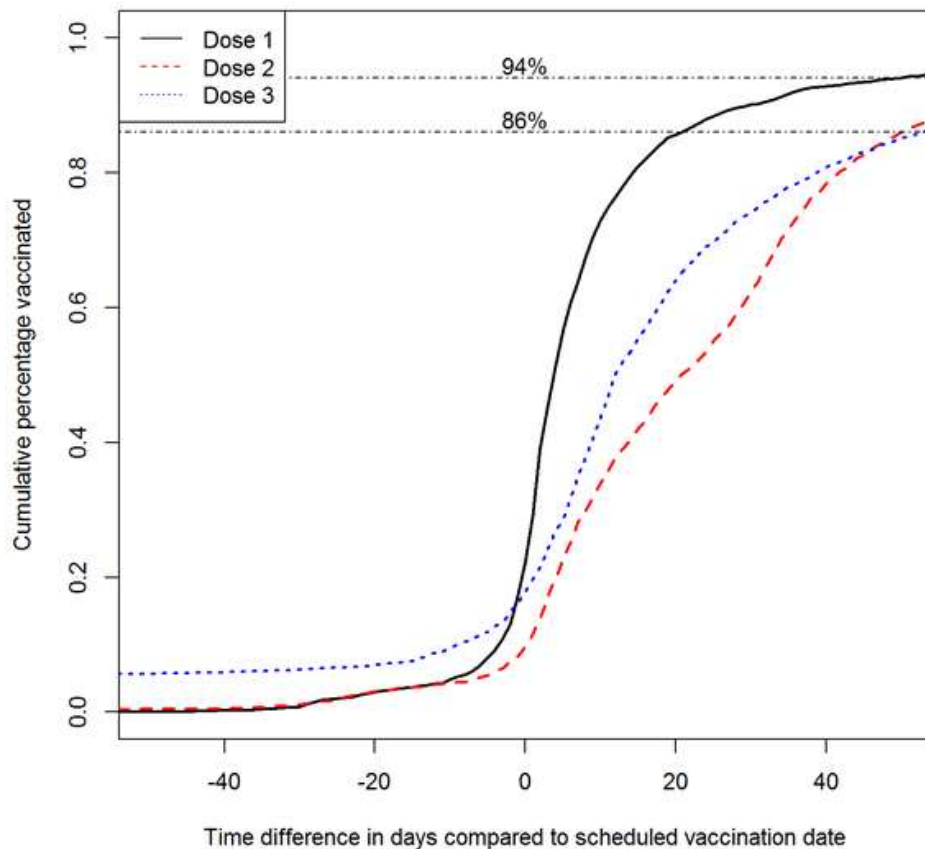
Figure 1.8 Cumulative proportion of children vaccinated in relation to scheduled day (Day 0) for the doses at 90 days, 150 days and 365 days, in children born from 1996 and until December 31, 2012, with a pertussis episode between October 1, 1997 and December 31, 2012.

The consistency over time is further illustrated in Table 1.1, comparing the median ages (in days) at dose 1-3 for children followed within the enhanced surveillance with the corresponding ages during the nation-wide Trial II in1993-1995.

	Dose 1 (90 days)	Dose 2 (150 days)	Dose 3 (365 days)
Trial 2 (n = 72,698 infants included in 3-5-12 month schedule)	100	174	386
Surveillance project from 1997-2012 (children, excl Gothenburg study area, with vaccination date)	94	167	375

Table 1.1 Median age at dose 1-3 in Trial II (1993-94) and during the 1997-2012 enhanced surveillance period. The scheduled ages are 3-5-12 months, corresponding to 90, 150 and 365 days.

1.5 Catch-up and booster vaccinations

Infants born during the latter part of 1995 were vaccinated against pertussis in most parts of the country, because the start of their vaccination program was delayed until the Pa vaccines were licensed in January 1996. At age 2 years, the

overall 3-dose coverage for the 1995 cohort was 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 [9]. Children were vaccinated to some degree also in the rest of the country.

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

The vaccination schedule in the national program was changed in 2007 (cohorts born from 2002) to include a 4th dose of DT and Pa at 5-6 years and furthermore to include a 5th dose at 14-16 years. Children born 1995-2001 have received a catch-up vaccination at 10 years of age from autumn 2005 until 2011-2012.

1.6 Case ascertainment

The laboratory reporting from the Swedish microbiological laboratories is based on culture, PCR or serology, as detailed in Figure 1.9. Cases reported on the basis of culture and/or PCR and from January 1, 2008 with serology are followed within the enhanced surveillance. Confirmation of B. pertussis by culture is slowly becoming replaced by PCR.
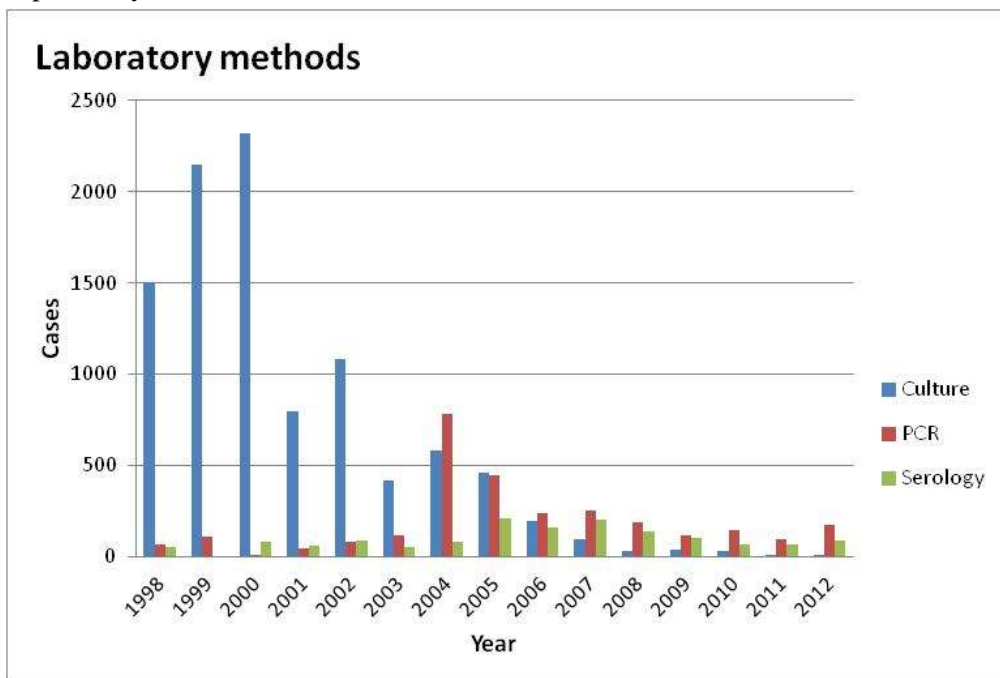
Figure 1.9 Laboratory methods used for verification of cases reported according to the Communicable Disease Act 1997-2012.

1.7 Pertussis disease in different ages and possible booster effects.

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

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

The first indications of a booster effect is shown in the figure below, Figure 1.10
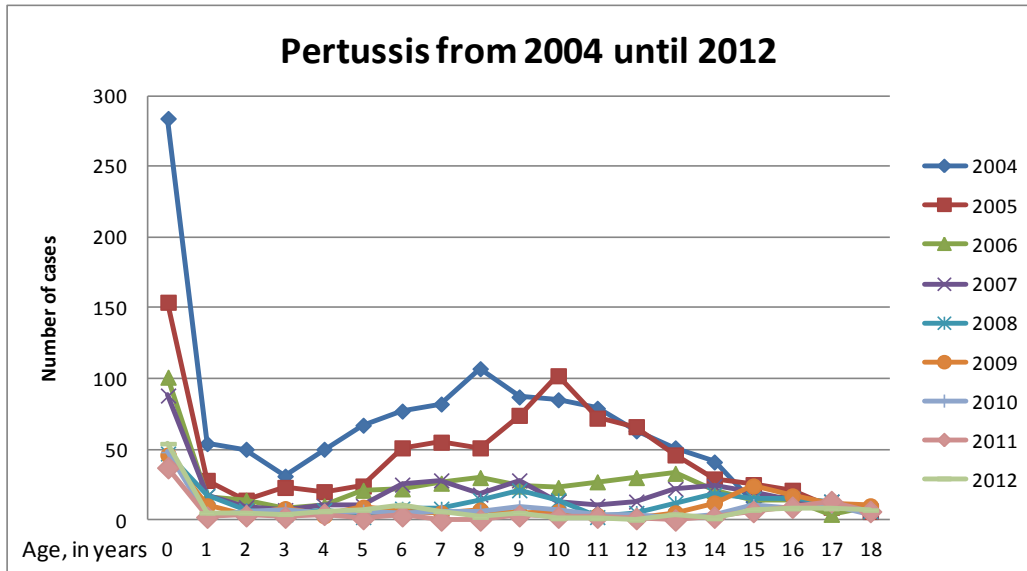
Figure 1.10: Number of laboratory verified pertussis cases between 2004 and 2012 has decreased since 2004 to 2006. An indication of a booster effect is shown in the figure after the 5-6 and the 10 year booster vaccinations.

Table 1:2 Overall and age-specific incidence of laboratory-reported pertussis per 100,000 from 1989 to 1995 before introduction and 1996 to 2012 after introduction of acellular pertussis vaccine.

	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
All ages	121.2	92	132.6	112.8	132.4	150.2	121.7	95.8	41.9	17.9	25	26.9	9.9	13.7	6.4	15.6	11.9	6.8	6,0	4,0	3,0	2.7	1.8	2.8
0	840.4	632.1	900.7	665.2	772.6	677.5	779.3	567.5	185.8	102.6	185.8	243.5	126.1	231.2	114.7	283.5	152.0	97.2	82.2	43.2	41.5	44.1	32.5	45.2
1	1427.1	1050.3	1375.9	1156.4	1305.2	1462.6	809.1	924.5	164.1	25.8	37.7	86.0	36.5	45.6	20.0	54.7	27.7	15.6	16.2	15.7	9.1	1.8	1.7	4.3
2	1678.2	1224.4	1700.5	1437.6	1567.4	1943.9	1456.9	599.5	394.1	74.4	34.3	39.7	41.1	58.3	19.4	52.4	14.1	13.7	8.7	6.6	2.7	5.4	2.7	3.4
3	1599.2	1153.6	1707.7	1384.1	1635.7	1760.8	1493.2	1126.3	316.0	190.0	94.4	55.5	32.9	40.9	9.8	33.3	24.0	8.0	6.8	3.8	7.5	6.4	1.8	3.5
4	1443.5	1028.6	1445.5	1203.8	1419.0	1622.0	1396.5	1190.7	547.3	133.1	269.3	153.1	30.8	50.2	22.0	54.4	21.4	10.4	9.9	6.8	2.9	4.6	3.6	4.5
5	1005.3	737.5	1048.2	904.5	1101.3	1187.7	1044.4	918.8	499.9	197.6	163.4	260.3	46.8	52.9	15.2	73.3	26.0	22.4	10.3	2.0	8.6	5.7	0.9	6.3
6	708.7	535.3	793.1	665.1	708.4	828.0	706.2	687.1	375.8	234.9	316.6	215.1	111.3	86.3	26.3	83.3	55.6	23.7	26.4	8.2	5.9	4.8	2.8	5.5
7	401.8	296.2	419.1	347.4	440.7	460.2	400.2	401.4	238.8	137.5	251.3	289.5	85.6	134.7	30.6	86.0	59.3	28.2	30.0	8.4	5.1	5.9	0	5.6
8	238.4	160.7	199.8	182.3	198.6	246.7	210.6	216.2	135.1	84.9	202.6	230.0	86.6	79.2	41.1	105.3	53.3	32.2	19.4	14.9	7.3	6.1	0	1.9
9	153.2	86.4	115.4	116.0	131.1	127.8	137.6	126.8	58.2	46.3	96.0	164.4	62.9	81.3	29.2	79.1	72.6	25.0	29.8	22.4	5.3	9.3	3.0	4.8
10	57.0	68.6	71.8	72.9	61.8	62.9	87.9	70.6	50.4	20.2	69.8	105.4	34.5	58.7	36.0	72.7	92.5	22.5	13.4	14.8	6.3	7.3	2.0	1.0
11	27.0	19.6	56.2	33.2	38.8	59.2	37.3	43.9	28.2	20.1	34.2	52.8	25.7	45.3	33.2	64.5	61.4	24.3	9.7	2.0	3.1	3.2	2.1	1.0
12	39.3	12.4	16.4	29.0	31.1	32.4	30.4	34.2	24.3	17.8	37.4	35.0	20.0	29.5	22.6	49.7	53.7	25.5	11.6	4.8	1.0	4.2	1.0	0
13	16.5	10.0	15.4	11.2	18.9	24.9	20.1	15.2	5.0	11.7	26.2	28.2	12.2	20.0	17.5	39.6	36.2	26.7	18.6	10.7	4.8	1.0	0	2.1
14	15.6	8.7	15.0	10.2	13.2	12.8	7.9	10.1	9.1	6.0	21.3	19.6	7.3	15.6	9.9	32.5	22.4	16.4	19.3	15.1	10.6	2.8	2.0	1.0
15	5.4	9.1	9.6	6.0	10.2	14.1	8.8	8.9	9.0	10.1	7.0	10.6	6.5	11.7	7.8	10.7	19.8	10.8	15.6	12.0	19.9	8.8	5.6	6.9
16	5.3	6.2	7.3	5.7	5.9	7.1	8.0	5.9	3.9	6.0	7.0	11.0	1.9	9.2	9.0	14.6	17.3	11.0	10.7	11.6	13.5	6.6	7.8	7.4
17	4.4	2.6	5.3	0.9	6.7	2.0	6.0	5.0	2.0	3.9	6.0	14.0	1.0	5.7	2.8	7.2	7.7	3.3	10.2	9.9	9.2	7.9	10.6	6.0
18	4.4	3.5	5.3	6.2	1.8	8.5	2.9	0.0	2.0	4.9	3.9	7.0	0.0	5.9	1.0	8.2	5.3	7.7	5.7	4.6	7.5	3.0	4.7	5.7
19	8.1	6.1	6.0	2.6	2.6	3.6	4.7	3.9	7.0	0.0	1.9	4.9	2.0	1.0	2.9	1.9	8.2	6.2	3.4	1.6	3.1	2.2	0.8	3.9
20-24	7.3	4.1	6.7	4.4	5.5	8.2	5.1	3.1	1.8	1.1	1.3	2.7	0.6	2.7	1.5	2.5	2.3	2.1	2.0	2.5	2.2	1.8	2.3	2.7
25-29	11.9	11.9	15.0	11.5	14.2	16.8	11.5	8.0	4.5	1.0	2.7	2.4	1.2	1.4	2.0	3.4	2.9	3.1	2.4	2.3	1.1	1.9	0.8	1.8
30-34	13.0	14.0	19.1	15.9	16.6	22.6	11.9	10.5	3.7	1.7	2.3	4.4	1.8	2.0	1.0	3.9	3.4	1.8	1.3	2.2	1.5	1.9	1.0	3.6
35-39	11.1	7.8	9.2	6.5	10.2	15.1	9.9	7.4	3.9	1.9	3.2	4.7	0.9	3.0	1.5	5.0	4.7	4.1	2.7	3.0	2.1	2.4	0.8	1.6
40-44	6.1	5.3	6.0	5.1	5.7	8.3	4.7	3.7	3.4	0.7	1.4	2.4	1.4	1.9	1.4	3.0	5.3	2.3	4.4	2.8	1.0	2.4	0.8	2.5
45-49	3.8	4.0	3.2	2.3	3.6	3.9	3.8	1.4	1.1	0.5	1.3	1.0	0.2	1.7	0.5	1.2	3.4	2.1	3.1	2.0	0.8	1.3	0.6	1.3
50-54	3.1	5.0	5.5	4.1	5.4	3.6	4.1	3.1	1.7	1.1	0.3	0.8	0.6	1.5	0.5	1.4	2.1	2.1	1.9	1.2	1.0	0.9	1.0	1.5
55-59	3.3	3.8	5.3	4.3	5.6	6.1	4.9	3.7	1.0	0.6	1.1	1.4	0.8	1.1	1.1	1.1	0.8	3.1	2.1	1.0	1.4	0.2	1.6	1.2
60-64	2.3	3.5	7.6	4.6	4.4	5.7	7.4	4.0	2.5	0.5	0.7	2.1	0.4	1.5	0.6	0.8	2.9	2.7	2.4	1.6	1.0	1.3	0.8	1.2
65+	2.0	2.5	2.6	2.9	2.4	4.7	4.0	3.5	1.4	0.6	0.9	0.9	0.1	0.7	0.8	0.9	1.7	1.5	2.4	1.4	0.7	0.6	0.6	1.4

Note for table 1.2 and 1.3! All age specific incidence figures in table 1:2 and 1:3 concern children from two yearly birth cohorts: Age specific incidence figures above, the red figures (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 below 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 – se Table 1 (M&M).

Table 1.3 No of lab reported pertussis cases in age groups from 1989- 1995 before introduction & 1996-2012 after introduction of vaccine

	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Age	10291	7875	11427	9781	11542	13185	10741	8473	3707	1582	2213	2388	878	1225	574	1404	1071	617	553	372	265	250	168	268
0	960	759	1120	821	928	778	839	566	173	91	165	217	115	217	111	284	155	101	88	47	45	48	37	51
1	1558	1208	1660	1443	1618	1763	931	992	160	25	34	76	33	42	19	54	27	16	17	17	10	2	2	5
2	1754	1344	1961	1738	1952	2417	1754	692	425	75	32	36	37	53	19	50	14	14	9	7	2	6	3	4
3	1636	1220	1886	1604	1985	2205	1864	1359	355	203	95	52	30	37	8	31	23	8	7	4	8	7	2	4
4	1423	1057	1536	1336	1658	1992	1769	1491	659	154	292	155	28	46	20	50	20	10	10	7	3	5	4	5
5	956	733	1083	965	1223	1391	1282	1156	618	236	186	281	48	50	14	67	26	21	10	2	8	6	1	7
6	673	509	790	688	757	933	838	842	478	295	383	253	122	86	25	77	50	22	25	8	4	5	3	6
7	380	284	401	344	458	491	449	471	291	173	313	345	98	148	31	83	55	26	27	10	4	6	0	6
8	232	152	193	176	198	260	231	244	158	104	257	289	105	92	45	107	49	30	19	12	6	6	0	2
9	150	86	113	112	133	129	142	135	66	56	119	208	79	99	34	86	75	24	28	24	6	9	3	5
10	55	67	70	72	55	62	90	78	56	23	83	131	44	74	44	86	102	23	13	12	5	7	2	1
11	25	19	55	31	38	58	38	42	31	22	39	62	32	58	43	78	73	28	10	1	3	3	2	1
12	39	12	16	29	31	32	29	35	24	19	41	41	24	36	28	63	65	29	14	5	1	4	1	0
13	17	10	15	11	19	25	20	13	5	12	28	30	14	25	22	51	46	33	21	13	5	1	0	2
14	17	9	15	10	13	14	8	10	9	6	22	21	9	18	12	43	29	21	25	19	10	3	2	1
15	6	10	10	7	10	13	9	9	9	10	7	11	6	13	9	11	26	14	19	13	23	10	6	7
16	6	7	8	5	6	7	8	6	4	6	7	11	2	10	10	16	20	14	14	16	16	8	9	8
17	5	3	6	1	7	2	6	5	2	4	7	14	1	6	3	9	9	4	13	12	12	10	13	7
18	5	4	6	7	2	9	3	0	3	5	3	7	0	6	1	9	6	9	7	6	9	4	6	7
19	9	7	7	3	3	4	5	4	6	0	2	5	2	1	3	2	9	7	4	2	4	3	1	5
20-24	45	25	40	26	32	48	30	18	10	6	7	14	3	14	8	13	12	11	11	13	12	11	15	18
25-29	70	73	94	74	92	108	73	49	27	6	16	14	7	8	11	19	16	17	13	14	6	11	5	11
30-34	75	80	110	92	98	137	74	68	24	12	15	28	11	12	6	24	21	11	8	13	9	11	6	21
35-39	65	46	54	38	59	89	57	42	23	10	19	29	6	20	10	33	30	26	17	19	12	15	5	10
40-44	41	35	39	32	35	50	28	23	20	4	8	14	8	11	8	18	33	15	29	19	7	16	5	16
45-49	21	24	20	15	24	25	26	8	7	3	8	7	1	10	3	7	20	12	18	12	5	8	4	9
50-54	15	24	26	20	28	20	23	19	12	7	2	4	4	9	3	8	12	13	11	7	6	5	6	9
55-59	13	15	22	18	24	27	22	17	4	3	6	8	5	7	7	7	5	17	14	6	7	1	9	7
60	10	15	32	19	18	23	30	17	10	2	3	9	2	7	2	4	16	17	14	10	6	8	5	7
65+	17	17	29	29	29	58	50	43	21	9	14	16	2	10	15	14	27	24	38	22	11	11	11	26

Chapter 2A Incidence of pertussis disease in the surveillance study 1997-2012 for children born from 1996.

2.A.1 Laboratory confirmed pertussis cases per calendar year, birth cohort & vaccination status

The number and composition of pertussis cases in this chapter is shown in Figure 2.A.1. As can be seen, the laboratory confirmed cases of pertussis with clinical data for children outside the Gothenburg area is split up into those that participated in Trial I/II and those born 1996 or later. Table 2.A.1 report cases among children born January 1, 1996 until December 31, 2012; the DTPa vaccination period. Table 2.A.2 represents cases among children in the Trial I cohort and cases among children born during the enrolment period of Trial II, June 1. 1993 until May 31. 1994 (and June 1994 for a subgroup), see Material and Methods.

Surveillance cases

```
                    ┌─────────────────┐
                    │      3255       │
                    │  cases followed │
                    └─────────────────┘
                     ↙               ↘
    ┌──────────────────────────┐   ┌──────────────────────────┐
    │  31  born during Trial I │   │          2553            │
    │  671  born during Trial II│  │  cases born 1996 or later│
    └──────────────────────────┘   └──────────────────────────┘
       ↙              ↘                          ↓
┌──────────────┐  ┌──────────────────┐   ┌──────────────┐
│ 8 unimmunized│  │ 363 unimmunized  │   │     976      │
│ cases born   │  │ cases born during│   │  unimmunized │
│ during       │  │     Trial II     │   └──────────────┘
│ Trial I      │  └──────────────────┘
└──────────────┘
```
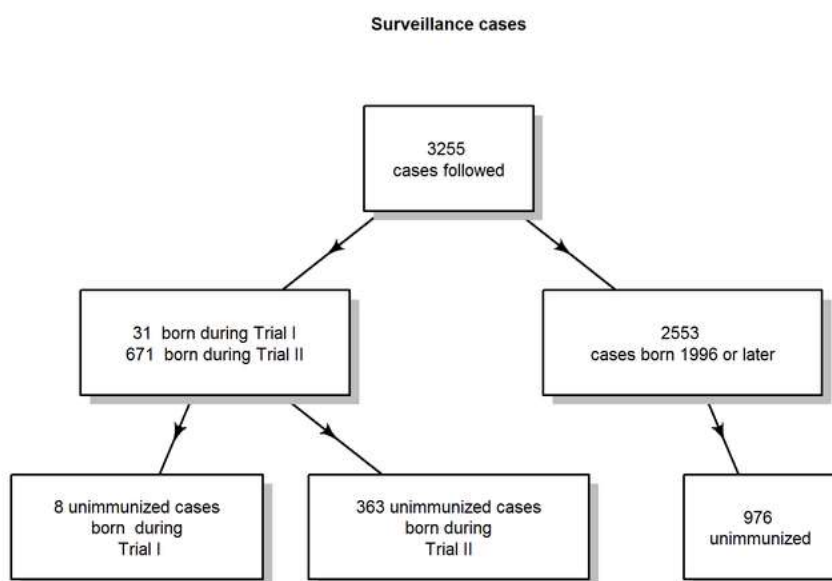
Figure 2.A.1: Flow chart for pertussis in unimmunized children and in all children

| | Year | | | | | | | | | | | | | | | | |
Birth cohort	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
1996	5 (3)	18 (15)	40 (35)	41 (35)	20 (16)	39 (39)	14 (14)	60 (55)	41 (38)	14 (13)	3 (3)	6 (5)	2 (2)	0 (0)	2 (2)	9 (8)	**314 (283)**
1997	23 (6)	29 (15)	19 (19)	25 (22)	17 (14)	32 (29)	7 (4)	25 (20)	26 (25)	16 (14)	14 (13)	8 (7)	0 (0)	5 (5)	2 (2)	7 (6)	**255 (201)**
1998		61 (7)	36 (20)	14 (12)	7 (4)	17 (15)	12 (11)	34 (33)	40 (40)	21 (19)	13 (12)	25 (23)	3 (3)	1 (1)	0 (0)	1 (0)	**285 (200)**
1999			96 (6)	65 (23)	9 (6)	19 (14)	8 (4)	18 (13)	25 (24)	12 (11)	18 (18)	20 (19)	4 (4)	5 (4)	2 (2)	2 (2)	**303 (150)**
2000				88 (5)	31 (6)	16 (9)	7 (6)	21 (14)	14 (11)	24 (17)	18 (17)	15 (12)	4 (4)	7 (6)	0 (0)	1 (1)	**246 (108)**
2001					33 (3)	21 (10)	8 (7)	16 (11)	13 (10)	10 (8)	10 (9)	12 (10)	5 (5)	3 (2)	4 (1)	0 (0)	**135 (76)**
2002						98 (3)	15 (3)	15 (10)	10 (9)	8 (7)	3 (3)	2 (2)	6 (3)	6 (2)	2 (1)	1 (1)	**166 (44)**
2003							52 (2)	40 (17)	11 (10)	6 (6)	7 (7)	4 (4)	7 (4)	3 (0)	0 (0)	4 (0)	**134 (50)**
2004								116 (4)	40 (16)	12 (11)	7 (6)	5 (5)	5 (5)	5 (2)	2 (0)	5 (0)	**197 (49)**
2005									74 (0)	14 (5)	4 (4)	4 (2)	3 (2)	3 (0)	2 (0)	3 (1)	**107 (14)**
2006										64 (4)	22 (6)	9 (7)	5 (5)	7 (2)	0 (0)	7 (3)	**114 (27)**
2007											46 (0)	17 (12)	4 (3)	4 (1)	3 (2)	7 (2)	**81 (20)**
2008												26 (1)	16 (8)	3 (2)	2 (0)	4 (2)	**51 (13)**
2009													29 (0)	11 (2)	2 (2)	5 (1)	**47 (5)**
2010														31 (1)	10 (3)	9 (3)	**50 (7)**
2011															28 (0)	7 (1)	**35 (1)**
2012																33 (0)	**33 (0)**
Total	28 (9)	108 (37)	191 (80)	233 (97)	117 (49)	242 (119)	123 (51)	345 (177)	294 (183)	201 (115)	165 (98)	153 (109)	93 (48)	94 (30)	61 (15)	105 (31)	**2553 (1248)**

Table 2.A.1 Laboratory confirmed pertussis cases per calendar year and birth cohort from October 1, 1997 until December 31, 2012 in children born from Jan 1 1996 until Dec 31, 2012. In brackets, number of children with two or more doses of a pertussis vaccine prior to the positive episode is given.

Cohort	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
Trial1	2 (1)	4 (3)	6 (4)	6 (5)	6 (4)	2 (2)	0 (0)	2 (2)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	31 (23)
1993.6-1994.5	21 (8)	80 (28)	167 (63)	138 (55)	51 (20)	43 (11)	18 (8)	36 (23)	37 (21)	17 (13)	8 (5)	17 (11)	13 (8)	8 (7)	10 (8)	7 (7)	671 (296)
Total	23 (9)	84 (31)	173 (67)	144 (60)	57 (24)	45 (13)	18 (8)	38 (25)	37 (21)	19 (14)	8 (5)	17 (11)	13 (8)	8 (7)	10 (8)	8 (8)	702 (319)

Table 2.A.2 Laboratory confirmed pertussis per calendar year in children from October 1, 1997 until December 31, 2012 for children in the Trial I cohort and for the birth-cohort covering the Trial II recruitment period, per period of onset of cough. In brackets, number of children with two or more doses of a pertussis vaccine prior to the positive episode is given.

2.A.2 Laboratory confirmed pertussis cases among unimmunised children born 1997-2012.

1347 (41.4%) of the cases in the surveillance stud, had not received a pertussis vaccine prior to the illness.

Tables for unimmunised children regarding year of birth and years of follow-up are given in Tables 2.A.3 and 2A.4.

Birth year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
1996	2	3	5	6	3	0	0	5	2	1	0	1	0	0	0	1	29
1997	12	8	0	3	3	3	3	5	1	2	1	1	0	0	0	1	43
1998		38	7	2	3	1	1	1	0	2	1	2	0	0	0	1	59
1999			61	26	3	5	4	5	1	1	0	1	0	1	0	0	108
2000				58	19	7	1	6	3	7	1	3	0	0	0	0	105
2001					22	5	1	4	3	2	1	2	0	1	3	0	44
2002						66	5	5	1	1	0	0	3	4	1	0	86
2003							41	16	1	0	0	0	3	3	0	3	67
2004								77	13	1	1	0	0	3	2	5	102
2005									60	5	0	2	1	3	2	2	75
2006										44	12	2	0	5	0	4	67
2007											35	5	1	3	1	5	50
2008												21	5	1	2	2	31
2009													19	6	0	4	29
2010														23	2	6	31
2011															24	3	27
2012																23	23
Total	14	49	73	95	53	87	56	124	85	66	52	40	32	53	37	60	976

Table 2.A.3 Children with confirmed pertussis with PCR or culture and from 2008 also serology among unimmunised children from October 1, 1997 until December 31, 2012 per birth-cohort since 1996 and per period of onset of cough for unimmunised children (i.e. children who have not received any pertussis vaccine before onset of cough). The first column after the birth year column describes children for the last three months of 1997 only.

Cohort	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
Trial1	1	1	2	1	2	0	0	0	0	1	0	0	0	0	0	0	8
1993.6-1994.5	12	51	101	80	31	32	9	12	16	3	3	5	5	1	2	0	363
Total	13	52	103	81	33	32	9	12	16	4	3	5	5	1	2	0	371

Table 2.A.4 Children with confirmed pertussis with PCR or culture and from 2008 also serology among unimmunised children in Trial I and II from October 1, 1997 until December 31, 2012 for the birth-cohort corresponding to trial I and to the recruitment period of Trial II and per period of onset of cough for unimmunised children (i.e. children who have not received any pertussis vaccine before onset of cough).

In the birth cohort June 1993 – May 1994, trial II, a majority, 363 of 671 (54.1 %), of the cases with laboratory confirmed pertussis had not been vaccinated before onset of disease, and were (thus) not participants in Trial II.

It should be noted that few of the cases from the 1996 birth cohort were unvaccinated (only 9.2 %). This is because most children in the cohort had in fact received three vaccine doses before the present follow-up started in October 1, 1997. In all, 976 of 2553 cases (38.2%), among children born 1996 or later, were unimmunised.

The minimum duration of cough, if cough, was 7 days and the median duration was 48 days. Spasmodic cough for 21 days or more (episodes according to the WHO-definition) was reported for 89.5% of the unvaccinated – with a median duration of 49 days. For 76 (5.6%) of the episodes there were no spasmodic cough at all.

Figure 2.A.2.a and 2A.2.b and table 2.A.5 shows the age distribution of laboratory confirmed cases at onset of cough, among 915 unimmunised children born since October 1, 1997. Most of the pertussis cases, 66% in this subgroup of unimmunised children, occurred before three months of age, i.e. before the scheduled first dose of a DTPa-containing vaccine. 13.7% occurred between 3 and 12 months of age, i.e. during the scheduled period for pertussis vaccinations and 20% occurred after one year of age.
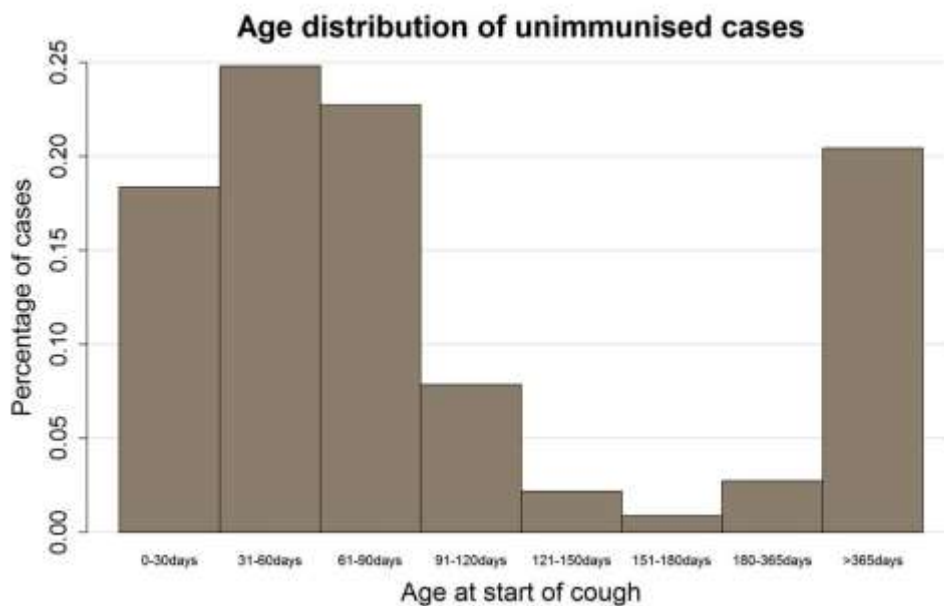
Figure 2.A.2.a Age distribution among 915 laboratory confirmed unimmunised children with pertussis born from October 1, 1997 until December 31, 2012 and follow-up during the same time period.
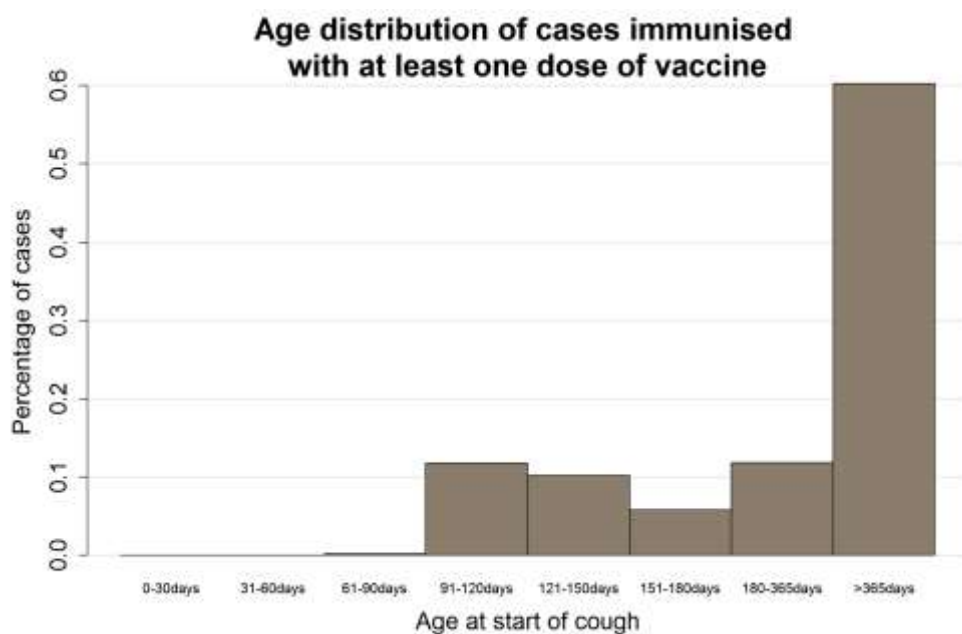
Figure 2.A.2.b Age distribution among laboratory confirmed immunised (with at least one dose) children with pertussis born from October 1, 1997 until December 31, 2012 and follow-up during the same time period. Nota bene: There are very few pertussis vaccinated cases before 3 months of age.

Age	Cases	Percent
0-30days	168	18
31-60days	227	25
61-90days	208	23
91-120days	72	8
121-150days	20	2
151-180days	8	1
180-365days	25	3
> 365days	187	20

Table 2.A.5 Age distribution among 915 laboratory confirmed unimmunised children with pertussis born from October 1, 1997 until December 31, 2012 and follow-up during the same time period.

2.A.3 Laboratory confirmed pertussis among vaccinated children born 1997-2012

Figure 2.A.3 below shows the distribution of the vaccinated cases and Table 2.A.1 and 2.A.2 show in brackets the number of children vaccinated with two or more doses of a pertussis vaccine prior to the pertussis episode. For both Trial I/II and those born from January 1, 1996 and followed-up from October 1, 1997, the majority of cases are among fully vaccinated children.

 Data on vaccination status among vaccine failures in Trial II with two or three doses (for 296 of the 308 children) are also given in Figure 2.A.3.

All children, except three of the vaccinated, were coughing during the pertussis episode. The minimum duration of cough, was 2 days – the median duration was 47 days. Spasmodic cough for 21 days or more (WHO-definition) was reported for 78.7% of the episodes (compared to 89.5% for the unimmunised children) – the median duration was 40 days. For 14.6% of the episodes there was no spasmodic cough compared to 5.6% 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.

Vaccinated cases

```
                    ┌──────────────────┐
                    │       3255       │
                    │   Cases total,   │
                    │  vaccinated and  │
                    │   unvaccinated   │
                    └──────────────────┘
```

┌────────────────────────────────┐   ┌────────────────────────────────┐
│ 23/31(74%) vaccinated Trial I   │   │   1577/2553(62%)   │
│ 308/671(46%) vaccinated Trial II│   │ vacc. cases born 1996 or later │
└────────────────────────────────┘   └────────────────────────────────┘

┌─────────────────┐ ┌─────────────────┐   ┌─────────────────┐
│ 22(71%)fully vacc.│◄─│ 288(43%)fully vacc.│   │ 1089(43%)   │
│ in Trial I   │ │   inTrial II   │   │ fully vacc.   │
└─────────────────┘ └─────────────────┘   └─────────────────┘

┌─────────────────┐ ┌─────────────────┐   ┌─────────────────┐
│ 1(3%)with two doses│◄─│ 8(1%)with two doses│   │   159(6%)   │
│ in Trial I   │ │   inTrial II   │   │ with two doses │
└─────────────────┘ └─────────────────┘   └─────────────────┘

┌─────────────────┐ ┌─────────────────┐   ┌─────────────────┐
│ 0(0%)with one dose│◄─│ 12(2%)with one dose│   │   329(13%)   │
│ in Trial I   │ │   inTrial II   │   │ with one dose │
└─────────────────┘ └─────────────────┘   └─────────────────┘
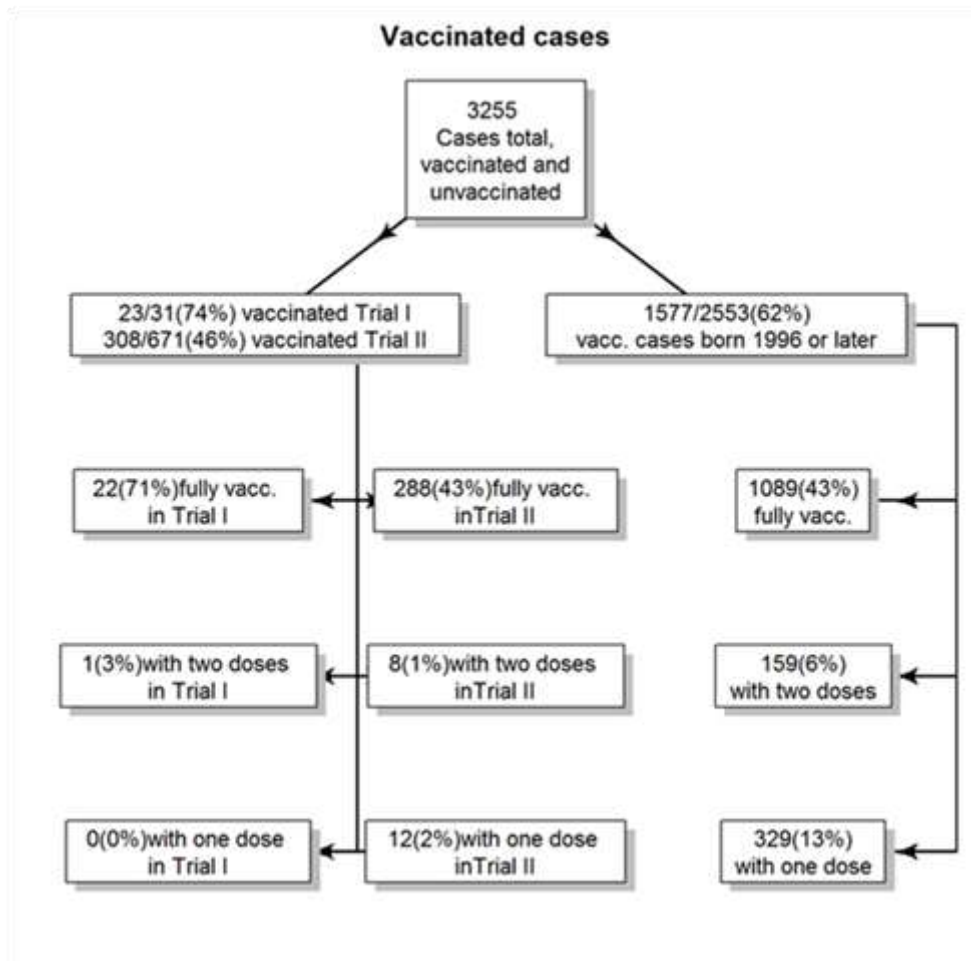
Figure 2.A.3 Distribution of vaccinated cases from the 3135 pertussis cases followed (1281 cases were unvaccinated, see chapter 2.A.2)

2.A.4 Laboratory confirmed pertussis cases in children born Jan 1. 1996 - Sept 30. 1997

This cohort of children was the first one in the universal 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 the Gothenburg study area. Available figures show vaccine coverage at about 98% for children born in 1996 until September 30, 1997. We regard this birth cohort a "pure" Infanrix® cohort. Figure 2.A.4 shows the distribution of these cases. Most cases are fully vaccinated, but 9.7% are unvaccinated children more than 12 months old. 87% of the unimmunised and 78% of the vaccinated children had spasmodic cough for 21 days or more.

Results of the laboratory confirmed cases are presented in Table 2.A.6

Cases born between Jan1 1996 and October 1,1997
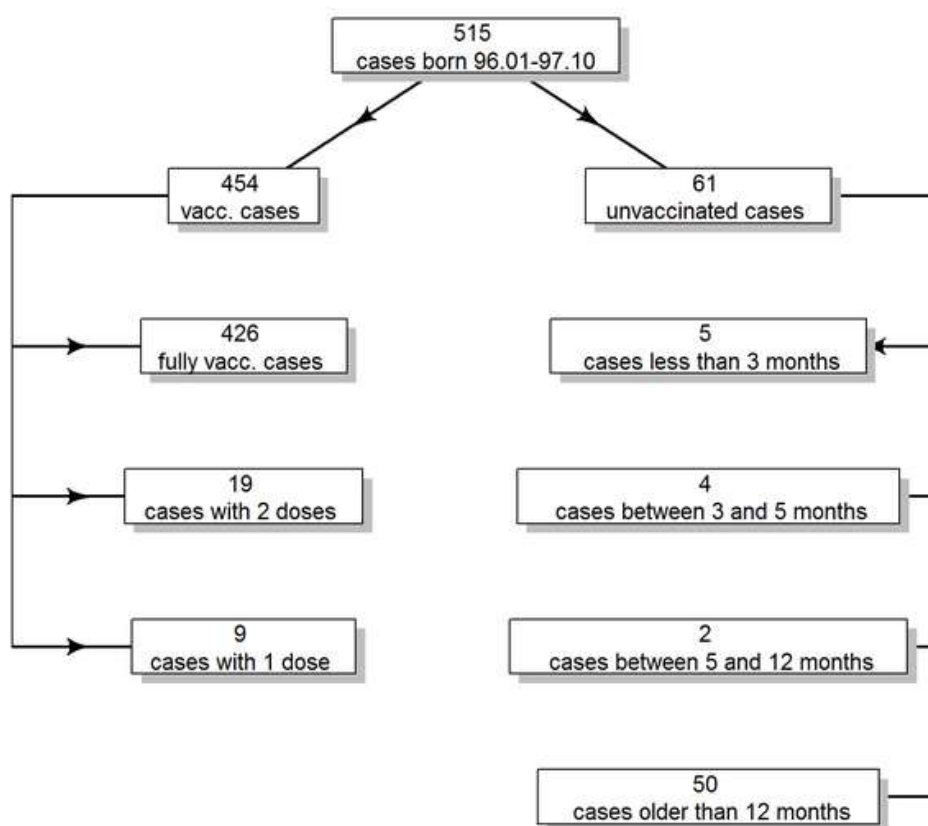
Figure 2.A.4: Immunisation and laboratory confirmed cases of pertussis in children born from Jan 1, 1996 to Sept 30, 1997 and followed from Oct 1, 1997 to Dec 31, 2012.

Birth cohort	Number of doses	Not immunised	Infanrix	Pentavac	Other/Mixed	Total
1996	0	29 (25)	0 (0)	0 (0)	0 (0)	**29 (25)**
"	1	0 (0)	1 (1)	1 (1)	0 (0)	**2 (2)**
"	2	0 (0)	5 (4)	0 (0)	0 (0)	**5 (4)**
"	3	0 (0)	271 (210)	0 (0)	7 (6)	**278 (216)**
1997.1-9	0	32 (28)	0 (0)	0 (0)	0 (0)	**32 (28)**
"	1	0 (0)	7 (5)	0 (0)	0 (0)	**7 (5)**
"	2	0 (0)	14 (7)	0 (0)	0 (0)	**14 (7)**
"	3	0 (0)	138 (112)	0 (0)	10 (9)	**148 (121)**
Subtotal	0	61 (53)	0 (0)	0 (0)	0 (0)	**61 (53)**
"	1	0 (0)	8 (6)	1 (1)	0 (0)	**9 (7)**
"	2	0 (0)	19 (11)	0 (0)	0 (0)	**19 (11)**
"	3	0 (0)	409 (322)	0 (0)	17 (15)	**426 (337)**
Total	-	61 (53)	436 (339)	1 (1)	17 (15)	**515 (408)**

Table 2.A.6 Laboratory confirmed cases of pertussis from October 1, 1997 until December 31, 2012, among children born from Jan 1, 1996 until September 30, 1997 by 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 brackets).

2.A.5 Incidence in children born January 1, 1996 - September 30, 1997

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

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

- Person-months from birth to three months of age (before Dose 1).

- Person-months between three and five months of age (between Dose 1 and Dose 2).

- Person-months between five and twelve months of age (between Dose 2 and Dose 3).

- Person-months after twelve month of age (after Dose 3) until December 31, 2012.

Children born January 1, 1996 until September 30, 1997 were followed from October 1, 1997 until December 31, 2012 for approximately 2,241,967 person-years. During follow-up 515 cases of laboratory confirmed pertussis have been reported to the surveillance system - 454 cases among vaccinated and 61 among unimmunised children (Table 2.A.6). Table 2.A.7 presents total number of person-years and laboratory confirmed pertussis cases divided in age/vaccination intervals described above. In Table 2.A.8 the interval after 1 year of age is divided in fifteen one-year intervals.

Onset of pertussis	Person years	Number of cases	Incidence	95% confidence interval
Before Dose 1 (0-90 days)	2552	0 (5)	0 (196)	0-145 (64-457)
Between 1 and 2 doses (91-150 days)	4537	9 (13)	198 (287)	91-377 (153-490)
Between 2 and 3 doses (151-365 days)	33,882	20 (22)	59 (65)	36-91 (41-98)
After dose 3 and/or after 1 year of age	2,200,996	425 (475)	19 (22)	18-21 (20-24)

Table 2.A.7 Incidence of pertussis, October 1. 1997-December 31, 2012, among children born between January 1, 1996 and September 30, 1997 with observed culture- or PCR-confirmed B.pertussis. From 2008 positive serology was added. The table shows person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person years and 95% confidence interval in the following age-/vaccine-groups at onset of the pertussis episode; 0-90 days of age (before dose 1); 91-150 days of age (between dose 1 and 2); 151-365 days of age (between dose 2 and 3); and after 1 year of age (after dose 3). In brackets, figures including the unimmunised children of respective age group (intent to treat), are given (in total 454 and 515 pertussis cases, respectively).

Onset of pertussis	Person years of follow-up	Number of cases	Incidence per 100,000	95% confidence interval
After Dose 3 and/or during 1 year of age	123,181	12 (17)	10 (14)	5-17 (8-22)
During 2 years of age	147,417	41 (45)	28 (31)	20-38 (22-41)
During 3 years of age	147,417	51 (58)	35 (39)	26-45 (30-51)
During 4 years of age	147,417	44 (52)	30 (35)	22-40 (26-46)
During 5 years of age	147,417	37 (43)	25 (29)	18-35 (21-39)
During 6 years of age	147,417	42 (43)	28 (29)	21-39 (21-39)
During 7 years of age	147,417	45 (51)	31 (35)	22-41 (26-45)
During 8 years of age	147,417	62 (68)	42 (46)	32-54 (36-58)
During 9 years of age	147,417	45 (48)	31 (33)	22-41 (24-43)
During 10 years of age	147,417	15 (15)	10 (10)	6-17 (6-17)
During 11 years of age	147,417	6 (8)	4 (5)	1-9 (2-11)
During 12 years of age	147,417	6 (6)	4 (4)	1-9 (1-9)
During 13 years of age	147,417	2 (2)	1 (1)	0-5 (0-5)
During 14 years of age	147,417	3 (3)	2 (2)	0-6 (0-6)
During 15 years of age	124,450	14 (16)	11 (13)	6-19 (7-21)

Table 2.A.8 Incidence of pertussis, Oct 1, 1997-Dec 31, 2012, among children born between Jan 1, 1996 and Sep 30, 1997 with observed culture- or PCR-confirmed B.pertussis. From 2008 positive serology was added. The data is presented by person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person years and 95% confidence interval after dose 3, or from 1 year of age for children divided in fourteen age intervals. In brackets, figures including the unimmunised children of respective age group (intent to treat), are given (in total 425 and 475 pertussis cases, respectively). (See also Table 2.A.7.)

2.A.6 Laboratory confirmed pertussis cases
in children born Oct 1. 1997 – Dec 31. 2012

For children in this cohort there were 2038 reports of laboratory confirmed pertussis in the database for episodes between October 1, 1997 and December 31, 2012, whereof 915 reports concern children without any pertussis vaccination prior to onset of the pertussis episode and 1123 reports concern children who had received at least one dose before the episode, Table 2.A.9.

Birth Cohort	Number of doses	Cases	Birth Cohort	Number of doses	Cases	Birth Cohort	Number of doses	Cases
1997.10-12	0	11 (10)	2003	0	67 (56)	2009	0	29 (24)
"	1	4 (4)	"	1	17 (14)	"	1	13 (10)
"	2	5 (4)	"	2	14 (11)	"	2	2 (2)
"	3	34 (30)	"	3	36 (29)	"	3	3 (2)
1998	0	59 (50)	2004	0	102 (90)	2010	0	31 (25)
"	1	26 (20)	"	1	46 (41)	"	1	12 (10)
"	2	21 (15)	"	2	18 (14)	"	2	3 (2)
"	3	179 (137)	"	3	31 (21)	"	3	4 (1)
1999	0	108 (98)	2005	0	75 (66)	2011	0	27 (23)
"	1	45 (42)	"	1	18 (16)	"	1	7 (5)
"	2	25 (18)	"	2	4 (2)	"	2	1 (1)
"	3	125 (96)	"	3	10 (8)	"	3	0 (0)
2000	0	105 (100)	2006	0	67 (61)	2012	0	23 (18)
"	1	33 (27)	"	1	20 (18)	"	1	10 (10)
"	2	9 (7)	"	2	8 (4)	"	2	0 (0)
"	3	99 (73)	"	3	19 (12)	"	3	0 (0)
2001	0	44 (39)	2007	0	50 (48)	Subtotal	0	915 (815)
"	1	15 (13)	"	1	11 (10)	"	1	320 (276)
"	2	11 (7)	"	2	10 (9)	"	2	140 (103)
"	3	65 (51)	"	3	10 (7)	"	3	663 (503)
2002	0	86 (80)	2008	0	31 (27)	Total	-	2038 (1697)
"	1	36 (30)	"	1	7 (6)			
"	2	4 (4)	"	2	5 (3)			
"	3	40 (31)	"	3	8 (5)			

Table 2.A.9 Laboratory confirmed pertussis, Oct 1. 1997-Dec 1. 2012, among children born 1. Oct 1997 until December 31, 2012, divided by birth-cohort and number of vaccine doses before episode. (No. of cases with 21 or more days of spasmodic cough in brackets).

Among the 915 unimmunised children, 603 (66%) were up to 3 months at the onset of the episode, i.e. cough started before the scheduled first dose of acellular pertussis vaccine. Of the cases, 92 were between 3 and 5 months of age, 33 between 5 and 12 months of age and 187 were older than 12 months at the onset.

Eighty-nine percent of the unimmunised children had spasmodic cough for 21 or more days during the episode.

2.A.7 Incidence in children
born October 1, 1997 – December 31, 2012

Data on number of newborns during 1997 until 2012, from Statistics Sweden (http://www.scb.se), have been used for person time of follow-up calculations. Detailed figures are presented in Appendix 1. Altogether approximately 1,394,478 children have been followed for approximately 10,103,654 years of follow-up from October, 1. 1997 until December 31, 2012.

Table 2.A.10 and 2.A.11 give the total number of person-years and laboratory confirmed pertussis cases by age/vaccination intervals and show the incidences for these intervals. Figure 2.A.5 and 2.A.6 are graphs of the same data,

Compared to data in Table 2.A.8, the incidence was about the same for the first age-interval but lower for the other age intervals up to 10 years of age. The observed differences between the two cohorts might depend on variations of the general exposure to pertussis in Sweden during follow-up from 1997 to 2012 as described in Chapter 1, Figure 1.1, 1.4 and 1.7.

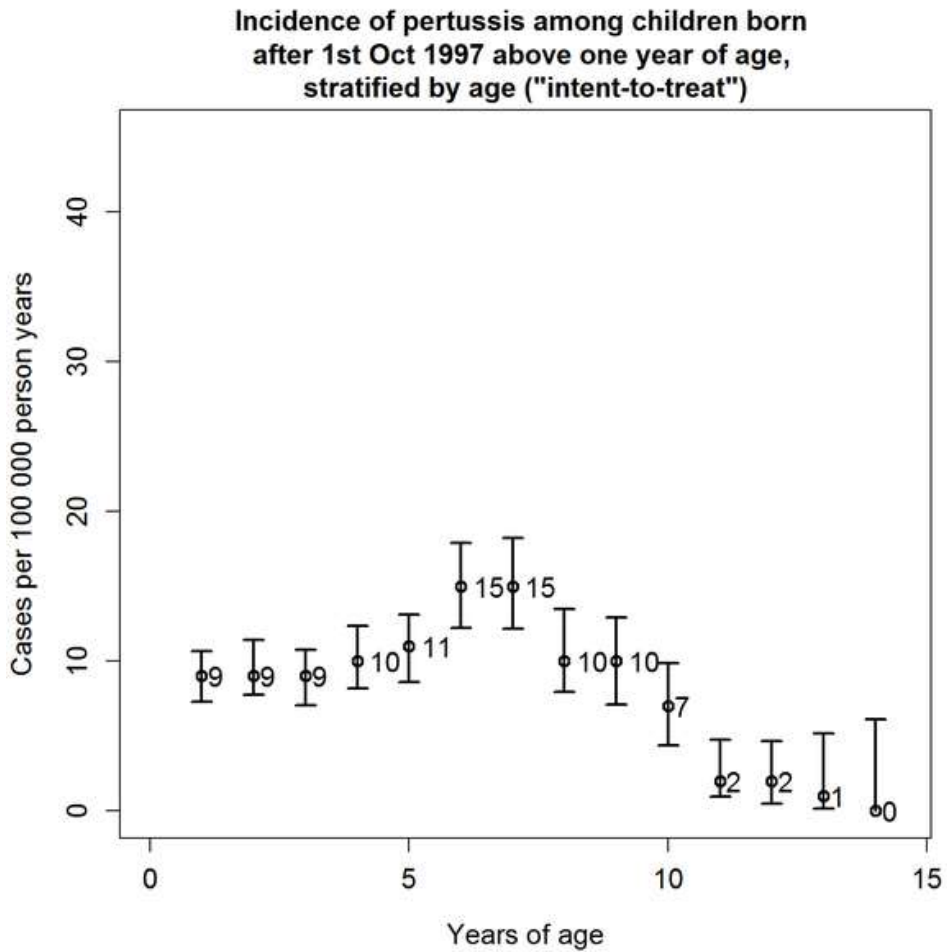| Onset of pertussis	Person years	Number of cases	Incidence	95% confidence interval
Before Dose 1 (0-90 days)	345,457	0 (603)	0 (175)	0-1 (161-189)
Between 1 and 2 doses (91-150 days)	226,784	320 (412)	141 (182)	126-157 (165-200)
Between 2 and 3 doses (151-365 days)	771,570	142 (175)	18 (23)	16-22 (19-26)
After dose 3 and/or after 1 year of age	8,759,843	661 (848)	8 (10)	7-8 (9-10)

Table 2.A.10 above and Figure 2.A.5 below Children born from October 1, 1997 until December 31, 2012 and followed from October 1, 1997 until December 31, 2012 with observed culture- or PCR-confirmed B.pertussis. From 2008 also positive serology was added. The table describes pertussis in relation to age divided in 0-90 days (before dose 1); 91-150 days (between dose 1 and 2); 151-360 days (between dose 2 and 3) and after 360 days of age (after dose 3). The columns include person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person years and 95% confidence interval in the age-/vaccine-groups at onset of the pertussis episode; in brackets also unimmunised children of respective age group are included.

Incidence and 95% CI of pertussis among children born after 1st Oct 1997 less than one years of age, stratified by age ("intent-to-treat").
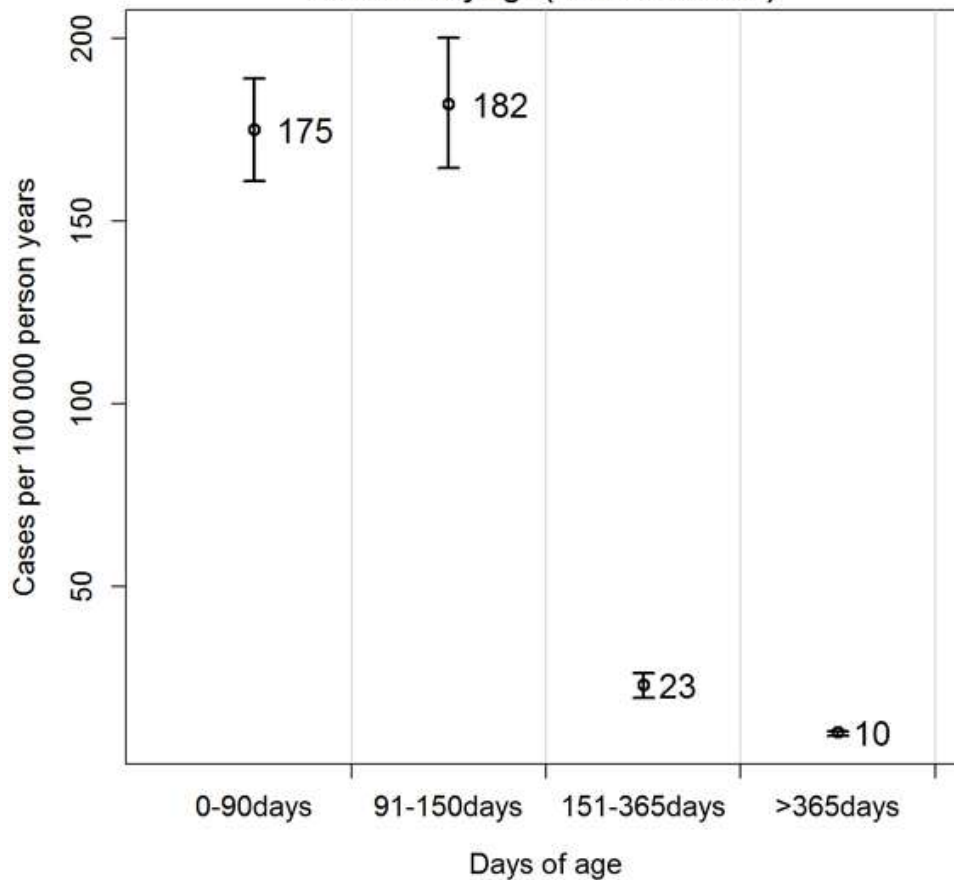
Onset of pertussis	Person years	Number of cases	Incidence	95% confidence interval
After Dose 3 and/or during 1 year of age	1,242,987	73 (110)	6 (9)	5-7 (7-11)
During 2 years of age	1,141,191	80 (108)	7 (9)	6-9 (8-11)
During 3 years of age	1,039,575	70 (91)	7 (9)	5-9 (7-11)
During 4 years of age	940,647	71 (95)	8 (10)	6-10 (8-12)
During 5 years of age	843,555	71 (90)	8 (11)	7-11 (9-13)
During 6 years of age	747,999	89 (111)	12 (15)	10-15 (12-18)
During 7 years of age	655,113	82 (98)	13 (15)	10-16 (12-18)
During 8 years of age	564,387	48 (59)	9 (10)	6-11 (8-13)
During 9 years of age	474,495	42 (46)	9 (10)	6-12 (7-13)
During 10 years of age	386,781	23 (26)	6 (7)	4-9 (4-10)
During 11 years of age	302,589	6 (7)	2 (2)	1-4 (1-5)
During 12 years of age	220,767	4 (4)	2 (2)	0-5 (0-5)
During 13 years of age	140,325	1 (2)	1 (1)	0-4 (0-5)
During 14 years of age	60,513	0 (0)	0 (0)	0-6 (0-6)
During 15 years of age	2552	1 (1)	39 (39)	1-218 (1-218)

Table 2.A.11 above and Figure 2.A.7 below. Children born from October 1, 1997 until December 31, 2012 and followed from October 1, 1997 until December 31, 2012 with observed culture- or PCR-confirmed B.pertussis. From 2008 also positive serology was added. The table shows pertussis in relation to age divided in years 1-15 in relation to person-years of follow-up, number of laboratory confirmed cases, incidence per 100,000 person years and 95% confidence interval in the age-/vaccine-groups at onset of the pertussis episode;. In brackets also unimmunised children of respective age group are included.

Incidence of pertussis among children born after 1st Oct 1997 above one year of age, stratified by age ("intent-to-treat")

Chapter 2B. Hospital admission and complications, duration of spasmodic cough and antibiotic treatment in the surveillance study 1997-2012 for children from 1996.

2.B.1 Hospital admission for pertussis

Data on complications and on hospitalisations, defined as at least one night at hospital due to pertussis disease during the episode, were available for 2525 of 2553 children born from Jan 1, 1996 until December 31, 2012 (see Material and Method, Exec sum and Figure 5 (Exec sum). Altogether 642 (25%) of the children had a hospital admission during the pertussis episode and 1883 had none.

Hospital admission and age at the pertussis episode

In all, 439 of 610 infants (72%), who were below 3 months of age at start of the pertussis episode, were hospitalised. The corresponding rates, **regardless of vaccination status** at the episode, for 346 children in age-group 3-<5 months, for 250 children in age-group 5-<12 months and for 1347 children from 12 months of age at the beginning of the pertussis episode were 39%, 16% and 2%, respectively (Figure 2.B.1, Figure 2.B.2 and table 2.B.1).

The age specific incidence rate of hospitalisation due to pertussis is highest, 126.1 per 100,000 years of follow-up, for children 0-<3 months of age and decreases by increasing age, to less than 0.2 per 100,000 years for children above one year of age at the pertussis episode (Figure 2.B.1). Circulating pertussis in the country has not decreased to a level that offers sufficient protection for the youngest, unimmunised infants.

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

Hospital admissions were also studied by age, duration of hospital stay as well as by vaccination status at start of the pertussis episode. Detailed data are given in Figure 2.B.1, Figure 2.B.2 and table 2.B.1.

The rate of hospital admission **among unimmunised children** aged 0-30, 31-60 and 61-90 days at beginning of the pertussis episode was 85%, 72%, 61% respectively, and drops to only 3% for unimmunised children above one year of age. For unimmunised children between 3-<5 and 5-<12 months of age the rate of hospital admission was still 45% and 37% respectively. 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 had received two or more doses of a pertussis vaccine before the pertussis episode. However, the hospitalisation rates are lower when compared to those for the unvaccinated children.
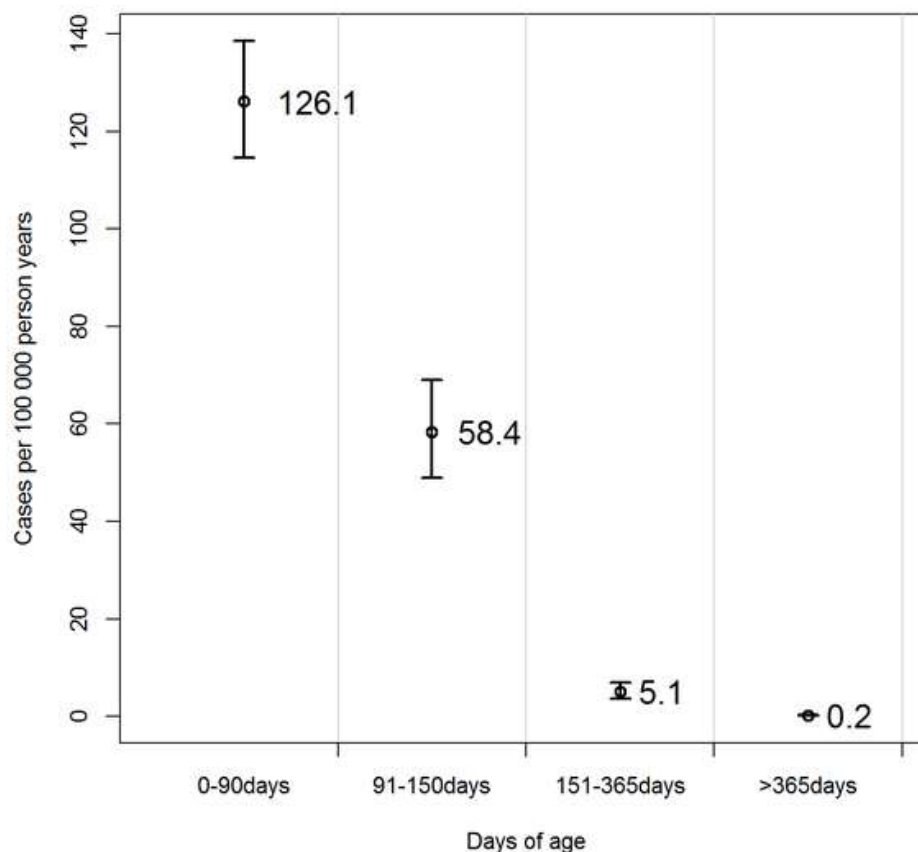
Figure 2.B.1: Incidence of hospital admissions due to pertussis in children with culture-, PCR- or from January 1, 2008 serology-confirmed pertussis per 100,000 cases among children born from 1996, during surveillance from October 1, 1997 until December 31, 2012. The x-axis defines the age of the child at onset of pertussis. The number of cases for 0-90 days was 610, for 91-150 days 346, for 151-365 days 250 and for more than 365 days 1347. The percentages of hospitalisations for the different age groups were 72%, 39%, 17% and 2 %, respectively.

The overall rate of hospital admission for unimmunised children was 51%. For these children, around 48% of the hospital admissions, had a duration longer than one week and this proportion was higher among the very young. Regardless of age, the rate of hospitalisation for children vaccinated with one dose was 32%, and about 26% of the admissions were longer than a week, For children vaccinated with 2 or more doses before the pertussis episode, 3% were hospitalized and 14% of these admissions were longer than a week. However, this striking association between rate of hospital admission and vaccination status before the episode was confounded by age. For e.g. children $\geq$ 12 months of age, the rate of hospital admission was low and independent of the vaccination status of the child.
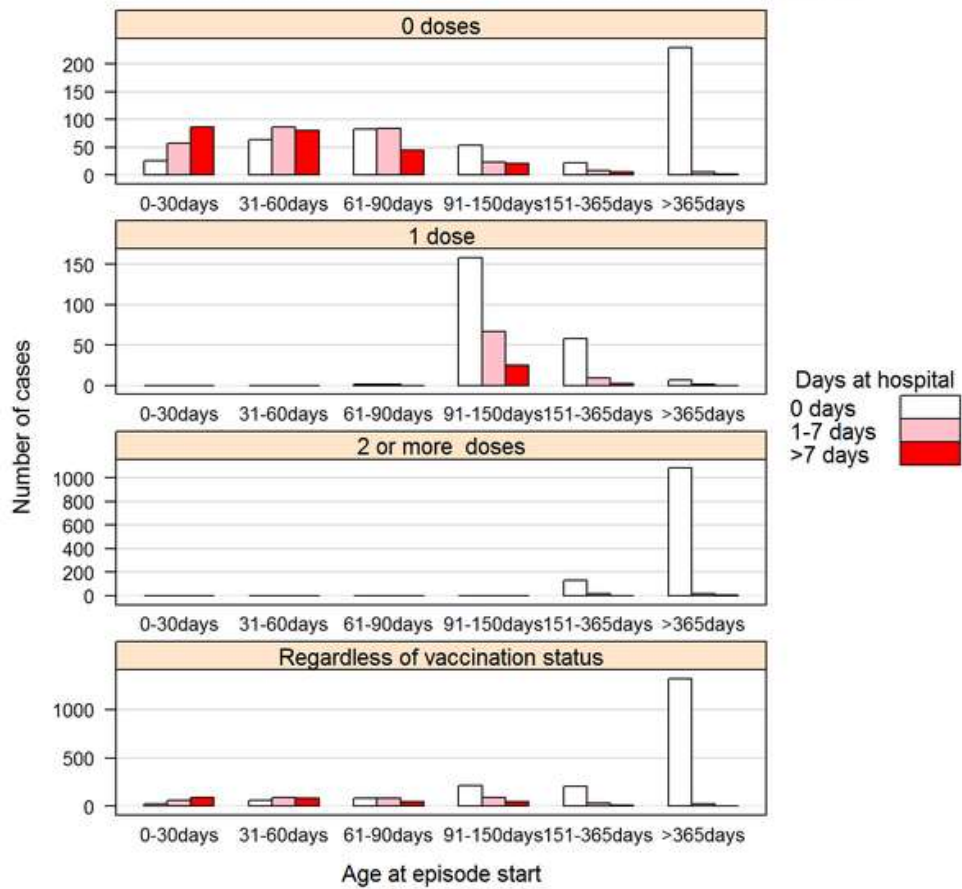
Figure 2.B.2 Duration of hospital stay stratified by age and vaccination status due to pertussis disease among children born from 1996 during surveillance from October 1, 1997 until December 31, 2012, by age at onset of cough and number of doses of a pertussis vaccine given prior to the pertussis episode.

Doses before episode:	Duration of Hospital Stay:	Age at episode start:						Sum
		0-30 days	31-60 days	61-90 days	91-150 days	151-365 days	> 365 days	
0 doses	0 days	25 (15%)	63 (28%)	82 (39%)	53 (55%)	22 (63%)	230 (97%)	475
"	1-7 days	57 (34%)	86 (38%)	84 (40%)	23 (24%)	8 (23%)	5 (2.1%)	263
"	> 7 days	87 (51%)	80 (35%)	44 (21%)	20 (21%)	5 (14%)	2 (0.8%)	238
"	Sum	169 (100%)	229 (100%)	210 (100%)	96 (100%)	35 (100%)	237 (100%)	976
1 dose	0 days			1 (50%)	158 (63%)	58 (84%)	7 (88%)	224
"	1-7 days			1 (50%)	67 (27%)	9 (13%)	1 (13%)	78
"	> 7 days			0%	25 (10%)	2 (2.9%)	0%	27
"	Sum			2 (100%)	250 (100%)	69 (100%)	8 (100%)	329
2 or more doses	0 days					129 (88%)	1083 (98%)	1212
"	1-7 days					15 (10%)	16 (1.5%)	31
"	> 7 days					2 (1.4%)	3 (0.3%)	5
"	Sum					146 (100%)	1102 (100%)	1248
	Total sum							2553

Table 2.B.1 Duration of hospital stay stratified by age and vaccination status due to pertussis disease among children born from 1996 during surveillance from October 1, 1997 until December 31, 2012, by age at onset of cough and number of doses of a pertussis vaccine given prior to the pertussis episode.

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

1. The median (mean) age at start of episode was 110 (144) days for unvaccinated versus 125 (131) days for children vaccinated with one dose before the episode. Thus, the two groups are "comparable" in age.

2. There were 43% of the children with a hospital admission for unimmunised and 32% for vaccinated children, with one dose during the pertussis episode which occurred in the age interval. This difference was statistically significant (p=0.045).

3. Given a hospital admission due to a pertussis disease at 3-<12 months of age, 45% of the admissions had a duration longer than a week for unimmunised and 26% for vaccinated children with one dose. This difference was statistically significant (p=0.029).

These results suggest that, there may be some protection against "severe" pertussis, expressed as requirement of hospitalisation, already after one dose of a pertussis vaccine.

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

2.B.2 Complications during the pertussis episode

Data on respiratory complications, neurological complications, dehydration with > 5 % loss of weight or other serious complications during the pertussis episode were registered in the database for 2525 of the 2553 children born January 1, 1996 until December 31, 2012 with vaccination and follow-up information. A respiratory complication (with apnea, n=185 or without apnea, n=195) was reported for 380 (15%) and a dehydration event for 104 (4.1%) of the children. Uncommon complications, i.e. neurological and other serious complications, were reported for 6 (0.2%) of the children.

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. Altogether 492 children (19.5%) had at least one complication due to the pertussis disease during their pertussis episode and 2033 (80.5%) had no complication at all and in 28 cases information was missing.

Any complication and age at the pertussis episode

In the 604 children who were below 3 months of age at beginning of the pertussis episode, 44% (263) had at least one complication. The corresponding rates for 341 children in age-group 3-<5 months, for 247 children in age-group 5-<12 months and for 1333 children aged 12 months and more at the beginning of the pertussis episode were 20%, 13% and 10%, respectively (Figure 2.B.3 and Table 2.B.2).

The age specific incidence rate of any complication due to pertussis was highest, 75 per 100,000 years of follow-up, for children 0-<3 months of age and decreased, by increasing age, to 0.2 per 100,000 years for children above one year of age at the pertussis episode.

Thus, there was an association between age of child at beginning of the pertussis episode and the risk of also suffering at least one complication due to the disease.

Any complication, age and vaccination status at the pertussis episode

The events "any complication" were studied in relation to age as well as vaccination status at beginning of the pertussis episode. Detailed data are given in Figure 2.B.3 and Table 2.B.2.

For <u>unimmunised</u> children aged 0-30, 31-60 and 61-90 days at the beginning of the pertussis episode the complication rates were 57%, 40% and 35% respectively, and dropped to 8% for children above one year of age. For children between 3-<5 and 5-<12 months of age, the rate of any complication was 24% and 34% - for the combined age group it was 27%.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. The overall rate of any complication for unimmunised children was 33%.

Regardless of age, the rate of any complication for children vaccinated with one dose was 17%, and 10% for children vaccinated with 2 or more doses before the pertussis episode (p<0.001). This significant difference was confounded by age. For children more than 12 months, the rate of any complication was at about 8 % for unimmunised children and 9.8% for children vaccinated with two or more doses. In the age interval 5-<12 months at the episode, the complication rate was 34% for unimmunised children, 12% for children vaccinated with one dose and 9% for those 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.

Cases with complications, stratified by age and vaccination status at episode start
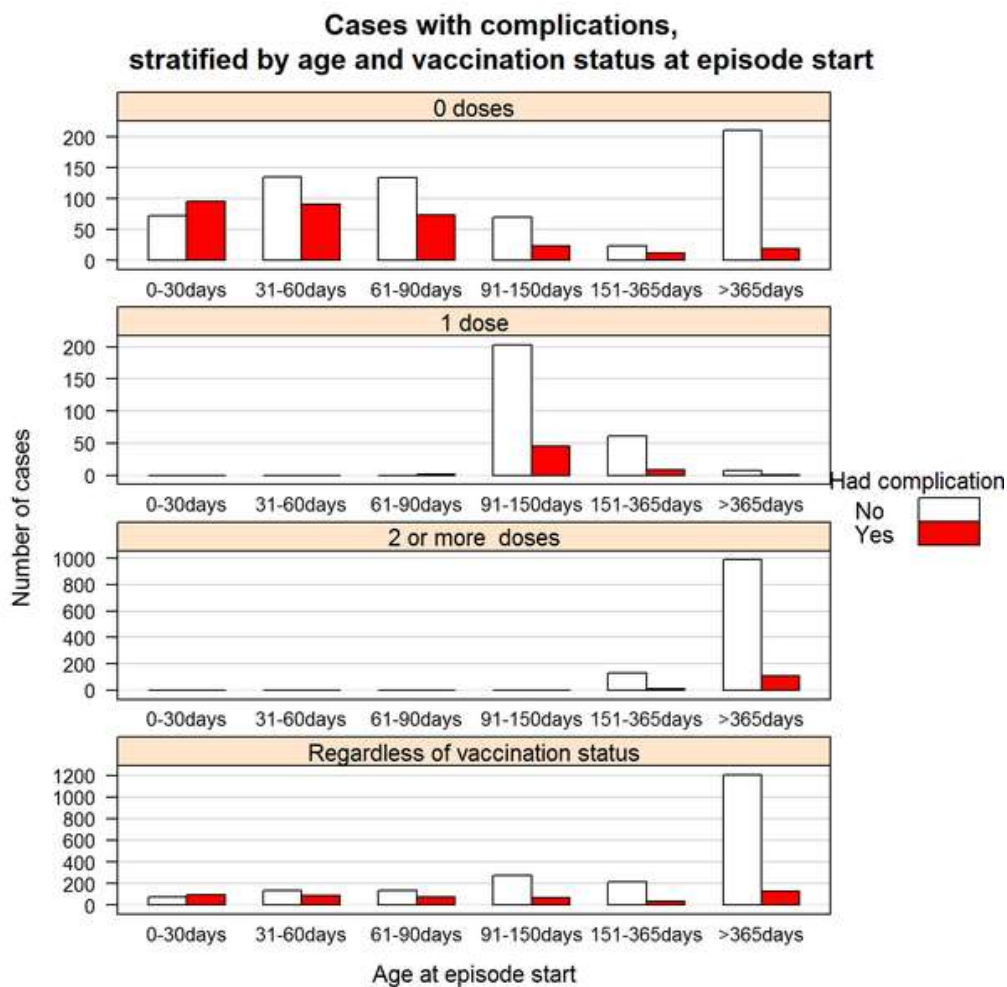
Figure 2.B.3 Any complication due to the pertussis disease and stratified by age and vaccination status among children born from January 1, 1996 during surveillance from October 1, 1997 until December 31, 2012, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

Doses before episode:	Complications after episode?	0-30 days	31-60 days	61-90 days	91-150 days	151-365 days	> 365 days	Sum
				Age at episode start:				
0 doses	No	72 (43%)	135 (60%)	134 (64%)	70 (75%)	23 (66%)	211 (92%)	645
	Yes	96 (57%)	91 (40%)	74 (36%)	23 (25%)	12 (34%)	19 (8%)	315
	Sum	168 (100%)	226 (100%)	208 (100%)	93 (100%)	35 (100%)	230 (100%)	960
1 dose	No			0%	203 (82%)	61 (88%)	7 (88%)	271
	Yes			2 (100%)	45 (18%)	8 (12%)	1 (13%)	56
	Sum			2 (100%)	248 (100%)	69 (100%)	8 (100%)	327
2 or more doses	No					130 (91%)	987 (90%)	1117
	Yes					13 (9.1%)	108 (9.9%)	121
	Sum					143 (100%)	1095 (100%)	1238

Table 2.B.2 Any complication due to the pertussis disease and stratified by age and vaccination status among children born from January 1, 1996 during surveillance from October 1, 1997 until December 31, 2012, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

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

1. The median (mean) age at start of an episode was 110 (144) days for unvaccinated children and 125 (131) days for children vaccinated with one dose before the episode. Thus, the two groups are "comparable" in age.

2. Overall 29% of the unimmunised children and 17% of children vaccinated with only one dose had a complication during the pertussis episode occurring in the age interval of 3-12 months. This difference was statistically significant (p=0.02).

These results suggest that, there was some protection against "severe" pertussis, expressed as any complication due to the disease, already after one dose of a pertussis vaccine.

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

Finally as could be expected there was also a strong association between any complication and a hospital stay during the pertussis episode. Seventy-two percent, 352 of 492, of children with at least one complication also had a hospital admission due to the disease during the episode. For 2033 children without any complication the hospitalisation rate was 14% (p<0.001). For children admitted to hospital with a complication, 54% of the admissions had a duration of 8 days or longer. For children without any complication 28% of the hospital admissions were 8 days or longer (p<0.001).

Deceased children

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

2.B.3 Spasmodic cough during the pertussis episode

Data on cough and spasmodic cough were available for all 2526 cases born January 1, 1996 until December 31, 2012. All children but 3 were coughing during their pertussis episode. 2256 (88.4%) of the children had spasmodic cough during the pertussis episode and 297 (11.6%) reported no spasmodic cough. Spasmodic cough for 21 or more days during the pertussis episode was reported for 82.5% of the children.

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

In all 543 of 610 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 346 children in age-group 3-<5 months, for 250 children in age-group 5-<12 months and for 1347 children aged 12- months at the beginning of the pertussis episode were 86%, 78% and 80%, respectively (Figure 2.B.4 and Table 2.B.3).

The age specific incidence rate of pertussis with 21 or more days of spasmodic cough was highest, 155 per 100,000 years of follow-up, for children 0 to <3

months of age and decreased to 9.6 per 100,000 years for children above one year of age at the pertussis episode.

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 Figure 2.B.4 and Table 2.B.3.
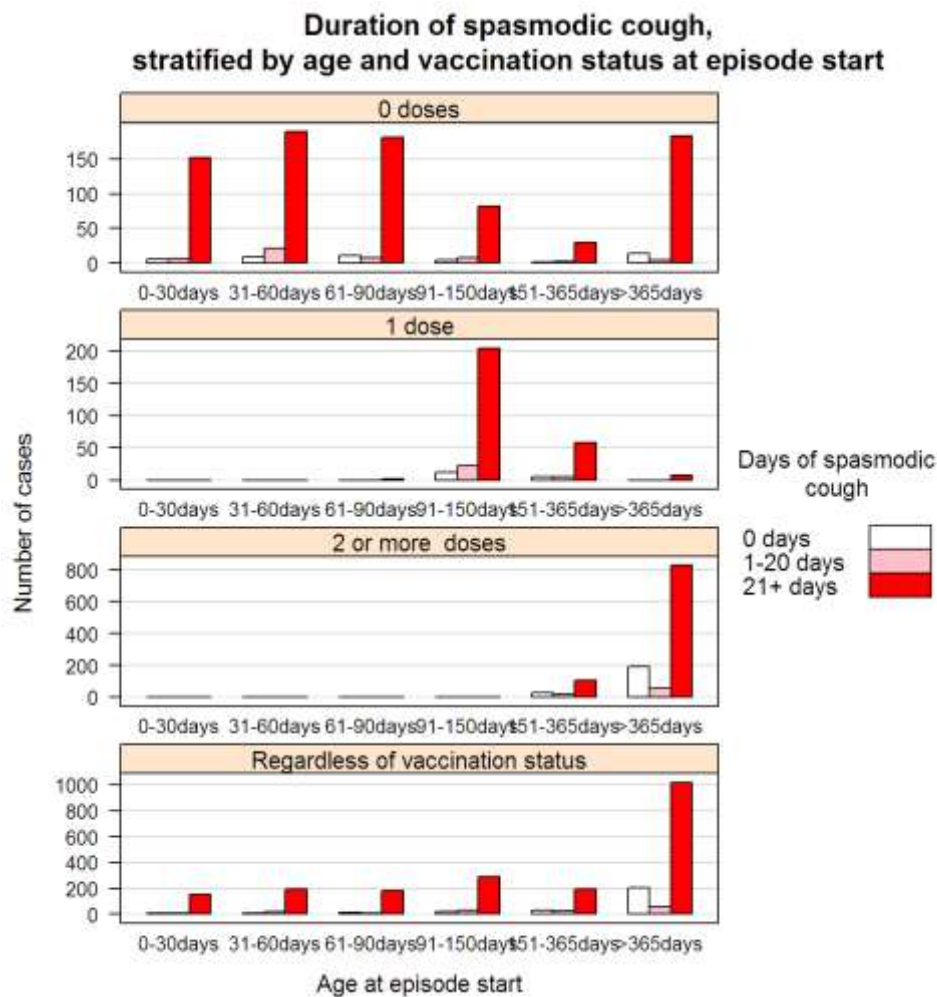
Figure 2.B.4 Duration of spasmodic cough due to pertussis disease and age-specific incidence of all pertussis per 100,000 years of follow-up regardless of vaccination status among children born from January 1, 1996, during surveillance from October 1, 1997 until December 31, 2012, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

Doses before episode:	Duration of spasmodic cough:	Age at episode start						Sum
		0-30days	31-60days	61-90days	91-150days	151-365days	>365days	
0 doses	**0 days**	8 (5%)	9 (4%)	13 (6%)	5 (5%)	1 (3%)	21 (9%)	**57**
"	**1-20 days**	6 (4%)	23 (10%)	8 (4%)	8 (8%)	2(5.71%)	4(1.69%)	**51**
"	**21+ days**	155 (92%)	197(86%)	189 (90%)	83 (86%)	32 (91%)	212(89%)	**868**
"	**Sum**	169 (100%)	229 (100%)	210 (100%)	96 (100%)	35 (100%)	237 (100%)	**976**
1 dose	**0 days**			0%	14 (6%)	5 (7%)	0%	**19**
"	**1-20 days**			0%	22 (9%)	5 (7%)	0%	**27**
"	**21+ days**			2 (100%)	214 (86%)	59 (86%)	8 (100%)	**283**
"	**Sum**			2 (100%)	250 (100%)	69 (100%)	8 (100%)	**329**
2 or more doses	**0 days**					25 (17%)	196 (18%)	**221**
"	**1-20 days**					18 (12%)	55 (5%)	**73**
"	**21+ days**					103 (71%)	851 (77%)	**954**
"	**Sum**					146 (100%)	1102 (100%)	**1248**

Table 2.B.3 Duration of spasmodic cough due to pertussis disease and age-specific incidence of all pertussis per 100,000 years of follow-up regardless of vaccination status among children born from January 1, 1996, during surveillance from October 1, 1997 until December 31, 2012, by age at onset of cough and number of doses of a pertussis vaccine prior to the pertussis episode.

The rate of episodes with 21 or more days of spasmodic cough among unimmunised children varied between 86% and 93% for the different age groups. The overall rate for unimmunised children was 89% (868/976). Also in vaccinated children no downward trends by age in this rate were observed. Regardless of age the rate of children with 21 or more days of spasmodic cough among vaccinated with one dose was 86% (283/329) and among those vaccinated with 2 or more doses 76% (954/1248). This downward "trend" in rate of a long duration of spasmodic cough by number of doses of a pertussis vaccine before the episode was statistically significant, p<0.001.

2.B.4 Duration of cough, spasmodic cough and antibiotic treatment

As stated in chapter 2.B.3, data on cough and spasmodic cough were available for all 2526 children born from January 1, 1996 until December 31, 2012, whereof 1206 were infants.

All children but three were coughing during their pertussis episode.

Duration of cough, spasmodic cough and antibiotic treatment

For 947 children, no antibiotic treatment was reported; of these, 186 were infants. Before further statistical analysis 42 treated cases with a short duration of treatment, 1 − 6 days with erytromycin, were excluded. Most often the described treatment period was shortened due to adverse events such as diarrhoea etc.

Figure 2.B.5 shows the result for antibiotic treatment and the duration of cough for

- 608 children aged 0-90 days at onset of the episode, without any pertussis vaccination prior to onset,

- 250 children aged 91-150 days at onset of the episode, with one dose of a pertussis vaccine prior to onset,

- 143 children aged 151-365 days at onset of the episode, with two doses of a pertussis vaccine prior to onset,

- 1086 children one year or older at onset of the episode, with three or more doses prior to onset.

- In all 2087 children were reported.
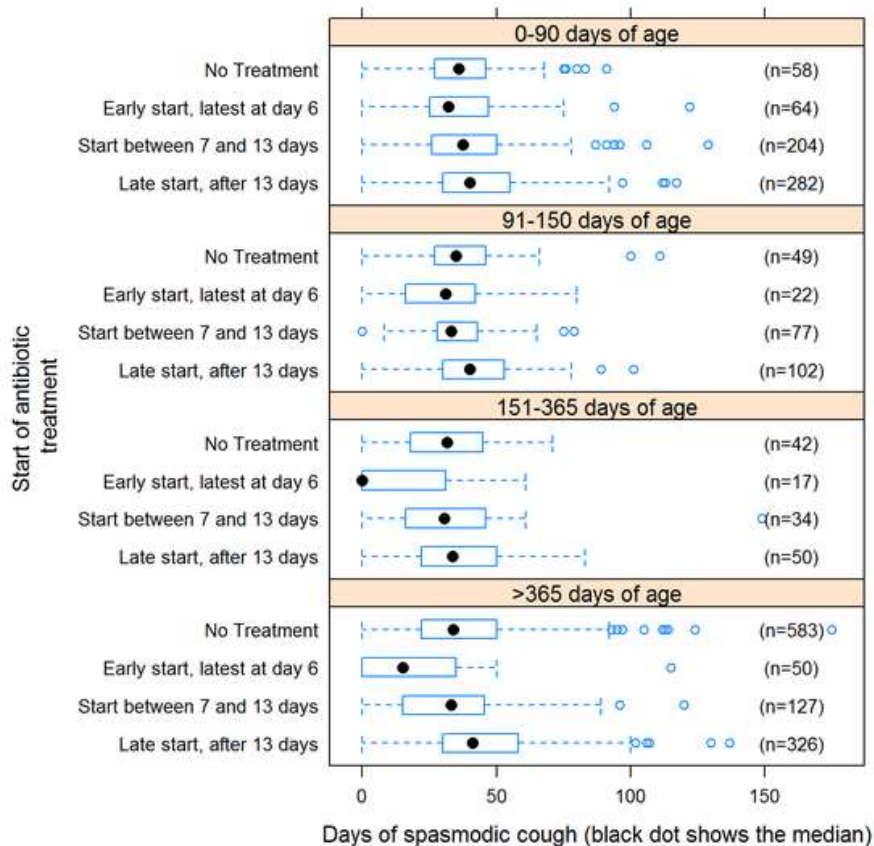
Figure 2.B.5: Duration of cough and spasmodic cough due to pertussis disease among infants born from January 1, 1996 under surveillance from October 1, 1997 until December 31, 2012, by age at onset of cough and day for start of antibiotic treatment in relation to onset of pertussis episode. Boxes show 1st and 3rd quartile. Whiskers extend the most extreme data point, or at most extreme data point within 1.5 times the interquartile range from the 1st resp. 3rd quartile.

An early start of the antibiotic treatment, within the first week (≤ 6 days) after onset of cough during the episode was, in all age groups, associated with a shorter duration of cough compared to both "no antibiotic treatment" and a late start, later than two weeks after onset. The same was true for spasmodic cough (data not shown).

Children below one year of age were in general treated with antibiotics, 852 (85%) of 1001 children. The treatment rates in the age-groups 0-<3 months, 3-<5 months and 5-<12 months were 90% (550 / 608), 80% (201 / 250) and 71 % (101 / 143), respectively. Among those aged one year or more at onset of cough during the episode, 46% (503 / 1086) children were treated.

72

Chapter 3 Trial I and Trial II data with results from 1997 to 2012.

Laboratory confirmed pertussis in previous trial cohorts

Tables, 3:1-4, summarise the number of cases reported among Trial I children born 1992, and among children born 1993.06-1994.05, who participated in Trial II.

Table 3:1 reports laboratory confirmed cases of pertussis during follow-up period from October 1, 1997 until December 31, 2012 among children vaccinated with 3 or 4 doses before onset of cough. During the fifteen year of follow-up, there were 6 more cases in the Trial II cohort compared to the fourteen year report. In all there were 296 cases of laboratory confirmed pertussis participants in Trial I and Trial II who had received 3 trial doses. Tables 3:1 and 3:3 include children vaccinated in either a 2, 4 and 6 or a 3, 5 and 12 months schedule.

The overall incidence was 22 per 100,000 person years of follow-up (Table 3:3). The trial participants were between 4 and 17 years old during the follow-up period and received the primary series of pertussis vaccine before 1 year of age.

Due to poor efficacy shown in Trial I, US DTPw, and in both trials, DTPa2 (unregistered vaccine) the recipients of these vaccines were offered a fourth dose of acellular pertussis vaccines at 3-4 years of age. The overall pertussis incidence for the trial children was similar to the incidence observed between dose 2 and 3, but higher than that measured after dose 3, among children born from 1996 until December 31, 2012, Table 1 (Exec sum). As expected, the estimated incidence after four doses in the DTPa2 trial arm (12/100,000 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 (24/100,000 person years).

Vaccines	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
3d CLI DTPwc	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	2
3d CLI DTPwc,1 d CLL Pa5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3d SKB DTPa2	0	0	1	0	0	0	0	0	0	1	0	0	0	0	0	1	3
3d SKB DTPa2,1d SKB Pa3	0	0	1	0	1	0	0	1	0	0	0	0	0	0	0	0	3
3d CLL DTPa5	1	1	1	4	2	1	0	1	0	0	0	0	0	0	0	0	11
Sum	1	1	3	5	3	2	0	2	0	1	0	0	0	0	0	1	19

Table 3:1 Cases of diagnosed pertussis among participants in the enhanced surveillance study Oct 1, 1997 to Dec 31, 2012 of children from Trial I.

Vaccines	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
3d Evans DTPwc	0	4	18	4	3	3	4	6	2	3	2	3	2	4	1	2	61
3d SKB DTPa2	0	6	5	5	1	1	0	6	7	3	1	0	3	1	1	1	41
3d SKB DTPa2,1d SKB Pa3	3	4	8	8	4	0	0	0	0	0	0	3	0	0	0	0	30
3d Chiron DTPa3	1	5	11	18	6	2	1	5	3	2	0	0	1	0	4	2	61
3d CLL DTPa5 II	4	6	18	18	6	4	3	4	6	4	2	4	2	0	2	1	84
Sum	8	25	60	53	20	10	8	21	18	12	5	10	8	5	8	6	277

Table 3:2 Cases of diagnosed pertussis among participants in the enhanced surveillance study Oct 1, 1997 to 31 Dec 2012 of children from Trial II

Trial	Vaccines	Enrolled children	Person years	Cases	Incidence (95% conf interval
Trial I	3d CLI DTPwc+/- 1d CII Pa5	2001	30,432	2	7 (1-24)
"	3d SKB DTPa2+/- 1d SKPB Pa3	2538	38,599	6	16 (6-34)
"	3d CLL DTPa5 I	2551	38,796	11	28 (14-51)
Trial II	3d Evans DTPwc	19,971	303,726	61	20 (15-26)
"	3d SKB DTPa2	6444	98,002	41	42 (30-57)
"	3d SKB DTPa2,1d SKB Pa3	13,731	208,826	30	14 (10-21)
"	3d Chiron DTPa3	20,239	307,801	61	20 (15-25)
"	3d CLL DTPa5 II	20,23	307,665	84	27 (22-34)
Both Trials	All	87,705	1,333,847	296	22 (20-25)

Table 3:3 Number of laboratory confirmed cases among participants in Trial I and Trial II from October 1, 1997 until December 31, 2012 , number of fully vaccinated children (3 doses at either 2-4-6 or 3-5-12 months), estimated person years of follow up, and incidence per 100,000 person years of follow up during the fifteen year period.

Table 3:4 shows the incidence figures during the fifteen-year follow up for children immunized at 3, 5 and 12 months of age in Trial II. The overall rate varies from 17/100,000 in the DTPw group compared to 20-42 /100,000 in the DTPa groups who had received three doses of a pertussis vaccine. It also demonstrates the relative risk of pertussis for acellular vaccine recipients compared to recipients of the British whole cell vaccine Evans DTPw.

Comparing recipients of 3 doses CLL DTPa5 recipients with 3 doses Evans DTPw gave the following result, RR=1.45 (0.99-2.13)).

Trial vaccines	No of Children	Person years	Cases	Incidence (95% conf interval)	Relative risk (95% conf interval)
3d Evans DTPwc	17,495	266,070	45	17 (12-23)	1.00
3d SKB DTPa2	5542	84,285	35	42 (29-58)	2.46 (1.57-3.82)
3d SKB DTPa2,1d SKB Pa3	12,122	184,355	23	12 (8-19)	0.74 (0.44-1.21)
3d Chiron DTPa3	17,739	269,781	55	20 (15-27)	1.20 (0.81-1.8)
3d CLL DTPa5 II	17,728	269,613	66	24 (19-31)4	1.45 (0.99-2.13)

Table 3:4 Incidence of pertussis, and Relative Risk ratios among children participating in Trial II and who followed a 3-5-12 months schedule. Number of culture- or PCR-confirmed pertussis cases and incidence per 100,000 person years of follow up in the 1993-96 randomised controlled pertussis vaccine trial [3] reported from October 1, 1997 until December 31, 2012 at 3 to 17 years of age. From 2008 positive serology was added. Relative risks are given for acellular pertussis vaccine recipients compared to recipients of the British whole cell vaccine Evans DTPw.

Chapter 4
Case-contact information in infants

Case-contact of pertussis in infants has been evaluated since Jan 1, 2009 by telephone interviews. All families with infants with laboratory verified pertussis, less than one year of age, were asked whether they had had any contact with anyone with more than 7 days of coughing and whether it is their first, second or 3rd contact with persons with cough more than a week. These questions were asked in association with all other questions in the surveillance project.

The study about a case-contact questionnaire has been approved by the Regional Ethical Committee in Stockholm.

In order to disentangle the path of infection the parents were asked how many persons in close contact with the child that had been coughing. Of 174 parents answering the question, 54 reported that they had no contact with coughing persons, 85 reported one coughing person, 23 reported two coughing persons and 10 reported three coughing persons.

Figure 5.1 illustrates the distribution of the one person that was reported as most likely to have infected the child. About 78% of these were family members of the case (parents or siblings). It is however worth to consider that in 133 cases (76%) the interviewer talked to the mother, in 38 cases (22%) to the father, and in three (2%) cases to someone other than the parents. This may potentially bias the information about who had been coughing, as it might be easier to recollect own coughing than coughing in another person.

In cases where other children were reported to have been a potential source of infection, an additional question was asked about the age of that child. Information is available for 36 contact children. Figure 5.2 illustrates the age distribution of the children. The material is quite small, and do not allow any firm conclusions to be drawn about the ages of the children. However, all ages in the age span seem to be represented, with a possible overrepresentation of young children.
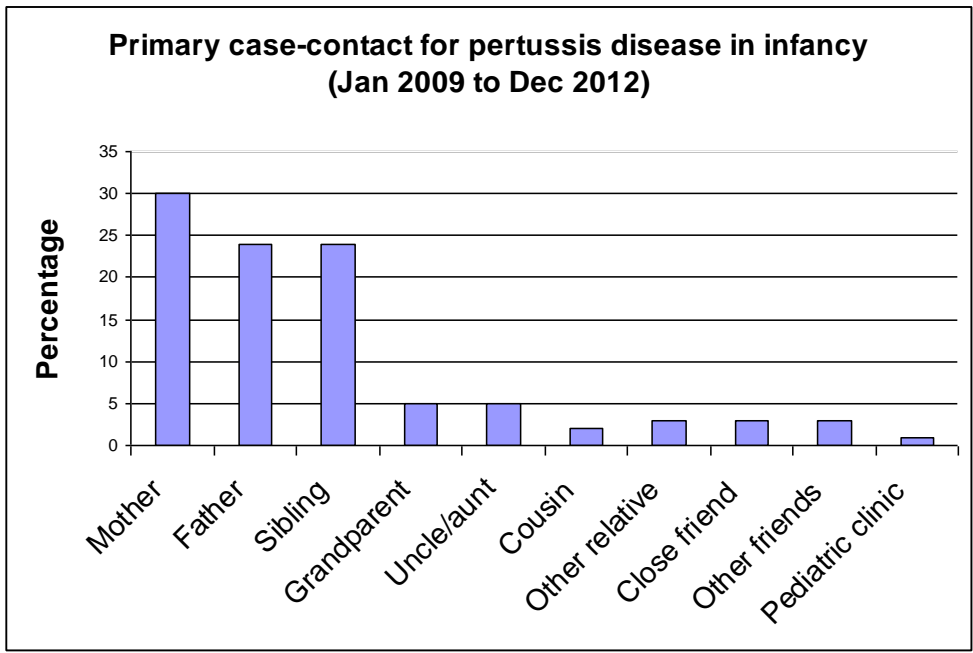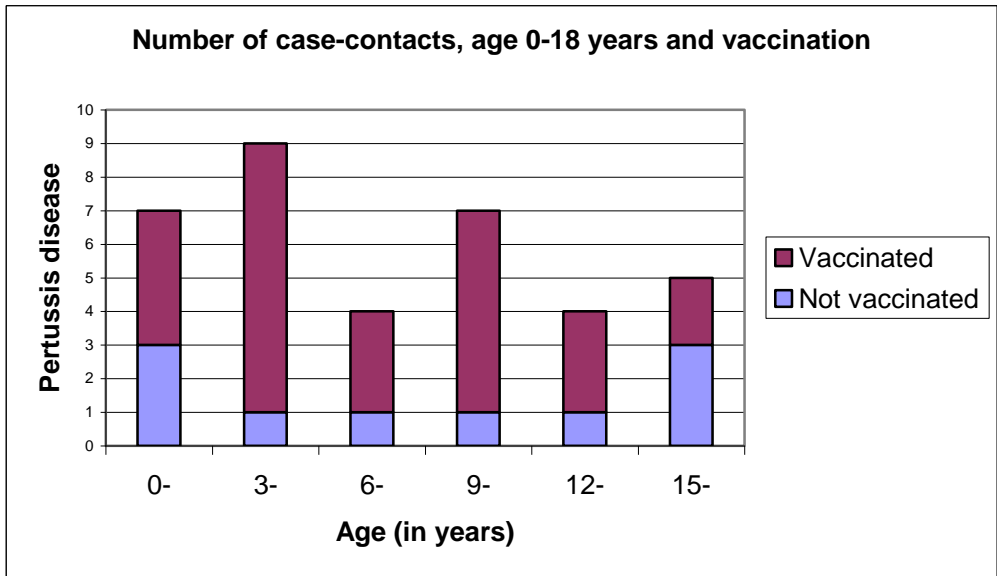
Figure 5.1: See the text above

Figure 5.2: See text above.

Chapter 5 Discussion

5.1 Discussion

We report a dramatic decline in pertussis incidence during the first years after introduction of acellular pertussis vaccination in Sweden. However, due to the increase of pertussis during the months August to December 2012 an increase of pertussis was seen in all ages. In infants, an increase of 1.4 times was seen in the number of infants with laboratory verified pertussis, i.e. from 37 to 51 infants compared with 2011. Correspondingly, there was a 1.3 times increase (53-71) in children 1-18 years of age, a 1.8 times increase (67-120) in adults 18-65 years of age and a 2.3 times increase (11-26) in persons more than 65 years of age. No continuation of this increase in incidence ratio has been shown for the first seven months in 2013 (preliminary data). The increase during 2013 has not substantially changed the overall decrease of laboratory confirmed pertussis, i.e. from 140/100,000 before these vaccines were introduced, to 2.8/100,000 in 2012. The reported incidences during the last seven years are lower than that observed in the late 1960's and early 1970's when a Swedish-produced whole-cell pertussis vaccine was used with a high coverage [1].

Our observations indicate that the acellular pertussis vaccines used in the Swedish National vaccination programme have markedly reduced the reported incidence of pertussis in immunised cohorts, and also to some extent reduced pertussis among unvaccinated and partially vaccinated infants, indicating herd immunity. The number of pertussis cases was around 3 per month for infants in 2011 and in the first half year of 2012 it was 2 per months but during the last six months of 2012 it was 7 per month. This increase does not seem to continue during the first seven months of 2013.

In order to achieve better control of the spread of *B. pertussis*, the Swedish National Board of Health and Welfare revised the booster schedule of the national vaccination program. From 2007 a preschool booster dose and also a school leaving booster was recommended to children born from 2002 (DTPa at age 5-6 years, reduced antigen vaccines at age 14-16 years), For children born 1995-2001 the booster dose (DTPa) was recommended at the age of 10 years [10]. Our data indicate a significant decrease in the incidence of pertussis following the implementation of these booster vaccinations (Figure 1.10 in chapter 1).

The number of children with pertussis disease is low during the second half of the first year of life (Figure 1.5b). In spite of this, most cases of pertussis are reported in infants due to many cases during the first 4-5 months of age, However, many other countries have their peak incidence among adolescents and young adults [36-38).

Resurgence of pertussis from the 1980ies in e.g. USA (39) and Australia (40), have been shown both in adolescents and adults. In 2012 in the UK, the highest mortality rate was registered since 1982 with 10 deaths, all occurred in infants less

than 12 months (41). Jackson and Rohani discuss in "Perplexities of pertussis…" the re-emergence of pertussis (42). They comment that awareness and diagnostic methodologies, composition of vaccines, differences in vaccine schedules and a change in immunity would be possible explanations for the increase in pertussis. They have doubts that awareness and diagnostic methodologies are the only explanations. They discuss that high coverage is important but also that every percent of the coverage less than 100% means a lot of unprotected individuals. Sweden has a very high coverage rate and together with an extraordinarily good timeliness for vaccinations this would presumably be of high importance for the good results with low reported incidence ratios of pertussis in children.

There seems to be a 2 to 4.6 year periodicity in pertussis incidence (41). In Sweden, we have had an increase in 1999-2000 with 25-27 pertussis cases/100,000 individuals, in 2004 with 15.6 pertussis cases/100,000 but no clear increased incidence ratio thereafter before the increase in autumn 2012, see table 1:2.

Hospitalisation due to pertussis disease is considerably dependent on age, i.e. the incidence is 126/100 000 person-years for infants 0-90 days in 1997-2012 and 0.2/100 000 in children from one year of age during the same time period. There is a significantly higher rate of hospitalisation for unimmunised infants 3-12 months of age compared with those vaccinated with one dose during the expected time interval for the first dose. Similarly, Dutch researcher have reported that among infants eligible for at least one dose of pertussis vaccine, a median duration of hospitalisation of 4 days was observed when receiving 1 dose versus 11 days in unvaccinated infants (p=0.03) (43).

Waning protection of pertussis has been suggested 5-6 years after the immunizations in infancy. In 2004-2007 we observed high reported age specific incidence for children 7-9 years old with an incidence of 19.4 to 105/100,000. These data, together with the earlier shown waning in immunity from 6 years of age, with an age-specific incidence at about or higher than that for 5-12 month-old infants (after the second dose of pertussis vaccine), strongly suggested that a booster dose would give protection by 5-6 years of age [17]. This suggestion has been shown to be true with our data showing no increase in pertussis during early school years and an estimated decrease of around 40% compared to before preschool booster in these children.

Previously reported randomised studies have shown that acellular pertussis vaccines are efficacious in young children [2-3, 7-8]. The very high efficacy estimates observed in the post-trial studies should be regarded with caution, since such studies are open to biases that predictably will over-estimate efficacy [14]. Our data indicate that the vaccines appear to be effective from the dose administered at 3 months of age, with a further reduction in disease incidence after the second dose of vaccine, (44) (Table 2.A.10). The reduction in the incidence of disease was more pronounced during the first year following vaccination, but

seemed to remain fairly stable for 4-5 years after the completion of the full vaccination schedule (Table 2.A.11). However, there is limited data on the effectiveness of the vaccines when given to school age children. In a small study an effectiveness between 60 and 92% has been shown (45).

These findings are in accordance with Italian, German, Norwegian and American experiences [46-49]. 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 [46], and after four doses of a four-component vaccine [47]. In a study in California including 277 children, 4 to 12 years of age, who were PCR-positive for pertussis with 3318 PCR-negative controls and 6086 matched controls it was estimated that the effectiveness against pertussis after 5 years was 42% if they assumed that the effectiveness of DTaP had an initial effect of 90%, i.e. the effectiveness waned substantially during the 5 years after vaccination (50).

Acellular pertussis booster at 4 years of age was introduced in the Netherlands in 2001. The relative risk of hospitalizations and notifications of pertussis declined in infants less than 6 months of age, relative risk 0.60 (95% CI 0.54-0.67) and 0.80 (95% CI 0.71-0.89), respectively (51) but the incidence has thereafter increased again, particularly among the youngest infants, 265/100,000 infants 0-2 months of age in 2012 compared with 126/100,000 infants 0-2 months in 2001. In the same period pertussis has increased among adolescents and adults (51).

In Australia, where a fifth dose of Pa has been recommended since 1994 at 4-5 years of age and the 18 month vaccine dose was removed in 2003 (and a 15-17 year old dose was added), no downward trend in the incidence in infants was seen but a clear increase in pertussis notifications from 2008-2011 for 5-14 year old children (52) This increase is accompanied with low IgG antibodies to pertussis, lower than 5 EU/ml in 40% of the children in these ages in 2007 compared with 20% in 1997. However, pertussis test requests increased with an odds ratio of 7.0 (95% CI, 5.5-8.8) from 2000/2004 to 2010/2011 and was highly correlated to pertussis notifications (r=0.99). PCR confirmed pertussis notifications increased during the same time from 16.3% to 65.3% (53). Fortunately, the incidence in the whole population is lower in 2012 than the last years, e.g. 23,900 in 2012 and 38,000 in 2011. The coverage of the first 3 pertussis doses is only 93% (WHO, update 2013/July/13).

In New Zealand both the incidence and the hospitalizations have increased in infants despite booster vaccination has been introduced at 4 years of age (54, 55). However, during the same period, the booster dose at 18 months has been removed from the national vaccine schedule. The primary intervention that has been suggested in New Zealand was to improve the immunization coverage and timeliness (55). The coverage is 90% and 60% of infants have the first 3 doses of vaccine administered within 4 weeks of the scheduled time (56).

The high rate of prescription of erythromycin in Sweden to treat pertussis in infants is noteworthy, but is in accordance with the recommendation from the Swedish National Board [6]. This recommendation was issued during the vaccine-free

period to reduce the morbidity and mortality among infants in an endemic setting. It is well known that erythromycin may reduce the severity and duration of disease if prescribed early during the course of pertussis. However, there is no consensus about the definition of early. In fact, it is generally believed that there is little or no reduction of severity from erythromycin if prescribed after the catarrhal phase. A beneficial effect of erythromycin, even when started during the paroxysmal phase, has previously been published [57].

From the sero-prevalence study in Sweden 2007 IgG to pertussis toxin (PT) has decreased compared with 1997 and a higher proportion of the population had non-detectable levels of IgG-PT. Also, in 2007 less adults between 20 and 64 years of age and also less children in the age groups 4-5 and 8-9 years had high PT-IgG (>50 EU/ml) compared with 1997. Only in the groups 14-18 years of age there were higher levels of PT-IgG in 2007 compared with 1997. The statistical analyses from the study in 2007 indicated that 3 of 100 adults had had a pertussis infection during the last year (58). However, we do not know if this infection was subclinical, mild or severe, only that it caused a strongly increased level of IgG to pertussis toxin. As a summary of the sero-prevalence studies, this indicates that the circulation of pertussis has decreased in the population but there is still a high circulation of pertussis after the introduction of the acellular pertussis vaccine in 1996. Also, there is an under-reporting of pertussis in adolescence and adults.

Limitations

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. From 2008, positive serology has been added as a diagnostic criterium. The children in the surveillance study diagnosed by serology were only four in 2011 and in 2012 nine were carefully controlled as children with obvious pertussis disease . The sampling rates may vary geographically and over time, according to the awareness of pertussis, local clinical practice, level of suspicion and laboratory experience in different parts of the country.

The problems with laboratory confirmation are mainly the lower sensitivity of culture-confirmation in vaccinated compared to unvaccinated individuals, and also the higher sensitivity of PCR-confirmation compared to culture-confirmation. PCR has replaced culture at an increasing number of laboratories during the last years, Figure 1.9.

On the other hand, the Swedish experience provide a reporting system that is stable over time, providing a unique opportunity to conduct a phase IV follow-up after introduction of acellular vaccines in an endemic setting. What we can learn from this long-term surveillance is the overall impact of an acellular pertussis vaccination program, including estimates of duration of vaccine-induced protection after vaccination in infancy and after introduction of pre-school booster, and – with the continuation of the project – after introduction of the "school-leaving" booster.

What we cannot learn from this type of follow-up is the vaccine effectiveness by percent reduction of disease rates among vaccinated compared to unvaccinated children, nor can we perform long-term comparisons of vaccines and geographic areas. However, taking these limitations into account, the results of this study provide valuable evidence on the impact of the pertussis vaccination programme which may serve as the basis for decisions on future vaccination strategies. Also, in spite of PCR as a sensitive diagnostic tool and that pertussis serology has been added in the diagnostics, the pertussis incidence has continued to decrease both in infancy and in school-aged children after the introduction of booster vaccination until summer 2012, thereafter it has been a transient increase in the incidence during autumn of 2012.

5.1.1 Future priorities

Potential differences in protective efficacy between vaccines was indicated by the data from the earlier efficacy studies. Efficacy from the trials may wane over the years, with little or no difference in the long run. Additional boosters may further decrease differences observed after priming. Another possibility could be the opposite, i.e. that differences of effectiveness between vaccines may remain unidentified for a number of years. Such late effects may only be detected by sustained disease surveillance combined with detailed national vaccination registry data [59]. A mandatory reporting to an immunization registry is introduced in Sweden in January 2013 which might improve data quality. Yet, the validity of comparing effectiveness of different vaccines will be limited by differences in completeness of case ascertainment.

Infants are especially vulnerable to pertussis and studies indicate that *B. pertussis* pneumonia triggers a cascade of events that includes acute pulmonary vasoconstriction and pertussis toxin-mediated increases in circulating leukocyte mass. Ultimately, these responses compromise pulmonary blood flow, exacerbate hypoxemia, and create a vicious cycle of refractory pulmonary hypertension in the infant [60].

Studies of neonatal vaccination are now on-going[61-63], evaluating the possibility to initiate a protective immune response already at birth. However, neonatal priming with acellular pertussis vaccine has shown to elicit bystander interference with Hepatitis B, Haemophilus type b, and diphtheria vaccine responses (64).

Also studies of maternal vaccination could be useful for protection of the newborn already from birth. In general, there is a need for better understanding of the epidemiology of pertussis in infancy and transmission routes. Studies relating vaccination of older age-groups are especially needed in relation to changes in infant epidemiology. Furthermore, changes in kinetics and magnitude of maternal antibodies over time may relate to changes in age-specific incidence in infancy. Recent publications have found a decreasing IgG to pertussis toxoid in women of child-bearing age in Sweden when serologic responses in 1997 were compared with the 2007 serology study (65).

While waiting for different immunisation strategies to be evaluated, such as neonatal vaccination, vaccination of the family of the newborn, and/or adult vaccination, extensive contact tracing should point to the the need for a stricter implementation of antibiotic chemo-prophylaxis around the exposed infant [66], and provide a better understanding of the infant transmission routes. The three first years of contact tracing in Sweden found that several families had not noted any cough in the environment and 80% of those infants with a contact person with more than 7 days of cough, originated from the family household. This would strengthen the value of a cocooning strategy around pregnant women.

Adult vaccination every 10th year has been recommended, e.g. in USA, Canada and Austria, but the coverage to this schedule is low, in USA around 10%. Therefore, the schedule is hard to evaluate. Elderly patients with pertussis have been shown to have more days of hospitalizations compared with younger persons with pertussis (67). In the Netherlands, 75 nuns were in the same convent, 9 of them had stayed in the same convent since young age. By the start of a pertussis outbreak in 1992, the convent had become a nursing home. All the nine nuns that were in the convent since several decades had pertussis and 4 of them died. However, only 55% of the nuns that had been working outside the convent had pertussis (68). The risk of pertussis during the outbreak was associated with duration of isolation from society and was independent of age. Natural boosters in adults could be an alternative to regular pertussis vaccinations in adults.

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. Cases with a milder clinical course because of antibiotic treatment may fall outside the reporting.

5:2 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 a previous study protocol from 8 September 1997, page 8:

1. The study is explorative, aiming at estimating the effectiveness of individual vaccines and the detection of potential changes in circulating Bordetella strains.

2. 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.

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

doses. This is however estimated recently for an evaluation of incidences in relation to vaccine doses (44).

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 study 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.

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

Chapter 6. Plan for continued work

Study objectives for 2012:

To continue the work in studying the long-term effects of a general infant acellular pertussis vaccination program implemented in 1996, with addition of a pre-school booster from 2007, on age-specific incidence in vaccinated cohorts and in the general population.

To seek background data and evaluate suitable intervals between booster vaccinations.

Analyses will 2013 also focus on:

 - pertussis in infants

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

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

 - Yearly progress reports will, as previously, summarise overall number and age-specific incidence of laboratory confirmed cases, detailed analyses in vaccinated cohorts, including hospital admission rates, and number of cases in trial cohorts, and procurement of vaccine per county will be provided. Case-contact information has been added for infants from January 1, 2009. Progress reports will be based on data collected per calendar year. We will also from 2013 follow all adults in the surveillance study born 1990-1995 with questions of vaccinations, case contacts etc.

Scientific publications and presentations:

Papers planned during the coming year include

1. A paper about the incidences of pertussis after no, one or two doses of pertussis vaccine has been published in 2012. This has also been as a poster to WSPID 2011 and at the Nordic Vaccine Meeting in 2012 .
2. A 15-year surveillance project paper will be submitted within the coming months and has been presented as a poster at ESPID 2012.
3. An evaluation of the booster effect of pertussis vaccination will be written and has been presented as a poster and poster session at ESPID 2010
4. A surveillance paper from the from the Gothenburg study area.

5. A paper in a Swedish Medical Journal about clinical cases of pertussis will be published week 37, 2013.
6. A paper about pertussis in a journal which we have been invited to write

Chapter 7. Administration

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

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

The advisory group should in advance be informed about public presentations of data from the study. Papers should be submitted to peer reviewed journals.

Chapter 9 Acknowledgments

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Abbreviations

CHC	Child Health Centre
DTPa	Diphtheria-, Tetanus and acellular Pertussis vaccine
FHA	Filamentous haemagglutinin
GSK	GlaxoSmithKline
Hib	Haemophilus influenzae type b
IPV	Inactivated Polio vaccine
ITT	Intention to treat
MSD	Merck Sharp & Dome
NRN	National Registration Numbers
Pa	Acellular pertussis vaccine
PCR	Polymerase chain reaction
PRN	Pertactin
Pw	Whole cell pertussis vaccine
PT	Pertussis toxoid
SMI	"Smittskyddsinstitutet" = Swedish Institute for Communicable Disease Control
SmiNet	Computer-linked reporting system for e.g. reports of pertussis infections
SSI	Statens Seruminstitut (Copenhagen)