What risk factors affect hospitalisation for confirmed pertussis cases among infants in the Czech Republic?

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ABSTRACT

Background: We estimated what risk factors affect hospitalisation for confirmed pertussis cases among infants (child up to 1 year) in the Czech Republic based on data from the questionnaire-based enhanced surveillance system (ESS) in years 2015, 2017 and 2019.
Methods: Retrospective cohort study was conducted in which we assessed demographic, clinical data, vaccination status and risk/protective factors. Vaccination status was extracted from the electronic nationwide notification system (NNS). We performed descriptive, univariable and multivariable analysis using risk ratio (RR) and logistic regression with odds ratio (OR).
Results: A total of 104 confirmed cases (27, 13, 64) were reported in the ESS during 2015, 2017 and 2019. Most cases were in age group 1 month (24), more males (57). Fifteen cases were vaccinated and 89 unvaccinated. Of 88 hospitalised cases, 31 cases reported stay in Intensive Care Unit (ICU). The median length of hospitalisation was 8 days. Although the variable vaccinated in infants was statistically significant in a univariable analysis for outcome hospitalisation, RR 0.76 (95% CI 0.53–1.10), it was not in multivariable. Hospitalisation was strongly associated with the younger age group of 0-3 months adjusted by a smoking family member in a household (OR = 9.72; 95% CI: 2.97–31.81). Stay in ICU was strongly correlated with the younger age group of 0–3 months (OR = 5.07; 95% CI: 1.44–17.87) and with a contact with confirmed or probable pertussis (OR = 7.05; 95% CI: 1.36–36.52).
Conclusions: Our study demonstrated younger age and contact with other pertussis case as risk factors for hospitalisation of infants with pertussis. It is necessary to consider adolescent and adult boosters, including vaccination during pregnancy. We suggest integrating the variables from the enhanced surveillance system into the nationwide notification system, in order to simplify the data reporting and evaluation. Further studies are needed to evaluate the ESS and to monitor the vaccination of pregnant women against pertussis.

KEYWORDS
pertussis – whooping cough – infant – hospitalisation – surveillance – risk factors

SOUHRN

Liptáková M., Špačková M., Balasegaram S., Malý M., Kynčl J., Fabiánová K.: Jaké rizikové faktory ovlivňují hospitalizaci u potvrzených případů černého kašle u kojenců v České republice?

Cíle: Rizikové faktory, které ovlivňují hospitalizaci u potvrzených případů černého kašle u kojenců (dětí do 1 roku) v České republice jsme stanovili na základě údajů z dotazníkové zesílené surveillance (ESS) v letech 2015, 2017 a 2019.
Metody: Byla provedena retrospektivní kohortová studie, ve které jsme hodnotili demografické, klinické údaje, stav očkování a rizikové/protektivní faktory. Stav očkování byl určen podle elektronického celostátního hlásicího systému (NNS). Provedli jsme deskriptivní, jednonásobnou a vícenásobnou analýzu s využitím relativního rizika (RR) a logistické regrese pomocí odds ratio (OR).
Výsledky: V letech 2015, 2017 a 2019 bylo v rámci ESS celkem hlášeno 104 potvrzených případů pertuse (27, 13, 64). Nejvíce případů bylo zaznamenáno ve věkové skupině 1 měsíc (24), více u mužů (57). Patnáct případů bylo očkováno a 89 neočkováno. Z 88 hospitalizovaných případů bylo 31 případů na jednotce intenzivní péče (JIP). Průměrná délka hospitalizace byla 8 dní. Ačkoli proměnná očkování kojenců byla statisticky významná v jednonásobné analýze pro výslednou hospitalizaci, RR 0,76 (95% CI 0,53–1,10), nebyla ve vícenásobné. Hospitalizace byla silně asociována s mladší věkovou skupinou 0–3 měsíce (OR = 9,72; 95% CI: 2,97-31,81) po odfiltrování vlivu kouření v domácnosti. Pobyt na JIP byl významně asociován s mladší věkovou skupinou 0–3 měsíce (OR = 5,07; 95% CI: 1,44-17,87) a s kontaktem s potvrzeným nebo pravděpodobným případem černého kašle (OR = 7,05; 95% CI: 1,36–36,52).
Závěr: Jako rizikové faktory pro hospitalizaci na pertusi u kojenců naše studie prokázala nižší věk (0–3 měsíce) a kontakt s jinými případy pertuse. Je nutné zvážit přeočkování u dospívajících a dospělých, včetně očkování v těhotenství. Pro zjednodušení vykazování a vyhodnocování dat doporučujeme začlenit proměnné ze zesílené surveillance (ESS) do celostátního hlásicího systému. K vyhodnocení ESS a ke sledování očkování těhotných žen proti pertusi jsou zapotřebí další studie.

KLÍČOVÁ SLOVA
pertuse – černý kašel – kojenec – hospitalizace – surveillance – rizikové faktory

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INTRODUCTION

Pertussis (whooping cough) is an acute highly contagious vaccine-preventable infectious disease caused by *Bordetella pertussis*. It affects the respiratory tract and spreads by sneezing or coughing, with strictly inter-human transmission. It may cause potentially severe consequences, especially in unvaccinated or not fully vaccinated new-borns and infants up to the age of 1 year. The complications may be even fatal. The case-fatality rate of pertussis in infants in 16 European countries in the period 1998–2002 varied between 0–21.3 per 1000 [1]. Based on data from the PERTINENT sentinel pilot surveillance system of 6 the European Union/the European Economic Area (EU/EEA) countries performed in December 2015 to December 2018 five (1%) of 466 cases of pertussis in infants died [2].

Surveillance of pertussis in the Czech Republic (CZ)

Pertussis is mandatorily notified disease in the CZ according to national legislation. The current pertussis surveillance system in the CZ is comprehensive, nationwide, case-based and harmonized with the EU requirements [3]. General practitioners and physicians from hospitals report pertussis cases to Local Public Health Authority (LPHA). LPHA collect information about pertussis cases and upload data in the electronic nationwide notification system (NNS).

Since 1993, the rate of pertussis in infants in CZ has steadily increased [4, 5]. The upward trend in pertussis in the CZ in the general population is also reflected in the increased number of cases in infants, including hospital admissions and pertussis-related complications [6].

Due to increased number of pertussis cases among infants the enhanced surveillance system (ESS) was established. The questionnaire-based ESS for laboratory confirmed pertussis cases among infants was introduced in CZ from 1st January 2015 onwards. ESS consists of active case finding and completion of a follow-up questionnaire of all infants with laboratory confirmed *B. pertussis* infection. Additional information is gathered on risk and protective factors for acquisition of pertussis. Between 1st January 2015 and 31st December 2019, a total 3,978 pertussis cases were notified in CZ, including 199 infants [7].

The proportion of infants among all reported pertussis cases from 2015 to 2019 from the NNS ranged from 3.3% in 2017; through 4.1% in 2016; 5.0% in 2015; 5.3% in 2019 to 6.5% in 2018 [7].

We aim to estimate risk and protective factors that affect hospitalisation of laboratory confirmed pertussis cases among infants in CZ in years 2015, 2017 and 2019 related on questionnaire-based ESS data.

METHODS

The retrospective cohort study included all confirmed infant pertussis cases reported by reporting week in CZ from 1st January to 31st December in 2015, 2017 and 2019, respectively. We chose to sample alternate years to reflect the upward trend of confirmed pertussis cases among infants in recent years.

The case was defined as any infant meeting clinical and laboratory criteria according to EU pertussis case definition (2008) [3]. The data reported to NNS under the code "A37.0" of the 10th revision of the International Classification of Diseases were processed.

Data for the analysis were extracted from a) ESS and b) from NNS**.** Records were matched via unique personal identification number (UPIN).

The ESS questionnaire was filled in by LPHA personnel that interviewed parents (usually mother or the other legal representative of infant) by phone. Completed questionnaire was sent to the National Institute of Public Health (NIPH). The analysis was restricted only to infant cases with completed questionnaire.

Variables available from NNS were: demographic case characteristics (age, gender, region of reporting), vaccination status of reported cases (if vaccinated, number of doses received), hospitalisation and likely source of infection. **Variables available from ESS questionnaire were:** antibiotic (ATB) treatment, admission in ICU, length of hospitalisation, clinical symptoms of pertussis, underlying chronic diseases, risk and protective factors for pertussis (preterm birth, smoking in household, pertussis vaccination among family members in household, infant's breastfeeding and likely source of infection).

Vaccination status available at the time of disease onset was categorized based on the number of age-appropriate doses within Czech childhood immunization programme.

Computerisation of the data collected from questionnaires was performed manually using Excel. Data cleaning, including searching for duplicates was done. In case of discrepancies between both systems, data from NNS were used. The matched and validated dataset was blinded for any personal information.

Data analysis was performed using Stata statistical software, release 16 (StataCorp LLC, College Station, TX, U.S.A.).

Descriptive analysis

We performed descriptive analysis of the data to assess selected demographic characteristics and potential risk and protective factors using hospitalisation as the primary outcome measure. The second outcome was a stay in the Intensive Care Unit (ICU), which is useful for assessing the severity of disease and the use of ICU resources. The disease incidence was calculated based on age-specific population data from

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Czech Statistical Office [8] counted on the 1st July of each year.

Following characteristics of the hospitalisation were evaluated:

– complications

– antibiotic (ATB) treatment: This indicator provides information about the possibility that pertussis in not considered or included in differential diagnosis. ATBs that were used for treatment of the infant case.

– length of ATB treatment

Cohort risk analysis

Based on the incubation period and at least partial onset of immunity after vaccination, we defined as vaccinated a person who received at least one dose of pertussis vaccine more than 21 days before the symptoms onset.

Within univariable analyses, an association between outcome and different risk factors was assessed using risk ratios (RRs). Chi-squared test or Fisher's exact test were used.

Multivariable analysis based on logistic regression model and where necessary, Firth logistic method, using odds ratio (OR) as a measure of association was proceeded for all variables with a significance level of p-value < 0.2 from univariable analysis. We used stepwise regression with selection of the variables for the model based on backward elimination. The Firth logistic regression model can address the separation issues that can arise in standard logistic regression [9] and has become a standard approach for the analysis of binary outcomes with small samples. We also checked for interactions and confounding using stratified analysis. The significance level was set to 5%.

RESULTS

Descriptive analysis

Within the study years 2015, 2017 and 2019, 121 confirmed pertussis cases were reported in NNS in CZ (27, 22 and 72, respectively). The annual incidence of cases reported in NNS was 26.3, 19.4, and 64.6 per 100,000 infants, respectively. However, only 104 questionnaires (for 86% of all reported cases) were received from ESS; 27 (100%), 13 (59%, n = 22) and 64 (89%, n = 72) respectively thus these were included in the analysis. Fifty-seven cases (55%) were males.

The median age of the 104 cases from ESS was 2 months (range 0–11, interquartile range IQR 3). The highest number of cases was reported in the age group 0-2 months (n = 62), with a peak in the second month of life (n = 24) – Figure 1.

Clinical symptoms, laboratory diagnosis and other characteristics of cases are presented in Table 1. Cases were detected in 13 of 14 regions; the only exception was Karlovy Vary region in western part of the Czech Republic.

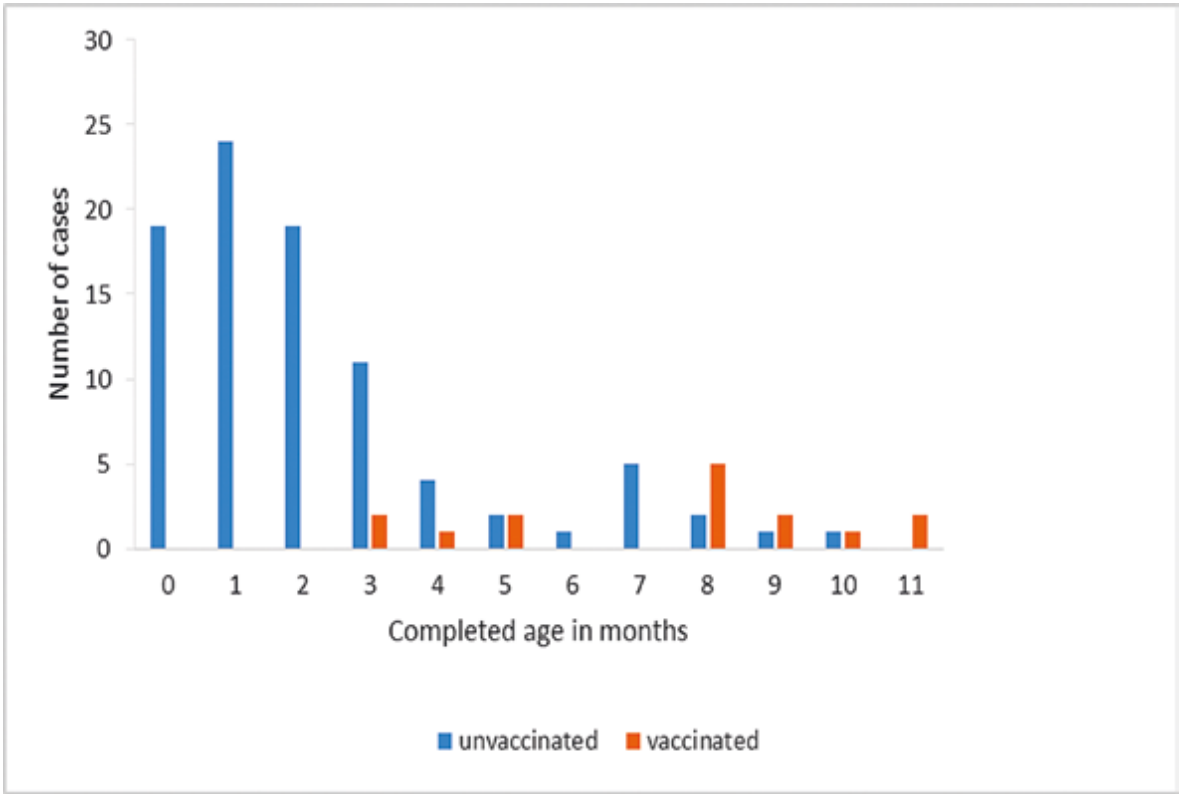


Figure 1. Vaccination status of confirmed pertussis cases by age using enhanced surveillance data in CZ in years 2015, 2017, 2019 (n = 104)

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Table 1. Characteristics of infants with confirmed pertussis in the CZ in years 2015, 2017 and 2019, data from enhanced surveillance

Clinical symptoms	N (%)	Other characteristics	N (%)
Paroxysm of coughing (n = 104)	101 (97%)	Vaccinated (n = 104)	15 (14%)
Inspiratory whooping (n = 96)	44 (46%)	Preterm birth* (n = 100)	20 (20%)
Post-tussive vomiting (n = 104)	49 (47%)	Low birth weight** (n = 44)	7 (16%)
Cyanosis (n = 102)	38 (37%)	Hospitalisation (n = 104)	88 (85%)
Apnoeic episode (n = 100)	32 (32%)	Chronic disease (n = 104)	9 (9%)
Choking (n = 55)	15 (27%)	Stay in the ICU (n = 102)	31 (30%)
Laboratory diagnosis	**N (%)**	Complications (n = 100)	14 (14%)
Culture (n = 82)	31 (38%)	ATB treatment (n = 104)	102 (98%)
PCR (n = 101)	88 (87%)	Contact*** (n = 66)	45 (68%)
Specific IgA (n = 85)	29 (34%)	Likely source of infection (n = 104)	34 (33%)

*Notes: n – number of respondents, N – Number of cases, ICU – Intensive Care Unit, ATB – Antibiotic(s), PCR - Polymerase chain reaction, * – < 37 week of pregnancy, ** – < 2,500 g, *** – contact with suspected or confirmed pertussis case*

ATB treatment was reported for 102 of 104 cases. The ATB treatment started in median 7 days after symptoms onset (range 1–57 days; IQR 8; n = 99) and this differed for unvaccinated (median 7 days), and vaccinated infants (median 13 days). The median length of ATB treatment was 14 days (range: 1–27; IQR 4; n = 96) and did not show differences between vaccinated vs unvaccinated infants.

The median gestational week at birth was 39th week (range 28–42; IQR 3; n = 68). Smoking in household was reported in 16 cases (37%, n = 43), all of which were hospitalised. Of 39 breastfed cases (83%, n = 47), the length of breastfeeding was reported in 31 cases. The median length of breastfeeding was 8 weeks (range 2–43; IQR 12).

Total of 28 (62%, n = 45) infants from ESS had a confirmed source of infection reported in NNS. The number of cases who were in a close contact with the person with confirmed or suspected pertussis in household and were hospitalised was 36 (65%, n = 66). In NNS, grandparents (in 12 cases), mother (10 cases), father (8 cases), siblings (2 cases), and other relatives (2 cases) were mentioned as sources of infection.

Fifteen (14%, n = 104) infants were vaccinated (Figure 1), of which 5 received one dose, 7 two doses and 3 received three doses. Ten (67 %) of vaccinated infants were hospitalised, 1 case received three doses, 4 cases two doses and 5 cases one dose. Of 88 hospitalised infants, 78 (89%) were unvaccinated. Vaccination status of family members was following: mother was vaccinated in childhood in 88 cases (100%, n=88), father in 47 cases (100%, n = 47) and siblings in 43 cases (80%, n = 54).

The total of 88 (85%, n = 104) infants were hospitalised. The median length of hospitalisation was 8 days (range: 3–83; IQR 6; n = 85). Of 54 cases (61% of all hospitalised cases) with length of hospitalisation longer than 7 days, 47 were aged ≤ 3 months in comparison with 7 cases aged 4–11 months. The median duration of hospitalisation was 9 days for unvaccinated vs 5 days for vaccinated infants. Among those who contracted disease during first three months of life (0–2), 60 infants (97%, n = 62) were hospitalised and among ill infants in the fourth month of age, 10 (77%, n = 13) were hospitalised.

Of hospitalised cases, 31 (35%, n = 88) reported stay in ICU. The median length of stay in ICU was 7.5 days (range: 2–26; IQR 4.5; n = 31). The median duration of stay in ICU was 7 days for unvaccinated vs 9 days for vaccinated infants. During first three month of life (0–2) reported stay in ICU in 23 infants (37%, n = 62) and in the fourth month of age 5 (38%, n = 13) infants.

Cohort risk analysis

In univariable analysis, the risk ratio (RR) for different exposures with outcome hospitalisation (Table 2) was calculated. The variables infant age > 3 months and vaccinated appeared to have a protective effect (RR < 1) and variables cyanosis and smoking in the household (RR > 1) appeared as potential risk factors. Further, the RRs for different exposure associated with outcome stay in ICU (Table 3) were assessed. Significantly protective (p-value <0.05) appeared to be age more than 3 months and as a risk factor, contact with confirmed or probable pertussis case in household was proved.

We found no evidence of effect modification and confounding in particular, when testing age and vaccination or age and contact.

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In the final multivariable regression model, infants in the age group 0–3 months were in significantly higher risk of hospitalisation (OR = 9.72; 95% CI: 2.97–31.81). Variable smoking within the household was borderline significant (p = 0.05).

In the final multivariable model, the outcome stay in ICU was strongly associated with the age group 0-3 months (OR = 5.07; 95% CI: 1.44–17.87) and with infants that had been in contact with another confirmed or probable pertussis case (OR = 7.05; 95% CI: 1.36–36.52).

Table 2. Univariable analysis of possible risk and protective factors for infant's pertussis hospitalisation in CZ in 2015, 2017 and 2019

Outcome hospitalisation	Exposed			Unexposed			RR	*p*-value	95% CI for RR
	Cases	Total	AR (%)	Cases	Total	AR (%)			
Age >3 months	**18**	**29**	**62.07**	**70**	**75**	**93.33**	**0.67**	**< 0.001**	**0.50–0.89**
Cyanosis	**36**	**38**	**94.74**	**50**	**64**	**78.13**	**1.21**	**0.026**	**1.04–1.41**
Smoking in household	**16**	**16**	**100.00**	**20**	**27**	**74.07**	**1.35**	**0.026**	**1.08–1.69**
Vaccinated	**10**	**15**	**66.67**	**78**	**89**	**87.64**	**0.76**	**0.037**	**0.53–1.10**
Chronic disease	**9**	**9**	**100.00**	**79**	**95**	**83.16**	**1.20**	**0.181**	**1.10–1.32**
Apnoea	29	32	90.63	55	68	80.88	1.12	0.215	0.95–1.32
1st sibling vaccination	42	49	85.71	4	6	66.67	1.29	0.234	0.72–2.29
Breastfeeding	33	39	84.62	8	8	100.00	0.85	0.235	0.74–0.97
Other people in household (grandparents)	27	32	84.38	6	9	66.67	1.27	0.236	0.78–2.06
*Contact	36	45	80.00	19	21	90.48	0.88	0.287	0.72–1.08
Birth weight (< 2.500 g)	7	7	100.00	32	37	86.49	1.16	0.302	1.02–1.31
Child regularly with grandparents	24	29	82.76	13	14	92.86	0.89	0.371	0.71–1.11
Cough	86	101	85.15	2	3	66.67	1.28	0.382	0.57–2.85
Preterm birth	18	20	90.00	67	80	83.75	1.07	0.484	0.90–1.28
2nd sibling vaccination	16	20	80.00	4	6	66.67	1.20	0.497	0.65–2.20
> 1 sibling	23	28	82.14	43	49	87.76	0.94	0.498	0.76–1.15
Grandparents in household	24	29	82.76	2	2	100.00	0.83	0.521	0.70–0.98
Mother pertussis in pregnancy	2	2	100.00	34	41	82.93	1.21	0.523	1.05–1.39
Whooping	38	44	86.36	43	52	82.69	1.04	0.622	0.88–1.24
Choking	13	15	86.67	33	40	82.50	1.05	0.710	0.82–1.34
Vomiting	42	49	85.71	46	55	83.64	1.02	0.769	0.87–1.21
Gender	48	57	84.21	40	47	85.11	0.99	0.900	0.84–1.17
Mother vaccinated in childhood	72	88	81.82	0	0	NA	NA	NA	NA

*Notes: AR (%) = Attack Rate, RR = Risk Ratio, 95% CI = 95% Confidence interval, *contact = contact with confirmed or probable pertussis case, NA = not applicable*

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Table 3. Univariable analysis of possible risk and protective factors for infant's pertussis stay in Intensive Care Unit in CZ in 2015, 2017 and 2019

Outcome stay in ICU	Exposed			Unexposed			RR	*p*-value	95% CI for RR
	Cases	Total	AR (%)	Cases	Total	AR (%)			
Age > 3 months	**3**	**29**	**10.34**	**28**	**73**	**38.36**	**0.27**	**0.006**	**0.09–0.82**
***Contact**	**15**	**45**	**33.33**	**2**	**20**	**10.00**	**3.33**	**0.048**	**0.84–13.23**
Cyanosis	16	38	42.11	15	62	24.19	1.74	0.060	0.98–3.10
1st sibling vaccination	18	48	37.50	0	6	0.00	NA	0.066	NA
Choking	6	15	40.00	7	40	17.50	2.29	0.080	0.92–5.71
Grandparents in household	11	29	37.93	2	2	100.00	0.38	0.085	0.24–0.60
Apnoea	13	23	40.63	17	66	25.76	1.58	0.134	0.88–2.83
Vomiting	18	49	36.73	13	53	24.53	1.50	0.181	0.82–2.72
Smoking in household	8	16	50.00	8	26	30.77	1.63	0.213	0.76–3.46
Preterm birth	8	20	40.00	22	78	28.21	1.42	0.307	0.75–2.70
Birth weight (< 2.500 g)	4	7	57.14	13	35	37.14	1.54	0.325	0.71–3.33
Vaccinated	3	15	20.00	28	87	32.18	0.62	0.343	0.22–1.79
> 1 sibling	8	28	28.57	18	47	38.30	0.75	0.392	0.37–1.49
2nd sibling vaccination	7	20	35.00	1	6	16.67	2.10	0.393	0.32–13.85
Breastfeeding	15	37	40.54	4	8	50.00	0.81	0.623	0.37–1.80
Mother pertussis in pregnancy	1	2	50.00	14	39	35.90	1.39	0.686	0.33–5.93
Child regularly with grandparents	12	29	41.38	5	14	35.71	1.16	0.722	0.51–2.65
Other people in household (grandparents)	14	32	43.75	3	8	37.50	1.17	0.749	0.44–3.10
Chronic disease	3	9	33.33	28	93	30.11	1.11	0.841	0.42–2.93
Whooping	14	44	31.82	15	50	30.00	1.06	0.849	0.58–1.94
Cough	30	99	30.30	1	3	33.33	0.91	0.910	0.18–4.63
Gender	17	56	30.36	14	46	30.43	1.00	0.993	0.55–1.80
Mother vaccinated in childhood	27	88	30.68	0	0	NA	NA	NA	NA

*Notes: AR(%) = Attack Rate, RR = Risk Ratio, 95% CI = 95% Confidence interval, ICU = Intensive Care Unit, *contact = contact with confirmed or probable pertussis case, NA = not applicable*

DISCUSSION

This study was the first investigation of confirmed pertussis cases in infants in CZ which were reported to NNS, based on the data from ESS. The highest incidence of confirmed pertussis cases in infants was observed in 2019, possibly due to regularly recurring epidemic pertussis cycles in whole Czech population, similarly as seen in other EU countries [10, 11]. Other factors that may contribute to the resurgence include decreasing vaccine coverage, improved diagnostic methods, and genetic changes in the organism [10, 11].

Within the study the risk of hospitalisation for pertussis was strongly associated with infants 0–3 months old, when results were adjusted for a smoking of a family member in the household. Stay in ICU was also strongly correlated with the age group of 0–3 months old and a contact with a confirmed or probable pertussis case in the household.

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Results in our study showed similar median age and gestational week of pertussis cases as in the EU PERTINENT study performed from December 2015 to December 2018 with the aim to assess incidence and severity of pertussis hospitalisations in infants < 1 year of age in 37 hospitals of six EU/EEA countries. PERTINENT study was performed in six University Hospitals in CZ, total of 73 infants were screened and 25 PERTINENT pertussis cases (8 cases in 2016, 7 cases in 2017 and 10 cases in 2018) were detected in CZ [2]. The highest complication and hospitalisation rates are usually found in infants too young to be vaccinated [1]. The peak incidence and hospitalisations are generally observed mainly during the second month of life [2, 12]. In our study the highest number of cases was also reported in the second month of life. Babies born on the proper time were hospitalised at younger ages (median 2.0 months) than those born preterm (3.0 months) [13]. Median duration of hospitalisation was 5 and 6 days for term and preterm (< 37 week of gestational age) infants, respectively in the Netherlands [13]. Median length of hospitalisation was 9 days (IQR 5–13 days) and 18% required intensive care treatment in German study [14]. The median length of hospitalisation within our study was comparable to the results of other studies [2, 14]. Median duration of hospitalisation was seven days for unvaccinated vs four days for vaccinated infants aged 3–5 months in Swedish study [12]. The younger the infant, the higher the proportion of cases hospitalised was detected in Sweden [12]. The length of hospital stay was longer ($p < 0.001$) in infants aged < 3 months (mean 8.7; SD 11.9) than in those aged 3–11 months (mean 6.5; SD 5.5) in the study based on Spanish data from the national registry of hospitalisations [15].

We describe higher proportion of hospitalised infants (85%) in comparison to the Swedish study. In Sweden 70% of all cases are under three month of age and 99% of cases with apnoea due to pertussis were admitted to hospital [12]. The true hospitalisation rates in Sweden may be underestimated in infants, as the trigger point for investigation was a positive laboratory sample [12]. In Sweden, antibiotics were prescribed to 85% of the infants, 77% had paroxysmal cough [12]. Of the 104 cases in our study, 97% had a paroxysm of coughing, 47% post-tussive vomiting and 46% inspiratory whooping which is again similar to PERTINENT results [2]. In our study ATBs were administered to 98% of the infants, which is a higher proportion than reported by the authors in Swedish study. Based on the study performed by the European Surveillance of Antibiotic Consumption Network (ESAC-Net) between 2014 and 2018, Sweden was among countries where statistically significant decrease in the total consumption of antibiotics was noted [16]. In our study the median duration of ATB treatment was 14 days (range 1–27; IQR 4) and did not show differences between vaccinated vs unvaccinated infants. Antibiotic treatment does not significantly shorten the clinical course in infected patients but aims to reduce transmission to other persons [17].

Notably, PCR has been increasingly used in the past decade, with culture-confirmed pertussis becoming rare as is mentioned in Swedish study performed in years 1998–2012 [12]. Based on the findings from our study, PCR was the most frequent laboratory method, used in 87% of cases, in PERTINENT PCR was used in 99% of confirmed cases [2].

In our study of 88 hospitalised cases, 31 cases (35%, n = 88) reported stay in ICU and the median length of stay in ICU was 7.5 days (range 2–26; IQR 4.5). In PERTINENT 83 (25%) of cases were admitted to ICU, the highest proportion of ICU cases was in infants aged 0–3 months [2].

We realized that preterm birth was reported in 20 cases (20%, n = 100), including 18 hospitalised and 2 cases isolated at home. In other study, preterm cases tended more often to have complications, to require artificial respiration or to need admittance to the ICU [13]. They experienced significantly longer ICU stay (15 vs 9 days; $p = 0.004$) [13]. In vaccinated preterms and terms a lower median length of hospital stay and lower crude risks of apneas and the need for artificial respiration, additional oxygen, and ICU admittance than those not vaccinated were reported [13].

In 2019, increase in pertussis in infants as well as increase in the total number of reported pertussis cases in CZ was detected. After the decline in morbidity in 2015 continuous increase of morbidity observed in 2016–2019. Despite the high level of vaccination coverage of the Czech population against pertussis [18], 2–5 years cycles of growth of pertussis cases are repeated regularly [10, 11] and a decrease in reported morbidity, as in other countries [10, 11]. These epidemic cycles indicate the persistent presence of *B. pertussis* in the population [7]. The disease trend in the youngest children thus clearly reflects the development of the disease in the whole population and confirms that the most common source of the disease for the youngest children is the adult population and adolescents [7].

Due to the possible serious complications of the disease and their rapid onset, pertussis treatment in the youngest children should always take place under the supervision of a specialized medical facility. Both, pertussis disease and vaccination provide only limited protection. It is therefore necessary to be revaccinated against the pertussis. The main purpose of giving the pertussis vaccine in pregnancy is to protect the smallest children by enhancing the transfer of maternal specific antibodies to the foetus through placenta and breast milk. An adequate level of maternal antibodies is considered to be the most important factor in the protection from infection in neonates and infants before vaccination. Most women of childbearing age have received a pertussis vaccine in their childhood, but neither vaccine nor post-infection immunity provides lifetime or

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at least long-term protection against pertussis [6]. We remind of existence of national recommendation for pertussis vaccination in pregnancy (since 8 December 2015 and updated on 10 June 2021) with aim to further promote this information in everyday clinical practice. Recommendation is publicly available on the webpage of the NIPH [6]. Pertussis presents the most serious threat in its course and possible complications for the smallest yet unvaccinated or incompletely vaccinated infants [19].

According to World Health Organization pertussis position paper from August 2015 [20], severe cases of pertussis and deaths in countries with a good vaccination coverage occur almost exclusively in the youngest children during the first weeks and months of life. The source of disease in children under 6 months of age are in 74–96% closest relatives living in the same household (household contacts) [7]. Similar findings were confirmed within our study and PERTINENT study, while in later as potential source of infection were mentioned sibling (31%), the mother (25%), the father (20%) and grandparents (10%) [2].

There are still significant challenges to controlling pertussis in Europe. High vaccination coverage is needed to provide indirect and direct protection for prone infants that tend to show the most severe symptoms [21]. In our study, only 15 (14%) cases were vaccinated at least 21 days before disease onset (defined based on the incubation period) and out of them 10 (67%) were hospitalised. In contrary, 89% of unvaccinated were hospitalised. Eight infants who received the vaccine less than 21 days before the disease onset, developed pertussis a few days later.

We did not find any associations with vaccination of family members, but we assume that this is due to a small number of cases included in the study, rather than there would not be any effect of it. As well the data are difficult to fully assess due to missing vaccination register in CZ.

Limitations. The main limitation of this study is that the study population only comprised 104 infant pertussis cases, with many missing values from ESS. The study power is therefore limited. Recall and selection bias tend to appear in observational studies, so we attempt to minimise interviewer bias by using a standardised questionnaire. During the data computerisation several different versions of the questionnaire were noted, as LPHAs created their own versions over time. Experiencing these, not all characteristics were available for each study year.

Of 121 cases reported in NNS only 104 questionnaires were obtained in ESS; the highest discrepancy was observed in year 2017. Nine reports in total have not been sent in 2017 from five regions in CZ.

Another major limitation was recall bias for questions related to vaccination status of family members as there is no vaccination register in CZ. Without a vaccination register, information on vaccination in adults was difficult to access, as many people did not remember their childhood vaccination, often did not have their childhood vaccination cards, or their medical records were not available for number of reasons.

The protective effect of vaccination against pertussis in infants on hospitalisation was demonstrated by the RR 0.76 (95% CI 0.53–1.10) and it was statistically significant ($p = 0.037$) in a univariable analysis. However, it was not seen in the multivariable analysis, because after controlling for age, vaccination status did not affect the model, and age appeared to be the stronger predictor. We assume that because vaccination status was strongly correlated with age, it was not possible to separate out the effects of this. If we had a larger sample size, it would be possible to restrict the analysis to those children by age and examine the effects of vaccination.

CONCLUSIONS

Our study confirmed that hospitalisation was strongly associated with the age group 0–3 months adjusted by a smoking family member in household; stay in ICU was predicted with the same age group and with infants that had been in contact with another confirmed or probable pertussis case.

Despite the number of cases reported, it is likely that the burden of pertussis in Europe is still considerably underestimated. Improved pertussis surveillance, associated with increased awareness and improved access to appropriate laboratory diagnosis, could contribute to a more accurate picture of the pertussis epidemiology and support policy decisions to optimise the impact of vaccination [21]. Perhaps the increased physician awareness may have contributed to the increased incidence of pertussis reported.

Consideration should be given to adolescent and adult boosters and the vaccination of healthcare workers and pregnant women, as well as ensuring that these recommendations are effectively implemented in accordance with national guidelines [21].

It is important to integrate the variables from ESS into NNS (data entry form), to have all relevant information in one place. This proposal could improve data quality and simplify the process of reporting and evaluating data from ESS. Further studies would be needed to evaluate ESS in infants to determine risk factors and assess information about the vaccination in the study participants and the characteristics of family members in households. In future the LPHAs employees and study co-workers should be updated about the ESS to improve questionnaire uptake, and to avoid producing modified questionnaires.

Further studies are needed to evaluate ESS and to monitor the vaccination of pregnant women against pertussis.

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Conflict of interest
The authors declare no conflicts of interest.

Ethical approval
Ethical approval was not required as in the Czech Republic public health agencies are able to access and use personal identifiable information for communicable disease outbreak investigations in the public interest. Completion of the questionnaire was considered as implied consent. Designated NIPH staff was authorized to work with individual case-based data under specific conditions protecting confidentiality of data.

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Authors contributions
KF created the questionnaire. KF designed the study in cooperation with ML and SB. ML and SB analysed data including all calculations and interpretations and drafted the initial version of the text. MS participated in all aspects of preparing the paper. MM and JK contributed to the text. All authors were involved in revising the manuscript and approved the final version.

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