Folkhälsomyndigheten

Pertussis surveillance in Sweden

22nd annual report

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Bindningar och jäv

För Folkhälsomyndighetens egna experter och utredare som medverkat i rapporter bedöms eventuella intressekonflikter och jäv inom ramen for anställningsförhållandet.

När det gäller externa experter och utredare som deltar i Folkhälsomyndighetens arbete med rapporter kräver myndigheten att de lämnar skriftliga jävsdeklarationer för potentiella intressekonflikter eller jäv. Sådana omständigheter kan föreligga om en expert t.ex. fått eller får ekonomisk ersättning från en aktör med intressen i utgången av den fråga som myndigheten behandlar eller om det finns ett tidigare eller pågående ställningstagande eller engagemang i den aktuella frågan på ett sådant sätt att det uppkommer misstanke om att opartiskheten inte kan upprätthållas. Folkhälsomyndigheten tar därefter ställning till om det finns några omständigheter som skulle försvåra en objektiv värdering av det framtagna materialet och därmed inverka på myndighetens möjligheter att agera sakligt och opartiskt. Bedömningen kan mynna ut i att experten kan anlitas för uppdraget alternativt att myndigheten föreslår vissa åtgärder beträffande expertens engagemang eller att experten inte bedöms kunna delta i det aktuella arbetet.

De externa experter som medverkat i framtagandet av denna rapport har inför arbetet i enlighet med Folkhälsomyndighetens krav lämnat en deklaration av eventuella intressekonflikter och jäv. Folkhälsomyndigheten har därefter bedömt att det inte föreligger några omständigheter som skulle kunna äventyra myndighetens trovärdighet. Jävsdeklarationerna och eventuella kompletterande dokument utgör allmänna handlingar som normalt är offentliga handlingarna finns tillgängliga på Folkhälsomyndigheten.

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Folkhälsomyndigheten, 2019 Artikelnummer: 19071

Förord (preface)

Folkhälsomyndigheten har en förstärkt övervakning av kikhosta sedan de acellulära vaccinerna mot kikhosta introducerades i det nationella barnvaccinationsprogrammet i Sverige år 1996. Övervakningen innefattar incidens av rapporterade fall av kikhosta per åldersgrupp samt en uppföljning via strukturerade telefonintervjuer av alla rapporterade fall 0–20 år. Denna rapport innehåller resultaten för år 2019 samt analys från de tjugotvå åren som studien pågått.

Kikhosta är en allvarlig och ibland livshotande sjukdom för ovaccinerade spädbarn under sex månader. Både sjukdomen kikhosta och vaccination mot kikhosta ger ett bra, men relativt kortvarigt skydd mot ny sjukdom. De senaste sex årens ökade incidens av kikhosta i Sverige, trots hög vaccinationstäckning, och ökningen av kikhosta i andra länder har aktualiserat vikten av fortsatt förstärkt uppföljning av kikhosta i Sverige.

Syftet med uppföljningen är att ge underlag för eventuella ändringar av vaccinationsprogrammet eller andra interventioner som kan skydda spädbarn mot kikhosta. Kunskap om sjukdomens epidemiologi och allvarlighetsgrad, vikten av provtagning och förebyggande antibiotikabehandling för de minsta barnen, sprids regelbundet via vetenskapliga publikationer, på Folkhälsomyndighetens webbplats och i samband med utbildningsdagar och kurser riktade till hälso- och sjukvårdspersonal.

Målgruppen för årsrapporten är hälso- och sjukvårdspersonal, och då särskilt personal inom mödra-, barnhälso-vård, elvhälsa och barnsjukvård samt primärvård och smittskyddsenheter.

Ansvariga för rapporten är utredare Bernice Aronsson och enhetschef Sören Andersson (enheten för vaccinationsprogram).

Folkhälsomyndigheten

Britta Björkholm, Avdelningschef, Avdelningen för smittskydd och hälsoskydd

Preface

The Public Health Agency of Sweden has conducted enhanced surveillance of pertussis since 1996, when acellular vaccines were introduced into Sweden's national immunisation programme for children. The surveillance includes the incidence of reported pertussis cases per age group and follow-up of all reported cases of pertussis in patients 0–20 years of age through structured telephone interviews. This report includes results for 2019, as well as analyses from the past 22 years.

Pertussis is serious and sometimes life threatening for unvaccinated infants under the age of 6 months. Both pertussis infection and vaccination provide good but relatively short-lived protection against reinfections of pertussis disease. The increased incidence of pertussis in Sweden during the last six years, despite high vaccination coverage, and the increase in pertussis in other countries has accentuated the importance of enhanced follow-up of pertussis cases.

The aim of the surveillance of pertussis is to provide knowledge to make informed changes in the national immunisation programme or other interventions to protect infants. Surveillance data on pertussis epidemiology, on severe disease progression, and on the importance of laboratory testing and prophylactic antibiotic treatment of infants, are disseminated regularly through scientific articles on the Public Health Agency's website and at conferences and in courses aimed at health care professionals.

This report is written for health care professionals, particularly those working in maternal and child health care, school health care (elevhälsan), and primary care, and those working in the counties' Departments of Communicable Disease Control and Prevention.

Responsible for this report are analyst Bernice Aronsson and head of unit for vaccination program Sören Anderssson.

The Public Health Agency of Sweden

Britta Björkholm, Head of the Department of Communicable Disease Control and Health Protection

Content

Abbreviations

aP Acellular pertussis (vaccine)

CHC Child health care

DTaP Diphtheria-, tetanus, and acellular pertussis vaccine

dTap Diphtheria, tetanus, pertussis vaccine (low-dose diphtheria and pertussis vaccine)

EPS Enhanced pertussis surveillance

FHA Filamentous haemagglutinin

Hib *Haemophilus influenzae* type b

IPV Inactivated polio vaccine

NIP National immunisation programme

PCR Polymerase chain reaction

PHAS Public Health Agency of Sweden

PRN Pertactin

PT Pertussis toxoid

SHC School health care

SMI *Smittskyddsinstitutet*, in English: Swedish Institute for Communicable Disease Control

SmiNet Computer-linked reporting system for reports of infections, including pertussis infections

wP whole-cell pertussis (vaccine)

Summary

During 2019, 749 laboratory-confirmed cases of pertussis in all ages were reported, of which 60 cases were among infants younger than one year of age. This 22nd annual report of enhanced pertussis surveillance summarises the epidemiology of pertussis in Sweden since the introduction of acellular pertussis vaccine in 1996. The current report will particularly focus on the most vulnerable age group with the highest risk for severe disease - infants (0–12 months of age).

The incidence of pertussis among infants as well as among the population overall has decreased since 1996 when acellular pertussis vaccine was introduced in Sweden. The incidence of pertussis was low during 2009-2013, but the number of reported cases increased threefold in 2014 for all ages. The higher incidence in the population overall has remained, which might partly be due to an increase in the number of samples taken since 2014.

There have been no infant deaths due to pertussis since 2015, and both the number of cases among infants and the incidence have had a noteworthy and significantly decreasing trend since 2014. As in previous years infants aged 3 months and younger had the highest overall incidence of pertussis in 2019 (160/100,000 person years), and the highest rate of hospitalisation and complications due to pertussis. This group of infants, younger than 3 months of age, contracted pertussis before they had received the first dose of vaccine.

The fifth dose of pertussis vaccine was implemented for teenagers 14-16 years of age in 2016. Between 2016 and 2018 there was an decreasing trend in the number of reported pertussis cases in the age group 15-19 years of age but with an increase in 2019. The pertussis incidence in teenagers will continue to be monitored closely since pertussis in this age groups might be of importance for the transmission of disease to infants.

Recommendations aiming to decrease the number of cases among infants were published in 2016. The timeliness of the first dose of vaccine was 97% but the time between onset of disease and start of antibiotic treatment is still more than 10 days and the awareness of the disease among caregivers needs to be improved. If an increase in pertussis among infants is observed in the future, other preventive measures and interventions, including recommendation of maternal vaccination, may have to be considered.

1 Background

1.1 The national immunisation programme, pertussis vaccine trials, and the mass vaccination project.

Whole-cell pertussis (wP) vaccine was introduced 1953 in Sweden and used with high vaccine coverage until 1979, when it was withdrawn due to concerns about safety and efficacy (Romanus 1987). Thereafter, there was no vaccination against pertussis in the National Immunisation Programme (NIP) until 1996 (Figure 1). A total of approximately 90,000 children were vaccinated against pertussis using various candidate vaccines during this period (1979-1996) (Trial I and Trial II as described below), and children in Gothenburg were vaccinated within the Gothenburg mass vaccination project (described below). More than one full dose diphtheria, tetanus, and acellular pertussis (DTaP) vaccine were registered in 1995 based on the results of large aP vaccine trials conducted in Sweden, -Trial I and -Trial II (Gustafsson 1996, Olin 1997, Trollfors 1995, Greco 1996). DTaP vaccinations were included in the NIP in January 1996 and administered to children at 3, 5, and 12 months of age (Figure 1, Figure 2). Some years after the introduction of the primary immunisation schedule, it became clear that aP vaccines induced protection for only a limited time. Therefore, in 2005 a revision of the NIP was initiated. As a first step, a booster dose was recommended for children 10 years of age starting in the autumn of 2005. The first cohort recommended for this fourth dose of DTaP were children born in 1995. The booster at 10 years of age was included in the NIP until 2011–2012 (Figure 1). Because a decay in antibody levels to non-protective levels was observed 4–5 years after vaccination with aP vaccine, with a corresponding decline in vaccine effectiveness and an increase in pertussis incidence (Olin 2003, Gustafsson 2006), a second step was taken in Jan 2007 when the schedule was revised to instead offer a fourth dose at 5–6 years of age and a fifth dose for teenagers 14–16 years old for children born from 2002 onwards. The fifth booster dose for teenagers was not implemented until 2016 (Figure 1). Many children born in 1995 were to a large extent (59%) immunised with monovalent pertussis (aP) vaccine before 2 years of age (Table 1). Furthermore, children that for some reason had delayed vaccination were until the spring of 2002 vaccinated with two doses of aP vaccine with a 2-month interval, followed by a third dose after 6 months, and from the age of 2 years according to a two-dose schedule.

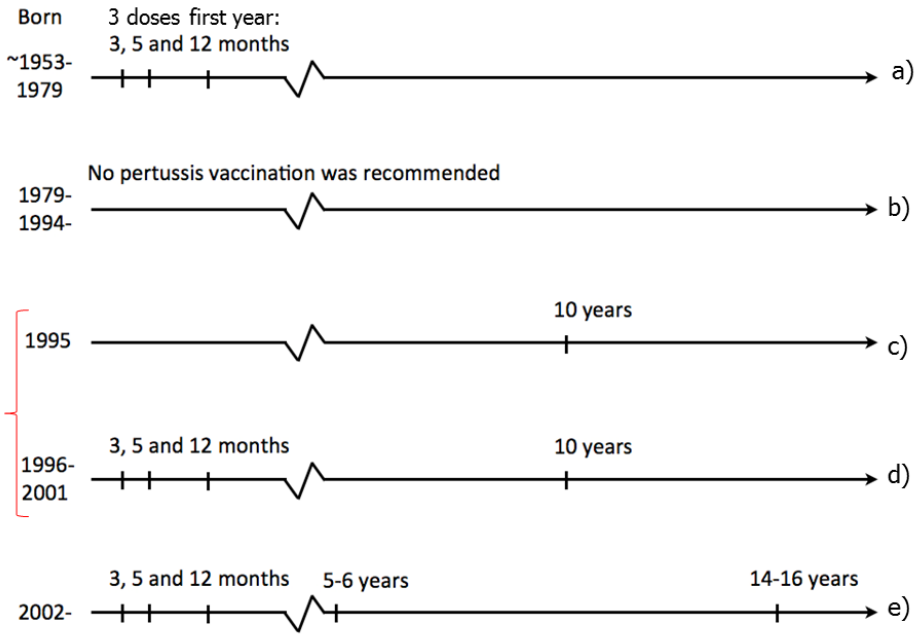

Figure 1: Pertussis vaccinations in childhood for those born from 1953 onwards in Sweden. During the time period from 1953 to 1979, wP vaccines were used in the NIP (a). During the time from 1979 to 1994, the use of pertussis vaccines in the NIP was interrupted (b). Large pertussis trials with aP vaccines were conducted in Sweden from 1979 to 1994 (b). After approval of the new vaccines in 1995, children born in 1995 received one dose at 10 years of age (c). In 1996, primary immunisation against pertussis was reintroduced in the NIP, and infants received the aP vaccines (DTaP) at 3 and 5 months of age and an early booster at 12 months followed by a fourth dose (DTaP) at 10 years of age (d). The booster-dose in the NIP was changed in 2007 with the fourth dose moved to preschool age and a fifth dose (dTap) introduced at 14–16 years of age (teenage booster) (e). In children born from 2002, the booster doses are administered at 5 years of age and from 2016 also at 14–16 years of age (e).

1.1.1 Pertussis vaccine Trial I and Trial II

In 1992, pertussis vaccine Trial I included 9,829 infants vaccinated at 2, 4, and 6 months of age with a five-component DTaP vaccine (Connaught Laboratories Limited (CLL)), a two-component DTaP vaccine (Glaxo Smith Kline, GSK), or a DTwP vaccine (CLL) (Gustafsson 1996).

Trial II included infants born from June 1993 to May-June 1994 and vaccinated with either a 3, 5, and 12-month schedule (72,698 infants) or a 2, 4, and 6-month schedule (10,194 infants) using a five-component vaccine (CLL), a two-component vaccine (GSK), a three-component vaccine (Chiron), or a DTwP vaccine (Evans) (Olin 1997) (Figure 2). Some of the children in Trials I and II (Gustafsson 1996, Olin 1997) were boosted in early childhood (almost all children vaccinated with DTwP in Trial I and almost all children vaccinated with DTPa2 in the two trials).

1.1.2 Gothenburg mass vaccination project

During the years 1996–1999, the Gothenburg mass vaccination project offered free catch-up vaccination with three doses to all children born in the Gothenburg area and surrounding communities (an area covering 11.4% of Swedish new-borns)(Taranger 2001) (Figure 2). There was no free catch-up offered in the rest of the country, but monovalent aP vaccine was available until the year 2000, and many children in the rest of the country were vaccinated at their parents' expense during these years. In the Gothenburg study area, infants were offered vaccination with a vaccine containing diphtheria, tetanus, and pertussis toxoids (DTP-toxoids) at 3, 5, and 12 months of age. Children aged 1 year were offered three doses of pertussis toxoid (PT) containing vaccine alone. Finally, for children who had been incompletely vaccinated with wP vaccine or with other aP vaccines, the vaccination series was completed with PT. Each 0.5 mL dose of pertussis vaccine contained 40 μg of PT inactivated by hydrogen peroxide. Each 0.5 mL dose of DTP-toxoids vaccine contained 40 μg of PT. The PT vaccine was produced by North American Vaccine, and the diphtheria and tetanus toxoids were produced by Statens Seruminstitut. The results and experiences from the follow-up in the Gothenburg study area have been published in scientific journals (Trollfors 1995, Taranger 1997, Taranger 2001) and as reports published on the Public Health Agency of Sweden (PHAS) website (reference in report list: 14-year report, Pertussis Surveillance, Pertussis in the Gothenburg study area).

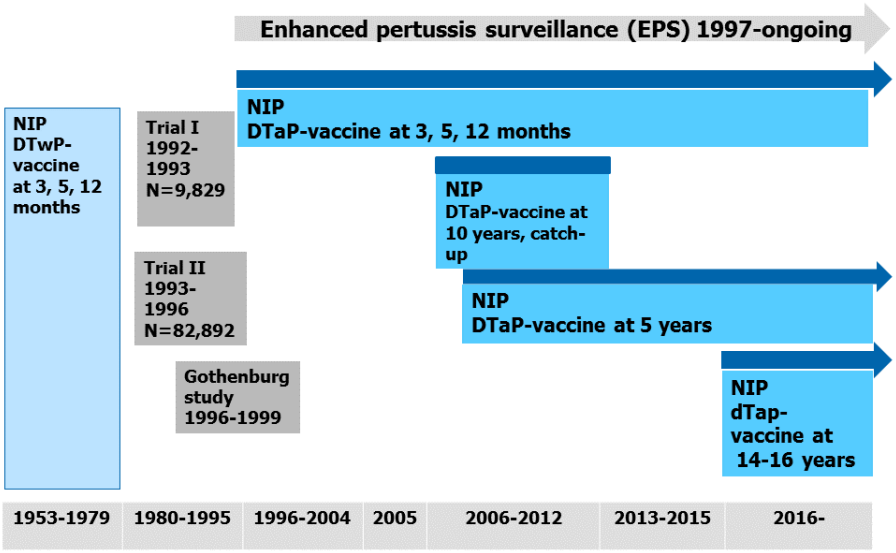

Figure 2: Visual description of different studies and the NIP from 1953 onwards. During the time period from 1953 to 1979, wP vaccines were used in the NIP. Between the years 1979 and 1996, there was no vaccination given against pertussis in the NIP with the exception of individuals participating in two larger studies (Trial I (1992–1993), Trial II (1993–1996)). In 1996, pertussis vaccination (aP) was reintroduced in the NIP and given at 3 and 5 months with an early booster given at 12 months of age followed by a booster at 10 years of age. The later booster dose given at 10 years of age was changed to 5 years of age in 2007. An additional booster was introduced to teenagers (15–16 years of age) in the NIP in 2016. The enhanced pertussis surveillance study started in 1997 and is still on-going today. During the years 1996–1999, the Gothenburg mass vaccination project described above was on-going

1.2 Vaccination registration and vaccine coverage in Sweden

For many years, Sweden has had a well established and internationally renowned Child Health Care (CHC) system covering >99% of all children in the country from new-borns to 6 years of age, and for decades Sweden has had a 97–99% coverage of the DTaP vaccinations recommended in infancy by the NIP. Health care is provided by the School Health Care (SHC) system for children from 6 to 18 years of age. CHC and SHC nurses vaccinate children and register the vaccinations in individual medical

record and report the vaccine doses given within the NIP to the regional health authorities. Vaccination coverage is then estimated at a national level by the PHAS. Since Jan 2013, it has been mandatory to report all vaccinations given within the NIP to the national immunisation register. A mandatory reporting directly to the national vaccination register at PHAS will in coming years replace the current reporting system from the regions.

In the pertussis vaccine studies (Trial I and II) performed in the 1990s, a large proportion of Swedish children were enrolled. The largest study, Trial II, comprised 46.9% of the infants born in 1993 and 42.0% of those born in 1994. Infants born during the latter part of 1995 were vaccinated against pertussis in most parts of the country, with the start of vaccination taking place in January 1996 when aP vaccines were introduced into the NIP. At the age of 2 years, the overall three-dose coverage for the 1995 cohort was 59.3% (Table 1).

With the introduction of a DTaP vaccine in 1996, the three-dose coverage for pertussis vaccination at 3, 5, and 12 months of age rapidly reached 98.7%. The national vaccination coverage has remained at a high and stable level over subsequent years during which a switch was also made to a combination aP vaccines (Folkhälsomyndigheten, Årsrapport 2018) (Table 1). Free catch-up vaccinations to more than 65,000 children born in the 1990s were offered in the Gothenburg study area from 1996 to 1999 (Taranger 2001). Likewise, children in the rest of the country were also catch-up vaccination to some degree.

The vaccination coverage for 5-year-old children according to the vaccination register is estimated to be above 90% for the fourth dose of aP-containing vaccine (DTaP-Polio). Vaccination of 14–16-year-old teenagers with the fifth booster dose (dTap) started in August 2016, and so far the coverage is about 90% according to the vaccination register. The lower coverage compared to infant vaccination may partly be due to underreporting.

Year of birth	aP coverage with 3 doses (%)
1993	46.9
1994	42.0
1995	59.3
1996	98.7
1997	98.6
1998	98.7
1999	98.5
2000	98.3
2001	98.4
2002	98.6
2003	98.7
2004	98.6
2005	98.3
2006	98.4
2007	98.0
2008	98.3
2009	98.3
2010	98.4
2011	98.4
2012	98.2
2013	98.1
2014	97.5
2015	97.3
2016	97.4
2017	97.5

Table 1: Vaccination coverage with the three-dose vaccination with aP-containing vaccines for children born from 1993 to 2017. The children should have had their second birthday before the evaluation of coverage in January each year.

1.3 Pertussis vaccines included in NIP

At the beginning of 1996 only one DTaP vaccine (Infanrix®, (GSK)) was used in most parts of Sweden except in the Gothenburg area.

Starting in Sep 1998 and continuing through 1999, some counties in Sweden switched to the first licensed combined pentavalent DTaP-Hib-IPV vaccine (Pentavac®, Sanofi Pasteur MSD). From the year 2000, another pentavalent combination vaccine (Infanrix-Polio+Hib®, GSK) was

licensed and came into use. During 2000–2001, the use of the pentavalent combination vaccines (DTaP-Hib-polio) for all infants was recommended in the NIP.

In the Gothenburg study area, a one-component DTaP vaccine containing 40 μg of PT (Di-Te-Kik®, Statens Seruminstitut, Denmark) was used. In the year 2000 there was a switch to Pentavac®, in this area.

Due to county-based procurements of vaccines, the use of the aP-containing vaccines within the NIP varied over time and county, ranging from the initial use of trivalent vaccines (DTaP) containing one or three pertussis components to the later use of five- or six-valent vaccines containing two or three pertussis components.

In Sweden, vaccination against hepatitis B is recommended for infants and children at risk, but it is not included in the NIP for all children. However, all of the counties have for some years offered hepatitis B vaccines to all children. According to information from GSK Sweden, based on the number of sold doses of Infanrix®hexa related to annual birth cohorts (data from Statistics Sweden, http://www.scb.se), 67% of all children were estimated to have received Infanrix®hexa in Jan 2014 with corresponding rates of 78% and 90% in January 2015 and December 2016, respectively. During 2018 it was estimated that 86% of the infants received Infanrix®hexa and 14% received Hexyon®, the corresponding numbers for 2017 were 80% and 20%. In 2019, according to data from the Swedish vaccination register 70% of the infants were vaccinated with Infanrix® and 30% were vaccinated with Hexyon®.

Children born in 1995–2001 have received a DTaP vaccine (Infanrix®) as a booster at 10 years of age. The two vaccines available for booster at 5–6 years of age Infanrix®polio, and Tetravac®. The vaccine current available for the fifth booster dose with a reduced dose vaccine against diphtheria, at 14-16-years of age is diTekiBooster®.

1.4 The enhanced pertussis surveillance study in Sweden

The main aims of the enhanced pertussis surveillance (EPS) study in Sweden are to evaluate the impact of pertussis vaccinations in the NIP on the epidemiology of the disease and its severity, to follow the long-term protection after vaccinations with aP-containing combination vaccines, and to document potential effects of changes made in the NIP. The results and experiences from the annual enhanced follow-up in Sweden have been published in scientific reports by PHAS (formerly the Swedish Institute for Communicable Disease Control (SMI)) and in reviewed papers, among which the following are the most important (Olin 1999, 2003, Trollfors 2001, Gustafsson 2006, Carlsson 2009, Nilsson 2012, and Carlsson 2015). The results from pertussis serology and other laboratory studies have been published in several papers (Advani 2004, 2009, Hallander 2005, Elomaa 2007, Hallander Andersson 2009, Hallander Gustafsson 2009, and Zeddeman 2014) and in pertussis serology reports with analyses from 1997 and 2007 (reports from the SMI).

The group with the highest incidence of pertussis -infants -is described in separate sections in the current report. The severity of the pertussis disease in infants is described with regard to vaccination status, hospitalisation, complications, spasmodic cough, and duration of cough.

1.5 Data sources and Methods

1.5.1 SmiNet - mandatory reporting of pertussis cases in Sweden

From 1980 to 1996, laboratory-confirmed pertussis was voluntarily reported from all bacteriological laboratories. There has also been a long-standing Swedish tradition of reporting pertussis by county medical officers since the early 20th century. In Sweden, pertussis became a notifiable disease in 1996. Pertussis is included as a notifiable disease in the Communicable Disease Act, and all cases of pertussis, including clinically suspected and/or laboratory-confirmed by culture, polymerase chain reaction (PCR), or serology, should be reported. From 2008 onward, positive serology has been included. Clinicians and laboratories report cases by notifications both to the PHAS and to the County Medical Officer of Communicable Disease Prevention and Control. The notifications are immediately available at both the national and regional level through a computer-linked reporting system, SmiNet, based on disease and personal identifiers (see Rolfhamre 2006) for a description of SmiNet) (Figure 3).

Contact tracing is also mandatory for pertussis, and the treating physician is responsible for taking reasonable measures for contact tracing of pertussis focusing on protecting infants. Attendance in school or day care

is not restricted for pertussis cases in general.

1.5.2 Collection of data and inclusion criteria in the enhanced surveillance study of pertussis

Cases aged 0–20 years are included in the EPS based on clinical reports and culture-positive and/or PCR-positive reports of pertussis, and from 2008 also including serology-positive cases, all retrieved from the SmiNet database. In the EPS, additional information is then collected through structured telephone interviews with the parents of children diagnosed with pertussis. Complementary information is also collected from medical records (Figure 3).

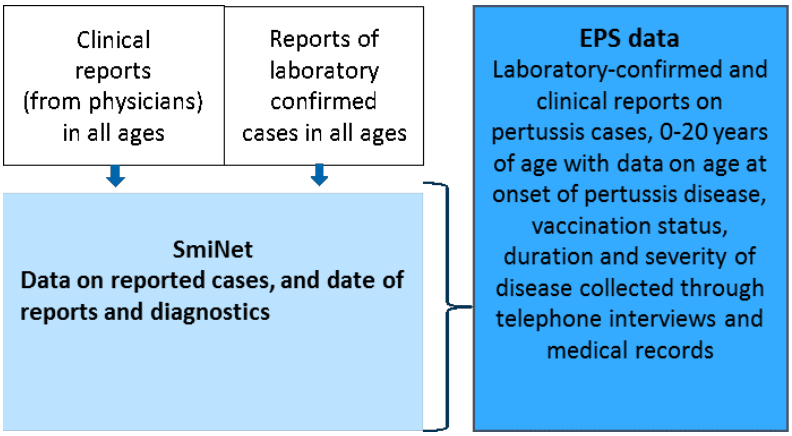

Figure 3: Flow chart of the reporting of pertussis cases to SmiNet and further to the EPS.

Inclusion criteria in the EPS are as follows:

1. Being born Jan 1, 1996, or later or being included in the pertussis vaccine trial cohorts and followed-up until 20 years of age.
2. Start of pertussis disease (episode start): a) outside the Gothenburg study area and having a pertussis episode starting Oct 1, 1997, or later or b) within the Gothenburg study area and having a pertussis episode starting Jan 1, 2003, or later.

As mentioned above, the Gothenburg study area used different vaccines until 2003 compared to the NIP. Hence, children from the Gothenburg study area were excluded from the EPS from Oct 1, 1997, to 2003. However, vaccine data were collected retrospectively for children in the Gothenburg area during this time period. Since Jan 1, 2003, and onwards the children from the Gothenburg study have been included in the EPS (Table 2).

Time period	Length of evaluation	Type of data	Area
Oct 1, 1997, until Dec, 31 2019	22 years	Prospective clinical and vaccine data	Sweden excluding Gothenburg study area
Oct 1, 1997, until Dec 31, 2002	5 years	Retrospective vaccine data, no clinical data	Gothenburg study area
Jan 1, 2003, until Dec 31 2019	17 years	Prospective clinical and vaccine data	Gothenburg study area

Table 2: Description of areas, dates, and length of evaluation for different studies carried out in Sweden between Oct 1997 and Dec 2019.

A total of 309 pertussis cases 0-20 years of age with onset of pertussis during 2019 were included in the EPS (309 laboratory-confirmed cases and 10 clinical report). Out of these 309 pertussis cases, 54 were infants and all infant cases except two were laboratory confirmed.

For ease of interpretation of the data, the pertussis vaccine trial cohorts (Trial I and Trial II) have been excluded from analyses in the current report. Individuals included in Trial I and Trial II were born in 1992 and 1993–1994, respectively, and thus did not fulfil the inclusion criterion of the EPS that only includes pertussis cases born Jan 1, 1996, or later (0–20 years of age).

The differences between the Gothenburg study area and the rest of Sweden have levelled out, and therefore it is no longer necessary to present data separately as in previous reports.

All data in this report encompass information obtained in two ways: A) within the regular Swedish surveillance of communicable diseases and B) within the EPS.

A Both clinically suspected cases and laboratory-confirmed cases are reported to SmiNet. However, only laboratory-confirmed cases are presented in this report and are referred to as "SmiNet data". A confirmed case is a case with a positive culture, PCR, or serology result (seroconversion or significant increase in IgG against PT). There is limited or no information in the reports to SmiNet on vaccination status or clinical details, including case contacts, but age-specific incidence rates can be calculated based on the age of the patient on the date of notification. **In this report, the annual numbers of laboratory-confirmed cases notified to SmiNet are presented based on the date of notification of the case.**

B **Within the EPS:** Every clinically reported or laboratory-confirmed pertussis case among those 0–20 years of age, born in 1996 or later, is identified in SmiNet for detailed follow-up, except for those occurring from Oct 1, 1997, to Dec 31, 2002, in the Gothenburg study area where a local surveillance project was in place.

All identified reports are matched against the population registry for parental contact details and to check that there has been no death notification. After approved consent from the parent/caregiver, a research nurse performs structured telephone interviews with one of the parents of each case using a standardised questionnaire. The clinical questions include the type and duration of cough, the presence of apnoea and other complications, the number and length of hospital admissions, the timing of antibiotic treatment if given, and the vaccination dates. Information on individual vaccination history allows for detailed evaluation of vaccinated and non-vaccinated children. If medical records are needed for complementary medical information, the parents are contacted to provide additional consent. The families of deceased children are not contacted. **With access to clinical information, data from the EPS study are based on the age at onset of symptoms**, which is important when analysing the age-specific severity of the disease in infants.

Vaccination history: The detailed vaccination histories of children born since 1996 were obtained from the medical records of the SHC centres by a telephone call to the nurse attending the individual child.

Severity of disease: Parameters reflecting the severity of disease included the duration of spasmodic cough and the total duration of cough and hospital admissions. Data on respiratory complications, neurological complications, dehydration with >5% of weight loss, or other serious complications during the pertussis episode were collected and registered in the database.

Antibiotic treatment: Information on antibiotic use was collected in pertussis cases among those 0–20 years of age born from Jan 1, 1996, with episodes starting between Jan 1, 2003, and Dec 31, 2019. Data on the time between the onset of an episode and the start of antibiotic treatment were collected along with data on the length of treatment and the type of antibiotics.

Source of transmission - case contact study: This has been included in the EPS study since 2009. A structured questionnaire was added to the telephone interview in the EPS with questions concerning the source of transmission. This information was added to the pertussis cases in infants younger than 1 year. All parents/caregivers were asked if someone who had been coughing for more than a week had been in close contact with the infant with confirmed pertussis disease in the month prior to the start of the episode in the infant. Questions were also asked whether it was none, one, two, or up to three contacts who had had a cough for more than a week.

1.6 Diagnostics

1.6.1 Diagnostic methods

The diagnostic methods used have changed over time across the different age groups. Until 2003, confirmation of *Bordetella pertussis* by culture was the dominant laboratory method in all age groups. In 1997 the proportion of PCR-confirmed cases was less than 5%, but in 2003 around 20% of all laboratory reports were based on PCR. In children, PCR is now the most common method for diagnosing pertussis. Since 2006, serology and PCR have been the most common methods used for diagnosing pertussis also in patients older than 10 years of age. Nowadays fewer than 5% of the pertussis reports are based on culture (Figures 4 and 5).

Table 3 shows the diagnostic methods for cases 0–20 years of age included in the EPS. PCR was the most common diagnostic method used in 2019 (Table 3).

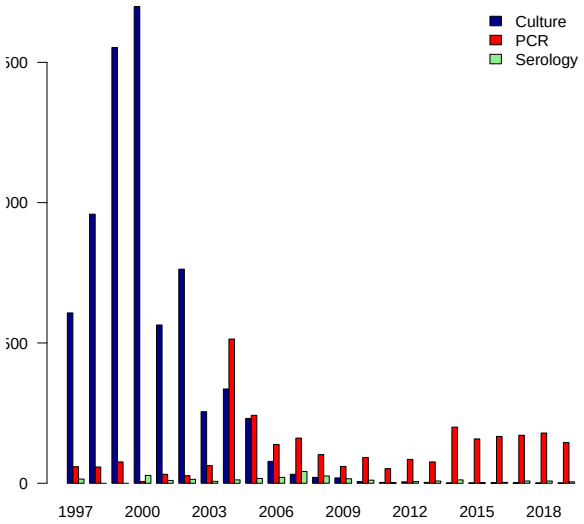

Figure 4: Laboratory methods used for verification of cases in children aged 0–10 years between 1997 and 2019. Data are based on laboratory-confirmed cases reported to SmiNet.

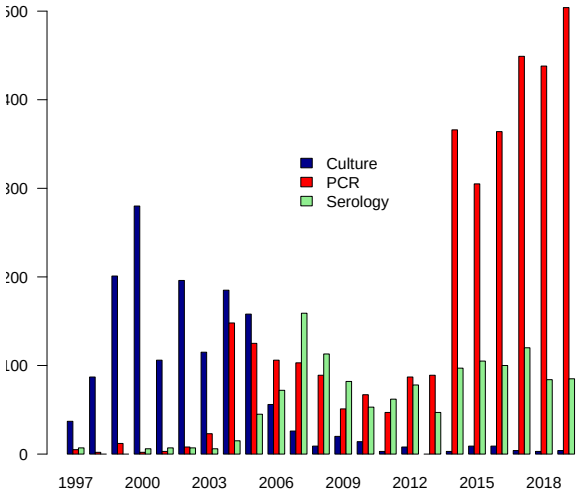

Figure 5: Laboratory methods used for verification of cases in children and adults aged 11 years or older between 1997 and 2019. Data are based on laboratory-confirmed cases reported to SmiNet.

Age (years)	Method	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19
0-1	Culture	41	69	146	263	121	229	94	112	82	33	14	12	12	4	2	1	2	1	0	1	1	1	0
	PCR	10	19	34	1	7	2	24	186	69	56	68	45	39	46	36	53	42	135	94	93	89	77	70
	Serology	0	0	0	1	1	0	0	0	1	4	12	6	2	1	1	2	0	4	0	0	2	1	0
2-6	Culture	456	661	795	653	210	224	61	69	43	23	10	5	6	1	0	2	1	0	1	1	1	0	0
	PCR	43	27	24	3	8	10	16	181	63	35	41	14	11	26	12	22	24	44	42	44	43	65	46
	Serology	12	0	0	5	1	3	0	3	7	2	8	9	6	2	1	2	6	4	0	2	2	3	4
7-12	Culture	121	255	671	873	282	383	144	236	163	38	10	4	1	1	2	3	0	0	1	0	1	0	1
	PCR	7	12	22	2	18	18	35	182	149	67	65	45	11	22	5	10	15	37	41	60	68	65	61
	Serology	3	0	0	22	10	16	9	13	17	24	30	15	11	13	1	2	2	8	5	3	5	7	3
13-16	Culture	7	17	54	56	25	44	38	64	46	19	8	4	5	4	0	2	0	0	3	0	0	0	0
	PCR	1	0	1	1	0	2	4	38	38	28	40	33	22	10	10	12	11	44	29	45	57	50	48
	Serology	0	0	0	2	0	0	1	4	16	12	29	21	22	6	7	5	3	7	6	11	15	16	8
16-20	Culture	2	5	12	24	3	10	5	4	9	2	3	1	5	2	0	1	0	1	2	1	0	0	0
	PCR	0	0	0	0	0	0	0	10	8	11	7	11	9	12	11	11	13	43	34	36	34	23	59
	Serology	0	0	0	1	1	1	1	0	2	6	13	8	11	6	11	11	5	9	9	6	7	6	9

Table 3: Laboratory methods used for verification of cases in children 0-20 years of age (number of tests by method).

1.6.2 Case definition in the enhanced pertussis surveillance study

A case in the EPS is defined as having a laboratory-confirmed or clinically reported pertussis diagnosis. Only positive samples that are taken more than 6 months after a previous positive sample are considered to be a new episode of pertussis. By this definition, every pertussis case in persons 0–20 years of age with laboratory-confirmed pertussis is defined as a case and can potentially be included in the EPS study except for those occurring from Oct 1, 1997, to Dec 31, 2002, in the Gothenburg study area.

1.6.3 Sample size considerations and the calculation of incidences

Formal a priori sample size calculations are not meaningful in a post-marketing follow-up of the NIP or the observational studies included in this report. Age-specific incidence rates of pertussis cases per 100,000 person years are based on the number of laboratory-confirmed reported pertussis cases during the study period from Oct 1, 1997, to Dec 31, 2019, reported to SmiNet. In addition, annual overall incidences and age-specific incidences of pertussis in Sweden are based on the number of notified culture-confirmed or PCR-confirmed cases of pertussis, and from 2008 also serology-confirmed cases, in the whole population and in all age groups. Furthermore, annual incidences are based on age at the notification of cases and on the corresponding mid-year populations derived from the mean of population numbers in two consecutive years divided by two (e.g. number of years). http://www.scb.se.

To simplify the calculations of person time of follow-up, we assumed an equal number of new-born infants each month of a calendar year i.e. 7,212 children per month during 1996 and 6,842 children per month during 1997. In addition, it was 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 3, 5, and 12 months of age. Only person time since Oct 1, 1997, was included because 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 3 months of age (before dose 1).
- Person-months between 3 and 5 months of age (between dose 1 and 2).
- Person-months between 5 and 12 months of age (between dose 2 and 3).

- Person-months after 12 months of age (after dose 3) until Dec 31, 2019.

2 Results

2.1 Number and incidence of reported pertussis cases to SmiNet in all ages

A total of 782 cases were reported to SmiNet during 2019, including both laboratory-confirmed and clinically suspected cases (reported by physicians) (Folkhälsomyndigheten, Epidemiologisk årsrapport 2019).

In the present report the data referred to as SmiNet data presented in Tables 4 and 5 are laboratory-confirmed cases reported during each year (*labsvarsdatum*). According to this definition, 749 laboratory-confirmed cases of pertussis were reported to SmiNet during 2019 (Table 4). After five years (2009–2013) with low incidence of reported cases of pertussis (2.5/100,000 person years on average), a significant three-fold increase in incidence was observed in the general population (7.1/100,000 person years) in 2014 as compared to 2013 (2.3/100,000 person years). This increase was partly sustained during both 2015 (5.9/100,000 person years) and 2016 (6.5/100,000 person years) and with a slight but stable increase in incidence for 2017 (7.5/100,000 person years), 2018 (7.0/100,000 person years) and 2019 (7.3/100,000 person years) (Table 5, Figure 6).

In infants 60 laboratory-confirmed cases were reported, which corresponds to an incidence of 51.7/100,000 person years which is considerably higher than in older age groups (Tables 4 and 5). In infants, incidences have varied between 104 and 284/100,000 person years during the years 1997–2006. In 2006, the age-specific incidence in infancy was below 100/100,000 person years for the first time since 1997. In 2007, the incidence in infants was 85/100,000 person years, and from 2008 to 2013 the incidence in infants was stable at below 50/100,000 person years. In 2014, the incidence in infants increased by three-fold (105.3/100,000 person years) compared to 2013 (34.3/100,000 person years), and the higher incidence in infants has remained, although at a slightly lower level, during 2015 (73.4/100,000 person years), 2016 (74.1/100,000), 2017 (69.6/100,000 person years), 2018 (58.3/100,000 person years) and 2019 (51.7/100,000 person years). There was no significant difference in infant incidence between 2018 and 2019 ($p = 0.08$), but when comparing 2015, 2016, 2017, 2018 and 2019 to 2014, respectively, the decrease in incidence was significant (2014 vs. 2015, $p = 0.004$; 2014 vs. 2016, $p = 0.002$; 2014 vs. 2017 $p=0.003$; 2014 vs. 2018, $p<0.001$; 2014 vs. 2019, $p<0.001$).

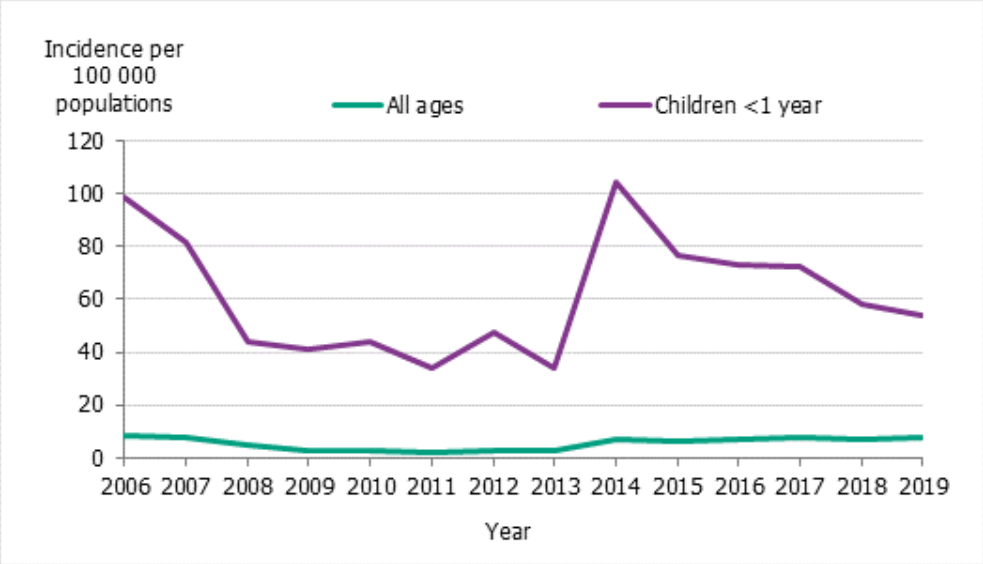

Figure 6: Incidence of pertussis in infants < 12 months of age (purple line) and all ages (including infants) (green line) between 2006 and 2019. Data are based on laboratory-confirmed cases reported to SmiNet.

Age	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
0	165	219	115	217	112	285	154	98	91	47	43	49	37	51	39	121	85	87	82	68	60
1	34	76	33	42	19	53	27	15	18	17	10	2	2	5	5	19	9	7	10	11	10
2	32	36	37	53	19	50	14	13	9	7	1	6	3	4	9	13	8	9	11	12	9
3	96	52	29	37	8	31	23	8	7	4	7	8	2	4	7	12	11	11	8	13	15
4	294	155	28	46	20	50	20	10	10	7	3	5	4	5	5	5	9	9	14	22	9
5	188	281	47	51	14	67	26	21	10	2	8	6	1	7	5	10	9	10	4	14	8
6	386	254	122	86	25	77	51	22	25	8	4	5	3	6	5	8	6	8	9	7	9
7	313	345	98	147	31	83	55	26	27	10	3	7	0	6	3	3	6	8	9	4	5
8	257	289	105	92	45	105	50	30	19	12	6	6	0	2	3	7	8	8	9	10	9
9	120	208	79	99	34	87	74	24	28	24	5	9	3	5	2	8	7	10	7	18	6
10	83	131	43	74	45	86	103	23	13	12	5	7	2	1	4	7	3	5	18	9	11
11	39	62	32	58	43	78	73	28	10	1	3	3	2	1	3	13	13	18	17	12	15
12	41	41	24	36	28	64	64	28	15	5	1	4	1	0	2	7	10	14	14	20	19
13	28	30	14	24	23	51	46	32	22	13	5	1	0	2	1	12	5	17	42	28	24
14	22	21	9	17	13	44	28	21	25	19	11	2	2	1	0	7	11	15	13	21	16
15	7	11	6	13	9	12	25	14	19	13	23	10	6	7	7	11	11	10	9	10	11
16	7	11	2	10	10	16	20	14	14	16	16	8	9	9	6	21	11	14	9	7	5
17	7	14	1	6	3	9	9	4	13	12	12	10	13	7	3	17	15	15	19	8	8
18	4	7	0	6	1	9	6	9	7	6	9	4	6	7	7	10	14	7	6	8	14
19	2	5	2	1	3	2	9	7	4	2	4	3	1	5	5	13	9	12	9	6	29
20-24	7	14	3	13	8	13	12	10	12	13	12	11	15	18	13	50	34	42	36	39	59
25-29	16	14	7	8	11	19	16	16	14	14	6	11	5	11	12	40	38	40	45	43	42
30-34	15	28	11	12	6	24	21	11	8	13	9	11	6	21	11	36	33	37	43	45	40
35-39	19	29	6	20	10	33	30	25	18	19	12	15	5	10	16	47	40	40	47	39	36
40-44	8	14	8	11	8	18	33	15	29	19	7	16	5	16	12	45	40	48	63	50	57
45-49	8	7	1	10	2	7	20	12	18	12	5	8	4	9	7	23	39	36	56	67	74
50-54	2	4	4	9	3	8	12	13	11	8	6	5	6	9	5	26	23	24	37	32	42
55-59	6	8	5	7	7	7	5	17	14	6	7	1	9	7	4	21	14	17	25	21	36
60-64	3	9	2	7	2	4	16	17	14	10	6	8	5	7	5	16	14	14	13	17	18
65+	14	14	2	10	14	15	26	24	38	22	11	11	12	26	17	60	47	55	71	54	53
Sum	2223	2389	875	1222	576	1407	1068	607	562	373	260	252	169	269	223	688	582	647	755	715	749

Table 4: Number of laboratory-reported cases of pertussis in defined age-groups reported to SmiNet between 1999 and Dec 31, 2019.

Age	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
0	185.8	244.6	126.1	231.2	114.7	284.5	152.0	94.3	85.0	43.2	38.8	43.0	32.5	45.2	34.3	105.3	73.4	74.1	69.6	58.3	51.7
1	37.7	84.9	36.5	45.6	20.0	53.7	26.7	14.6	17.1	15.7	9.1	1.8	1.7	4.3	4.4	16.5	7.7	5.9	8.3	9.1	8.4
2	34.3	39.7	41.1	58.3	20.5	52.4	14.1	12.8	8.7	6.6	0.9	5.4	2.7	3.4	7.7	11.3	6.9	7.6	9.1	9.8	7.4
3	96.4	55.5	31.8	40.9	8.7	33.3	24.0	8.0	6.8	3.8	6.5	7.3	1.8	3.5	6.0	10.2	9.4	9.3	6.6	10.7	12.2
4	272.1	155.1	29.8	50.2	22.0	54.4	21.4	10.4	9.9	6.8	2.9	4.6	3.6	4.5	4.4	4.2	7.6	7.6	11.6	18.0	7.3
5	163.4	259.3	46.8	54.0	15.2	73.3	28.2	22.4	10.3	2.0	7.7	5.7	0.9	6.3	4.4	8.6	7.5	8.3	3.3	11.5	6.5
6	320.0	220.3	112.2	85.3	26.3	83.3	55.6	23.7	26.4	8.2	3.9	4.8	2.8	5.5	4.5	7.0	5.1	6.6	7.3	5.7	7.3
7	250.5	285.3	84.7	134.7	30.6	87.1	59.3	28.2	28.9	10.5	3.0	6.8	0.0	5.6	2.7	2.6	5.2	6.7	7.3	3.2	4.0
8	202.6	230.8	86.6	79.2	41.1	103.4	52.3	32.2	20.4	12.7	6.2	6.1	0.0	1.9	2.8	6.3	7.0	6.8	7.5	8.0	7.2
9	96.8	163.6	62.9	81.3	29.2	79.1	72.6	25.0	29.8	25.6	5.3	9.3	3.0	4.8	1.9	7.3	6.2	8.6	5.9	14.7	4.8
10	69.8	105.4	33.7	58.7	36.8	73.5	93.4	22.5	13.4	12.7	5.3	7.3	2.0	1.0	3.8	6.5	2.7	4.4	15.2	7.4	8.9
11	34.2	52.0	25.7	45.3	34.0	63.7	62.2	25.2	9.7	1.0	3.1	3.2	2.1	1.0	3.0	12.2	11.8	16.0	14.7	10.0	12.3
12	37.4	35.9	20.0	28.8	21.8	50.4	52.1	23.8	13.4	4.8	1.0	4.2	1.0	0.0	2.0	6.8	9.3	12.6	12.3	17.0	15.7
13	26.2	27.3	12.2	20.0	18.3	39.6	36.2	25.9	18.6	11.6	4.8	1.0	0.0	2.1	1.0	11.9	4.8	15.6	37.2	24.3	20.2
14	21.3	19.6	8.2	14.7	10.8	34.9	21.7	16.4	20.1	15.9	9.7	1.9	2.0	1.0	0.0	7.0	10.8	14.2	11.7	18.3	13.7
15	7.0	10.6	5.6	11.7	7.8	9.9	19.8	10.8	14.8	10.4	19.1	8.8	5.6	6.9	7.1	11.1	10.9	9.6	8.4	8.9	9.5
16	7.0	11.0	1.9	9.2	9.0	13.8	16.5	11.0	10.7	12.4	12.7	6.6	7.8	8.3	5.8	20.8	10.9	13.5	8.4	6.4	4.4
17	7.0	14.0	1.0	5.7	2.8	8.1	7.7	3.3	10.2	9.1	9.2	7.9	10.6	6.0	2.7	16.3	14.5	14.4	17.8	7.3	7.2
18	3.9	7.0	0.0	5.9	1.0	8.2	5.3	7.7	5.7	4.6	6.8	3.0	4.7	5.7	5.9	9.0	13.1	6.6	5.6	7.3	12.6
19	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	4.0	10.9	8.0	11.1	8.3	5.4	25.7
20-24	1.3	2.7	0.6	2.5	1.5	2.5	2.3	1.9	2.2	2.3	2.0	1.8	2.3	2.7	1.9	7.4	5.1	6.5	5.7	6.4	10.0
25-29	2.7	2.4	1.2	1.4	2.0	3.4	2.9	2.9	2.5	2.5	1.1	1.9	0.8	1.8	1.9	6.2	5.7	5.7	6.2	5.8	5.7
30-34	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	1.8	6.0	5.4	5.9	6.6	6.7	5.7
35-39	3.2	4.7	0.9	3.0	1.5	5.0	4.7	3.9	2.9	3.0	1.9	2.4	0.8	1.6	2.6	7.7	6.6	6.5	7.5	6.1	5.6
40-44	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	1.9	7.0	6.1	7.4	9.8	7.8	9.0
45-49	1.3	1.2	0.2	1.7	0.3	1.2	3.4	2.1	3.1	2.0	0.8	1.3	0.6	1.3	1.0	3.4	5.9	5.4	8.5	10.2	11.2
50-54	0.3	0.6	0.6	1.5	0.5	1.4	2.1	2.2	1.9	1.4	1.0	0.9	1.0	1.5	0.8	4.3	3.6	3.7	5.5	4.7	6.2
55-59	1.1	1.4	0.8	1.1	1.1	1.1	0.8	2.7	2.3	1.0	1.2	0.2	1.6	1.2	0.7	3.6	2.4	2.9	4.3	3.5	5.9
60-64	0.7	2.1	0.4	1.5	0.4	0.8	2.9	2.9	2.3	1.6	1.0	1.3	0.8	1.2	0.9	2.8	2.5	2.5	2.3	3.0	3.2
65+	0.9	0.9	0.1	0.7	0.9	1.0	1.7	1.5	2.4	1.4	0.7	0.6	0.7	1.4	0.9	3.2	2.4	2.8	3.6	2.7	2.6
Total	25.1	26.9	9.8	13.7	6.4	15.6	11.8	6.7	6.1	4.0	2.8	2.7	1.8	2.8	2.3	7.1	5.9	6.5	7.5	7.0	7.3

Table 5: Incidence of laboratory-reported cases of pertussis in defined age-groups reported to SmiNet between 1999 and Dec 31, 2019.

2.1.1 Incidence and number of cases of pertussis distributed by age, time intervals, and vaccination program

In 2019, the distribution of the number of reported pertussis cases was lower in all age groups except for 15–19 years of age and older (Figure 7).

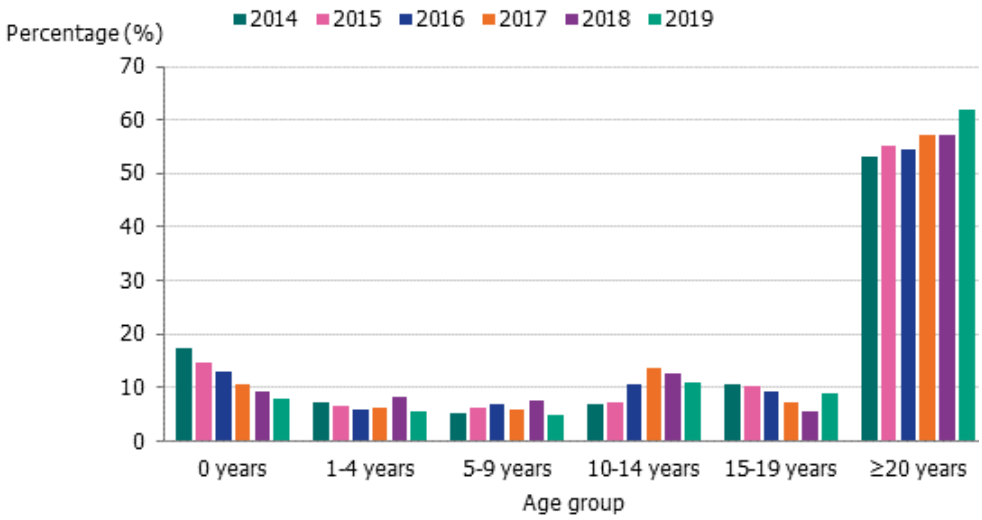

Figure 7: Percentage of cases in different age groups during 2014–2019. Data are based on laboratory-confirmed cases reported to SmiNet.

In figure 8 the incidences in age groups 1 year and older are illustrated. As in 2018 the incidence in 2019 was high in 10–14 year olds and in 40–49 year olds. In the age group 14–19 year olds, the incidence was not significantly higher compared to previous years (Figure 8).

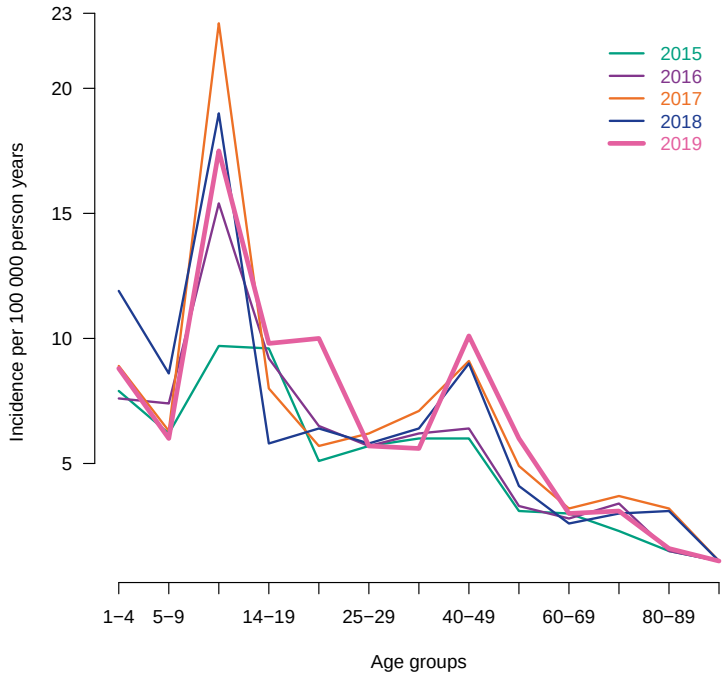

Figure 8: Incidence of pertussis in age groups above 12 months of age, by years 2014–2019. Data were based on laboratory-confirmed cases.

2.1.2 Incidence and cases on a monthly basis

Monthly assessment of the number of reported cases of pertussis is important in order to detect potential seasonal patterns as well as outbreaks. In the first 6 months of 2014, about 2–5 infants with pertussis were reported per month, whereas in the last 6 months of 2014 about 10–26 infants were reported with pertussis each month. The number of cases reported per month in all ages clearly indicated a peak in August 2014 to February 2015 (66–156 reported cases).

In the following months in 2015, between March and July, the number of reported cases per month in all age groups decreased (31–41 reported cases) until a peak in the number of reported cases per month (53–69 reported cases) was observed in August and October, although the peak was much smaller in comparison to the peak in 2014.

In 2018, the number of monthly reports peaked with 90 cases in August.

The increase was sustained from August to December 2018 (65–90 cases per month). In 2019 the peak of reported cases was also reported in August with 124 reported cases. During the fall of 2019 the number of reported cases on a monthly basis varied between 72 and 111 cases. A peak in monthly reports among infants was also seen during the fall of 2019 when 3-13 cases were reported per month in August to December. The peaks in recent years during the last 5 months of each year might indicate a tendency for a seasonal pattern from August to December. The pattern is easier to observe during years with high numbers of pertussis cases (Figure 9).

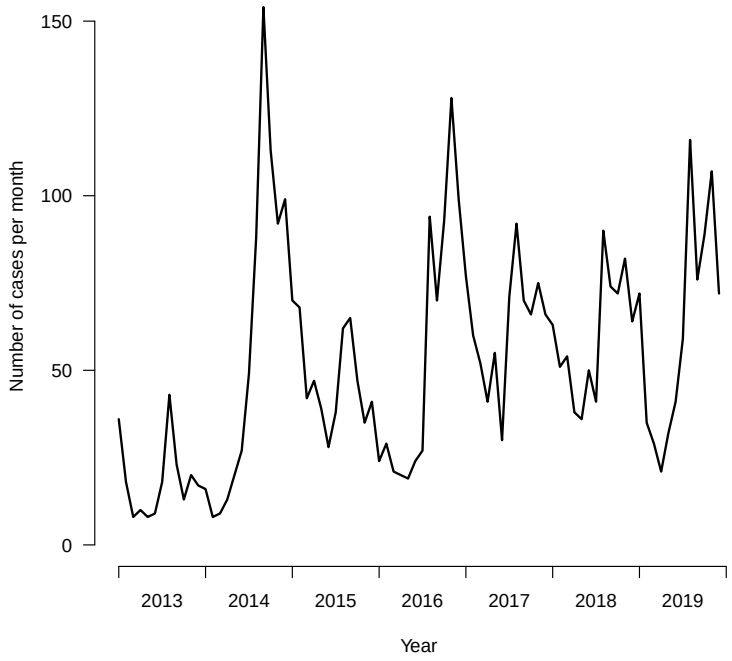

Figure 9: Number of laboratory-confirmed cases (all ages) on monthly records during 2013-2019)

2.1.3 Geographic differences in Sweden for laboratory-confirmed pertussis cases

At the regional level there are variations in the incidence both between counties and across time. Figure 10 illustrates the geographic variations in

reported pertussis cases (laboratory-confirmed pertussis cases) during the years 1997–2019.

During 2019, most of the pertussis cases (21%) were reported from the Stockholm region followed by the Scania region (Skåne) (17%) and the Västra Götaland region (14%). The Västernorrlands region had the highest incidence of 25/100,000 person years followed by the Jönköpings region and Västerbotten with 21/100,000 and 19/100,000 person years, respectively.

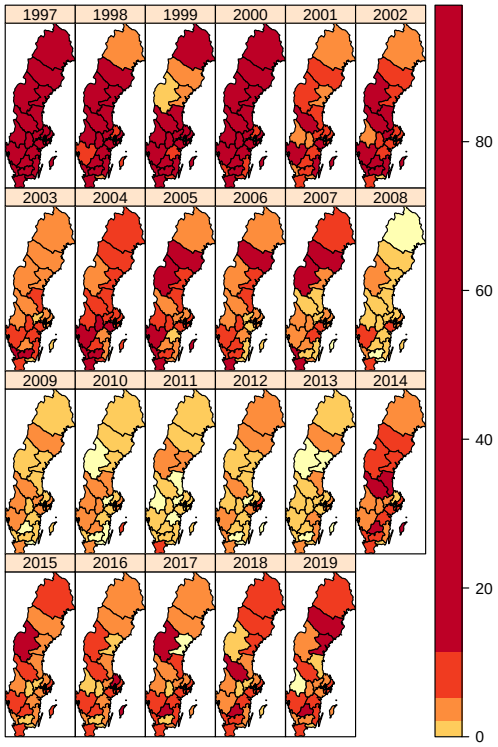

Figure 10: Incidence of reported pertussis cases (laboratory reports) in different Swedish counties from 1997-2019 with episodes starting between Oct 1, 1997 and Dec 31, 2019, reported to SmiNet. Colour changes indicate the 25%, 50%, and 75% quartiles. Source: SmiNet.

2.1.4 Incidence of pertussis cases reported to SmiNet in defined age-groups before and after the introduction of DTaP vaccination

The overall annual incidence of pertussis during the period when no pertussis vaccine was included in the NIP reached more than 100/100,000 person years. Infant vaccination with aP vaccines was thus introduced in an endemic setting. Since the introduction of aP vaccination at 3, 5, and 12 months of age in 1996, there has been a dramatic decline in the overall pertussis incidence in the Swedish population. There was a rapid drop from 121/100,000 person years in 1995–1997 to an overall annual incidence of 10–27/100,000 person years in 1998–2001, with a further reduction to 6.7/100,000 person years and 2.3/100,000 person years in 2006 and 2013, respectively. These incidences are lower compared to when the Swedish wP vaccine was still effective during the late 1960s and early 1970s (9.4–12.2/100,000 person years). The decline in incidence after 1996 has been more rapid than when DTwP was introduced during the 1950s (Figure 11). One explanation might be that vaccination coverage in those days was only gradually rising over decades until reaching 90% among infants, whereas the coverage for DT in the 1990s quickly reached more than 98% and remained so after the reintroduction of pertussis vaccination by adding aP to the DT vaccine.

Peaks of pertussis occurred every third winter in the pre-vaccination period, including 1987–1988, 1990–1991 (continuing into 1992), and 1993–1994. After the introduction of DTaP vaccine, the pattern of cyclic peaks every third year changed, and there was a small peak at about 25/100,000 person years in the winter of 1999–2000 and thereafter additional minor peaks in 2002, 2004–2005, and 2012. After five years (2009–2013) with low incidence of reported cases of pertussis, a three-fold increase in incidence was observed in 2014. During the period 2015–2019, this increase was sustained in the total population but with a decreasing trend in infants (Figure 6, Table 5).

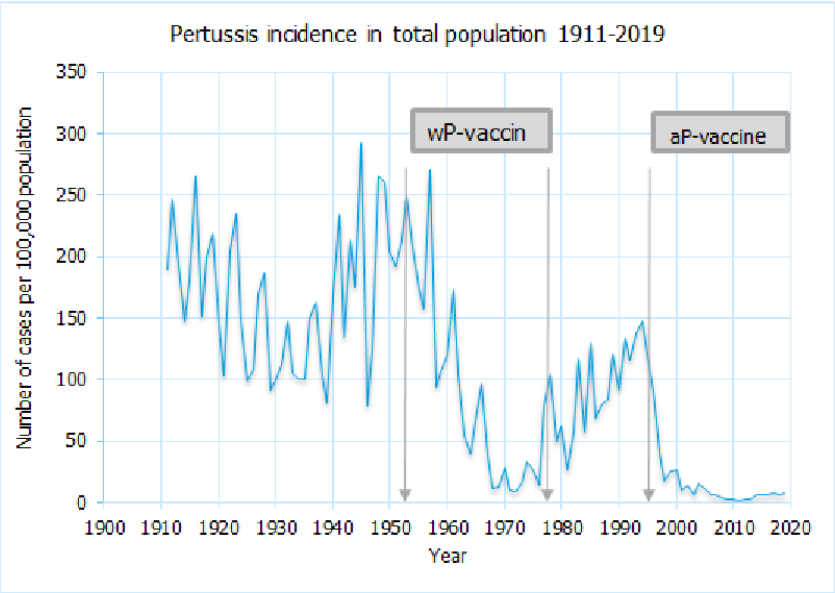

Figure 11: Overall pertussis incidence in Sweden. Case reports from general practitioners until the mid-1980s, from laboratory-reports since 1980, and according to the Communicable Disease Act from 1997.

DTaP vaccine was introduced in 1996 into the NIP, and in 2007 a preschool booster was introduced including a catch-up program for children born before 2002, who received a booster at close at 10 years of age (2007–2012). The incidences of pertussis for different age groups during 1997–2006 were much higher than during 2007–2019 for the corresponding age groups with the exception of the age group of 16–39 years (Figure 12).

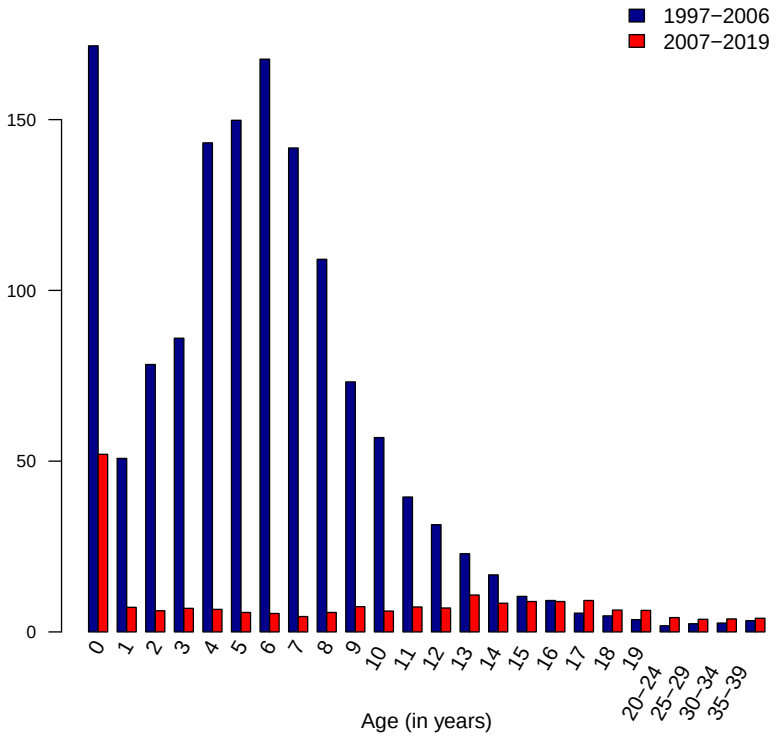

Figure 12: Mean incidence per 100,000 person years of pertussis in defined age groups during 1997–2006 (blue bars) and during 2007–2019 (red bars). Data are based on laboratory-confirmed cases reported to SmiNet according to the Communicable Disease Act.

The vaccinated birth cohorts born from 1996 had a lower age-specific incidence of laboratory-confirmed pertussis in preschool and early school age than the corresponding age groups prior to the implementation of aP vaccination in 1996. The age-specific incidence for preschool children (excluding 0–1 years) dropped from >1,000/100,000 person years to approximately 100/100,000 person years in 1998–2000, to 50/100,000 person years in 2001, to approximately 20/100,000 person years in 2003, and to fewer than 10/100,000 person years in 2009–2013. The incidences in 5–6-year-old children decreased after the introduction of the booster vaccine in 2007 (Table 5, Figure 12). The effect of the booster at 5–6 years of age introduced in 2007 was described in the EPS report for 2010 and was reported at the European Society for Paediatric Infectious Diseases (ESPID) meeting in 2010 (Rydevik, abstract 2010). The implementation of the booster at preschool age was shown to have a strong effect, and the risk of pertussis decreased in children who had received the booster.

From Jan 1, 2010, to Dec 31, 2015, the incidence of pertussis increased significantly among 15–17 year olds possibly due to waning immunity after the 10-year booster administered to children born from 1995. In 2016–2019, this increase levelled out, but whether this is a result from booster vaccination of 14–16 year olds that started during 2016 is too early to say.

2.2 Pertussis in fully vaccinated children 1–18 years of age

It is well known that immunity wanes after pertussis vaccination, but there is limited information available about pertussis in fully vaccinated children. Therefore, the reported cases in the EPS study were analysed to identify pertussis in fully vaccinated individuals 1–18 years of age between 2007 and 2019. The time period was set from 2007 because this corresponds to the year in which the booster dose in children aged 5–6 years was implemented. Fully vaccinated children were defined as children aged 1–5 years who had received at least three doses of aP vaccine and children aged 6–18 years who had received at least four doses of aP vaccine. Children with onset of pertussis less than 4 weeks after the last dose of pertussis vaccine were excluded.

During the period 2007–2019, a total of 1,890 pertussis cases were reported in children 1–18 years of age. Of these, 881 (47%) were fully vaccinated. The proportion of children who were fully vaccinated in the different age groups varied greatly, especially in the older age groups. In children aged 1–5 years, the proportion of fully vaccinated varied between 59% and 68%, with the highest proportion in the 3 year olds. In the 6–18 year olds, the proportion of fully vaccinated varied between 13% and 57%. The 17–18 year olds had the lowest proportion of fully vaccinated, 13%, but very few cases were reported in this age group. The proportion of fully vaccinated children decreased considerably when comparing the 5-year-old children (60%) to the 6-year-old children (28%) (Table 6). More detailed data on pertussis in fully vaccinated children are given in Table 7.

Age	Cases, n	Fully vaccinated, n	Fully vaccinated (per cent)	Median of disease duration (days)	Median of days with cough	Median of hospitalisation days
1	114	67	59	47	32	0
2	102	61	60	45	32	0
3	118	80	68	55.5	44	0
4	113	74	65	53	41	0
5	85	51	60	45	31	0
6	104	29	28	52	32	0
7-9	315	100	32	56	37.5	0
10-13	460	264	57	59	47	0
14-16	301	131	44	62.5	53	0
17-18	178	24	13	63.5	53.5	0
Total	1890	881	47	-	-	-

Table 6: Number of reported pertussis cases for children 1-18 years of age with data on vaccination status and median days of disease duration, paroxysmal cough and hospitalisation. Data are displayed for the period 2007–2019. Data collection was performed in the EPS. Fully vaccinated children were defined as children aged 1–5 years who had received at least three doses of aP vaccine and children aged 6–18 years who had received at least four doses of aP vaccine.

Year	Number of cases	Number of fully vaccinated cases	Number of female cases	Number of male cases	Number of cases by positive PCR	Number of cases by serology	Number of cases by isolation of Bordatella perussis in culture	Number of cases by other diagnostic method
2007	124	38	63	61	0	6	0	118
2008	163	48	84	79	82	58	17	8
2009	74	31	43	31	33	29	12	0
2010	72	16	41	31	49	16	4	3
2011	39	14	22	17	26	9	2	2
2012	91	31	50	41	62	19	7	3
2013	75	30	34	41	55	12	1	7
2014	208	133	101	107	170	26	2	12
2015	162	84	77	85	138	13	5	6
2016	211	114	113	98	183	20	4	7
2017	246	109	140	106	195	31	3	1
2018	221	113	125	96	176	21	1	0
2019	204	120	111	93	171	22	1	0
Total	1890	881	1004	886	1340	282	59	167

Table 7: Number of reported pertussis cases with data on vaccination status collected during the period 2007 to 2019. Data collection was performed in the EPS. Fully vaccinated children were defined as children aged between 1–5 years who had received at least three doses of aP vaccine and children aged between 6–18 years who had received at least four doses of aP vaccine.

2.3 Pertussis in infants

In 2019, infants had the highest incidence of all age groups. The data analysis and presentation in this report focuses on reported cases of pertussis among infants, markers of severity in relation to age at onset of disease, and individual vaccination histories.

There were 60 cases of laboratory-confirmed pertussis reported to SmiNet in infants (younger than 1 year of age) during 2019. As in previous years, the incidence of laboratory-confirmed pertussis was greatest among infants (51.7/100,000 person years), and this was a decrease in comparison with 2018 (58.3/100,000 person years), 2017 (69.6/100,000 person years), 2016 (74.1/100,000 person years) and 2015 (73.4/100,000 person years), and a significantly lower incidence compared to 2014 (105.3/100,000 person years) (Table 5, Figure 6).

The EPS study included a total 54 infants with laboratory-confirmed pertussis with onset of pertussis disease during 2019.

Between 2003 and 2019 in the youngest age groups, 0–3 and 3–5 months of age, the incidences were higher compared to the older age group 6–12 months of age (Figure 13). The increase of incidence seen in 2019 (Figure 13, Table 8) is due to technical issues assuming number of months. It is not possible to use all months for 2019 when assuming equal number of births each month over the year related to number of vaccines given. Infants born in October will not have the possibility to have had their second or third vaccination dose despite that they are born in 2019. There were also fewer births in Sweden 2019 which increase the incidence despite fewer cases.

While zero or one dose of vaccine still left children apparently susceptible to some risk of disease, as seen by the 2014–2015 peak and subsequently higher incidence, as soon as two doses age is reached, the epidemiologic patterns seem much decreased.

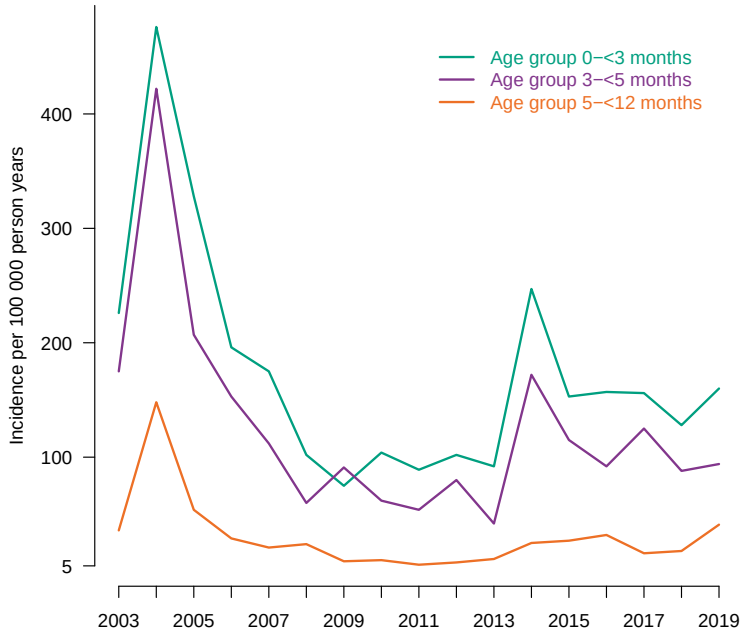

Figure 13: Incidence in pertussis in laboratory-confirmed pertussis cases in infants, 0–3 months, 5–12 months and 6–12 months of age. Data collection was performed in the EPS in infants with onset of pertussis disease between Jan 01, 2003, and Dec 31, 2019.

Age groups (months)	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
0-<3	226	476	328	196	175	102	75	104	89	102	92	247	153	157	156	128	160
3-<5	175	422	207	153	112	60	91	62	54	80	42	172	115	92	125	88	94
5-<12	36	148	54	29	21	24	9	10	6	8	11	25	27	32	16	18	41

Table 8: Incidence in pertussis in laboratory-confirmed pertussis cases in infants in different age groups, 0-<3, 5-<12 and 6-<12 months of age. Data collection was performed in the EPS in infants with onset of pertussis disease between Jan 01, 2003, and Dec 31, 2019.

2.3.1 Cases of pertussis in infants and among children older than 1 year of age, distributed by age and vaccination status

The number of cases reported in 2019 in unvaccinated and vaccinated infants (one dose or more) for different ages (in days) is shown in Figure 14. Out of all 60 laboratory-confirmed infant cases reported in 2019, 40 (67%) infants had their first symptoms of pertussis during the first 90 days of life, and all of these cases were unvaccinated infants. Another 12 infants had their first symptoms of pertussis before they were 150 days of age, i.e. 52 of 60 (87%) of infants with reported pertussis in 2019 contracted the disease before 150 days of age (Figure 14). In 2018, 57% of the cases were infected within the first 90 days (p = 0.33 for comparing 2019 and 2018). In 2019, 12 (20%) of all infants reported with pertussis had been vaccinated with at least one dose, which was slightly less than the 24 cases (36%) reported in 2018.

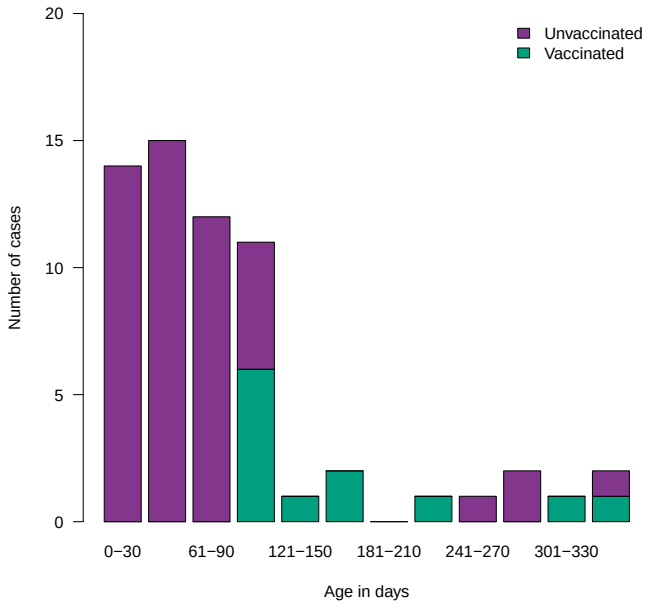

Figure 14: Number of reported pertussis cases in infancy in 2019 by vaccination status (not vaccinated or vaccinated with at least one dose of aP vaccine) and age (days). SmiNet data for reported pertussis infant cases and vaccination status from EPS data base.

A substantial proportion of pertussis cases reported in the Swedish EPS study were among the unvaccinated children who are too young to be fully

vaccinated with three doses of aP vaccine at 3, 5, and 12 months of age (90, 120, and 365 days of age) according to the NIP.

The proportion of pertussis cases in unvaccinated children during infancy and in pertussis cases 1–20 years of age in the EPS study (1997–2019) is shown in Table 9. Sixty two per cent of the unvaccinated pertussis cases were younger than 1 year of age, and 51.1% were infants younger than 3 months of age.

Age	Number of cases	Per cent of cases
0-30 days	310	14.3
31-60 days	419	19.3
61-90 days	380	17.5
91-120 days	128	5.9
121-150 days	37	1.7
151-180 days	17	0.8
180-365 days	58	2.7
>365 days	822	37.9

Table 9: Age (days) at episode start for 2,171 unvaccinated cases with pertussis. Data collection was performed in the EPS, with episodes starting between Oct 1, 1997, and Dec 31, 2019. Data are presented for pertussis cases 0–20 years of age.

The median ages of pertussis cases with none, one, or two vaccinations were 95, 127, and 270 days, respectively. In contrast, for children who had received three doses of aP vaccine during their first year of life, the median age for onset of pertussis was 2,150 days of age (6 years) (range = 1–7,928 days) (Table 10).

Doses before episode of pertussis	Median age in days at onset of pertussis	Cases (n)
0	95	2015
1	127	586
2	270	430
3	2150	2430

Table 10: Median age in days at the onset of pertussis and the number of aP vaccination doses prior to the onset of pertussis. Data collection was performed in the EPS, with episodes starting between Oct 1, 1997, and Dec 31, 2019, and from 2003 in the Gothenburg study area. Data are presented for pertussis cases 0–20 years of age.

2.3.2 Incidence of pertussis in infancy by year and after changes to the national immunisation programme

The age-specific incidence of laboratory-confirmed pertussis cases among infants was around 700–800/100,000 person years during the 10-year period prior to 1996. The incidence decreased rapidly after the introduction of pertussis vaccination and oscillated around 200/100,000 person years from 1996 to 2005, after which time the incidence decreased further (Figure 15, Table 5). This decrease could be due to the new vaccination schedule that included preschool booster vaccinations for children born in 2002 and a booster vaccination at 10 years of age leading to a higher proportion of vaccinated children in the population during 2007–2012.

In 2014 the incidence was around three times higher than the mean incidence during the time period 2008–2013 ($p = 0.002$) and slightly higher than the incidence in 2005, which was when the vaccine booster in 10 year olds was introduced (Figure 15, Table 5).

During the increase in pertussis incidence in infants in 2014, the NIP in Sweden was well established, using a 3, 5, 12-month programme with a booster dose at 5–6 years of age and with high vaccination coverage. In 2016, 2 years after this increase, the booster dose at 14–16 years of age was implemented, but it is still too early to evaluate the effect of this booster dose on infant pertussis.

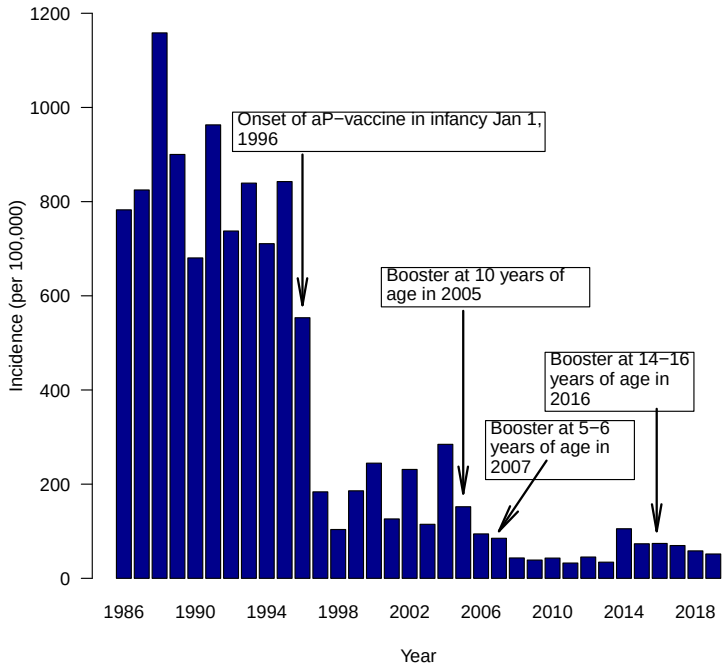

Figure 15: Incidence of pertussis in infants younger than 1 year of age by year. Changes in the NIP are indicated. Data are from case reports of pertussis reported to SmiNet in 1997–2019. Data before 1997 are from voluntarily reports from bacteriological laboratories.

The decline in the incidence among infants after 1996 is to a large extent explained by a decreasing number of infant cases from the age of 5–12 months, i.e. from the scheduled age of the second dose of DTaP. The mean number of infants with laboratory-reported pertussis per age (in months) during infancy is illustrated in Figure 16, and data are shown for the 10 years before and the 22 years after the introduction of aP vaccination in infancy. Most cases were reported in the youngest birth cohort in each calendar period, with a marked decline at about 5 months of age.

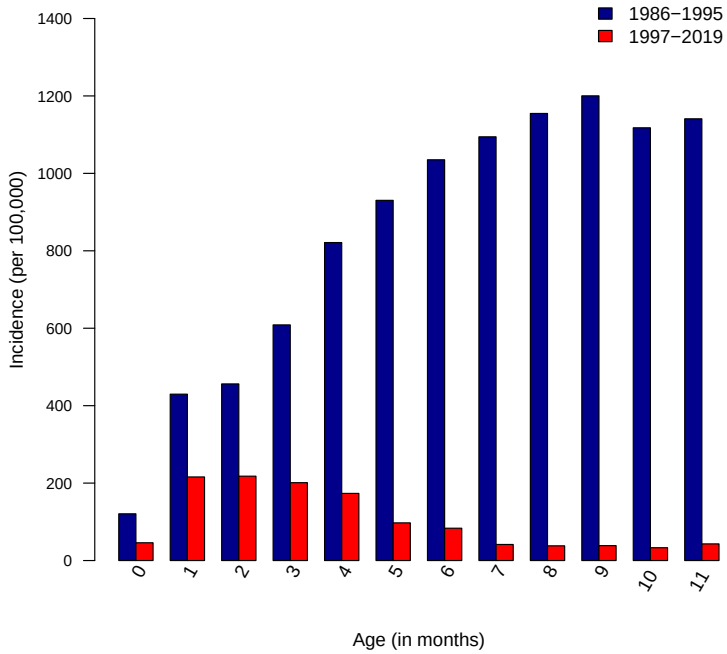

Figure 16: Mean incidence (per 100,000 person years) of pertussis in infants in defined age groups during the 10 calendar years before (1986–1995) and during the 23 years after (1997–2019) the introduction of DTaP in 1996. Before 1997, data are from voluntarily reports from bacteriological laboratories, and after 1997 the data are from case reports of pertussis reported to SmiNet.

2.3.3 Severity of pertussis cases in infants and among cases in children 1–20 years of age

In the following sections, data are presented for age-specific complication and hospitalisation rates in vaccinated (one dose or more) and unvaccinated infants, with information on length of hospital stay and the duration of cough in infants. In the EPS study, data on the first day with symptoms are collected and described as the age at episode start.

In the Gothenburg study area, different vaccines were used compared to the NIP until 2003, as described above. Children from the Gothenburg study area have thus been reported within the EPS from Jan 1, 2003, onwards when the vaccines used in this area was aligned with the rest

of Sweden (according to the NIP) (Table 3). Data on complications are therefore in this section presented for the period 2003–2018.

Clinical data were analysed according to cough definitions from the World Health Organization (WHO 2015) and according to the definition of 21 days of paroxysmal cough as recommended by the WHO (WHO 1991) for use in previous efficacy trials.

During the period from Jan 1, 2003, to Dec 31, 2019, the age-specific incidence of any complication due to pertussis was highest in children 0-<3 months of age at 63/100,000 person years. The incidence decreased thereafter to 1/100,000 person years for children 1–20 years of age (Table 11).

Age groups (months)	All pertussis cases	>=21 days of spasmodic cough	Hospital admission	Complication
0-<3	160 (148-171)	131 (121-142)	109 (99-119)	63 (56-71)
3-<5	116 (104-128)	89 (79-100)	41 (34-48)	25 (19-31)
5-<12	27 (24-30)	17 (14-19)	3 (2-4)	3 (2-4)
+12	10 (10-10)	7 (7-7)	0 (0-0)	1 (1-1)

Table 11: Incidence of pertussis in relation to severity and age per 100,000 person years (95% confidence interval). Incidences are presented for all reported cases with pertussis, reported cases of pertussis with paroxysmal cough for 21 days or more, hospital admissions due to pertussis, and complications due to pertussis. Data collection was performed in the EPS with episodes starting between Jan, 01, 2003, and Dec, 31, 2019. Data are presented for pertussis cases 0–20 years of age.

2.3.4 The rate of complications due to pertussis by age

To analyse the association between complications during the pertussis episode and age and/or vaccination status of the child at the start of the episode, individuals were grouped into either having no complication during the pertussis episode or having at least one noted complication. Data collection was performed in the EPS with episodes starting between Jan 01, 2003, and Dec 31, 2019. Data are presented for pertussis cases 0–20 years of age.

Age at episode start (days)				
0-90	**91-150**	**151-365**	**>365**	**Total**
309/787 (39%)	79/374 (21%)	30/298 (10%)	191/2613 (7%)	609/4072 (15%)

Table 12: Numbers and proportions of children with at least one complication due to pertussis, by age at onset of disease. Data collection was performed in the EPS with episodes starting between Jan, 01, 2003, and Dec, 31, 2019. Data are presented for pertussis cases 0–20 years of age.

2.3.5 Severity of pertussis in infant cases less than 6 months of age at the start of the pertussis episode

The greatest burden of morbidity and mortality related to pertussis is among the youngest infants prior to their primary immunisation series. The number of hospitalisation, complications, and spasmodic cough for 21 days or more in infant pertussis cases younger than 6 months of age with episodes starting between Jan 1, 2011, and Dec 31, 2019, are presented in Table 13, with the aim to evaluate the severity of pertussis in the youngest infants during the last 9-year period.

During the time period 2011–2013, the rate of infants with any complication in this age group was 23–31%. During the time-period 2014–2019, the corresponding rate was 20–63%, with the highest rate in 2016. The hospitalisation rate was 59–65% during the time period 2011–2019, and the median duration of hospital stay was 5.5–7.5 days.

Almost all infants had spasmodic cough for 21 days or more during the studied time period 2011–2019. There was no significant difference in the proportion of hospitalised infants younger than 6 months of age. The proportion of infants with respiratory complications with apnoea varied during this studied time period (6–41%) but with no significant trend over the years.

	2011 N=36	**2012** N=48	**2013** N=35	**2014** N=109	**2015** N=71	**2016** N=70	**2017** N=64	**2018** N=52	**2019** N=46
No complication	25	36	27	79	43	26	41	39	37
Any complication	11	12	8	30	28	44	23	13	9
Respiratory, with apnoea	8	4	7	21	21	29	8	3	6
Respiratory, without apnoea	2	7	1	6	4	12	15	8	3
Dehydration	1	1	0	3	2	0	0	1	0
Other severe events	0	0	0	0	1	3	0	1	0
Spasmodic cough for 21 days or more	32	37	34	93	66	62	56	48	43
Hospitalized	22	29	21	66	43	42	42	33	27
Median days of hospitalization	7.5	7	7	7	7	6	5.5	7	6

Table 13: Number of infants aged 6 months or less with and without complications, spasmodic cough and median days of hospitalisation during 2007–2017. Data collection was performed in the EPS with episodes starting between Jan 01, 2011, and Dec, 31, 2019.

2.3.6 Hospital admission due to pertussis in all infant pertussis cases

In 2019, 27 infants (59%) with pertussis were hospitalised and the corresponding numbers in 2018 were 33 (63%).

In the EPS study (Jan 1, 2003, to Dec 31, 2019), 751 of the children (17%) were admitted to hospital during the pertussis episode (Table 14). A total of 544 of 800 infants (68%) who were younger than 90 days of age at the start of the pertussis episode were admitted to hospital. The corresponding admission rates, regardless of vaccination status at the start of the episode, for the 382 children in the age group 91–150 days of age, for the 303 children in the age group 151–365 days of age, and for the 2,835 children older than 365 days of age at episode start were 35%, 10%, and 1%, respectively (Table 14).

	Age at episode start (days)			
0-90	**91-150**	**151-365**	**>365**	**Total**
544/800 (68%)	135/382 (35%)	31/303 (10%)	41/2835 (1%)	751/4320 (17%)

Table 14: Hospital admissions by age at episode start (number and per cent). Data collection was performed in the EPS with episodes starting between Jan, 01, 2003, and Dec, 31, 2019. Data are presented for pertussis cases 0–20 years of age with data on hospital admission.

The age-specific incidence rate of hospitalisation due to pertussis was highest for children 0–90 days of age (108.3/100,000 person years). The incidence decreased with increasing age to less than 1/100,000 person years for children older than 1 year of age at the start of the pertussis episode (Figure 17).

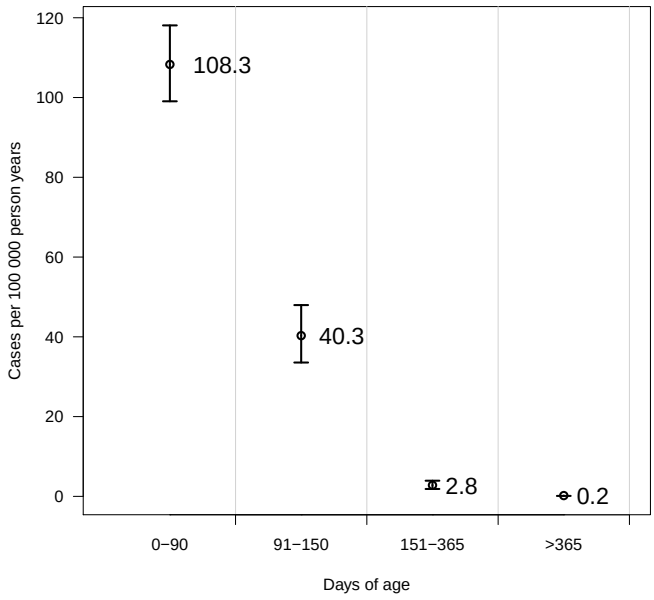

Figure 17: Incidence of hospital admission per 100,000 person years due to pertussis stratified by age at episode start. Data collection was performed in the EPS study of pertussis, with episodes starting between Jan 1, 2003, and Dec 31, 2019. Data are presented for pertussis cases among those 0-20 years of age.

2.3.7 Complications due to pertussis in all infant cases by hospitalisation

For the time period 2003–2019, respiratory complications (with apnoea, n = 264, or without apnoea, n = 230) were reported in 494 (12%) of the children, and dehydration was reported in 96 (2,4%) of the children. Uncommon complications, e.g. neurological and other serious complications, were reported in 14 (0.3%) children (Table 15).

Altogether, most of the children with respiratory complications with apnoea were admitted to the hospital (86%). The majority of the children with dehydration were also hospitalised (Table 15).

Complication type	Hospitalised	Not hospitalised	Total
Respiratory, with apnoea	227 (86%)	37 (14%)	264
Respiratory, without apnoea	99 (43%)	131 (57%)	230
Dehydration	59 (61%)	37 (39%)	96
Other severe events	10 (71%)	4 (29%)	14
No complication	354 (10%)	3110 (90%)	3464
Total	749 (18%)	3319 (82%)	4068

Table 15: Number of children with pertussis by complication type and rate of hospitalisation. Data collection was performed in the EPS with episodes starting between Jan, 01, 2003 and Dec, 31, 2019. Data are presented for pertussis cases 0–20 years of age with data on hospital admission and complications.

2.3.8 The probable source of infection linked to age at onset and severity

The on-going EPS study was extended in January 2009 to also investigate infant pertussis case contacts. The aim of the study is to investigate pertussis in infants younger than 6 months of age stratified by information on probable source of infection.

Preliminary data from this study show that the mother was most commonly identified as contact source of infection. This study is now under preparation for publication in a peer-reviewed journal, and detailed data will be published when accepted for publication.

2.4 Recommendations to improve pertussis disease control among infants

Due to the remaining cases of pertussis disease among infants in Sweden and the increase of pertussis since 2014, the PHAS issued recommendations in August 2016 to improve pertussis disease control among infants (Folkhälsomyndigheten, Rekommendationer 2016). The recommendations were based on the EPS data, conclusions from a systematic literature review (Link to review), and a health economic analysis performed by the PHAS in 2015. The proposed interventions are aimed at strengthening the current recommendations in Sweden, that is, to increase the timeliness of the first vaccine dose, to increase the awareness of pertussis among caregivers, and to increase testing for pertussis in infants and the use of early post-exposure antibiotic prophylaxis. In this report we analyse the data to determine if this recommendation has made any changes regarding vaccination (timing of first dose) or awareness of pertussis (delay of antibiotic treatment, delay of diagnosis, or number of visits before diagnosis). Data were collected to evaluate the effect of these recommendations on infant pertussis both from the EPS study and the vaccination register.

2.4.1 Timing of vaccinations

The cumulative proportion of infants (n = 453,122) that received their first dose within 40 days from the planned vaccination day was 97% (Jan 1, 2016, to Dec 31, 2017 (Figure 18).

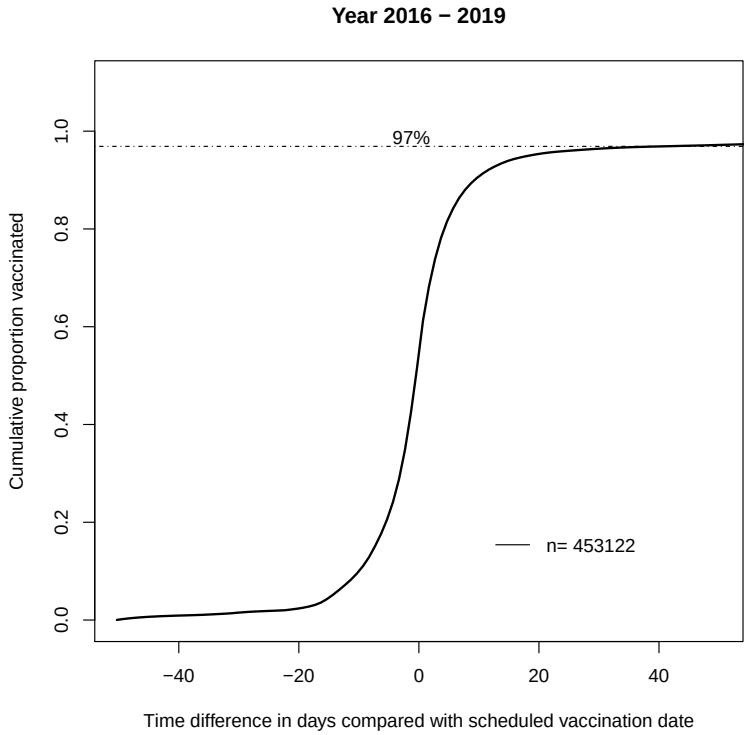

Figure 18: Cumulative proportion of vaccinated children for the first dose of aP vaccination with differences in actual vaccination dates from the planned date according to the NIP (2016 – 2019). The horizontal line indicates the percentage of infants vaccinated within 40 days after the planned vaccination. Data are from the Swedish vaccination register.

2.4.2 Treatment of pertussis in infants and in children above 1 year of age

The time between the onset of the pertussis disease and the start of antibiotic treatment is shown in Figure 19. The treatment period tends to start rather late, and there is no clear difference between the youngest infants (0–3 months of age) and the older infants based on the median values (10–12 days between the onset of pertussis and the start of antibiotic treatment). However, there are some extreme values. Furthermore, in the youngest age group and in the age groups 5-<12 months and older than 12 months of age, one child in each group had received prophylactic treatment before episode start.

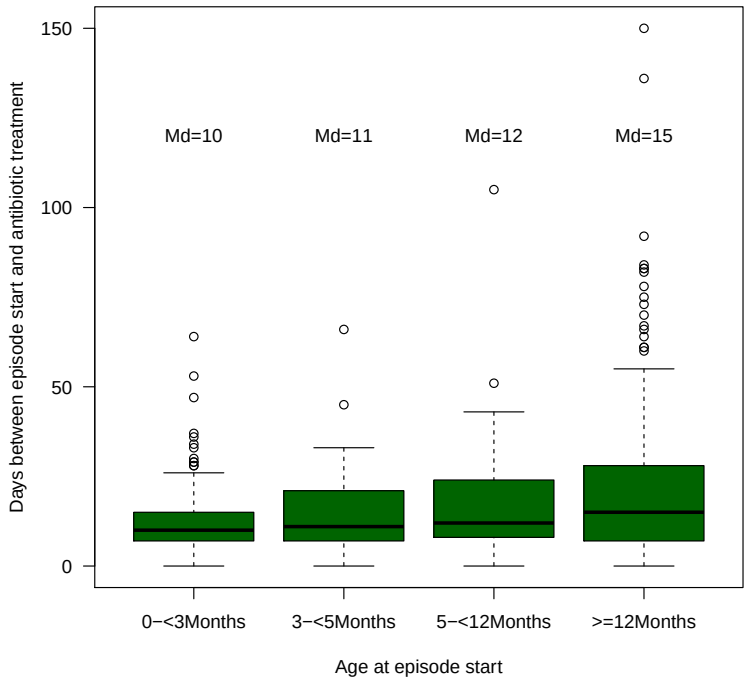

Figure 19: Number of days between episode start and start of antibiotic treatment. Data collection was performed in the EPS with episodes starting between Jan 1, 2003, and Dec 31, 2019. Data are presented for pertussis cases among those 0–20 years of age. Md = Median.

2.4.3 Number of times parents have sought medical care for their sick child before a pertussis diagnosis was established.

The awareness of pertussis among health-care workers can be evaluated by analysing the number of times parents have sought medical care for their sick infant before a pertussis diagnosis was established. Since January 2016, data regarding the number of visits have been collected within the EPS study. During the time period 2016–2019, 56% (151/271) of reported infant cases had to seek medical care more than one time before a pertussis diagnosis was established.

2.4.4 Number of samples analysed for pertussis

Starting in Jan 1, 2014, the PHAS began to collect data from all laboratories in Sweden on the total number of samples analysed for *B. pertussis* (PCR, culture, and/or serology). During 2018, a total of 20,668 samples were tested for pertussis, 185 samples by culture, 19,101 by PCR, and 1,382 by serology (data from the Linköping area and Unilab Stockholm are not included). A total of 13,194 samples were tested for pertussis in 2014, 12,935 were tested in 2015, 14,508 were tested in 2016, and 18,791 were tested in 2017. Due to COVID-19 pandemic this data has not been collected from 2019.

3 Discussion

Pertussis vaccine is included in the Swedish national immunization program (NIP), but despite having had a high and stable vaccination coverage at 97–98% for aP-containing vaccines since 1998, pertussis is the least controlled of all vaccine-preventable bacterial diseases (Folkhälsomyndigheten, årsrapport 2018). Although pertussis incidence varies by age group, unvaccinated or undervaccinated infants are at greatest risk of infection and associated complications.

During 2019, 749 laboratory-confirmed cases of pertussis were reported to SmiNet, of which 68 cases were in infants younger than 1 year of age. As in previous years, the incidence of laboratory-confirmed pertussis in Sweden during 2019 (51.7/100,000 person years) was the greatest among infants but decreased in comparison to 2015–2018 and was significantly lower compared to 2014.

After five years (2009–2013) with low incidence of reported cases of pertussis (2.5/100,000 person years on average), a threefold increase in the incidence was seen in the general population in 2014. Since then, the increase in the general population has been sustained in 2015–2019. Since 2014, there has been a significant increasing trend in the numbers of samples analysed for *B. pertussis*. The sustained higher incidence of pertussis in the general population from 2015 onwards might partly be due to the increased number of samples taken. However, due to pandemic situation corresponding data for 2019 has not yet been collected.

Pertussis in infants

The greatest burden of morbidity and mortality caused by pertussis is in infants prior to their primary immunisation series with pertussis-containing vaccines (Cantey 2014). Over the past few years, several countries have reported an increase in pertussis cases and pertussis-related deaths among infants. In most countries, infants receive their first pertussis vaccine between 6 weeks and 2 months of age, followed by additional immunisations given at 1- or 2-month intervals (WHO 2015). Therefore, the most vulnerable age group is not sufficiently protected or is not protected at all against the disease (Juretzko 2002).

In this report, incidence of pertussis in different age groups of infants was studied between 2003 and 2019. In the youngest age groups, 0–3 and 3–5 months of age, the incidences were significantly higher compared to the older age group, 6–12 months of age. The incidence for the two youngest age groups increased in 2014, but not in the oldest age group, indicating that two doses of aP vaccine can protect from disease also during outbreaks.

In 2017, infants below 1 year of age had the highest incidence (53.9/100,000 person years) compared to older age groups based on data from 30 EU/EEA countries. Luxembourg (146.9) and Austria (145.1), followed by Denmark (138.7) and Ireland (126.8) had the highest incidence in infants among reporting countries (ECDC 2019). Norway reported an incidence of 70/100,000 person years during 2018 in infants 0–5 months of age.

In Norway the incidence for infants ranged between 67–175/100,000 person years during 2009–2018 (Folkehelseinstituttet 2019). In Sweden the corresponding incidence was 32–105/100,000 person years for the same time period. In comparison to the EU/EEA countries with the highest incidence rate of pertussis in infants, the incidence in Sweden is still relatively low and at a similar level as Norway, a country with exactly the same pertussis vaccination schedule and similar structure of the health care system.

In 2019, 27 infants (61%) below 1 year of age with pertussis were hospitalised in Sweden, the proportions of hospitalised infants being similar in the previous four years (2014–2017). The hospitalisation rate for infants was 63% based on data during 2017 from EU/EEA countries (ECDC 2019). In Sweden, during 2003–2018, the age-specific mean hospitalisation rate was highest in infants younger than 3 months of age (70%). The overall hospitalisation rate for unvaccinated children was 39%. However, the majority (92%) in this group were younger than 3 months of age and thus too young to be vaccinated. Consequently, the high hospitalisation rate among infants is mainly represented by infants too young to have received one dose of pertussis vaccine.

In Sweden, the mean incidence of hospitalised infants younger than 3 months was 108.3/100,000 person years during 2003 to 2019. In infants >3–5 months of age the corresponding mean incidence of hospitalised infants was lower (40.3/100,000 person years). In Norway, the hospitalisation incidence in infants 0–5 month of age was low during 2018 (36.0/100,000 person years) and ranged between 30 and 109/100,000 person years (Folkehelseinstituttet 2019). The proportion of infants who are hospitalised is dependent on the age at the onset of disease, but might also vary depending on national guidelines and criteria for the child to be admitted to hospital. In the coming years, other markers for the degree of severity such as pertussis-related apnoea will be studied in more detail.

Pertussis in children aged 1–20 years and effects of catch-up and booster vaccination schedules It has been known for several years that the protective immunity following aP vaccines wanes over time (Misegades 2010, Witt 2012, Klein 2012, Sheridan 2012, Baxter 2013, Koepke 2014, McGirr 2015, Burdin 2016). Worldwide surveillance data suggest that the use of aP vaccines will result in a resurgence of pertussis after a number of years and that this resurgence might also lead to an increased risk of death

in infants who are too young to be vaccinated (WHO 2015).

The preschool booster has been shown to have a significant effect, with less than half the number of pertussis cases being reported compared to before the introduction of the booster vaccination (Carlsson 2009). The age-specific incidence for all reported cases in preschool children (1–6 years of age) dropped from >1,000/100,000 person years in the time period before the aP vaccine was introduced in 1997 to approximately 100/100,000 person years in 1998–2000, to fewer than 10/100,000 person years in 2009– 2013. In 2016, 2017, and 2018, the incidence in preschool children increased slightly but still remained below 10/100,000 person years.

In 2019 the incidence in 10–14 year olds was lower compared to 2017 and 2018 but higher compared to 2015 and 2016. In other EU countries an increase of pertussis in school children, 10–14 years old, has been indicated, but it is too early to determine if the trend will continue (ECDC 2019).

In 2019 the incidence in 14–19 year olds was higher compared to 2018 but only somewhat higher compared to 2015–2017, that seems to be driven by the 19 year-olds, rather than consistent across the age group. The incidence of pertussis in teenagers will be studied, and the data in future reports will give the possibility to evaluate the effictiveness of the dTap booster vaccination of teenagers who have received aP vaccine as infants.

Pertussis in fully vaccinated children The resurgence of pertussis infections in Sweden as well as in several other countries with high vaccination coverage has raised questions about the nature and durability of vaccine-induced immunity (de Celle's 2016, Locht 2016). Epidemiological studies have shown that aP vaccines are protective in the first years after vaccination, but the protection is only temporary and the immunity wanes rapidly (Plotkin 2014).

This report shows that the proportion of children who were fully vaccinated in the different age groups has varied greatly over the last 12 years (2007–2019). Among children aged 1–5 years, the proportion of fully vaccinated individuals varied between 51% and 70%, with the highest proportion in the 3 year olds. The number of pertussis cases in fully vaccinated children aged 1–5 years is reasonable considering a vaccine efficacy of 80% after three doses of aP vaccines and in relation to the number of children vaccinated annually and the size of the vaccinated cohorts in Sweden. The proportion of fully vaccinated children decreased in 5-year olds (51%) and in 6-year olds (29%), which is most likely due to the booster vaccine administered at 5 years of age according to the NIP.

In 2017, 64% of individuals age between 5 and 19 years and reported with pertussis, had been vaccinated with four or more doses according to data from 30 EU/EEA countries. This age-specific proportion was above 70% for

10 of the reporting countries (ECDC 2019).

In a pertussis outbreak in the state of Washington, in the US, in 2012, a valid vaccination history was available for 91.2% of the patients aged 3 months to 19 years. Overall, 75.8% of the patients aged 3 months to 10 years were up-to-date with the childhood DTaP doses (CDC 2012). Similarly, a high proportion of pertussis cases was observed among fully vaccinated children aged 7–10 years in the pertussis epidemic in California in 2010, with 66% of the cases being fully vaccinated (Winter 2012). Furthermore, in another California epidemic in 2014, 87% of the pertussis cases in adolescents had previously received the dTap booster vaccine, and the median length of time since the prior dTap dose was 3 years (range = 0–7 years) (Winter 2014).

In comparison to the previous US studies, the proportions of fully vaccinated pertussis cases in this EPS report are lower but they are similar when compared to data from other EU countries. Based on the aP vaccine efficacy and the observation that immunity for pertussis appears to wane over time after vaccination, our data might be reasonable even though pertussis vaccine uptake is high and timely in Sweden. Nonetheless, the occurrence of pertussis among fully vaccinated children warrants further close observation and analysis and studies on vaccine effectiviness estimated by the screening method are ongoing.

Strategies to protect infants from pertussis in Sweden Those at highest risk of severe disease are infants (Marshall 2015) who might be too young to receive their first vaccination; as such, protecting infants is the key priority in pertussis-related public health interventions. In addition, early post-exposure antibiotic prophylaxis provides good protection against clinical pertussis in infants (Bergquist 1987, Wirsing von König 2005).

Due to the sustained increase of pertussis among infants in Sweden since the sharp increase in 2014, the PHAS issued recommendations in August 2016 to improve pertussis disease prevention and control among infants. The proposed interventions aimed at strengthening the recommendations in Sweden, that is, to enhance the timeliness of the first vaccine dose, to increase the awareness of pertussis among caregivers, and to increase testing for pertussis in infants and the use of early post-exposure antibiotic prophylaxis (Folkhälsomyndigheten 2016).

Using data from the EPS and the Swedish vaccination register, the effect of the recommendation published in 2016 has been evaluated for the past three years as well as the incidence of reported pertussis cases and hospitalisations among infants.

The proportion of all infants included in the vaccination register who had received their first dose within 40 days from the intended vaccination date

was 97% during 2016–2019.

The time between the onset of pertussis disease and the start of antibiotic treatment in infants varied between 10 and 12 days during 2003–2019.

During the time period 2016–2019, 56% of the infants had to seek medical care more than once before a pertussis diagnosis was obtained.

Even though more samples were analysed for pertussis among the population (all ages) in 2018 than in the previous years, the awareness of infant pertussis among caregivers can still be improved. Most important is to increase awareness so that infants are diagnosed when they first seek medical attention and receive antibiotic treatment or post-exposure antibiotic prophylaxis early. Results from the case-contact study highlight the importance of being observant of coughing among close family members during a child's first few months of life, as well as offering generous testing, rapid diagnostics, and early antibiotic treatment to prevent infant deaths. It is also important that coughing pregnant women and other family members with cough are examined and tested for pertussis disease before the baby is born. Strategies for spreading information to health care professionals at the clinics who assess sick children about how to prevent severe pertussis in infants need to be further developed.

In a recent and thorough literature review of pertussis vaccination during pregnancy based on relevant literature published from 1946 until April 2017, 46 studies with a total of 345,000 participants were included to obtain a comprehensive evaluation of vaccine effectiveness, vaccine safety, immunogenicity, and interference after pertussis vaccines given during pregnancy (Campbell, 2018). Currently, neither maternal vaccination nor cocooning immunisation strategies are recommended in Sweden (Link to recommendations). This EPS report shows that the pertussis incidence in infants is still at lower levels compared to corresponding data in countries that have already decided to recommend maternal vaccination. Although the incidence in infants younger than three months of age is high in Sweden. Cases among infants in Sweden are being closely monitored through both routine surveillance and the EPS, and the PHAS is continuously working to increase the awareness of pertussis among health care professionals. If an increase in pertussis among infants is observed in the future, other preventive measures and interventions, including recommendation of maternal vaccination, will be re-evaluated.

The methodology for pertussis surveillance in Sweden has been stable for many years and therefore offers a unique opportunity for conducting an enhanced follow-up after the introduction of aP vaccines in an endemic setting with high vaccination coverage. The long-term surveillance provides insights into the overall impact of the aP vaccination programme,

including estimates of the duration of vaccine-induced protection after vaccination in infancy, after the introduction of a preschool booster, and after the school-leaving booster. The unique EPS data with date of onset of disease allows for detailed evaluations of the effects of vaccination strategies and recommendations to prevent severe pertussis in infants.

4 Plan for continued work

In accordance with the overall objective of the study, the plan for 2020 is:

- To monitor epidemiological trends over time for pertussis in Sweden (at the broader population level and specifically in vaccinated cohorts)
- To monitor the impact of any changes in the NIP
- To monitor the impact of any new recommendations
- To provide insight into the ability of the timing/dosing schedule to control pertussis
- To provide particular insight into the awareness of pertussis among caregivers

The analyses are primarily descriptive/qualitative and are designed to monitor epidemiological trends for pertussis and to provide insight into how they might be changing with time and vaccination schedule.

Age-specific incidence will be studied in order to monitor the impact of the preschool booster and the adolescent booster on the incidence of pertussis in infants, to monitor the trends of pertussis and the impact of the entire schedule of vaccinations, and to evaluate the effect of booster doses on pertussis epidemiology. Specifically, we will measure the incidence of pertussis during and after the first year of life presented as the time intervals according to changes in the NIP, the incidence and cases of pertussis in children by age and by vaccination status, and the incidence of pertussis in infancy by time and by changes to the NIP.

Antibiotic treatment. The use and the effect of antibiotic treatment in all children will be studied, including the time interval between the onset of disease and the start of antibiotic treatment and the relation between the timing of antibiotic treatment and disease severity.

Timing of vaccinations and the impact of vaccination status. Due to regional vaccine procurements, exposure to different pertussis vaccines varies with birth cohort and geographical area. Therefore, comparison between vaccines will not be possible, and the outcome of the analyses will instead include the following:

- We will determine the number of pertussis cases and severity of pertussis in infancy by vaccination status.
- In fully vaccinated children (according to the NIP and Summaries of Product Characteristics) with laboratory-confirmed pertussis from

2007 and onwards, we will study the time from last vaccine dose administered until the episode start of pertussis disease. The data will be analysed and reported by age group.

- We will use mathematical modelling to analyse the impact of different vaccination schedules on pertussis incidence in age groups 0–20 years of age.

Severity of pertussis disease will be studied with a special focus on infants and will include the duration of disease, the rate of hospital admission, the duration of hospital stay, the duration of cough, and the rate of severe complications. Markers of severity will be studied and related to the age at onset of disease and to individual vaccination histories as well as to the scheduled ages of the NIP.

Infant pertussis cases leading to admission to intensive care will be studied as a complementary evaluation of severity and to evaluate if there are other relevant markers of severity of pertussis disease in hospitalised infants.

Case-contact information for infants will be used to study the probable source of infection and will be related to the severity of disease, to age at onset of disease, and to individual vaccination histories.

Collaboration with other Nordic and EU countries will be used to compare and evaluate trends in infant pertussis incidence and in hospitalisation incidence and the incidence of other severity markers

Additional analyses might be added to the project as decided at the annual review meetings. Annual progress reports will, as previously, summarise the overall number and age-specific incidence of laboratory-confirmed cases with detailed analyses in vaccinated cohorts.

4.1 Scientific publications and presentations

Papers planned during the coming year include

1. Publication of data from the analysis of case contact data of the probable source of pertussis infection for the youngest infants.
2. Publication of data from the analysis of aP vaccine effectiveness. By using data on pertussis cases in fully vaccinated children reported within the framework of the enhanced pertussis surveillance and data from the Swedish vaccination registry, it will be possible to evaluate vaccine effectiveness in different age groups, describe the cyclic-patterns of pertussis cases in Sweden from 1997 to 2018, describe the proportion of fully vaccinated cases observed among

12–60 months-old and 6–15 years-old children and adolescents in contrast with expected proportions, taking into account the cyclic patterns and changes in vaccination schedule over the 1997–2018 period.

3. Publication of Control of pertussis – lessons learnt from a 20-year surveillance programme in Sweden. Sweden was the only country in the world without any general pertussis vaccination when aP vaccines were introduced. The PHAS has conducted enhanced surveillance of pertussis since 1996, when acellular vaccines were introduced into Sweden's NIP for children. The unique combination of high vaccinaton throughout this time period and long-term enhanced surveillance gives the opportunity to evaluate the age-specific burden of pertussis over a 20-year time period.

4.2 Limitations

While it is likely that the mandatory reporting system is reasonably reliable in reporting diagnosed cases, there is substantial risk that infected individuals are not diagnosed in the first place. One reason for not being diagnosed is because infected persons can have no, mild, or atypical symptoms. While mild symptoms reduce the probability that the disease will be diagnosed, these cases might still be relevant in the circulation of the disease. Also, there appears to be a conception among both medical professionals and the public that pertussis disease does not affect vaccinated individuals. It is therefore likely that even patients with typical symptoms are not tested for pertussis if they have already been vaccinated. Because there are no data on the true incidence of pertussis, we cannot quantify the magnitude of such under diagnosis, but it is likely that failure to obtain a diagnosis is more common in adults than in children and that it might be increasing with time as the awareness of pertussis has decreased because a large proportion of the population has been vaccinated. Possible consequences of under-diagnosis include overly optimistic conclusions about pertussis incidence, vaccine effectiveness, and the duration of vaccine immunity.

Adverse events in vaccinated children are reported directly to the Medical Product Agency in Sweden by the child's nurse or doctor. These reported data are confidential, and the surveillance team at PHAS has no access to these data. The study on pertussis in fully vaccinated children can be reported on a group level (by age), but not on an individual level. If a parent reports an adverse event (any symptoms), the team at PHAS will contact the reporting doctor or nurse for proper action.

5 Administration

The EPS in Sweden started on Oct 1, 1997, and is on-going with annual reconsideration of continuation. Financial support has been obtained from the vaccine manufacturers Sanofi of France and GlaxoSmithKline, Belgium. Contracts for the project Pertussis surveillance in Sweden have been agreed upon for the continued follow-up of clinical epidemiology since 1997 by the manufacturers named above. Major policy decisions relating to the conduct of the study are made by the team at PHAS, including the Internal Steering Committee at PHAS, and are discussed with representatives from the supporting manufacturers at annual review meetings. Study staff on the PHAS team: Bernice Aronsson (principal investigator, project leader), Kerstin Drakes Jämtberg (study nurse), Emma Byström (research assistant), Henrik Källberg (statistician), and Bo Östlund (administrative coordinator). Annual reports are published every year on the PHAS website, (http://www.folkhalsomyndigheten.se/).

6 Published reports based on the enhanced surveillance data

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

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First signs of waning immunity at 6-7 years of age: Olin P, Gustafsson L,Barreto L, Hessel L, Mast C, Van Rie A, et al. Declining pertussis incidence in Sweden following the introduction of acellular pertussis vaccine. Vaccine 2003;21:2015-21

Pertussis toxoid causes a small but significant reduction in the immunogenicity of diphtheria toxoid and tetanus toxoid. Trollfors B, Taranger J, Lagergård T, Sundh V. Reduced immunogenicity of diphtheria and tetanus toxoids when combined with pertussis toxoid. Pediatr Infect Dis J. 2005 Jan;24(1):85-6

A booster dose of acellular pertussis vaccine is warranted from 5 to 7 years of age: Gustafsson L, Hessel L, Storsaeter J, Olin P. Long term follow-up of Swedish children vaccinated with acellular pertussis vaccines at 3, 5, and 12 months of age indicates the need for a booster dose at 5 to 7 years of age. Pediatrics September 2006; 118:3 978-984

Complementary strategies are needed to achieve further reduction in morbidity from circulation of Bordetella pertussis: Carlsson RM, Trollfors B. Control of pertussis–lessons learnt from a 10-year surveillance programme in Sweden. Vaccine. 2009; 27:5709-18

A universal adolescent booster vaccination will reduce the incidence of pertussis in the target group but the duration of immunity is uncertain: Hallander HO, Nilsson L, Gustafsson L. Is adolescent pertussis vaccination preferable to natural booster infections? Expert Rev Clin Pharmacol. 2011 Nov;4(6):705-11

The first dose of vaccine has a significant effect on the incidence and associated complications of pertussis, and we find 38% fewer hospitalised infants in the 3-<9 month age group Nilsson L, Lepp T, von Segebaden K, Hallander H, Gustafsson L. Pertussis vaccination in infancy lowers the incidence of pertussis disease and the rate of hospitalisation after one and two

doses: analyses of 10 years of pertussis surveillance. Vaccine. 2012 May 2;30(21):3239-47

Age-specific contact patterns alone can explain shifts in prevalence and age-stratified incidence: Rohani P, Zhong X, King AA. Contact network structure explains the changing epidemiology of pertussis. Science. 2010 Nov 12;330(6006):982-5

Pertussis among infants could be further reduced by increasing awareness of pertussis in adults and adolescents and by strictly following the recommended vaccination schedule: Nilsson L, von Segebaden K, Blennow M, Linde A, Uhnoo I. Review Läkartidningen 2013; 110

Pertussis immunisation in infancy does not increase the risk of asthma medication use in adolescents: Vogt H, Bråbäck L, Kling A-M, Grunewald M, Nilsson L. Pertussis immunisation in infancy and adolescent asthma medication. Pediatrics 134; 2014: 721 -728

The probability of infection upon contact is age-independent, and we find elevated probabilities among children, adolescents and young adults whose contacts might be more intimate than others: Feng Z, Glasser JW, Hill AN, Franko MA, Carlsson RM, Hallander H, et al. Modeling rates of infection with transient maternal antibodies and waning active immunity: application to Bordetella pertussis in Sweden. Theor Biol. 2014 Sep 7; 356:123-32

Surveillance of infant pertussis in Sweden 1998–2012: the severity of disease in relation to the national vaccination programme: Carlsson R-M, von Segebaden K, Bergström J, Kling AM, Nilsson L. Euro Surveill. 2015;20(6):pii=21032. 12 February 2015

Cost-Effectiveness Analyses of Different Vaccination Strategies to Reduce Pertussis among Infants in Sweden: Wolff E, Aronsson B, Hultstrand M, Brouwers L (2019). J Infect Dis Epidemiol. 5:065. doi.org/10.23937/2474-3658/1510065.

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Årsrapporten för övervakningen av kikhosta (pertussis) beskriver utfallet av antal rapporterade fall av kikhosta för alla åldersgrupper med förstärkt övervakning av kikhosta hos barn och ungdomar som pågått i Sverige under tjugoett års tid. Rapporten beskriver i detalj förekomst av kikhosta utifrån ålder, vaccinationsstatus och sjukdomsbörda med särskilt fokus på barn yngre än ett år. Rapporten ar avsedd som kunskapsstöd för forskare och vårdgivare. Målgruppen för årsrapporten är hälso- och sjukvårdspersonal, och då särskilt personal inom mödravård, barnhälsovård och barnsjukvård samt primarvård och smittskyddsenheter.

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