

## Decline of pertussis in hospitalised children following the introduction of immunisation in pregnancy – results from a nationwide, prospective surveillance study, 2013–2020

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### Summary

**AIMS OF THE STUDY:** Surveillance of pertussis at a national level is important to collect information on the epidemiology of the disease and to design optimal immunisation strategies. After an initial surveillance period for pertussis in hospitalised children in Switzerland from 2006 to 2010, new recommendations (including immunisation in pregnancy) were implemented in the national pertussis immunisation schedule in 2013. To monitor its effects, surveillance was resumed in 2013 and concluded in 2020.

**METHODS:** From 1 January 2013 to 31 December 2020, hospitalised children under the age of 16 years with suspected or proven *Bordetella pertussis* infection were reported to the Swiss Paediatric Surveillance Unit. We analysed epidemiological and clinical characteristics for all patients who fulfilled the clinical case definition of pertussis (physician diagnosis, cough lasting  $\geq 14$  days in combination with at least one of the following symptoms: paroxysmal cough, whooping or post-tussive vomiting, or apnoea not otherwise explained in patients under the age of 12 months) with and without laboratory confirmation (polymerase chain reaction, culture or serology).

**RESULTS:** 220 of the 306 reported cases met the inclusion criteria. Of these, 214 (97%) were laboratory-confirmed *B. pertussis* infections: 209 by polymerase chain reaction and 5 by culture from nasopharyngeal specimens. 172/220 (78%) patients were infants under six months of age at the day of hospitalisation. The mean annual hospitalisation rate for pertussis was 27.9 per 100,000 children for infants and 2.1 per 100,000 in all children  $< 16$  years of age. Of the 115 cases with precise records of immunisation, 50 (43%) were unimmunised, 3 (3%) were incompletely immunised and 62 (54%) were up to date with their immunisation status according to their age, including 10 (9%) whose next doses were due. However, most patients with an up-to-date immunisation status (85%) were still too young to have completed their primary series, leaving only eight cases of vaccine failure. Only 5 of the 172 infants

$< 6$  months of age had mothers who had been vaccinated during pregnancy.

**CONCLUSIONS:** After the introduction of immunisation in pregnancy in Switzerland, hospitalisation rates in infants declined. However, the remaining cases call for increased efforts towards more complete and timely immunisation of children, those in close contact with children, and pregnant women.

### Introduction

The control of pertussis, a respiratory tract infection mainly caused by the bacterium *Bordetella pertussis*, remains a global challenge despite the availability of effective vaccines [1]. In this regard, longitudinal surveillance of pertussis at a national level is important [2, 3] to collect information on the epidemiology of the disease and to design an optimal immunisation strategy. The Swiss Sentinel Surveillance Network (SSSN) has been monitoring the incidence of pertussis in the general population in Switzerland since 1991. As pertussis is most severe in infants and children, we utilised the Swiss Paediatric Surveillance Unit (SPSU) to assess reported hospitalisations due to pertussis to survey the characteristics of the disease. After an initial surveillance period covering the years 2006–2010 [4], new recommendations regarding pertussis were implemented in the Swiss national immunisation schedule in 2013. Specifically, pertussis booster doses were introduced for anyone in close contact with infants  $< 6$  months of age and for pregnant women to protect the most vulnerable age group [5]. To assess the effects of these new recommendations, surveillance was resumed from 2013 to 2020. Having previously published some preliminary data [6], we now report the detailed and final results.

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## Methods

### Data collection and ethics

The SPSU is an active reporting system under the auspices of the Swiss Federal Office of Public Health (FOPH). It monitors nationwide hospitalisations of children due to defined childhood diseases in Switzerland. All paediatric hospitals or units in Switzerland participate on a voluntary basis. SPSU projects have been exempt from ethical approval throughout the duration of this study. Pertussis was reported to the SPSU from 2006 to 2010, and this resumed on 1 January 2013 until 31 December 2020.

### Case definition

Laboratory confirmation of a *B. pertussis* infection by polymerase chain reaction, culture or serology and/or a fulfilled clinical case definition in a hospitalised child under 16 years of age was mandatory for inclusion. The clinical case definition comprised (1) signs and symptoms compatible with pertussis (physician diagnosis) or (2) a cough lasting  $\geq 14$  days in combination with at least one of the following symptoms: paroxysmal cough, whooping or post-tussive vomiting or (3) apnoea in a patient under the age of 12 months not explained otherwise.

### Data analyses

A standardised, anonymous questionnaire was sent to participating hospitals for every new case notification. All questionnaires were returned to the principal investigator (UH) and checked for completeness. In the case of missing data, the reporter was contacted for clarification. The data was converted into an Excel datasheet at the FOPH.

The statistical methods used have been reported before [6]. Briefly, we performed descriptive analyses for epidemiological data and used frequencies or proportions to report patient characteristics. Also, to compare the number of hospitalised cases of pertussis during the first and second halves of the total study surveillance period, we calculated age-specific proportionate changes. We used the GraphPad Prism software (version 8.4.3., San Diego, CA, USA) to calculate the 95% confidence intervals and the method of Wilson with modifications by Brown et al. for selected percentages, as appropriate [7]. Population statistics from the Swiss Federal Statistical Office were used to calculate age-dependent pertussis hospitalisation incidence values [8].

## Results

All paediatric units and hospitals in Switzerland participated in this SPSU project throughout the study period from January 2013 to December 2020. Compliance through the return of the monthly reporting forms was 100% over the whole study period.

### Epidemiology

In total, 306 cases of pertussis were reported to the SPSU. Of these, 86 were excluded for various reasons (fig. 1). The following analyses are based on the remaining 220 cases (95 females, 43%). Laboratory confirmation of *B. pertussis* infection was provided in 214 (97%) cases (209 by polymerase chain reaction and 5 by culture from nasopharyngeal specimens), of which 192 (87%) also met criteria for a clinical case of pertussis, as did a further six cases without laboratory confirmation (see supplementary table S1 in the appendix).

Figure 2 shows seasonal variations in incidence and the overall decline in reported cases across the whole surveillance period. The intermittent increase observed for the years 2016 and 2017 was also seen in outpatient pertussis cases reported via the SSSN (appendix, table S2). Notably, the last case of pertussis was reported to the SPSU in May 2020. The mean annual incidence of hospitalisation for pertussis was 27.9 per 100,000 in infants (<1 year of age) and 2.1 per 100,000 in all children under 16 years of age.

To evaluate the effects of the introduction of pertussis immunisation in pregnancy in 2013, we divided the surveillance period into two parts, 2013 to 2016 (early) and 2017 to 2020 (late). The decrease in case numbers from the early to the late surveillance period was most pronounced in infants (table 1).

### General patient characteristics

Age at day of hospitalisation ranged from 16 days to 15 years, with a median of 11.6 weeks (IQR: 6.4–20.6 weeks). The great majority of hospitalised children (172 out of 220, 78%) were infants <6 months of age, including 86 (39%) <2 months of age and 23 (10%) newborns, i.e. <1 month of age (table 1). The time interval between the onset of clinical signs or symptoms of pertussis and hospitalisation was known in 213 (97%) patients. The mean interval was 11.1 days (median: 10; range: 0–48) across all ages, with a mean of 5.4 days in neonates (median: 4.5; range: 1–16) and a mean of >10 days in children over two months of age (appendix, table S3). Mean and median duration of hospitalisation were highest in neonates and decreased with increasing age (table 2).

### Disease characteristics

Paroxysmal cough was not only the main reason for hospitalisation, but also the most frequent symptom (97%), followed by rhinitis (65%) and post-tussive vomiting (43%), whereas fever was infrequent (17%), especially in infants <6 months of age (appendix, table S4). Only 15% of patients did not suffer from any complications due to pertussis. The most common complications were cyanosis and dyspnoea (both >50%). Severe complications, such as pneumonia, cerebral convulsions and encephalopathy, were rare (each  $\leq 5\%$ ) (table 3). Over the whole surveillance period, three children died: two neonates (whose mothers were not vaccinated against pertussis during pregnancy) and an 18-month-old unvaccinated patient. All of them suffered from severe complications leading to death less than two weeks after admission to hospital. Therefore, the case fatality rate was 1.4% among all children hospitalised with pertussis, and 8.7% in neonates.

Two hundred and twelve patients (97%) received antibiotic treatment, most commonly a macrolide (appendix, table S5). Intensive care treatment was required in 52% of all

neonates, with the proportions requiring this decreasing with increasing age (appendix, table S6).

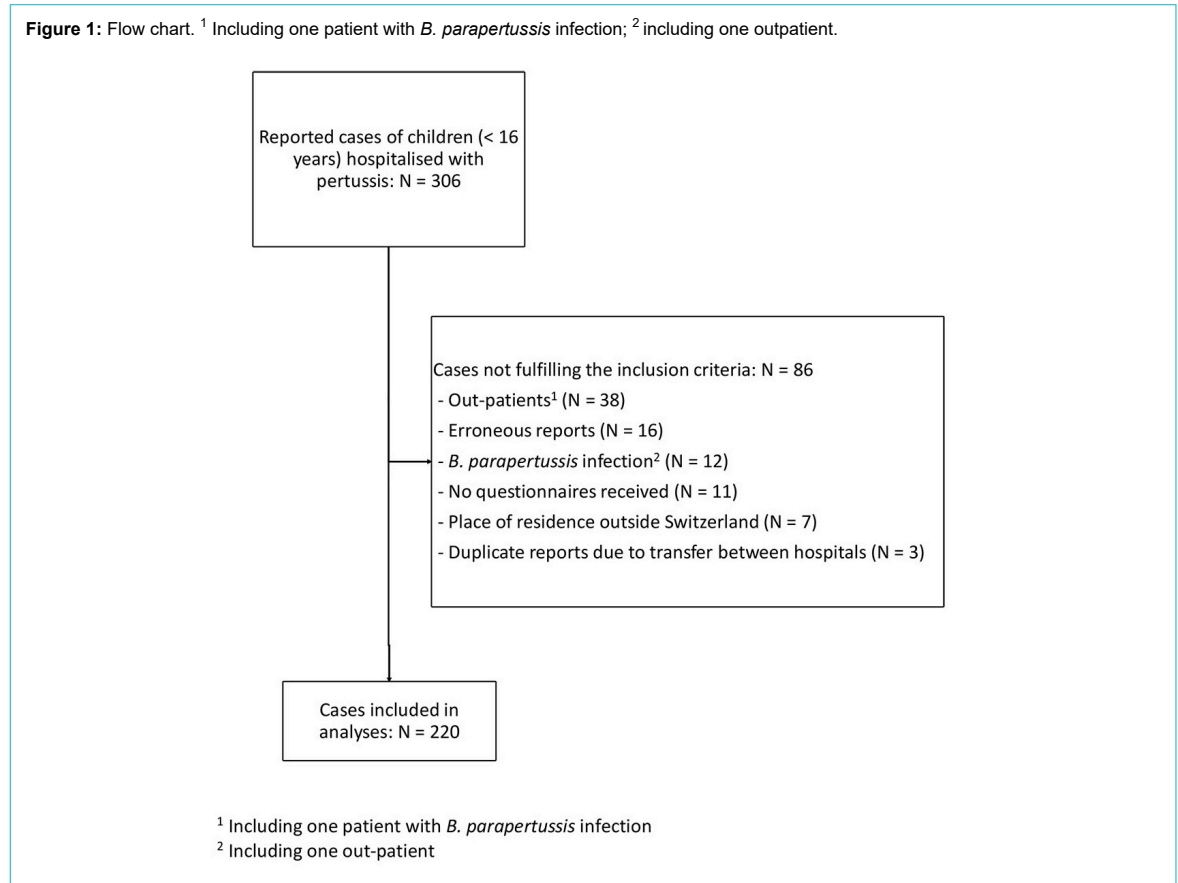
A likely source of infection was identified in 162 patients (74%) and was most commonly a member of the same household (140 cases; 86%) (appendix, table S7).

**Immunisation status**

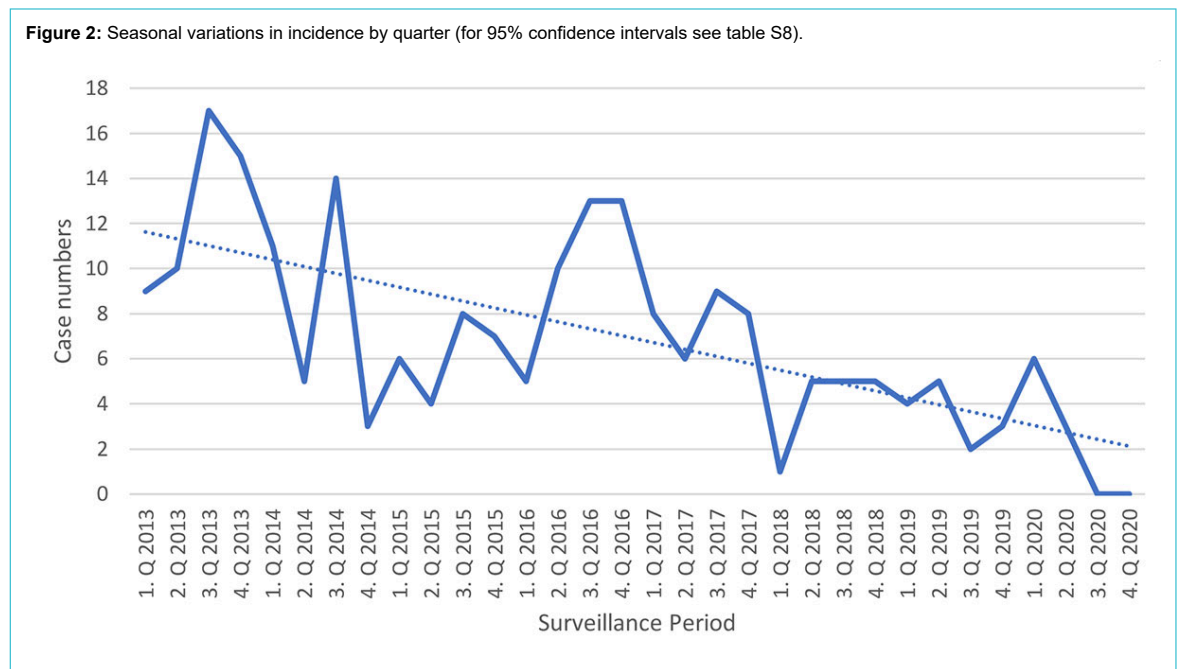
Ninety-five patients (43%) were <2 months of age at onset of symptoms and therefore too young to be vaccinated.

In 115 of the remaining 125 cases, all necessary information, such as number of doses, date of immunisations and exact age, was available (fig. 3). Of these, 50 patients (43%) were unimmunised. Three children (3%) had an incomplete pertussis immunisation status according to their age and a further 10 (9%) were still up to date but their next doses were due. Finally, 52 patients (45%) had an up-to-date pertussis immunisation status according to their age (fig. 3). Forty-four (85%) of these, however, were still

**Figure 1:** Flow chart. <sup>1</sup> Including one patient with *B. parapertussis* infection; <sup>2</sup> including one outpatient.



**Figure 2:** Seasonal variations in incidence by quarter (for 95% confidence intervals see table S8).



too young to have completed their primary series. The remaining eight cases were vaccine failures (four after the third dose, three after the fourth dose and one after the sixth dose). Notably, no vaccine failures occurred after

**Table 1:**

Case counts by age category and surveillance period (modified from table 1 in [6]).

	01.01.2013–31.12.2016	01.01.2017–31.12.2020	Increase or decrease	Total (01.01.2013–31.12.2020)
Age category	N (%)*	N (%)*	% (95% CI)	N (%)
<1 month	16 (11)	7 (10)	–56 (–33 to –77)	23 (10)
1 month	43 (29)	20 (29)	–54 (–39 to –68)	63 (29)
<2 months (cumulative)	59 (39)	27 (39)	–54 (–42 to –66)	86 (39)
2 months	28 (19)	10 (14)	–64 (–46 to –79)	38 (17)
3–5 months	34 (23)	14 (20)	–59 (–42 to –74)	48 (22)
<6 months (cumulative)	121 (81)	51 (73)	–58 (–49 to –66)	172 (78)
6–11 months	13 (9)	4 (6)	–69 (–42 to –87)	17 (8)
12–23 months	5 (3)	5 (7)	0 (0 to –43)	10 (5)
≥2 years	11 (7)	10 (14)	–9 (–0.5 to –38)	21 (10)
Total**	150 (68)	70 (32)	–53 (–45 to –61)	220 (100)
Extrapolated number of cases according to Swiss Sentinel system***	34,845 (65)	18,791 (35)	–46 (–46 to –47)	53,636 (100)

\* Percentage of all reported cases in that period

\*\* Percentage of total surveillance period 2013–2020

\*\*\* Personal Communication Damir Perisa and Tania Villeneuve (Federal Office of Public Health, Switzerland, March 16, 2021)

**Table 2:**

Duration of and reasons for hospitalisation.

	Patients*	Duration of first hospitalisation**	Cough/coughing spells	Cyanosis	Monitoring and observation	Feeding difficulties and/or vomiting	Apnea	Dyspnoea	Others	Reason Unknown
Age category	N (%)	Mean/Median (Range)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
<1 month	23 (10)	14.2/11 (3–46)	15 (68)	4 (18)	1 (5)	3 (14)	4*** (18)	2 (9)	6 (27)	1 (4)
1 month	63 (29)	10.9/9.5 (2–34)	36 (59)	14 (23)	16 (26)	12 (20)	7 (11)	3 (5)	8 (13)	2 (3)
2 months	38 (17)	6.6/4.5 (2–32)	21 (60)	8 (23)	9 (26)	3 (9)	8 (23)	0 (0)	3 (9)	3 (8)
3–5 months	48 (22)	5.2/4 (2–21)	33 (72)	14 (30)	11 (24)	4 (9)	8*** (17)	2 (4)	0 (0)	2 (4)
6–11 months	17 (8)	4.5/4 (2–11)	13 (76)	2 (12)	4 (24)	3 (18)	1 (6)	1 (6)	2 (12)	0 (0)
12–23 months	10 (5)	5.1/4 (2–12)	5 (50)	1 (10)	1 (10)	0 (0)	1 (10)	2 (20)	3 (30)	0 (0)
≥2 years	21 (10)	5.7/3 (2–47)	14 (70)	4 (20)	1 (5)	5 (25)	1 (5)	2 (10)	7 (35)	1 (5)
Total	220 (100)	8/5 (2–47)	137 (65)	47 (22)	43 (20)	30 (14)	30 (14)	12 (6)	29 (14)	9 (4)

\* In some patients more than one reason for hospitalisation was reported

\*\* Duration in one patient unknown

\*\*\* Including one patient with an Apparent Life Threatening Event (ALTE)

Table updated from [4]

**Table 3:**

Complications by age category.

Age category	Patients	Cyanosis	Dyspnoea	Sleep disturbed	Apnoea	Pneumonia	Cerebral convulsions	Encephalopathy	Others	Any
	N (%)	N/N known (%)	N/N known (%)	N/N known (%)	N/N known (%)	N/N known (%)	N/N known (%)	N/N known (%)	N/N known (%)	N/N known (%)
<1 month	23 (10)	18/22 (82)	16/23 (70)	10/22 (45)	18/22 (82)	6/23 (26)	0/23 (0)	2/23 (9)	3 <sup>1,2</sup> /23 (13)	21/23 (91)
1 month	63 (29)	38/60 (63)	38/63 (60)	31/59 (53)	35/63 (56)	1/63 (2)	1/63 (2)	0/63 (0)	1 <sup>3</sup> /63 (2)	56/63 (89)
2 months	38 (17)	16/37 (43)	16/38 (42)	13/38 (34)	12/38 (32)	2/38 (5)	1/38 (3)	0/38 (0)	1 <sup>3</sup> /38 (3)	26/38 (68)
3–5 months	48 (22)	26/48 (54)	20/48 (42)	20/48 (42)	17/48 (35)	0/48 (0)	0/48 (0)	0/48 (0)	0/48 (0)	41/48 (85)
6–11 months	17 (8)	9/16 (56)	10/17 (59)	10/14 (71)	6/17 (35)	0/17 (0)	0/17 (0)	0/17 (0)	0/17 (0)	17/17 (100)
12–23 months	10 (5)	5/10 (50)	5/10 (50)	2/9 (22)	2/10 (20)	0/10 (0)	2/10 (20)	1/10 (10)	2 <sup>4,5</sup> /10 (20)	9/10 (90)
≥2 years	21 (10)	8/21 (38)	9/21 (43)	13/21 (62)	1/21 (5)	2/21 (10)	0/21 (0)	0/21 (0)	2 <sup>5,6</sup> /21 (10)	18/21 (86)
Total	220 (100)	120/214 (56)	114/220 (52)	99/211 (47)	91/219 (42)	11/220 (5)	4/220 (2)	3/220 (1)	9/220 (4)	188/220 (85)

<sup>1</sup> Hyperleucocytosis

<sup>2</sup> Neonatal respiratory distress syndrome (NRDS), arterial hypertension

<sup>3</sup> Weight loss

<sup>4</sup> Hypoxia

<sup>5</sup> Syncope during coughing spell

<sup>6</sup> Fear of death

the switch from the 3+1 to the reduced 2+1 immunisation schedule in Switzerland in March 2019 [9].

Although information on the pertussis immunisation status was only known in 47 of the 220 (21%) mothers, we identified 5 out of 172 (3%) infants under the age of six months whose mothers had been vaccinated during the pregnancy. Three of these five mothers had received their vaccine dose at 17 to 31 weeks of gestation, whereas in the other two cases time points of the immunisation during pregnancy were not reported.

## Discussion

Here we report the results of a nationwide pertussis surveillance study in hospitalised children in Switzerland after the introduction of immunisation during pregnancy in 2013.

Figure 2 shows some seasonal variations but overall, a clear decrease in reported cases during the eight-year surveillance period was seen. We previously compared the mean hospitalisation rate of the current study period up to 2019 with the preceding period (2006–2010) and showed a decline in incidence, especially in infants, i.e. <1 year of age [6]. Here, with the case numbers from 2020 included, the decline is further extended, from mean annual hospitalisation rates of 38.8 per 100,000 children <1 year and 2.6 per 100,000 patients <16 years between 2006 and 2010 to 27.9 and 2.1 per 100,000 children <1 year and <16 years respectively between 2013 and 2020.

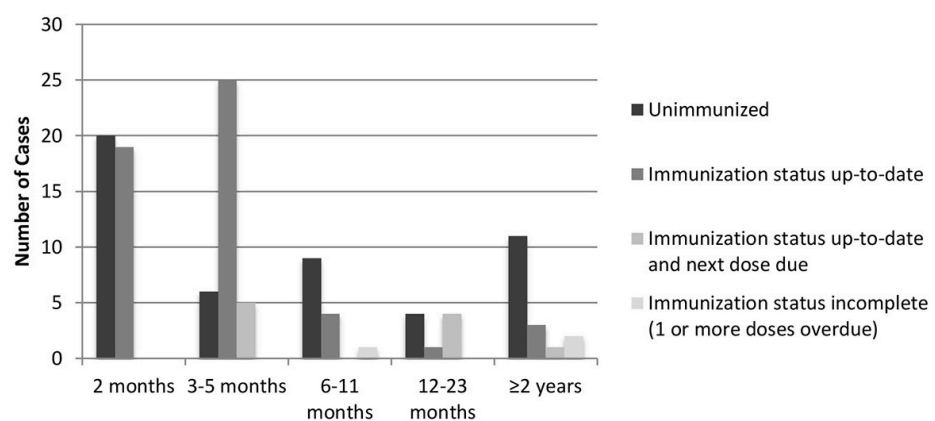
Different studies have shown that the implementation of public health measures to slow down the COVID-19 pandemic also had an impact on the transmission of other infectious diseases [10, 11], including pertussis [12]. With the introduction of strict measures (e.g. working from home, closing leisure facilities, limiting social gatherings etc.) in Switzerland in mid-March 2020, reported pertussis case numbers declined from six cases to three from the first to the second quarter of the year. After May 2020, no further cases were reported. This indicates a massive reduction in the transmission of *B. pertussis* in the Swiss paediatric population due to the public health measures established during 2020, as was also noted in the general population (table S2) and continues to be the case in 2021 [13].

Young infants are the age group at highest risk for complications and death due to pertussis and at the same time, they are too young to be completely immunised. In our surveillance study, 78% of all hospitalised children were under the age of six months and therefore not or incompletely immunised. Protecting this age group indirectly by immunising their close contacts, a strategy called “cocooning”, is challenging and – at least in our region – complicated by the lack of knowledge among parents about the importance of their own immunisation status [14, 15]. As in our previous surveillance period, covering the years 2006–2010 [4], the main suspected source of infection was members of the child’s household. However, even if cocooning was implemented with very high compliance, the limited efficacy of the currently used pertussis vaccines against disease – and especially against *B. pertussis* infection and transmission – would not prevent the exposure of infants in their own households sufficiently [16]. Moreover, the relatively high proportion of cases (26%) in which the source of infection was not known suggests that silent transmission (i.e. sporadic contact with unrecognised pertussis cases) of *B. pertussis* is a common phenomenon. This makes protecting young infants through cocooning even more difficult.

A more promising way to protect these infants from pertussis is via immunisation of their mothers against pertussis in every pregnancy. Studies have shown that this measure successfully reduces the risk of hospitalisation due to pertussis by approximately 80–90% [17, 18, 19]. Currently, pertussis immunisation in pregnancy can only be achieved by use of tetanus-diphtheria-acellular pertussis combination vaccines (Tdap) due to the lack of a stand-alone pertussis vaccine in most parts of the world, including Europe. For further pregnancies, repeated immunisation against pertussis alone would suffice, whereas pregnant women and their unborn children would not benefit from repeated tetanus and diphtheria toxoid doses. Although repeated doses of Tdap within a short period of time do not lead to increased reactogenicity when compared to longer intervals, i.e. up to 10 years, a stand-alone acellular pertussis vaccine would be highly welcome [20].

In Switzerland, immunisation during pregnancy was implemented in 2013 and acceptance of this recommendation during the early surveillance period was poor [15]. In the meantime, however, compliance has improved substantially. Although our study was not designed to formally assess

**Figure 3:** Immunisation status of children hospitalised due to pertussis.



the effectiveness of pertussis immunisation in pregnancy, the continuous decline in cases in infants under two months of age throughout the course of our study (table S2) is in accordance with this observation.

Similar to the findings from the previous surveillance period (2006–2010) [4], vaccine failure in children with complete primary immunisation series was infrequent.

We are not aware of any similar comprehensive, longitudinal, national pertussis surveillance data covering the whole paediatric age spectrum from other countries published in the recent past. However, a comparison between reports from the pre-acellular vaccine era, about three decades ago, in Germany and the USA [21, 22] and our current findings reveals very similar and unchanged clinical characteristics and epidemiological features of pertussis in children.

Our study has strengths and limitations. The duration of the study, over eight years, the high proportion of laboratory-confirmed cases and the nationwide reporting through SPSU make the results highly reliable. Although underreporting, underrecognition and underdiagnosis of pertussis may have led to falsely low numbers, there is no reason to believe that this is any different from previous years and other similar studies. One limitation is that white blood cell counts were not systematically demanded from the reporters. Extreme leucocytosis is a risk factor for severe pertussis and even death in young infants [23] and therefore, such information should be recorded in future pertussis surveillance projects.

In conclusion, respectable improvements have been achieved with the introduction of immunisation against pertussis in pregnancy. However, to better protect young infants from this life-threatening disease, further efforts to achieve better compliance through timely and complete immunisation in pregnant women, infants themselves and those in close contact with them are needed.

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#### Conflict of interest

Both authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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## Appendix: supplementary data

Table S1:

Case definitions by age groups.

Age category	Patients	Laboratory confirmed <i>B. pertussis</i> infection, clinical case definition fulfilled	Laboratory confirmed <i>B. pertussis</i> infection, clinical case definition not fulfilled	Clinical case definition fulfilled, no laboratory confirmation
	N (%)	N (%)	N (%)	N (%)
<1 month	23 (10)	22 (96)	1 (4)	0 (0)
1 month	63 (29)	60 (95)	3 (5)	0 (0)
2 months	38 (17)	30 (79)	8 (21)	0 (0)
3–5 months	48 (22)	43 (90)	3 (6)	2* (4)
6–11 months	17 (8)	15 (88)	1 (6)	1 (6)
12–23 months	10 (5)	5 (50)	4 (40)	1 (10)
≥2 years	21 (10)	17 (81)	2 (10)	2 (10)
Total	220 (100)	192 (87)	22 (10)	6 (3)

\* Including one patient with unknown duration of cough and physician diagnosed pertussis

Table S2:

Case counts by age categories, sex, and surveillance years.

Age category	2013	2014	2015	2016	2017	2018	2019	2020	Total	Female	Incidence
	N (%)*	N (%)*	N (%)*	N (%)*	N (%)*	N (%)*	N (%)*	N (%)*	N (%)**	N (%)***	N†
<1 month	6 (12)	4 (12)	3 (12)	3 (7)	0 (0)	2 (13)	5 (36)	0 (0)	23 (10)	8 (35)	40.8
1 month	16 (31)	9 (27)	9 (36)	9 (22)	9 (29)	5 (31)	2 (14)	4 (44)	63 (29)	26* (41)	111.6
<2 months (cumulative)	22 (43)	13 (39)	12 (48)	12 (29)	9 (29)	7 (44)	7 (50)	4 (44)	86 (39)	34 (40)	76.2
2 months	9 (18)	4 (12)	4 (16)	11 (27)	6 (19)	1 (6)	1 (7)	2 (22)	38 (17)	16 (42)	67.3
3–5 months	13 (25)	4 (12)	4 (16)	13 (32)	8 (26)	3 (19)	3 (21)	0 (0)	48 (22)	22 (46)	28.3
<6 months (cumulative)	44 (86)	21 (64)	20 (80)	36 (88)	23 (74)	11 (69)	11 (79)	6 (67)	172 (78)	72 (42)	50.8
6–11 months	1 (2)	6 (18)	3 (12)	3 (7)	1 (3)	1 (6)	2 (14)	0 (0)	17 (8)	8 (47)	5.0
12–23 months	1 (2)	1 (3)	2 (8)	1 (2)	3 (10)	1 (6)	0 (0)	1 (11)	10 (5)	5 (50)	1.5
≥2 years	5 (10)	5 (15)	0 (0)	1 (2)	4 (13)	3 (19)	1 (7)	2 (22)	21 (10)	10 (48)	0.2
Total**	51 (23)	33 (15)	25 (11)	41 (19)	31 (14)	16 (7)	14 (6)	9 (4)	220 (100)	95 (43)	2.1
Extrapolated Cases by Swiss Sentinel System§. **	10'140 (19)	9'391 (18)	7'001 (13)	8'313 (15)	8'873 (17)	3'995 (7)	4'374 (8)	1'549 (3)	53636 (100)	Not reported	–

\* Percentage of all reported cases in that year

\*\* Percentage of total surveillance period 2013–2020

\*\*\* Percentage of all reported cases in that age group

° Information not available in one patient

\* Per 100'000 children in this age category

§ Personal Communication Damir Perisa and Tania Villeneuve (Federal Office of Public Health, Switzerland, March 16, 2021)

Table S3:

Duration from onset of signs and symptoms to hospitalisation (in days).

Age category	Patients N (%)	Mean	Median	Range	Duration unknown
<1 month	23 (10)	5.4	4.5	1–16	1 (4)
1 month	63 (29)	10.5	9	1–48	3 (5)
2 months	38 (17)	10.7	9	1–36	0 (0)
3–5 months	48 (22)	11.8	11.5	3–29	0 (0)
6–11 months	17 (8)	14.8	11.5	4–43	1 (6)
12–23 months	10 (5)	14.4	16	1–33	1 (10)
≥2 years	21 (10)	14.2	14.5	0–31	1 (5)
Total	220 (100)	11.1	10	0–48	7 (3)



**Table S4:**  
Signs and symptoms by age categories.\*

Age category	Patients	Paroxysmal cough	Rhinitis	Post-tussive vomiting	Whooping	Fever (≥38 °C)	Others
	N (%)	N/N known (%)	N/N known (%)	N/N known (%)	N/N known (%)	N/N known (%)	N/N known (%)
<1 month	23 (10)	22/23 (96)	18/23 (78)	15/22 (68)	9/22 (41)	2/23 (9)	1 <sup>1</sup> /23 (4)
1 month	63 (29)	62/63 (98)	41/63 (65)	29/61 (48)	15/59 (25)	5/63 (8)	2 <sup>1,2</sup> /63 (3)
2 months	38 (17)	37/38 (97)	25/37 (68)	14/38 (37)	9/37 (24)	5/37 (14)	1 <sup>2</sup> /38 (3)
3–5 months	48 (22)	48/48 (100)	28/46 (61)	17/48 (35)	10/47 (21)	6/47 (13)	4 <sup>2,3,4</sup> /48 (8)
6–11 months	17 (8)	17/17 (100)	11/17 (65)	8/16 (50)	4/14 (29)	4/17 (24)	0/17 (0)
12–23 months	10 (5)	7/10 (70)	8/10 (80)	2/10 (20)	1/10 (10)	5/10 (50)	1 <sup>3</sup> /10 (10)
≥2 years	21 (10)	20/21 (95)	10/20 (50)	7/21 (33)	4/19 (21)	9/21 (43)	3 <sup>1,5</sup> /21 (14)
Total	220 (100)	213/220 (97)	141/216 (65)	92/216 (43)	52/208 (25)	36/218 (17)	12/220 (5)

\* Presence of signs and symptoms not in all patients known.

<sup>1</sup> Feeding difficulties

<sup>2</sup> Bradycardia

<sup>3</sup> Exanthema

<sup>4</sup> Reduced appetite, hypoxaemia

<sup>5</sup> Aggressive behavior, nausea, pain

**Table S5:**  
Antibiotic treatment.

Age category	Patients	Clarithromycin	Azithromycin	Macrolides and/or other antibiotics <sup>1</sup>	Treated but drug unknown	No antibiotic treatment	Unknown if treated
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
<1 month	23 (10)	9 (39)	10 (43)	4 (17)	0 (0)	0 (0)	0 (0)
1 month	63 (29)	38 (60)	23 (37)	1 (2)	1 (2)	0 (0)	0 (0)
2 months	38 (17)	26 (70)	8 (22)	3 (8)	0 (0)	0 (0)	1 (3)
3–5 months	48 (22)	34 (72)	11 (23)	0 (0)	0 (0)	2 (4)	1 (2)
6–11 months	17 (8)	12 (71)	4 (24)	0 (0)	0 (0)	1 (6)	0 (0)
12–23 months	10 (5)	6 (60)	2 (20)	0 (0)	1 (10)	1 (10)	0 (0)
≥2 years	21 (10)	10 (48)	6 (29)	2 (10)	1 (5)	2 (10)	0 (0)
Total	220 (100)	135 (62)	64 (29)	10 (5)	3 (1)	6 (3)	2 (1)

<sup>1</sup> Usually other antibiotic was followed by a macrolide when a diagnosis of pertussis had been made

**Table S6:**  
Intensive care and respiratory support.

Age category	Patients	Intensive care	Duration of intensive care (in days)	Intubation	Duration of intubation (in days)	CPAP	Duration of CPAP (in days)	Oxygen substitution
	N (%)	N (%)	Mean/median (range)	N (%)	Mean/median (range)	N (%)	Mean/median (range)	N (%)
<1 month	23 (10)	12 (52)	12.5/9 (1–39)	4 <sup>1</sup> (17)	4/4 (2–6)	3 (13)	6/5 (1–12)	7 (30)
1 month	63 (29)	12 (19)	7.7/7 (2–19)	1 (2)	2/2 (2)	3 <sup>2</sup> (5)	4.7/5 (2–7)	8 (13)
2 months	38 (17)	3 (8)	7.7/7 (2–14)	2 (5)	6.5/6.5 (4–9)	0 (0)	0/0 (0)	4 (11)
3–5 months	48 (22)	1 (2)	7/7 (7)	0 (0)	0/0 (0)	0 (0)	0/0 (0)	1 (2)
6–11 months	17 (8)	0 (0)	0/0 (0)	0 (0)	0/0 (0)	0 (0)	0/0 (0)	2 (12)
12–23 months	10 (5)	1 (10)	8/8 (8)	0 (0)	0/0 (0)	1 <sup>3</sup> (10)	8/8 (8)	2 (20)
≥2 years	21 (10)	0 (0)	0/0 (0)	0 (0)	0/0 (0)	0 (0)	0/0 (0)	1 (5)
Total	220 (100)	29 (13)	9.7/7 (1–39)	7 (3)	4.4/4 (2–9)	7 (3)	5.7/5 (1–12)	25 (11)

<sup>1</sup> Including one patient with Extracorporeal Membrane Oxygenation (ECMO)

<sup>2</sup> Including one patient with Biphasic Positive Airway Pressure (BiPAP)

<sup>3</sup> This patient had BiPAP

**Table S7:**  
Source of infection\*

Age category	Patients	Parent(s) only	Sibling(s) only	Sibling(s) + parent(s)	Adults other than household members	Children other than household members	Source unknown
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
<1 month	23 (10)	9 (45)	2 (10)	7 (35)	3 (15)	1 (5)	3 (13)
1 month	63 (29)	20 (42)	7 (15)	15 (31)	7 (15)	8** (17)	15 (24)
2 months	38 (17)	11 (39)	4 (14)	8 (29)	7 (25)	3 (11)	10 (26)
3–5 months	48 (22)	10 (26)	12 (32)	10 (26)	8 (21)	1 (3)	10 (21)
6–11 months	17 (8)	5 (50)	2 (20)	3 (30)	1 (10)	1 (10)	7 (41)
12–23 months	10 (5)	2 (33)	2 (33)	2 (33)	2 (33)	0 (0)	4 (40)
≥2 years	21 (10)	3 (25)	4 (33)	2 (17)	1 (8)	4 (33)	9 (43)
Total	220 (100)	60 (37)	33 (20)	47 (29)	29 (18)	18 (11)	58 (26)

\* Some patients had more than one potential source of infection

\*\* Including two patients with nosocomially acquired pertussis

**Table S8:**  
95% confidence intervals for figure 2.

	Lower 95%CI	Upper 95%CI
2013 Q1	0.2	1.1
2013 Q2	0.3	1.2
2013 Q3	0.7	1.9
2013 Q4	0.65	1.7
2014 Q1	0.3	1.3
2014 Q2	0.05	0.7
2014 Q3	0.5	1.6
2014 Q4	0	0.5
2015 Q1	0.1	0.8
2015 Q2	0	0.6
2015 Q3	0.2	1.0
2015 Q4	0.1	0.9
2016 Q1	0.05	0.7
2016 Q2	0.3	1.2
2016 Q3	0.5	1.5
2016 Q4	0.5	1.5
2017 Q1	0.2	1.0
2017 Q2	0.1	0.8
2017 Q3	0.2	1.1
2017 Q4	0.2	1.0
2018 Q1	0	0.2
2018 Q2	0.05	0.7
2018 Q3	0.05	0.7
2018 Q4	0.05	0.7
2019 Q1	0	0.6
2019 Q2	0.05	0.7
2019 Q3	0	0.4
2019 Q4	0	0.5
2020 Q1	0.1	0.8
2020 Q2	0	0.5
2020 Q3	0	0
2020 Q4	0	0