

Original Article

When will the coughing stop? Characteristics of children with pertussis (whooping cough) in Armenia (2014-2018)

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Abstract

Introduction: Despite the reported cases of whooping cough in Armenia, there has been no formal evaluation of “who these cases are and their load on hospital wards”. In a tertiary reference hospital, we determined the trend in hospitalized pertussis cases stratified by vaccination status and risk factors associated with apnea and hospital stay.

Methodology: Retrospective cohort study of children (< 18 years) with confirmed pertussis hospitalized at the Republican Infectious Diseases Hospital between 2014 and 2018. Multivariate logistic regression was used to identify risk factors.

Results: The majority (62%) of 116 children (44% female, mean age 21 months) were from regions outside the capital city of Yerevan. Standardized pertussis admissions increased by almost fivefold, from 2.2/1,000 in 2014 to 10.6/1,000 in 2018. The cumulative average percentage (2014-2018) of children not vaccinated against pertussis was 33%, while 29% were completely vaccinated. Twenty-five children (21%) had apnea, two of whom died. Younger age (Odds Ratio (OR) = 1.04; P = 0.05), not having been vaccinated (OR = 3.57; P = 0.01) and having comorbidities (OR = 4.1; P = 0.09) were associated with apnea. After adjusting for age, the longer hospital stay (>8 days) was significantly associated with non-vaccination (OR = 5.0, P = 0.002).

Conclusions: There is a progressive increase in rate of hospital admissions for pertussis meriting closer vigilance on a national scale. Unvaccinated children of younger age are predisposed to apnea and longer hospitalization and would benefit from early referral to specialized infectious units. This may improve clinical outcomes and reduce hospital burden.

Key words: whooping cough; pertussis; vaccination; infant mortality; hospital burden; SORT IT.

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Introduction

Whooping cough (also known as pertussis) is an airborne highly contagious bacterial disease caused by *Bordetella pertussis*. Typically, the symptoms start with cough and runny nose and evolve into paroxysmal and severe cough followed by high-pitched whoop [1]. The most common complications of pertussis include apnea, which occur in about 61% of cases, followed by pneumonia (23%), convulsion (1.1%), death (1%) and encephalopathy (0.3%) [2].

Pertussis remains a major cause of preventable infant mortality worldwide, causing an estimated of 160,700 deaths in under-fives in 2014 [3]. Despite being a vaccine-preventable disease, there has been a

paradoxical increase in the incidence of pertussis globally over the past two decades, even in countries with strong health systems and high vaccination rates [4-6].

Vaccination remains the most effective means of preventing pertussis-related complications [7]. The efficacy of the current acellular pertussis vaccine (in combination with diphtheria and tetanus vaccines – DTPa) ranges from 80 to 90% [8], with greater effectiveness for more severe strains [9]. Neither vaccination nor infection provide long-term immunity, therefore booster regimens are required to control *B. pertussis* [10]. Whooping cough may occur in those

who have been vaccinated, but the symptoms are typically milder.

Armenia has historically maintained a high rate of infant DTPa vaccination: 94% of one-year-old children received three-part immunization in 2016 [11]. Nevertheless, in recent years, the country has reported a steady increase in the incidence of pertussis.

Despite the public health concern about whooping cough in Armenia, there has been no formal evaluation of “who these cases are, their severity and the load they pose on the hospital ward”. Furthermore, a key question is whether these characteristics are associated with vaccination status. Studies from Europe and North America have shown that decreasing efficacy of the current vaccine could be the reason for rising incidence [5,12,13], however this issue has not yet been studied in Armenia.

Furthermore, as pertussis cases become more frequent, they pose a burden for the healthcare system due to the lengthy hospital stay and the need to prevent and control the infection in specialized infection control units. Apnea (the most common complication of pertussis) and duration of hospital stay can serve as proxy measures of the burden of this disease on the health system in Armenia.

A PubMed search revealed no studies from Armenia, nor from the Eastern Europe and Central Asian region assessing these parameters. In a tertiary reference hospital in the capital city of Yerevan, Armenia we thus determined a) the trend in hospitalized pertussis cases stratified by vaccination status, b) their sociodemographic and clinical characteristics and c) risk factors associated with apnea and duration of hospitalization (as proxies of hospital burden).

Methodology

Study Design

A retrospective cohort study using inpatient data from the Nork Republican Infectious Diseases Hospital (RIDH) in Yerevan, Armenia.

Study Setting

General

Armenia is a former Soviet, upper middle-income country located in the Eastern Europe. It is home to about three million people, of whom about 64% live in urban areas, and a fifth of the population is under 18 years of age [14]. Since the collapse of the Soviet Union in 1991, immunization rates have steadily increased in the country. From 2000 to 2010, the immunization coverage for the three dose regimen of the DTPa

vaccine has increased from 92% to 96% and has remained high [11].

Specific

Pertussis vaccination is offered as a major preventive measure and is included in the national vaccination schedule in accordance with the World Health Organization (WHO) recommendations. This includes a three dose regimen, with the first vaccination done at 6 weeks of age; with subsequent doses given 4-8 weeks apart, and then at 18 months [1,9]. This activity is supervised by a pediatrician and offered at 850 primary health facilities around the country. Pertussis cases can be identified at all health facility levels, and depending on clinical severity, the attending clinician can decide on outpatient management or refer the patient for hospitalized care. Hospitalization is restricted to tertiary health facilities that have infectious disease department. There are 11 such hospitals with one in each region and the RIDH in Yerevan. Diagnostic confirmation is done using Polymerase Chain Reaction and/or Pertussis specific immunoglobulin M testing at reference laboratories.

Patients with confirmed whooping cough are admitted to an isolation ward in the infectious disease unit where there is a specialized nursing and medical staff. They receive antibiotics and supportive treatment, and severe cases are referred to the intensive care unit.

Study site, population and period

The study site was the Nork RIDH, which is a tertiary level governmental healthcare facility. The infectious disease unit has 30 beds dedicated to airborne diseases, and there are about 15 beds in intensive care unit.

The study population included all children (< 18 years), admitted to the Nork RIDH with clinically and laboratory confirmed pertussis. The study covered the period January 2014 to May 2018.

Data collection, sources and statistical analysis

Data related to the study objectives was sourced by two clinicians from patient files. A data collection sheet was used for this purpose and data were then entered into a dedicated Epi Data database. Data were double-entered and cleaned. Variables included year of admission, age in months, gender, region, comorbidities, vaccination status, contact with coughing person, clinical features, complications and length of hospital stay.

Vaccination status was classified as none (no vaccine doses received), partially vaccinated (1-3

doses) or completely vaccinated (received all four doses).

Numbers of admitted pertussis cases were standardized per 1,000 pediatric admissions. Data were analyzed using the STATA software (Version 12, StataCorp, TX, College Station, USA) and online statistical application EasySTAT (<https://easystat.app/>) and expressed descriptively. Multiple logistic regression analysis was conducted to evaluate the relationship between apnea status and vaccination, as well as apnea status and length of hospitalization. Best fitting final model was identified and assessed using the Hosmer-Lemeshow test.

Ethics Approval

The study was approved by the Institutional Review Board of the Yerevan State Medical University, Yerevan, Armenia. As this study included anonymized routine secondary data, the issue of informed consent did not apply.

Results

Table 1 shows the trends in hospitalization of pertussis cases stratified by vaccination status for the period 2014-2018. The numbers of admitted pertussis children showed a variable trend with marked increases in 2017 and 2018. Pertussis admissions standardized per 1,000 pediatric admissions increased by almost fivefold between 2014 (2.2/1,000) and 2018 (10.6/1,000).

Over the study period, a cumulative average of 33% of admitted children were non-vaccinated while 29% had complete vaccination. Of the total number of 116 hospitalized children (44% female, mean age 21 months), the majority (62%) originated from regions outside Yerevan (Table 2).

A total of twenty-five children (22%) had apnea. After multi-variate adjustment, factors associated with apnea included vaccination status, age and comorbidity.

Younger children had a 4% higher odds (OR = 1.04; P = 0.05) of developing apnea, unvaccinated had more than threefold higher odds (OR = 3.57; P = 0.01) and those comorbidities – fourfold higher (OR = 4.1; P = 0.09) (see Table 2).

Two non-vaccinated infants (aged 2 and 5 months) with apnea died.

Of 116 children, 68 (59%) were hospitalized for ≤ 8 days, while 48 (41%) for more than 8 days. After adjusting for age, the unvaccinated group had five times higher odds of longer hospital stay (Table 3).

Discussion

This is the first study from Armenia that assessed a 5-year trend in pertussis among children admitted to a tertiary infectious disease hospital. It revealed that between 2014 and 2018, hospitalizations standardized per 1,000 pediatric admissions increased by five-fold. Roughly one out of three hospitalized children was unvaccinated, and this group had a considerably higher risk of apnea and longer hospital stay. Two children with apnea died, both of whom were non-vaccinated infants.

The study findings have healthcare system implications. On average, 33% of admitted children were never vaccinated, which represents a healthcare system gap. Did they have appropriate access to vaccination services, or were their parents simply unwilling to vaccinate their offsprings? The other side of the coin is that an average of 29% of the sample size contracted pertussis despite being completely vaccinated. Could this be explained by inadequate efficacy of the current DTPa vaccine, differences between administrative and operational vaccination coverage or other factors? Whatever the reasons for these findings are, these gaps will need to be bridged if the Sustainable Development Goals (SDGs) of eliminating deaths from preventable disease is to be achieved and “none are left behind”.

Table 1. Trend in pertussis hospitalization stratified by vaccination. Nork Republican Infectious Diseases Hospital (RIDH), Yerevan, Armenia (2014-2018).

Hospitalization	Number of cases, n				
	2014	2015	2016	2017	2018
Annual hospital admission	3,658	5,309	4,385	4,702	3,584
Pertussis	8	23	14	33	38
Pertussis admissions per 1,000*	2.2	4.3	3.2	7.0	10.6
Vaccination	Number of cases, n (%)				
None	2 (25)	9 (39)	5 (36)	10 (30)	14 (37)
Partial	1 (12)	8 (35)	7 (50)	14 (42)	8 (21)
Complete	5 (63)	4 (17)	2 (14)	6 (18)	13 (34)
Missing	0	2 (9)	0	3 (10)	3 (8)

*Per 1,000 pediatric admissions at Nork RIDH, Yerevan, Armenia.

Table 2. Risk factors for apnea among children with pertussis (n = 116) at Nork Republican Infectious Diseases Hospital, Yerevan, Armenia (2014-2018).

Variable	Apnea, n (%)		Crude OR*	90% CI**	Adjusted OR	90% CI	P-value
	No (n = 91)	Yes (n = 25)					
Region							
Yerevan	35 (38)	9 (36)	1	0.4-2.8	-	-	-
Other	56 (62)	16 (64)	1.1	-	-	-	-
Mean age, months (SD***)	23.9 (25)	9.5 (19)	14.4	5.1-23.7	0.96	0.92-0.99	0.05
Gender							
Male	51 (56)	14 (56)	1	-	-	-	-
Female	40 (44)	11 (44)	1	0.4-2.7	-	-	-
Comorbidities							
No	88 (97)	21 (84)	1	-	-	-	-
Yes	3 (3)	4 (16)	5.6	1.2-26.9	4.10	1.01-16.7	0.09
Vaccination status							
None	24 (26)	16 (64)	1	-	-	-	-
Complete/ Partial	60 (66)	8 (32)	0.2	0.1-0.5	0.28	0.12-0.68	0.01
Missing	7 (8)	1 (4)	-	-	-	-	-
Cyanosis							
No	60 (66)	9 (36)	3.4	1.3-9.8	-	-	-
Yes	31 (34)	16 (64)	1	-	-	-	-
Pneumonia							
No	76 (84)	14 (56)	3.92	1.3-11.5	-	-	-
Yes	15 (16)	11 (44)	1	-	-	-	-
Hospitalization, days							
≤8 days	63 (69)	5 (20)	-	-	-	-	-
>8 days	28 (31)	20 (80)	9	3.1-26.4	-	-	-

*OR = Odds Ratio. **CI = Confidence Interval. ***SD = Standard Deviation.

Table 3. Length of hospitalization in relation to vaccination status and age among children with pertussis (n = 116) at Nork Republican Infectious Diseases Hospital, Yerevan, Armenia (2014-2018).

Variable	Hospital stay, n (%)		Crude OR* (95% CI**)	Adjusted OR (95% CI)	P-value
	≤8 days (n = 68)	>8 days (n = 48)			
Vaccination status					
None	16 (24)	24 (50)	1	1	-
Partial	28 (41)	10 (21)	0.24 (0.08-0.68)	0.2 (0.07-0.54)	0.002
Complete	20 (29)	10 (21)	0.34 (0.11-0.99)	-	-
Missing	4 (6)	4 (8)	-	-	-
Mean age, months (SD***)	25.6 (27.3)	14.1 (17.6)	0.98 (0.95-0.99)	0.96 (0.94-0.99)	0.024

*OR = Odds Ratio. **CI = Confidence Interval. ***SD = Standard Deviation; The Hosmer-Lemeshow goodness of fit test (p = 0.85).

The strengths of the study are that all pertussis cases were diagnosed using case definitions and were laboratory confirmed allowing comparison of trends. Data were sourced from patient files, double entered and validated and thus, we believe, robust. We adhered to STROBE guidelines for the reporting of observational studies [15].

The study limitations are that our data is restricted to one of the 11 infectious disease hospitals in the country and as such, we do not know whether the situation in other infectious hospitals is similar. This aspect merits wider operational research, which is further justified in view of the fact that the majority of admitted children came from outside Yerevan. Another limitation is the small sample size, which limits study power to have more precise estimates of factors related to apnea and the length of hospitalization.

The study findings have a number of policy and practice implications.

First, the finding that on average about a third (29%) of children with pertussis were completely vaccinated calls for national vigilance. Since the efficacy of the current vaccine is around 80-90%, it is natural to see cases of pertussis despite complete vaccination [8]. However, in the last two years of study, we observed a tendency to increase the number of such cases in Nork RIDH. Is this a reflection of waning immunity, issues around vaccine efficacy or other factors? In any case, ensuring close surveillance and monitoring of all reported pertussis cases throughout the country and their relation to the vaccination state deserve attention. If this reveals growing trends in new cases of whooping cough despite complete vaccination, it would be a “red flag” and a call to action.

It also raises the question of whether pertussis vaccination should be offered to pregnant women. This may confer maternal antibodies to newborns and have advantages for unvaccinated “young” infants. Operational feasibility and scientific rationale for such complementary action will require further study [16,17].

Second, the risk of apnea was higher in those who were not vaccinated, had comorbidities and were of younger age. This finding largely consistent with the previous studies [2,3]. In fact, despite hospitalization and treatment in a tertiary reference hospital, the two infants with a fatal outcome were from apnea group. Although this association needs further exploration, the message for clinicians is clear: if you see a child with pertussis who is young, has concomitant disease(s) and is unvaccinated, start antibiotics to prevent further transmission and urgently refer the patient to a

specialized infectious care unit. From the patient perspective, the benefits will include earlier presentation, avoidance of possible complications and a favorable hospital outcome. From the healthcare system perspective, this might translate into shorter hospital stay and, subsequently, reduced burden on the health system.

Finally, a universal measure that should be considered is to raise public awareness of the importance of vaccinations, including pertussis, with focused campaigns targeting specific regions where cases of illness originate.

Conclusion

In conclusion, there is a progressive increase in rate of hospital admissions for pertussis meriting closer vigilance on a national scale. Unvaccinated children of younger age are predisposed to apnea and longer hospitalization. This may improve clinical outcomes and reduce hospital burden.

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