Folkhälsomyndigheten
PUBLIC HEALTH AGENCY OF SWEDEN

Methods and analysis of the long-term follow up of the effectiveness of one whole cell and two acellular pertussis vaccines

Technical report

Article number: 21289

About this publication

This long-term follow up is based on the large, blinded randomized infant pertussis vaccination trial that is internationally known as “Stockholm Trial II”. The trial included pertussis vaccines from different producers and was conducted in Sweden during 1993–1996. The Public Health Agency of Sweden (former Swedish Institute for Infectious Disease Control) has conducted enhanced pertussis surveillance (EPS) since October 1997 to collect clinical details and vaccination histories of children with pertussis in Sweden.

In November 2021, a short article on the long-term follow-up of the effectiveness of one whole-cell and two acellular pertussis vaccines was published (1). The present report aims to provide more details about the methods used for the long-term surveillance of vaccine-specific effectiveness.

This report is written for national health authorities, vaccine producers, epidemiologists, and researchers.

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Introduction

A large, blinded, randomized infant vaccination trial including pertussis vaccines from different producers was performed in Sweden during 1993–1996. This trial was internationally known as "Stockholm Trial II" (2). Trial II included the majority of Swedish counties, with the exception of Gothenburg and adjacent areas, where other trials were conducted at the same time. The children included in Trial II were born between June 1, 1993, and June 30, 1994. Trial II included at the start 82,892 children aged 2–3 months. The children were randomized to receive four different vaccines in two different vaccine schedules, hence eight groups were randomized (see Table 1 for the descriptions of three of the vaccines). The results of Trial II have been reported previously (3, 4). One of the four study vaccines had shown low efficacy in another trial (2), and vaccinees belonging to this group were therefore offered an early booster vaccine against pertussis already during 1995.

The three remaining vaccine groups – one licensed whole-cell vaccine group (wP) and two investigational acellular vaccine groups (aP) – were kept blinded until code-breaking on October 7, 1996. Pre-planned analyses were performed for relative efficacy, immunogenicity, and safety. It was concluded that the reliance on passive case identification of culture-confirmed pertussis in Trial II had decreased the number of diagnosed cases more than previously expected. All three remaining candidate vaccines had reasonably high efficacy against culture-confirmed pertussis with at least 21 days of paroxysmal cough.

The Swedish authorities made pertussis a mandatory reportable disease according to the Communicable Disease Act starting on January 1, 1997. After code-breaking and after renewed informed consent, the Swedish Institute for Infectious Disease Control (SIIDC) had the opportunity to continue to follow participants in Trial II in an unblinded fashion. Starting in October 1997, a special program – the so-called Enhanced Pertussis Surveillance programme (EPS) – was set up at the SIIDC with support from vaccine manufacturers to collect clinical details and vaccine histories on children with pertussis in Sweden.

Trial II participants who received pertussis vaccines according to the 3, 5, and 12-month schedule without any additional booster doses were followed for culture/PCR-positive pertussis until 2007 by use of the Swedish personal ID codes (5). The results have been published (1).

The aim of the present technical report is to give details about the methods chosen for long-term surveillance of vaccine-specific effectiveness. In this report we concentrate on three investigational vaccines: The Evans-Wellcome (Evans) whole-cell vaccine (wP) was licensed and used in UK at the time of Trial II but is no longer produced. The Chiron-Biocine (Chiron) acellular three-component investigational vaccine (aP) was later licensed and used in Italy, but it too is no longer produced. The Connaught Laboratories Limited (CLL/Connaught) acellular five-component investigational vaccine (aP) was later licensed and used in Canada and many other countries. This product is currently (as of December 2020) licensed

by Sanofi and is used in combination childhood vaccines under different trade names.

The follow up-period for each child was calculated from the day he or she received dose 3 of the study vaccine. The follow-up methodology will be described for five different periods:

Time Period 1, Trial II proper: From 1994 to the end of blinded follow-up on October 7, 1996 (previously published in Ref 3,4).

Time Period 2: From October 8, 1996, to December 31, 1996 (unblinded follow up, not previously published, not part of the EPS).

Time Period 3: From January 1, 1997, to October 1997 (unblinded follow-up, not previously published, part of the EPS).

Time Period 4: From October 1, 1997, to September 30, 2004 (unblinded follow-up, previously published as Ref 6, part of the EPS).

Time Period 5: From October 1, 2004, to December 31, 2007 (unblinded follow-up, not previously published, part of the EPS).

Methods

Surveillance methods: Time Period 1 (1994–October 7, 1996)

The surveillance methods were described in Ref 3. Paediatricians and primary-care physicians in Trial II areas were encouraged to collect nasopharyngeal samples when whooping cough was suspected in children born on or after June 1, 1993. Letters and leaflets were sent to parents in the study emphasizing the importance of getting laboratory confirmation of whooping cough in order to ascertain vaccine effectiveness.

Laboratory reports of positive *B. pertussis* culture were referred to the SIIDC as part of the routine national surveillance system. The register of reports was matched daily to the register of enrolled children by each infant's Swedish personal identity number. If any numbers matched, a study nurse would contact the parents for weekly follow-up until the end of the episode (usually the end of daily coughing). Serological confirmation was not used in Trial II. The main reason for that decision was that serological results, as recommended based on acute and convalescent samples, would not be available in time to start adequate clinical follow-up.

In the 3, 5, and 12-month vaccine groups the numbers randomized to receive at least one vaccine dose were 18,175 in the Chiron aP group, 18,183 in the Connaught aP group, and 18,159 in the Evans wP group (3). There was some loss of person time between doses 1 and 3. In Table 12.1.2 of the Technical Report (4), the numbers of vaccine recipients at risk after dose 3 are given as 17,679 in the Chiron group, 17,686 in the Connaught group, and 17,453 in the Evans group. Table 12.1.2 from Ref 4 also gives the numbers of culture-confirmed cases stratified by time after dose 3 as 0–<6 months, 6–<12 months, 12–<18 months, and 18 months or more (Appendix A). The cumulative numbers of pertussis break-through cases in Trial II were 49 cases in the Chiron group (7, 12, 13, and 17 cases per stratified time period, respectively) compared to 27 cases in the Connaught group (7, 4, 8, and 8 cases per time period) and 19 cases in the Evans group (2, 4, 9, and 4 cases per time period). Ref 4 states that the majority of culture-confirmed breakthrough cases during Trial II proper had more than 21 days of cough, but a percentage was not given.

Surveillance methods: Time Period 2 (October 8, 1996–December 31, 1996)

During the last two and a half months of 1996 there was no surveillance system in place in Sweden that specifically followed former Trial II vaccine recipients. However, the parents had received a letter already in March 1996 with an offer valid for the period April–December 1996 in which the Trial II organization offered to pay for visits to physicians for culturing if a vaccinated child had had a

cough for 7 days or more or if pertussis was suspected for other reasons. There were two alternative ways for refunding physicians by the SIIDC. Also, the Swedish microbiology laboratories in Trial II areas performed culturing during the whole year of 1996 without asking for reimbursement. In the end, however, no breakthrough cases of pertussis were identified and documented in this manner during November or December 1996.

Surveillance methods: Time Period 3 (January 1, 1997–October 22, 1997)

General pertussis vaccination was reintroduced in the Swedish childhood vaccination program in January 1996 after a 17 year hiatus. Three different newly licensed DTaP vaccines were used in different areas of the country, but general catch-up vaccination of previously unvaccinated children was not conducted in Sweden except for the Gothenburg region. At the same time there was an outbreak of pertussis in the Netherlands (7), and as a consequence there were additional European requirements from the European Medicines Agency (EMA) to document possible strain changes in vaccine breakthrough cases. Hence, the SIIDC applied for funding to do a long-term follow up of effectiveness of the new vaccines, one of which was the Connaught product described above (Table 1).

A protocol was written, and dedicated personnel were trained for this purpose after the necessary permissions were granted. During the period January–October 1997, while still waiting for all necessary permissions, cases of *B. pertussis* infections were notified to the SIIDC. The strains were serotyped at the SIIDC laboratory and documented in the SIIDC computer-linked reporting system SmiNet (5). It was possible to link the breakthrough cases with the vaccine history documented in Trial II by using the Swedish personal ID code for each case. The date that the SIIDC got the report was noted and used in later statistical analyses, but clinical details were not collected during this period (see Appendix B for the data variables collected). The numbers of breakthrough cases among fully vaccinated Trial II vaccinees during this period were 13 cases in the Chiron group, 13 cases in the Connaught group, and 5 cases in the Evans group.

Table 1: Description of vaccines in the follow up

Name of vaccine	Chiron-Biocine	CLL/Connaught	Evans-Wellcome
Type of vaccine	acellular DTP	acellular DTP	whole cell DTP
Lots No.	DTP26/PFK/AH & DTP29/PFK/AH	003-11 & 003-31	BA4473 & BA4479
Contain per dose :	PT-9K/126G, 5 µG FHA, 2.5 µG 69 kDa Pertactin, 2.5 µg Diphtheria toxoid, 25 Lf Tetanus toxoid, 10 Lf Thiomersal ~0.01% v/v Aluminium hydroxide, ~1 mg	Glutaraldehyde inactivated PT, 20 µg Formalin treated FHA, 20 µG 69 kDa Pertactin, 3 µg Fimbriae 2 and 3/6, 5 µg Diphtheria toxoid, 30 IU, 15 Lf Tetanus toxoid, 40 IU, 5 Lf 2-phenoxyethanol, 0.61% v/v Aluminium phosphate, ~1 mg Glutaraldehyde, 0.1%	Pertussis, 4 IU Diphtheria toxoid, 30 IU 32.5Lf Tetanus toxoid, 60 IU 4.4Lf Thiomersal, 0.01% w/ Aluminium hydroxide ~0.6 mg aluminium/dos

Surveillance methods: Time Period 4 (October 1, 1997–September 30, 2004)

The surveillance method was described in Ref 6. The main research purpose stated in Ref 6 was to evaluate the long-term effectiveness of vaccination with aP vaccines given at 3, 5, and 12 months of age. Age-specific incidence rates of pertussis were estimated and generally limited to aP vaccination irrespective of product/brand name because of the potential bias related to the fact that different vaccines were used in different areas of Sweden starting in January 1996.

For children with culture/PCR-confirmed pertussis born during 1996 or later, or children born between June 1993 and June 1994 in Trial II areas (see Ref 4), the clinical course and vaccination history was documented by telephone by study nurses at the SIIDC according to the same procedures as in Trial II as outlined in the EPS protocol (the English variable list is given in Appendix C). Parental permission was obtained to request medical charts as needed. For the three study groups of interest for us, Ref 6 documented 44 cases of culture/PCR positive breakthrough cases in the Chiron group, 47 cases in the Connaught group, and 27 cases in the Evans group.

An exact list of which children were included as cases in Table 2 of Ref 6 cannot be recreated today because of data protection rules. However, it was noted that at least 78% of the breakthrough cases had more than 21 days of cough (6).

Surveillance methods: Time Period 5 (October 1, 2004–December 31, 2007)

The surveillance method was continued as performed previously and based on the EPS protocol. The clinical course and vaccination history of culture/PCR-positive breakthrough cases of pertussis was documented by telephone by study nurses at the SIIDC as mentioned above. In the current EPS dataset that combines Time Period 4 and Time Period 5, we identified altogether 186 breakthrough cases, including 58 cases in the Chiron group, 76 cases in the Connaught group, and 52 cases in the Evans group. It has previously been published that at least 83% of the cases during those time periods had 21 days or more with cough (8).

Statistical analysis of Time Period 1 with imputed data

Based on Table 12.1.2 from the technical report (4) (the table is enclosed here as appendix A), we show time to disease onset of the pertussis cases according to the lower time interval plus three months (3, 9, 15, and 21 months). The numbers of cases for each vaccine group are given in the previous section *Surveillance methods: Time Period 1 (1994–October 7, 1996)*.

Statistical methods

We used two different approaches to estimate time to onset of pertussis. The first approach was a case-only analysis where only cases were used and followed for 150 months from the third and final dose of vaccine. In this approach we used Kaplan–Meier curves to estimate differences between the three vaccine groups (Figure 1).

In the second approach we used Cox proportional regression using all individuals (including the whole cohort of study participants). In this approach all individuals that were not registered with a pertussis diagnosis were censored at the end of follow up (Figure 2).

In addition to these approaches, we calculated pair-wise differences between median time to onset of pertussis and vaccine group using the Mann–Whitney U-test for cases. We used a p-value of less than 0.05 as the level of significance.

Results

Overall description

A brief description of the data used in the report is provided in Table 1.

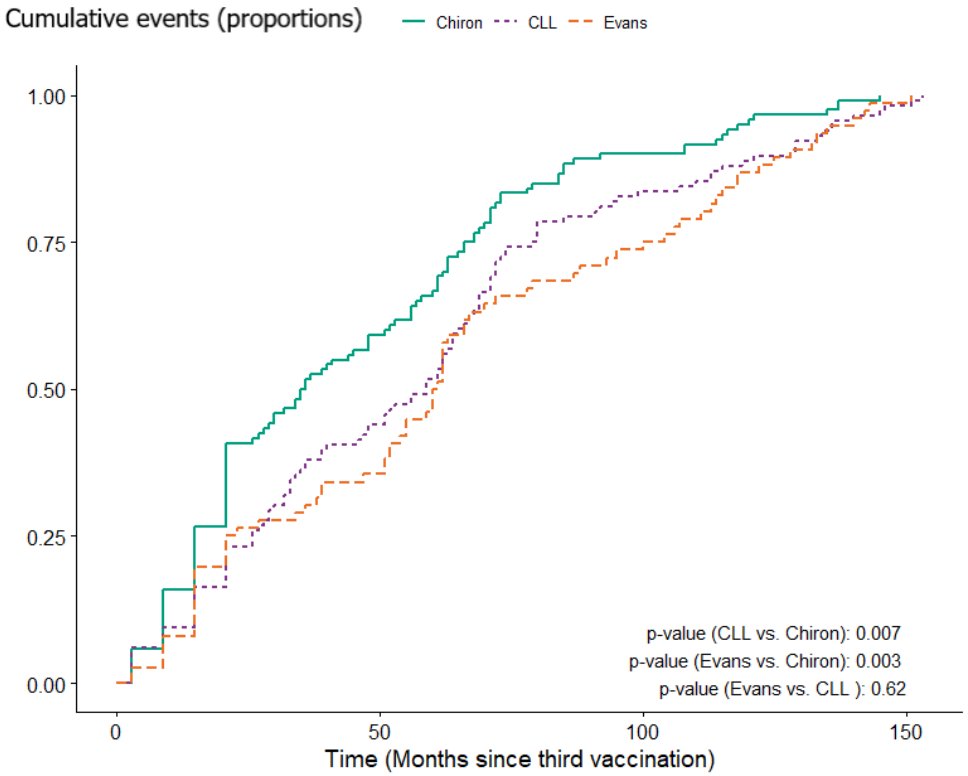
Table 2. Vaccines used in the follow up, number of children at risk, and number of cases

Description	Chiron	CLL	Evans
Vaccine	3 component aP	5-component aP	wP
Number of children at risk	17,679	17,686	17,453
Number of confirmed cases in total follow up	120	116	76
Of which were confirmed cases in Trial II	49	27	19
Median time (months) to pertussis onset	35.5	59	60.5

Inverse survival curves and log-rank test (cases-only analysis)

In Figure 1 we present inverse survival curves for the three different vaccine groups (Chiron, CLL, and Evans). P-values in the figure are based on the log-rank test.

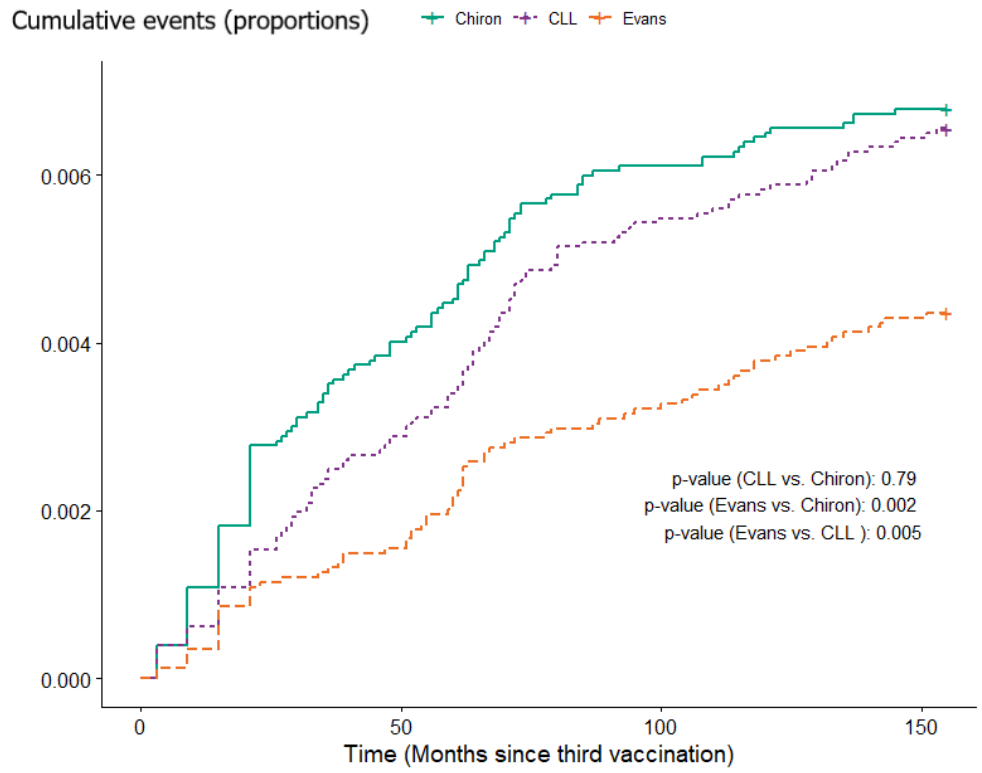
Figure 1: Kaplan–Meier curves for the three different vaccine groups against pertussis.



Inverse survival curves and Cox regression

In Figure 2 we present inverse survival curves for the three different vaccine groups (Chiron, CLL, and Evans). P-values in the graph are based on Cox proportional hazard regression models.

Figure 2: Cox proportional hazard regression for the three different vaccine groups against pertussis.



Discussion

This long-term follow up gave us a unique opportunity to assess pertussis vaccine-specific effectiveness over time based on three randomized groups that were followed with similar methods by the SIIDC since 1996 until adolescence in 2007. The personal identity of the breakthrough cases among fully vaccinated children was guaranteed by use of the Swedish unique ID numbers, and no child was counted twice in the national reporting system (5). While randomization theoretically eliminates many of the biases connected with epidemiological cohort studies, this study has some limitations. First, to be counted as a case of pertussis a child had to have symptoms of some duration and severity, the parents had to have sought medical care, a valid sample had to have been taken and processed, and the positive result had to have been reported by use of the Swedish ID number to the SIIDC. Most cases of pertussis infection in vaccinated children are assumed to be asymptomatic and/or of little clinical significance, and therefore this study‘s inclusion criterion (culture/PCR positivity) limited the numbers to only a small proportion of the true numbers of pertussis infections in Sweden. However, there is no a priori scientific reason to believe that the diagnostic procedures or the bacterial yield differed between the three vaccine groups under study, even though such a possibility cannot be entirely discarded (3). Therefore, comparing three different vaccine groups is assumed to be valid and non-biased. Second, the SIIDC does not have direct information on the children or their families after the end of the follow up in Trial II in 1996, and some children from the original cohort may have emigrated from Sweden. Likewise, some vaccine breakthrough cases may have been offered booster vaccines not documented in the Swedish registries.

A strength of this study is that the cohorts were exposed to natural pertussis during follow up. For the 1993 birth cohort, national pertussis incidences per 100,000 person years ranged between 839 and 1484 for the years 1993–1996, between 203 and 543 for the years 1997–2000, and between 20 and 87 for the years 2001–2007 (9).

Australian investigators have reported that priming with DTwP is associated with a lower risk of subsequent pertussis than in DTaP-only primed children and that this difference has been evident for more than a decade (10). Our study to some degree supports this finding. We found that an efficacious wP vaccine performed somewhat better compared to two efficacious aP vaccines.

However, it should be stated that the number of breakthrough cases during 11 years of follow up was actually quite small in all three vaccine groups. Most cases occurred after 6 years of follow up and would have been avoided if a booster dose against pertussis had been offered to the three cohorts of children, as is now routinely done in Sweden and elsewhere (6).

An interesting observation is the different kinetics between the two aP vaccine groups under study. The Kaplan–Meier estimates indicate a statistically significant difference between the Chiron vaccine and the Connaught CLL vaccine, mirroring

more breakthrough cases in the Chiron group during the first years of follow up (Figure 1). The cumulative numbers of cases were, however, quite similar between the two aP groups, and significantly higher compared to the wP group (Figure 2).

In January 1996, Sweden introduced general vaccination against pertussis using aP vaccines from different manufacturers and in different combinations. After some years satisfactory control of pertussis was attained, although there have been small outbreaks of pertussis among vaccinated children and unfortunately also some cases of deaths in infants too young to be vaccinated. Complementary strategies are thus needed to achieve a reduction in morbidity and mortality (9).

In conclusion, this study is supportive of the current Swedish vaccination program, with aP vaccines given at 3, 5, and 12 months of age with a booster at pre-school age, given the high vaccine coverage.

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Appendix

Appendix A

N01-AI-15125, Technical Report Trial II, Appendix 12.1

Number of cases in 6-month intervals from Dose 3 in Trail II until 7 October 1996 (end of blinded follow-up)

Table 12.1.2 Number of culture-confirmed cases of the two primary case definitions for the Chiron acellular three-component vaccine (DTPa3), the CLL acellular five-component vaccine (DTPa5) and the Evans–Wellcome whole-cell vaccine (DTPwc), in six months intervals (1 month = 30 days) from Dose 3 until 7 October 1996 in the 3, 5, and 12-month schedule.

Number of cases	DTPa3	DTPa5	DTPwc
Children at risk who got 3 doses	17,679	17,686	17,453
0–<6 months after Dose 3	7	7	2
6–<12 months after Dose 3	12	4	4
12–<18 months after Dose 3	13	8	9
≥18 months after Dose 3	17	8	4

Appendix B

Variable List 1997, Lab reports

- Date of registration
- Laboratory diagnosis
- Laboratory
- Type of notification
- Type of patient-ID
- Sex
- Year of birth
- Age
- Name
- Sample identification number
- Arrival date of sample
- Type of sample
- Diagnostic method
- Species/type
- Name of physician responsible
- Clinic of referral for notification
- County medical officers responsible for notification
- Date of notification

Appendix C

Clinical follow-up of pertussis in persons born from 1996

(including participants in pertussis vaccine trials KVPI and KVPII)

Version dated 2008-08-29

I. BASIC INFORMATION OF THE CASE (* = field i SmiNet)

88 = report missing ("no data"), 99 = missing in report ("missing")

Patient* (name)

Personal identity number* (alternatively other number)

Phone (home)*

County* (*where patient lives*)

Guardian

Other phone numbers (work/mobile)

Childcare centre/school

Lab* (name)

Lab-identification number*

Method*

Date sample was taken* (YYMMDD)

Date of diagnosis of clinical report* (YYMMDD)

County medical officers responsible for notification* (*where case was notified*)

1. Form number

2. Study area (Gothenburg, rest of Sweden)

II. EXCLUSION CRITERIA

3. Family could not be reached for an interview (end the form)

1 Unknown address/phone, 2 No answer despite repeated calls, 3 Language barriers

4. Is the patient deceased 0 = no, 1 = yes

5. If the patient is deceased, provide date (YYMMDD)

(Do NOT contact the family. If possible, ask the childcare centres, department for communicable diseases, or other source for information regarding vaccination status including if born premature or "full-term" for infants, fill out #55 and end the form.)

III. FIRST INTERVIEW WITH THE FAMILY

not asked ("no data/not relevant"), 99 = asked but person did not know ("missing")

6. Date for first contact with family/individual during this pertussis episode (YYMMDD)

7. Spoke to; 1 mother, 2 father, 3 other, 4 the person him/herself

8. If spoken to other:

9. OK to ask questions regarding the child's pertussis as well as to retrieve vaccination information from childcare centres/school?

1 Yes, both ; 2 Yes, clinical questions only; 3 Yes, vaccination information only; 0 No (End form)

10. Are cough or daily cough attacks present at the time of the first contact

0 No, 1 Yes, 2 Cough and daily cough attacks, 3 Only cough during episode, 4 Cough but daily cough attacks have ended

11. If cough, when was date of onset (YYMMDD)

12. If cough attacks, when was date of onset (YYMMDD)

13. Has the child participated in a pertussis vaccine trial?

0 No, 1 KVP1, 2 KVP2, 3 Gothenburg, 4 Other city

IV. VACCINATION INFORMATION FROM CHILD CARE CENTER/SCHOOL

88 = not received current dose ("no data/not relevant"), 99 = vaccinated but information missing for current dose ("missing")

14. Date of contact with childcare centre/school (YYMMDD)

15. Dose 1, Date (YYMMDD)

16. Dose 1, Pertussis vaccine (use code from list)

17. Dose 1, Batch number

18. Dose 2, Date (YYMMDD)

19. Dose 2, Pertussis vaccine (use code from list)

20. Dose 2, Batch number

21. Dose 3, Date (YYMMDD)

22. Dose 3, Pertussis vaccine (use code from list)

23. Dose 3, Batch number

24. Dose 4, Date (YYMMDD)

25. Dose 4, Pertussis vaccine (use code from list)

26. Dose 4, Batch number

27. Dose 5, Date (YYMMDD)

28. Dose 5, Pertussis vaccine (use code from list)

29. Dose 5, Batch number

30. Dose 6, Date (YYMMDD)

31. Dose 6, Pertussis vaccine (use code from list)

32. Dose 6, Batch number

V. SECOND INTERVIEW WITH FAMILY

88 = not asked ("no data/not relevant"), 99 = asked but person did not know ("missing")

33. Date for second contact with family/individual during this pertussis episode (ÅÅMMDD) (write 88 if form ended after the first contact)

34. Spoke to; 1 mother, 2 father, 3 other, 4 the person him/herself

35. If spoken to other

36. Are cough or daily cough attacks present at the time of the first contact
0 No, 1 Yes, 2 Cough and daily cough attacks, 3 Only cough during episode, 4 Cough but daily cough attacks have ended

The following questions are filled out at the second contact (or with the first contact if the child has had paroxysmal cough for at least 21 days)

37. What date did daily cough attacks end, or if only cough during the episode, what date did it end (YYMMDD) (Write 88 if no cough or cough attacks. If ongoing cough, write 99)

38. Duration of disease from start of cough to last day of cough attacks or cough (including last day) (Days)

39. Number of days with cough attacks (Days)

40. Has the child had spasmodic cough
0 No, 1 Yes, several/day, 2 Yes, several/week , 3 Yes, occasionally throughout the period

41. Has the child had cough/cough attacks that resulted in vomiting, 0 No, 1 Yes, several/day, 2 Yes, several/week, 3 Yes, occasionally throughout the period

42. Hospitalized during the episode? If yes, how many days (Days) (write 0 if the child was not hospitalized)

43. If hospitalized, which date (YYMMDD) (write 88 if not hospitalized)

44. Ok to request a copy of the journal for the hospitalization for pertussis? 0 No, 1 Yes (submit request)

45. Respiratory complications 0 No, 1 Yes, 2 Yes, with apnoea

46. Dehydrated, >5% weight loss, 0 No, 1 Yes

47. Other serious complications, 0 No, 1 Yes

48. If yes, which complications (write)

49. Treated with antibiotics for pertussis; from what date (YYMMDD)

50. Completed antibiotic treatment for pertussis; number of days (Days)

51. Treated with antibiotics for pertussis; 1 Erythromycin, 2 Other macrolide, e.g. Azithromycin/Clarithromycin/Roxithromycin, 3 Trimethoprim/sulfa, 4 Other antibiotic

52. If other antibiotics, which ones? (write 88 if no treatment for pertussis)

53. For infants: Ok with contact tracing questions? 0 No, 1 Yes (fill out separate form)

VI. OTHER

54. Other relevant information (vaccination status/length of pregnancy if deceased, etc.):

55. Date when form was ended (YYMMDD)

Appendix D

Number of cases reported per year of follow-up, name and type of vaccine.

Year post last (third) dose	Evans (wP)	Chiron (3-aP)	CLL (5-aP)
≤1	15	32	19
2	6	23	16
3	5	11	12
4	6	8	8
5	13	14	15
6	6	13	16
7	3	6	6
8	3	1	5
9	5	2	4
10	6	6	3
11	4	3	7
≥12	4	1	5
Total	76	120	116

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