

Retrospective Study of the Clinical Epidemiological Characteristics of Pertussis in Infants Prior to Their First Vaccination in the Russian Federation

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ABSTRACT

Introduction: The coverage of pediatric pertussis vaccination in the Russian Federation is high, generally using a diphtheria, tetanus, and whole-cell pertussis vaccine in a 3-, 4.5-, and 6-month primary series and with a booster at 18 months of age. However, with no registered pertussis vaccines for adults, unvaccinated adolescents and adults can be a

major source of infection of infants under 3 months of age.

Methods: A multicenter, retrospective, clinical epidemiological analysis to characterize pertussis in infants aged up to 3 months who contracted pertussis and were hospitalized in four different cities in the Russian Federation was performed. Archived medical records and a questionnaire were used to collect the relevant epidemiological and clinical aspects for each case of pertussis over a 2-year period.

Results: Infants in four different regions of the Russian Federation in the first 3 months of life, prior to their first pertussis vaccination, are at

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risk of pertussis infection. The severity is generally worse in neonates, and can lead to complications that can require intensive care.

Conclusion: Prior to vaccination, young infants in the Russian Federation remain vulnerable to severe pertussis, which may be worsened by their proximity to unvaccinated adults.

Keywords: Epidemiology; Infants; Pertussis; Pre-vaccination; Russia; Three months of age

INTRODUCTION

Pertussis is a bacterial respiratory infection caused by *Bordetella pertussis* that is preventable by vaccination, and which is most severe in infants and young children. Following the introduction of the whole-cell pertussis (wP) vaccine in the 1940s the incidence of pertussis worldwide has fallen significantly, and in the Russian Federation the current rate of vaccination, based on an evaluation of the administration of three doses of a diphtheria–tetanus–pertussis (DTP) vaccine in the first year of life, is very high (97%) [1]. However, pertussis infection is not under complete control [2, 3], for example, due to gaps in vaccination coverage [4].

In the Russian Federation the wP vaccine is administered as a DTP combination vaccine [purchased once per year by the Russian Ministry of Health by federal tender from a single producer (Microgen, Moscow, Russia)] in a 3, 4.5, and 6 months primary series and with a booster at 18 months of age [5, 6]. This has proven very effective in controlling pertussis outbreaks [7], however, since the first vaccination is not until 3 months of age infants can be vulnerable prior to this age to severe pertussis that can lead to serious complications and even fatal outcomes. There

are currently no registered pertussis vaccines for adults in Russia, and unvaccinated mothers who are infected with pertussis can be a major source of infection of infants aged less than 3 months who have not yet received their first vaccination.

However, the introduction of routine pediatric vaccination in the Russian Federation has led to reduced pertussis infection rates in the general population, with herd protection having a positive effect even on unvaccinated infants. Surveillance data have shown that the incidence of pertussis has decreased dramatically since the 1950s and has been generally stable from 2005 to 2013 [cases per 100,000 population (year): 3.2 (2005), 5.7 (2006), 2.4 (2007), 2.5 (2008), 2.9 (2009), 3.4 (2010), 3.3 (2011), 5.05 (2012), 3.16 (2013)] [3, 6].

But in some cities and regions, including Saint Petersburg and Moscow, the pertussis incidence rates are two- to threefold above the average national level, both for the general population and for children aged under 14 years [7]. This can be attributed not only to the higher population density in large cities but also to substantially increased diagnostic opportunities. This persisting incidence of pertussis has necessitated a comparative assessment of the clinical epidemiological characteristics of the course of pertussis in non-immunized children in their first few months of life in different cities and regions of the Russian Federation, against a background of mass vaccine prophylaxis and reduction in the absolute number of afflicted infants in their first year of life.

The aim of this multicenter, retrospective, clinical epidemiological analysis, therefore, was to characterize pertussis in infants in the first 3 months of life in different cities and regions in the Russian Federation.

METHODS

The retrospective analysis was conducted using in-patient medical records archived at the following cities of the Russian Federation: Moscow (Central Okrug), Saint Petersburg (North-Western Okrug), Krasnodar (Southern Okrug), and Krasnoyarsk (Siberian Okrug). In Russia, infants with infectious diseases are hospitalized in specified hospitals and so we can be confident that this analysis includes data from the overwhelming majority of pertussis patients hospitalized in their first 3 months of life in these cities, since the hospitals included have respiratory infection departments and are specified for infectious diseases. The annual birth cohorts/overall populations in the four cities are approximately 91,000/10.5 million (Moscow), 42,000/4.6 million (Saint Petersburg), 12,000/754,000 (Krasnodar), and 2600/973,000 (Krasnoyarsk). Infants with a final diagnosis of 'pertussis' were included in the analysis [8].

A questionnaire was used to collect the relevant epidemiological and clinical aspects for each case of pertussis and to ensure that data were collected in a consistent and systematic manner. The questionnaire included the following: the infant's residence, gender and age, date of admission and date of discharge, principal diagnosis, severity on admission, duration of hospital stay (in days), time from the onset of disease to hospitalization, and whether or not the infant's family had other children aged under 18 years. The questionnaire also specified the etiological diagnosis methods used for pertussis and treatment options: administration of antibacterial therapy, need for and time of treatment in resuscitation/intensive care departments, and duration of mechanical lung ventilation (MLV) when it was necessary. Specific and non-specific complications of pertussis were also registered.

The analysis was descriptive and included data from infants aged less than 3 months and 29 days who contracted pertussis and were hospitalized over a 2-year period from January 1, 2007 to December 31, 2008. The age range definitions used were the following: newborn (within the first 29 days of life); 1 month of age (from 30 days to 1 month and 29 days); 2 months of age (from 1 month and 30 days to 2 months and 29 days); and 3 months of age (from 2 months and 30 days to 3 months and 29 days). These definitions are widely used in the Russian Federation and correspond to reference intervals developed by the Saint Petersburg State Pediatric Medical Academy. All infants, including those aged 3 months, had not been vaccinated against pertussis.

A diagnosis of pertussis was made based on standard clinical epidemiological data, in accordance with the World Health Organization International Classification of Diseases (ICD-10) and the literature [9–16]. All cases of pertussis were community acquired, and the study included cases verified by laboratory analysis (if facilities were available) or diagnosed only clinically (if laboratory facilities were not available); if laboratory data were negative but characteristic clinical symptoms were present the diagnosis was maintained. If performed, laboratory analysis was done preferably by polymerase chain reaction (PCR), or by serology or culture.

Cases of pertussis were classed as severe if at least one of the following was present: paroxysmal cough of 30 episodes/24 h, severe intoxication, decrease of body weight, apnea, encephalitis reactions and hemorrhage, leukocytes 40,000–80,000 cells/mL, or lymphocytes 70–80% of all white blood cells. All cases of severe pertussis were confirmed by laboratory analysis. Other criteria used for the assessment of severity included: frequency and

nature of whooping cough attacks; frequency of vomiting accompanying cough; the patient's condition during the attack-free periods; severity of oxygen insufficiency symptoms; complications of specific and non-specific nature, duration of the pre-attack period; and severity of hematological abnormalities [17, 18].

The analysis in this article is based on previously conducted studies, and does not involve any new studies of human subjects performed by any of the authors.

RESULTS

There were a total of 116 cases of pertussis identified following the review of patients' records and included in this study.

Distribution of Pertussis Cases

Distribution by Age and Site

The overall distribution of study subjects by age is presented for each city and overall in Table 1. Overall, 4.3% of subjects were newborn, 19.8% were 1 month of age, 35.3% were 2 months of age, and 40.5% were 3 months of age.

In all of the cities, newborn infants accounted for the lowest proportion of the

total number of patients; there were no such patients in the Krasnodar site. The proportion of infants aged 1–2 months was highest in Moscow and Krasnoyarsk (28.9% and 27.3%, respectively). In each city, most of the subjects were 2–3 months of age: 77.2% in Saint Petersburg, 66.6% in Moscow, 96% in Krasnodar, and 63.6% in Krasnoyarsk.

Of the 116 cases of pertussis in infants within 3 months after birth included in this study, there were 45 cases in Moscow, 35 in Saint Petersburg, 25 in Krasnodar, and 11 in Krasnoyarsk (Fig. 1).

Distribution by Link to Pertussis Infection in a Close Relative

A total of 11 subjects had a close relative with a long history of cough (9 in Moscow and 2 in Saint Petersburg). The mother was identified as the source of the infection in 5/11 cases. In 4/11 cases, the source was identified as other children in the family, and in 2/11 cases the grandfather or father was the source.

Distribution of Pertussis Cases by Severity

In terms of the distribution of pertussis by severity, moderate disease was the most common being diagnosed in 59% of patients.

Table 1 The age distribution of the study population in different cities

Age	City								Total (N = 116)	
	Saint Petersburg (N = 35)		Moscow (N = 45)		Krasnodar (N = 25)		Krasnoyarsk (N = 11)			
	n	%	n	%	n	%	n	%	n	%
Newborn	2	5.7	2	4.4	0	0.0	1	9.1	5	4.3
1 month	6	17.1	13	28.9	1	4.0	3	27.3	23	19.8
2 months	10	28.6	15	33.3	10	40.0	6	54.5	41	35.3
3 months	17	48.6	15	33.3	14	56.0	1	9.1	47	40.5
Total	35	100.0	45	100.0	25	100.0	11	100.0	116	100.0

N number of participants, n number of participants fulfilling criterion, % percentage of participants fulfilling criterion

Severe forms were registered in 37% of patients, and mild forms were extremely rarely seen (in 3% of patients). The proportion of severe disease cases was 14.3% in Saint Petersburg; 37.8% in Moscow; 44% in Krasnodar, and 72.7% in Krasnoyarsk. In Saint Petersburg and Moscow, moderate pertussis was 6 and 2.4 times, respectively, more frequent than severe disease; in Krasnodar the split was about equal; in Krasnoyarsk, there were more infants with severe than moderate pertussis.

All newborn infants presented with severe disease. Severe pertussis was diagnosed in 52.2%

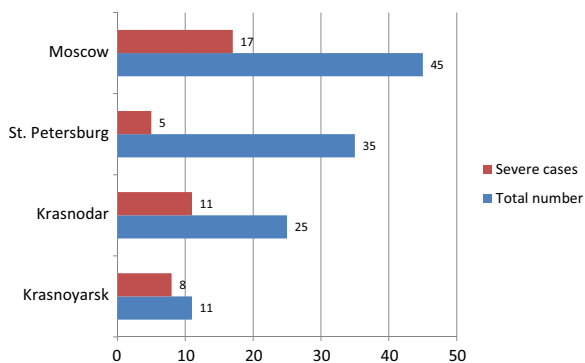


Fig. 1 Distribution of absolute number of total and severe cases of pertussis by city

of 1-month-old subjects, 36.6% of subjects aged 2 months, and 19.1% of subjects aged 3 months. Among 3-month-old infants, most severe pertussis was diagnosed in Krasnodar (6 out of 9 infants), while the other cities each had one such patient.

No significant gender-specific differences were observed in patients with severe pertussis: 21 boys and 19 girls were afflicted.

Distribution of Pertussis Cases by Hospital Stay

The median length of hospital stay was 12 days, and ranged from 1 day to 46 days. The median hospital stay was found to be 17.8 days in Saint Petersburg; 17 days in Krasnodar; 14.5 days in Krasnoyarsk; and 9.3 days in Moscow (Table 2).

Distribution of Pertussis Cases by Intensive Care Unit Stay and Complications

The intensive care requirement rates of Saint Petersburg, Moscow, and Krasnodar were similar across cities (11.4% for Saint Petersburg, 13.3% for Moscow, and 12% for Krasnodar; Table 2).

Table 2 Intensive care requirement rates and intensive care duration

		City				Total (N = 116)
		Saint Petersburg (N = 35)	Moscow (N = 45)	Krasnodar (N = 25)	Krasnoyarsk (N = 11)	
Median hospital stay	Days	17.8	9.3	17	14.5	18.3 ^a
RICD stay requirement	n	4	6	3	4	17
	%	11.4	13.3	12.0	36.4	14.7
RICD stay duration	Days	5.5	4.7	4.0	4.7	4.7 ^a
MLV requirement	n	1	1	2	1	5
	%	2.9	2.2	8	16.7	4.3
MLV duration	Days	5.0	1	2	21	7.3 ^a

N number of participants, n number of participants fulfilling criterion, % percentage of participants fulfilling criterion, MLV mechanical lung ventilation, RICD Resuscitation and Intensive Care Department

^a Mean value across sites

There were differences in duration of Resuscitation and Intensive Care Department (RICD) stay, the maximum stay (5.5 days) being in Saint Petersburg and the minimum duration (4.0 days) in Krasnodar. In Krasnoyarsk, the percentage of infants who received intensive care was the highest (36.4%) [but the small number of infants in the group ($N = 11$) should be taken into account] with 72.7% of this group being cases of severe pertussis. Among infants treated in Krasnoyarsk, one was a newborn in whom pertussis became complicated by bilateral pneumonia, leading to a 46-day intensive care period, including 21 days on MLV. Other infants with severe disease did not require MLV, while their length of RICD stay (4.7 days) did not differ compared with the other cities.

The classification and nature of complications observed in the participating cities are presented in Table 3. The most frequent complications were pertussis-induced encephalopathy, bronchitis, and pneumonia. The spectrum of specific complications was best characterized in patients in Saint Petersburg: breathing pattern impairment prevailed among specific complications, and pneumonia and acute bronchitis were most common among the non-specific complications. Both patients with pertussis-induced encephalopathy stayed in the RICD for 1 week receiving intensive care, including MLV, for 4–5 days. Encephalopathy was accompanied in these patients by respiratory pattern impairment. Two infants with short-term respiratory arrest were administered prednisolone in short courses

Table 3 The classification and nature of complications of pertussis

Complication	City				Total ($N = 116$)	
	Saint Petersburg ($N = 35$) <i>n</i>	Moscow ($N = 45$) <i>n</i>	Krasnodar ($N = 25$) <i>n</i>	Krasnoyarsk ($N = 11$) <i>n</i>	<i>n</i>	%
Specific						
Encephalopathy	2	2	5	2	11	9.5
Respiratory pattern impairment	4	0	0	0	4	3.4
Hemorrhage	1	0	0	1	2	1.7
Hernia (umbilical)	2	0	0	0	2	1.7
Atelectasis	1	3	0	0	4	3.4
Non-specific						
Pneumonia	4	4	0	1	9	7.8
Acute bronchitis	8	0	1	2	11	9.5
Obstructive bronchitis	2	0	0	0	2	1.7
Otitis media	3	0	0	0	3	2.6
Total	27	9	6	6	48	41.4

N number of participants, *n* number of complications, % percentage of cases with complications (one participant can have more, than one complication)

(3–5 days) and required no intensive care or MLV. Seven patients had multiple specific or non-specific complications or combinations (e.g., encephalopathy, apnea, pneumonia, atelectasis). Atelectasis and pneumonia were the most frequently diagnosed complications in Moscow. It should be noted that only one infant who developed atelectasis had a history of pneumonia. Among 2 patients with pertussis-induced encephalopathy, only 1 received intensive care in the RICD for 24 h, and this patient did not need MLV. Pertussis-induced encephalopathy was the main specific complication in patients with pertussis in Krasnodar; two infants were treated for this in the RICD, including the use of MLV, for 2 days. The Krasnoyarsk spectrum of specific complications was broader and included encephalopathy, subconjunctival hemorrhage, acute bronchitis, and pneumonia. Of two patients with pertussis-induced encephalopathy in Krasnoyarsk, one received intensive care in the RICD for 7 days (without MLV). One newborn infant in Krasnoyarsk with bilateral pneumonia in whom no other (including specific) complications of pertussis were diagnosed was given MLV for 21 days, spending a total of 46 days in the RICD; the course of the disease in this patient appeared to be due to a background condition(s) (probably an intrauterine infection and/or developmental defects). Overall, 27 complications were diagnosed in of Saint Petersburg patients, 9 in Moscow subjects, 6 in Krasnodar patients, and 6 complications in Krasnoyarsk subjects.

Two patients experienced hemorrhages—a 3-month-old infant in Saint Petersburg and a 2-month-old infant in Krasnoyarsk. Both were cases of subconjunctival hemorrhage.

The occurrence of complicated disease was significantly higher than that of severe pertussis in Saint Petersburg (19 patients vs. 5). In

Moscow, Krasnodar, and Krasnoyarsk patients, the incidence of severe pertussis was above the rate of complicated forms (17 vs. 6, 11 vs. 7, 7 vs. 5, respectively).

Distribution of Pertussis Cases by Urban/Rural Location

Overall, 16.8% of the study sample ($N = 116$) were from a rural population in whom severe pertussis was registered in 70% of cases, in contrast to those from the cities who had a 30% proportion of severe cases. Rural dwellers accounted for 17.1% of the Saint Petersburg patients, half of them with severe pertussis forms. Only two newborn infants (6.9%) had severe pertussis among the urban population. All Moscow patients were regarded as urban (including two coming from other localities). The urban Moscow population had severe pertussis in 39% of all cases divided as follows: 12.5% newborn infants, 50% 1-month-old infants, and 37.5% 2-month-old infants. Individuals aged 3 months presented with mild to moderate pertussis. In Krasnodar, the urban-to-rural ratio was balanced (13 and 12 patients, respectively). Among urban patients, 3 infants had severe pertussis and 10 patients presented moderate pertussis. Among rural inhabitants of Krasnodar, however, severe disease was observed in eight infants (aged 2 and 3 months) and moderate pertussis in just four patients. Predominantly severe forms of the disease were observed in Krasnoyarsk. Among 11 patients, just 1 was a villager suffering from severe pertussis; among urban inhabitants, 8 were severely and 2 moderately affected.

Distribution of Pertussis Cases by Diagnosis Type

Among all laboratory verification methods, PCR demonstrated the highest sensitivity and was

Table 4 The distribution of study subjects by pertussis verification method

Verification method	City								Total (<i>N</i> = 116)	
	Saint Petersburg (<i>N</i> = 35)		Moscow (<i>N</i> = 45)		Krasnodar (<i>N</i> = 25)		Krasnoyarsk (<i>N</i> = 11)			
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
PCR	11	31.4	4	8.9	5	20	0	0	20	17.2
Bacteriological	3	8.6	9	20	9	36	5	45.5	26	22.4
Serological	2	5.7	3	6.7	3	12	6	54.5	14	12.1
Clinical	22	62.9	18	40	13	52	5	45.5	58	50

N number of participants, *n* number of participants with verification method, % percentage of participants with verification method

the most commonly used in Saint Petersburg, bacteriological investigation was the most common in Moscow and Krasnodar, and serological and bacteriological testing the most common in Krasnoyarsk. The etiological diagnosis was confirmed by two laboratory methods in one patient in Saint Petersburg (PCR + culture), in two patients in Moscow (PCR + serology), in four individuals in Krasnodar (PCR + serology), and in five subjects in Krasnoyarsk (culture + serology). Serological methods were effective primarily when enzyme immunoassay (EIA) was used (Table 4).

DISCUSSION

This retrospective analysis demonstrated that in a range of cities and regions of the Russian Federation cases of pertussis in infants are still registered during the first 3 months of life, despite the decreases in pertussis incidence that have been described for the population as a whole, against a background of vaccination conducted in a considerable proportion of infants and children after 3 months of age. This finding is in accordance with previous data from countries other than the Russian

Federation that show that severe pertussis is a particular problem in young, unimmunized infants [19–21]. The cities selected for this analysis were representative of different climate zones in the Russian Federation (central, north-west, north-east and south) and the absolute number of registered patients varied substantially between different Russian cities, not only because of different population size but also due to varying incidence levels in the different regions.

In Moscow and Krasnoyarsk the proportion of patients under 1 month of age was higher than in the other cities, which could be a factor leading to the higher percentage of severe disease cases in these cities. However, overall the distribution of severity is in agreement with previously described specifics of pertussis found in infants under 1 year of age [9, 22]. Interestingly, no obvious relationship was observed in any city between the incidence of pertussis in infants aged under 3 months and the presence of other children aged under 18 years in the family (only 11 of the 116 participants had the source identified as a close family member), although the reverse may be true, that is, unvaccinated adolescents and adults may be at increased risk of contracting

pertussis if in close contact with an infected infant.

Specific complications of pertussis are known to characterize both the severe and moderate forms of the infection, and all severe forms are complicated. It would appear that some of the centers underestimated the complications of pertussis and probably overestimated the severity of the underlying disease. However, increased severity of pertussis and related complications are not uncommon in a young, unvaccinated population such as the one in this analysis, and previous studies have suggested that severity of pertussis may be worsened by low maternal antibody transfer [23], which is likely to be the case in the Russian Federation and is a factor that could be addressed by more wide vaccination of the adolescent and adult population. The incidence of encephalopathy was unusually high, particularly in Krasnoyarsk and Krasnodar; this reflects the higher percentage of infants with severe pertussis in these two sites.

Early diagnosis, particularly in infants within their first 3 months of life, is a pressing problem of health care. The bacteriological method, which was always regarded as a 'gold standard' in laboratory diagnosis, has diagnosis verification rates not exceeding 60%, and in recent years, its efficacy has fallen to 6–12%. Nevertheless, the main bacteriological findings are obtained in non-immunized infants under 1 year of age [9, 22].

As this study is descriptive and retrospective, limitations include an uncontrolled sample size and patient distribution across the four cities and a small sample size for individual sites. For this reason, no statistical analyses have been performed. The data we describe, however, are in agreement with others' findings, although future studies could be prospective in nature and include statistically powered sample size and full statistical analyses. Another limitation

is the definition of pertussis severity; this used Russian medical standards, which are in line with other severity scores but not identical.

CONCLUSION

Despite the ever-decreasing pertussis incidence rates against a background of widespread pediatric vaccination, infants in their first 3 months of life still suffer from severe pertussis with development of both specific and non-specific complications that require intensive care. However, in Moscow and Saint Petersburg infants aged above 2 months of age more frequently developed uncomplicated moderate and, less commonly, mild forms of this disease. Most newborn infants developed severe disease forms, which makes vaccination for adults who are in contact with neonates and infants within their first few months of life a valuable option [24]. Timely and adequate diagnosis of pertussis is only possible with a complex approach including not just modern laboratory investigations but also using clinical epidemiological data.

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Compliance with ethics guidelines. The analysis in this article is based on previously conducted studies, and does not involve any new studies of human subjects performed by any of the authors.

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