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Evaluation of the diagnostic utility of the new clinical case definition of pertussis – experience from sentinel and hospital-based pertussis surveillance

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SUMMARY

Introduction/Objective Global surveillance systems use different clinical case definitions of pertussis. The aim of this study was to identify sign and symptom combinations with best relation with laboratory-confirmed pertussis.

Methods A one-year prospective observational study, proposed by the Global Pertussis Initiative (GPI) for three age groups (0–3 months, four months to nine years, and ≥ 10 years) was performed in Novi Sad to evaluate the performance of the clinical case definition of pertussis. Laboratory confirmation of *B. pertussis* infection was obtained using the DNA polymerase chain reaction (PCR) or ELISA serology tests.

Results From October 1, 2013 to September 30, 2014, 103 (32.3%) out of 319 participants with suspected pertussis had laboratory-confirmed pertussis. Combined whooping, post-tussive emesis, and worsening of symptoms at night was the best predictor of pertussis in outpatients aged four months to nine years (positive likelihood ratio (LR+) 11.6), while among inpatients of the same age group it was apnoea (LR+ 13.5). The LR+ in outpatients aged ≥10 years for combinations of apnoea and post-tussive emesis, or a combination of whooping and sweating episodes between paroxysms and post-tussive emesis was 16.8, while among in-patients LR+ was < 2.3 for all combinations in the same age group.

Conclusions The GPI case definitions for pertussis are good predictors for laboratory-confirmed pertussis and are useful for the purpose of pertussis surveillance.

Keywords: pertussis (whooping cough); Global Pertussis Initiative; case definition; surveillance

INTRODUCTION

Pertussis remains an important cause of morbidity and mortality among infants and children, even in countries with high vaccination coverage rates. The World Health Organization (WHO) estimates that 50 million cases and 300,000 deaths occur every year because of pertussis, and case-fatality rates of pertussis in developing countries are estimated to be as high as 4% in infants [1]. Consequently, establishing a reliable diagnosis of pertussis has become increasingly important [2, 3].

Because of the heterogeneity in clinical manifestations of pertussis, lack of general availability of laboratory confirmation of the disease, mixed infections, and a low index of suspicion among many physicians, pertussis is under-recognized worldwide. In addition, the absence of a sensitive clinical case definition of pertussis has contributed to missed or misdiagnosed pertussis cases [4, 5, 6].

Existing clinical case definitions of pertussis are based on clinical presentation in infants and children, but they are also used for adolescents and adults who may manifest distinct signs and symptoms. Therefore, in an effort to improve the diagnosis of pertussis, the Global Pertussis Initiative (GPI) proposed an algorithm based on the most common signs and symptoms of pertussis for three age groups, i.e. 0–3 months, four months to nine years, and ≥ 10 years old [7].

Until 2012, the epidemiology of pertussis in Novi Sad has not been described well, when an improved surveillance method for pertussis was introduced following the GPI recommendations [7]. We then determined that pertussis was widespread in our population, affecting patients of any age [8, 9].

The aim of this study was to determine the most predictive signs and symptoms of pertussis, and to evaluate the diagnostic performance of certain combinations of signs and symptoms based on the case definitions of pertussis proposed by the GPI.

METHODS

Study design, specimen collection, and laboratory testing

The recruitment period was from October 1, 2013 to September 30, 2014 (52 weeks). According to the GPI, methods have previously been described in detail [7, 9]. Briefly, we

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simultaneously conducted prospective surveillance at both primary (outpatients) and tertiary (inpatients) health care levels in the city of Novi Sad. Participants were identified and sampled by the physicians in the two health care levels as a part of their daily routine. Hospital surveillance for the entire Novi Sad area (341,624 inhabitants) was conducted in two inpatient facilities: pulmonology clinic of the Institute of Child and Youth Health Care of Vojvodina (pediatric inpatient facility) and the Institute of Pulmonary Diseases of Vojvodina (adult inpatient facility). We only included patients who fulfilled one or more criteria of clinical case definitions for three age groups (0–3 months, four months to nine years, and ≥ 10 years old) [7].

Patient data collection, sampling, and transport of patient material, as well as the laboratory testing of samples and interpretation of results was performed according to the previously used methodology [7, 9].

We classified participants as "fully vaccinated" according to their age, "partly vaccinated" (cases who had received ≥ 1 but not all the vaccinations required for their age), and "unvaccinated." Due to waning immunity after vaccination against pertussis, only vaccination status for participants < 18 years was recorded. All participants aged ≥ 18 years were considered as participants with an unknown vaccination status.

Verbal informed consent was obtained from patients before swab taking in accordance with national regulations and written consent from parents or guardians was obtained.

Statistical analysis

Because we registered only five laboratory-confirmed pertussis cases in infants aged 0–3 months, we did not perform a validation of certain sings and symptoms in this age group. A two-tailed P value $p < 0.05$ was considered to indicate statistical significance for all statistical tests. Data analysis was performed using the SPSS for Windows, version 22.0 software (IBM Corp. NY, USA) and MedCalc for Windows, version 12.3.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

During the study period, 319 participants with suspected pertussis were enrolled, and 103 (32.3%) had laboratory-confirmed pertussis by PCR or serology. Among the laboratory-confirmed cases, 29, 71, and three patients were positive by PCR and the enzyme-linked immunosorbent assay (ELISA) respectively. *B. parapertussis* or *B. bronchiseptica* infections were not detected. No participant with suspected pertussis had been vaccinated against pertussis during the 12 months before inclusion into the study, and there were no deaths. Patients with laboratory-confirmed pertussis were younger than those without laboratory confirmation ($p = 0.030$), and the proportion of pertussis was higher among hospitalized patients compared to outpatients ($p < 0.001$), and higher among "unvaccinated" and "partly vaccinated" children compared to those where "fully vaccinated," although the difference was not significant (OR 1.87, 95% CI 0.97–3.60, $p = 0.062$) (data not shown).

Pertussis was confirmed in 31.3% (5/16), 27.4% (34/124) and 35.8% (64/179) in individuals 0–3 months, four months to nine years, and ≥ 10 years old, respectively.

In infants 0–3 months of age, the mandatory signs and symptoms (MSS) in combination with pneumonia (OR 6.75, 95% CI 0.64–71.18) and close exposure to a person with a prolonged afebrile cough illness (contact) (OR 2.50, CI 0.12–50.45) had a strong association with pertussis, but due to a limited number of participants, differences between positive and negative cases were not statistically significant ($p > 0.05$).

In the four months to nine years and ≥ 10 years age groups, the MSS accompanied by whoop or apnoea or post-tussive emesis or worsening of the symptoms at night were significantly associated with having a laboratory-confirmed pertussis ($p < 0.05$). Among the participants aged four months – nine years, only combination of MSS and pneumonia was not associated with pertussis, and in the ≥ 10 years age group, only MSS accompanied by sweating episodes between paroxysms was not a predictor of laboratory-confirmed pertussis ($p > 0.05$) (Table 1).

The diagnostic performance of the selected sign and symptom combinations for pertussis in the participants aged four months to nine years is shown in Table 2 and for those ≥ 10 years in Table 3.

Among the outpatients, the MSS of pertussis in the age group from four months–nine years accompanied by whoop, post-tussive emesis and worsening symptoms at night had the highest diagnostic value of laboratory-confirmed pertussis (LR+ 11.6, 95% CI 2.6–51.8). A combination of the MSS and apnoea was the strongest predictor of pertussis among inpatients (LR+ 13.5, 95% CI 1.8–99.6). When stratified by the surveillance sites, the MSS along with apnoea was significantly more sensitive in the hospital than in the sentinel sites (42.1% *vs.* 6.7%, $p = 0.022$). The MSS in combination with post-tussive emesis or accompanied by post-tussive emesis and contact were significantly more specific among the outpatients than in the inpatients (77.6% *vs.* 43.8%, $p = 0.001$ and 100% *vs.* 90.6%, $p = 0.018$, respectively).

According to the values of LR+ for participants aged ≥ 10 years, among the inpatients there was no combination with LR+ greater than 2.3. In the outpatients, including the MSS in combination with one or more signs and symptoms through sentinel surveillance, we have determined that five different combinations from the proposed case definition were the strongest predictors of pertussis in the ≥ 10 years age group (LR+ above 10).

Compared to the values of sensitivities and specificities among the participants aged ≥ 10 years in the two surveillance systems, including the MSS of pertussis, post-tussive emesis was significantly more sensitive among the out-patients than in the in-patients (61.3% *vs.* 27.3%, $p = 0.007$, respectively). The combination of MSS along with worsening of symptoms at night was significantly more sensitive (84.9% *vs.* 61.3%, $p = 0.034$, respectively), and the combination of MSS accompanied by whoop and post-tussive emesis was

Table 1. Signs and symptoms associated with laboratory confirmed pertussis infections in the sentinel and hospital surveillance of pertussis by age group

Age group with mandatory and other signs and symptoms of pertussis	Total (n = 319)	Positive (n = 103)	Negative (n = 216)	crude OR (95% CI)	p	adjusted OR[a, b] (95% CI)	p
1) 0–3 months Cough and coryza with no or minimal fever plus:	(n = 16) n (%)	(n = 5) n (%)	(n = 11) n (%)	Ref.			
Whoop	7 (43.8)	2 (40)	5 (45.5)	0.80 (0.09–6.85)	0.839	-	-
Apnoea	3 (18.8)	3 (60)	0 (-)	NA	ND	-	-
Post-tussive emesis	7 (43.8)	1 (20)	6 (54.5)	0.21 (0.02–2.52)	0.217	-	-
Cyanosis	5 (31.3)	1 (20)	4 (36.4)	0.44 (0.04–5.40)	0.519	-	-
Seizure	1 (6.3)	1 (20)	0 (-)	NA	ND	-	-
Pneumonia	5 (31.3)	3 (60)	2 (18.2)	6.75 (0.64–71.18)	0.112	-	-
Contact[c]	2 (12.5)	1 (20)	1 (9.1)	2.50 (0.12–50.45)	0.550	-	-
2) four months to nine years Paroxysmal cough with no or minimal fever plus:	(n = 124) n (%)	(n = 34) n (%)	(n = 90) n (%)	Ref.			
Whoop	55 (44.4)	23 (67.6)	32 (35.6)	3.79 (1.64–8.76)	**0.002**	3.63 (1.48–8.90)	**0.005**
Apnoea	13 (10.5)	9 (26.5)	4 (4.4)	7.74 (2.20–27.26)	**0.001**	10.11 (2.40–42.63)	**0.002**
Post-tussive emesis	52 (41.9)	21 (61.8)	31 (34.4)	3.07 (1.36–6.96)	**0.007**	3.51 (1.44–8.57)	**0.006**
Worsening of symptoms at night	58 (46.8)	21 (61.8)	37 (41.1)	2.31 (1.03–5.20)	**0.042**	3.29 (1.31–8.25)	**0.011**
Pneumonia	8 (6.5)	1 (2.9)	7 (7.8)	0.36 (0.04–3.04)	0.347	-	-
Seizure	0 (-)	0 (-)	0 (-)	NA	ND	NA	ND
Contact[c]	20 (16.1)	10 (29.4)	10 (11.1)	3.33 (1.24–8.95)	**0.017**	5.68 (1.76–18.35)	**0.004**
3) ≥ 10 years Non-productive, paroxysmal cough of ≥ 2 weeks duration without fever plus:	(n = 179) n (%)	(n = 64) n (%)	(n = 115) n (%)	Ref.			
Whoop	76 (42.5)	44 (68.8)	32 (27.8)	5.71 (2.93–11.12)	**< 0.001**	4.64 (2.29–9.41)	**< 0.001**
Apnoea	17 (9.5)	14 (21.9)	3 (2.6)	10.45 (2.88–38)	**< 0.001**	10.68 (2.74–41.54)	**0.001**
Sweating episodes between paroxysms	79 (44.1)	24 (37.5)	55 (47.8)	0.65 (0.35–1.22)	0.184	-	-
Post-tussive emesis	51 (28.5)	28 (43.8)	23 (20)	3.11 (1.59–6.10)	**0.001**	2.73 (1.32–5.67)	**0.007**
Worsening of symptoms at night	105 (58.7)	47 (73.4)	58 (50.4)	2.72 (1.40–5.28)	**0.003**	3.66 (1.74–7.69)	**0.001**

Values that differ significantly between positive and negative pertussis cases are marked in bold;
NA – not applicable; ND – not determined;

[a]adjusted for the following variables: age, gender, duration of cough and vaccination status (fully vaccinated persons compared with unvaccinated, partly vaccinated, and persons with unknown vaccination status together) for characteristics with significance difference according to univariate analysis;
[b]not calculable and omitted in logistic regression analyses in the 0–3 months age group;
[c]close exposure to an adolescent or adult (usually a family member) with a prolonged afebrile cough illness

significantly less specific (81.8% *vs.* 97.1%, p = 0.019, respectively) in hospitalized than in outpatient cases.

DISCUSSION

The main aim of the study was to validate the pertussis case definitions of the GPI. A very important aspect of our study was the estimation of the sensitivity and specificity of various combinations of signs and symptoms of the clinical case definitions proposed by the GPI.

One of the first published studies, in which certain signs and symptoms of pertussis case definition were evaluated, was conducted during two community outbreak years in Wisconsin and Delaware (in 1985 and 1986) [10]. In this study, participants were enrolled in the outbreak settings with wide inclusion criteria (one or more symptoms of acute respiratory illness, regardless of the age of participants), and a total of 50% of patients had laboratory evidence of pertussis, while the prevalence of laboratory-confirmed pertussis in our study was 32.3%. Except for the pertussis outbreak in the families, there were no registered

Table 2. Diagnostic accuracy of signs and symptoms and their combinations of proposed case definitions of patients aged four months to nine years with suspected pertussis infection

Surveillance system	Mandatory signs and symptoms plus:	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR- (95% CI)
Sentinel surveillance (outpatients)	Whoop	73.3 (44.9–92.1)	63.8 (50.1–76)	34.4 (18.6–53.2)	90.2 (76.9–97.2)	2 (1.3–3.2)	0.4 (0.2–0.9)
	Apnoea	6.7 (1.1–32)[a]	94.8 (85.6–98.9)	25 (4.1–79.7)	79.7 (68.3–88.4)	1.3 (0.1–11.5)	1 (0.9–1.1)
	Post-tussive emesis	60 (32.3–83.6)	77.6 (64.7–87.5)[b]	40.9 (20.8–63.6)	88.2 (76.1–95.5)	2.7 (1.4–5)	0.5 (0.3–0.9)
	Worsening of symptoms at night	66.7 (38.4–88.1)	55.2 (41.5–68.3)	27.8 (14.2–45.2)	86.5 (71.2–95.4)	1.5 (0.9–2.4)	0.6 (0.3–1.3)
	Pneumonia	0 (-)	91.4 (81–97.1)	NA	77.9 (66.2–87.1)	NA	1.1 (1–1.2)
	Contact[c]	40 (16.4–67.7)	89.7 (78.8–96.1)	50 (21.2–78.8)	85.3 (73.8–93)	3.9 (1.5–10.3)	0.7 (0.4–1)
	Whoop + apnoea	6.7 (1.1–32)	94.8 (85.6–98.9)	25 (4.1–79.7)	79.7 (68.3–88.4)	1.3 (0.1–11.5)	1 (0.9–1.1)
	Whoop + post-tussive emesis	46.7 (21.3–73.4)	93.1 (83.3–98.1)	63.6 (30.9–88.9)	87.1 (76.1–94.2)	6.8 (2.3–20.1)	0.6 (0.4–0.9)
	Whoop + worsening of symptoms at night	40 (16.4–67.7)	82.8 (70.6–91.4)	37.5 (15.3–64.5)	84.2 (72.1–92.5)	2.3 (1–5.4)	0.7 (0.5–1.1)
	Whoop + contact[c]	33.3 (12–61.6)	96.6 (88.1–99.5)	71.4 (29.3–95.5)	84.9 (73.9–92.5)	9.7 (2.1–45)	0.7 (0.5–1)
	Post-tussive emesis + worsening of symptoms at night	53.3 (26.7–78.7)	89.7 (78.8–96.1)	57.1 (28.9–82.2)	88.1 (77.1–95.1)	5.2 (2.1–12.6)	0.5 (0.3–0.9)
	Post-tussive emesis + contact[c]	20 (4.6–48.1)	100 (-)[b]	100 (-)	82.9 (72–90.8)	NA	0.8 (0.6–1)
	Worsening of symptoms at night + contact	20 (4.6–48.1)	96.6 (88.1–99.5)	60 (15.4–93.5)	82.4 (71.2–90.5)	5.8 (1.1–31.7)	0.8 (0.6–1.1)
	Whoop + post-tussive emesis + worsening of symptoms at night	40 (16.4–67.7)	96.6 (88.1–99.5)	75 (35.1–96.1)	86.2 (75.3–93.5)	11.6 (2.6–51.8)	0.6 (0.4–0.9)
	Whoop + post-tussive emesis + worsening of symptoms at night + contact[c]	13.3 (2.1–40.5)	98.3 (90.7–99.7)	66.7 (11.6–94.5)	81.4 (70.3–89.7)	7.7 (0.6–79.7)	0.9 (0.7–1.1)
Hospital surveillance (inpatients)	Whoop	63.2 (38.4–83.7)	65.6 (46.8–81.4)	52.2 (30.6–73.2)	75 (55.1–89.3)	1.8 (1–3.3)	0.6 (0.3–1.1)
	Apnoea	42.1 (20.3–66.5)[a]	96.9 (83.7–99.5)	88.9 (51.7–98.2)	73.8 (57.9–86.1)	13.5 (1.8–99.6)	0.6 (0.4–0.9)
	Post-tussive emesis	63.2 (38.4–83.7)	43.8 (26.4–62.3)[b]	40 (22.7–59.4)	66.7 (43–85.4)	1.1 (0.7–1.8)	0.8 (0.4–1.7)
	Worsening of symptoms at night	57.9 (33.5–79.7)	65.6 (46.8–81.4)	50 (28.3–71.8)	72.4 (52.8–87.2)	1.7 (0.9–3.1)	0.6 (0.4–1.2)
	Pneumonia	5.3 (0.9–26.1)	93.8 (79.2–99.1)	33.3 (5.5–88.5)	62.5 (47.4–76)	0.8 (0–8.7)	1 (0.9–1.2)
	Contact[c]	21.1 (6.2–45.6)	87.5 (70.9–96.4)	50 (16–83.9)	65.1 (49.1–78.9)	1.7 (0.5–5.9)	0.9 (0.7–1.2)
	Whoop + apnoea	31.6 (12.7–56.5)	96.9 (83.7–99.5)	85.7 (42.2–97.6)	70.5 (54.8–83.2)	10.1 (1.3–77.7)	0.7 (0.5–1)
	Whoop + post-tussive emesis	36.8 (16.4–61.6)	81.3 (63.6–92.8)	53.9 (25.2–80.7)	68.4 (51.4–82.5)	2 (0.8–5)	0.8 (0.5–1.1)
	Whoop + worsening of symptoms at night	31.6 (12.7–56.5)	84.4 (67.2–94.7)	54.6 (23.5–83.1)	67.5 (50.9–81.4)	2 (0.7–5.7)	0.8 (0.6–1.1)
	Whoop + contact[c]	10.5 (1.6–33.2)	93.8 (79.2–99.1)	50 (8.3–91.7)	63.8 (48.5–77.3)	1.7 (0.3–11)	1 (0.8–1.1)
	Post-tussive emesis + worsening of symptoms at night	36.8 (16.4–61.6)	78.1 (60–90.7)	50 (23.1–76.9)	67.6 (50.2–82)	1.7 (0.7–4.1)	0.8 (0.6–1.2)
	Post-tussive emesis + contact[c]	21.1 (6.2–45.6)	90.6 (75–97.9)[b]	57.1 (18.8–89.6)	65.9 (50.1–79.5)	2.3 (0.6–9)	0.9 (0.7–1.1)
	Worsening of symptoms at night + contact[c]	15.8 (3.6–39.6)	96.9 (83.7–99.5)	75 (20.3–95.9)	66 (50.7–79.1)	5.1 (0.6–45.2)	0.9 (0.7–1)
	Whoop + post-tussive emesis + worsening of symptoms at night	21.1 (6.2–45.6)	87.5 (71–96.4)	50 (16–84)	65.1 (49.1–79)	1.7 (0.5–6.)	0.9 (0.7–1.2)
	Whoop + post-tussive emesis + worsening of symptoms at night + contact[c]	10.5 (1.6–33.2)	100 (-)	100 (-)	65.3 (50.4–78.3)	NA	0.9 (0.8–1)

NA – not applicable; PPV – positive predictive value; NPV – negative predictive value; LR+ – positive likelihood ratio; LR- – negative likelihood ratio;
[a]sensitivity significantly different between the two surveillance systems;
[b]specificity significantly different between the two surveillance systems;
[c]close exposure to an adolescent or adult (usually a family member) with a prolonged afebrile cough illness

Table 3. Diagnostic accuracy of signs and symptoms and their combinations of proposed case definitions of patients aged ≥ 10 years with suspected pertussis infection

Surveillance system	Mandatory signs and symptoms plus:	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR- (95% CI)
Sentinel surveillance (out-patients)	Whoop	71 (52–85.8)	74 (64.5–82.1)	44.9 (30.7–59.8)	89.5 (81.1–95.1)	2.7 (1.8–4.1)	0.4 (0.2–0.7)
	Apnoea	16.1 (5.5–33.7)	97.1 (91.8–99.4)	62.5 (24.7–91)	79.5 (71.5–86.2)	5.6 (1.4–22.1)	0.9 (0.7–1)
	Sweating episodes between paroxysms	35.5 (19.3–54.6)	51.9 (41.9- 61.8)	18 (9.4–30)	73 (61.4–82.6)	0.7 (0.4–1.2)	1.2 (0.9–1.7)
	Post-tussive emesis	61.3 (42.2–78.1)[a]	81.7 (73–88.6)	50 (33.4–66.6)	87.6 (79.4–93.4)	3.4 (2.1–5.5)	0.5 (0.3–0.7)
	Worsening of symptoms at night	61.3 (42.2–78.1)[a]	51 (41–60.9)	27.1 (17.2–39.1)	81.5 (70–90.1)	1.3 (0.9–1.8)	0.8 (0.5–1.2)
	Whoop + apnoea	12.9 (3.7–29.9)	99 (94.7–99.8)	80 (28.8–96.7)	79.2 (71.2–85.8)	13.4 (1.6–115.7)	0.9 (0.8–1)
	Whoop + post-tussive emesis	38.7 (22–57.8)	97.1 (91.8–99.4)[b]	80 (51.9–95.4)	84.2 (76.4–90.2)	13.4 (4–44.6)	0.6 (0.5–0.8)
	Post-tussive emesis + worsening of symptoms at night	32.3 (16.7–51.4)	90.4 (83–95.3)	50 (27.2–72.8)	81.7 (73.5–88.3)	3.4 (1.5–7.3)	0.8 (0.6–1)
	Apnoea + post-tussive emesis	16.1 (5.5–33.7)	99 (94.7–99.8)	83.3 (36.1–97.2)	79.8 (71.9–86.4)	16.8 (2–138.3)	0.9 (0.7–1)
	Whoop + sweating episodes between paroxysms + worsening of symptoms at night	9.7 (2–25.8)	95.2 (89.1–98.4)	37.5 (8.5–75.5)	78 (69.7–84.8)	2 (0.5–8)	1 (0.8–1.1)
	Whoop + sweating episodes between paroxysms + post-tussive emesis	16.1 (5.5–33.7)	99 (94.7–99.8)	83.3 (36.1–97.2)	79.8 (71.9–86.4)	16.8 (2–138.3)	0.9 (0.7–1)
	Whoop + worsening of symptoms at night + post-tussive emesis	19.4 (7.5–37.5)	98.1 (93.2–99.7)	75 (35.1–96.1)	80.3 (72.3–86.8)	10.1 (2.1–47.4)	0.8 (0.7–1)
	Apnoea + sweating episodes between paroxysms + post-tussive emesis	3.2 (0.1–16.7)	99 (94.8–99.9)	50 (1.3–98.7)	77.4 (69.4–84.2)	3.4 (0.2–52.1)	1 (0.9–1)
Hospital surveillance (in-patients)	Whoop	66.7 (48.2–82)	54.6 (23.5–83.1)	81.5 (61.9–93.6)	35.3 (14.3–61.7)	1.5 (0.7–2.9)	0.6 (0.3–1.2.7)
	Apnoea	27.3 (13.3–45.5)	100 (-)	100 (-)	31.4 (16.9–49.3)	NA	0.7 (0.6–0.9)
	Sweating episodes between paroxysms	39.4 (22.9–57.9)	54.6 (23.5–83.1)	72.2 (46.5–90.2)	23.1 (9–43.7)	0.9 (0.4–1.9)	1.1 (0.6–2)
	Post-tussive emesis	27.3 (13.3–45.5)[a]	63.6 (30.9–88.9)	69.2 (38.6–90.7)	22.6 (9.6–41.1)	0.8 (0.3–2)	1.1 (0.7–1.9)
	Worsening of symptoms at night	84.9 (68.1–94.8)[a]	36.4 (11.2–69.1)	80 (63.1–91.5)	44.4 (14–78.6)	1.3 (0.8–2.1)	0.4 (0.1–1.3)
	Whoop + apnoea	21.2 (9–38.9)	100 (-)	100 (-)	29.7 (15.9–47)	NA	0.8 (0.7–0.9)
	Whoop + post-tussive emesis	18.2 (7–35.5)	81.8 (48.2–97.2)[b]	75 (35.1–96.1)	25 (12.2–42.2)	1 (0.2–4.3)	1 (0.7–1.4)
	Post-tussive emesis + worsening of symptoms at night	24.2 (11.1–42.3)	72.7 (39.1–93.7)	72.7 (39.1–93.7)	24.2 (11.1–42.3)	0.9 (0.3–2.8)	1 (0.7–1.6)
	Apnoea + post-tussive emesis	6.1 (0.9–20.3)	100 (-)	100 (-)	26.2 (13.9–42)	NA	0.9 (0.9–1)
	Whoop + sweating episodes between paroxysms + worsening of symptoms at night	21.2 (9–38.9)	90.9 (58.7–99.8)	87.5 (47.4–99.7)	27.8 (14.2–45.2)	2.3 (0.3–16.9)	0.9 (0.7–1.1)
	Whoop + sweating episodes between paroxysms + post-tussive emesis	6.1 (0.9–20.3)	90.9 (58.7–98.5)	66.7 (11.6–94.5)	24.4 (12.4–40.3)	0.7 (0.1–6.7)	1 (0.8–1.3)
	Whoop + worsening of symptoms at night + post-tussive emesis	18.2 (7–35.5)	90.9 (58.7–98.5)	85.7 (42.2–97.6)	27 (13.8–44.1)	2 (0.3–14.8)	0.9 (0.7–1.2)
	Apnoea + sweating episodes between paroxysms + post-tussive emesis	0 (-)	100 (-)	NA	25 (13.2–40.3)	NA	NA

NA – not applicable; PPV – positive predictive value; NPV – negative predictive value; LR+ – positive likelihood ratio; LR- – negative likelihood ratio;
[a]sensitivity significantly different between the two surveillance systems;
[b]specificity significantly different between the two surveillance systems

outbreaks in the population in the city of Novi Sad during our study period [8, 9]. Because participants in our study were enrolled during an epidemic free year and because we included only those who fulfilled the required signs and symptoms for the three age groups, we are convinced that mentioned differences would have contributed to the discrepancy of the results in the cited study [10].

Surveillance of pertussis in many countries across the world is based on the clinical case definitions of pertussis recommended by the WHO, the US Centers for Disease Control Prevention, or the European Centre for Disease Prevention and Control. Unlike these commonly applied case definitions, which include cough duration of two weeks or longer for all age groups, in the clinical case definitions of pertussis proposed by the GPI, cough duration depends on the age of the patients [7]. Thus, we included all patients aged ≥ 10 years, which had a non-productive, paroxysmal cough of that lasted two weeks or longer without fever. Among the participants younger than 10 years, MSS were paroxysmal cough with no or minimal fever (patients aged four months to nine years), and cough and coryza with no or minimal fever (patients 0–3 months of age), regardless of the duration of cough. The differences between case definitions did not allow us to compare our results with the published studies by other investigators. Certain clinical criteria of the GPI case definitions helped us to detect pertussis more efficiently in patients younger than 10 years old, in whom coughing duration was shorter than two weeks.

The primary objective of our study was to estimate the highest values both of sensitivity and specificity, complimented by PPV and LR+ for a certain sign and symptom combinations from the case definitions proposed by the GPI.

We provided evidence that whoop in combination with prerequisite signs and symptoms had the highest sensitivity of pertussis in the four months to nine years age group who have visited the primary or tertiary health care levels (73% *vs*. 63%, respectively). Nonetheless, among the in-patients, post-tussive emesis had the same sensitivity as a whoop. Among the outpatients, seven different sign and symptom combinations had specificities of 95% or more, while in the in-patients four different combinations had specificities above 96%.

As is known, the significance of a high PPV is helpful for clinical case management to maximize the detection of laboratory-confirmed cases among the tested participants [11]. We found that the outpatients aged four months–nine years with a combination of different symptoms which included MSS, whoop and contact had a high number of true positive pertussis cases (PPV > 71%). On the other hand, the inpatients had a highest PPV for apnoea in combination with MSS (89%) and for MSS combined with whoop, post-tussive emesis, worsening of the symptoms at night and contact (PPV = 100%).

For the participants aged ≥ 10 years, MSS combined with whoop had the highest sensitivity and a moderate PPV (71% and 45%, respectively) in outpatients, whereas the MSS in combination with worsening of symptoms at night had the highest sensitivity and high PPV (85% and 80%, respectively) among inpatients. Apnoea in combination with MSS, or in combination with other signs and symptoms had the highest specificity among the inpatients and outpatients, and was exceeding the value of 97% in all observed combinations.

Ghanaie et al. [4] reported that cough that lasted two or more weeks, with whoop had a sensitivity of 71% and a specificity of 46%, after examining the performance of the WHO pertussis case definition (cough ≥ 14 days with either paroxysmal cough, inspiratory whoop, or post-tussive emesis without other apparent causes), among the outpatients between the ages of six and 14 years. We found that the sensitivity and specificity of MSS combined with a whoop among the outpatients were 73% *vs*. 64%, respectively (four months to nine years age group) and 71% *vs*. 74%, respectively (≥ 10 years age group).

Our results showed that MSS combined with apnoea was a better predictor of pertussis among the inpatients than in the outpatients aged four months to nine years, possibly reflecting milder disease among the outpatients registered at primary health care centers.

Although the existing GPI case definition includes minimal fever or absence of fever depending on the age, many medical conditions can still resemble pertussis [12]. The differences in awareness and subjectivity of some signs and symptoms could influence the defined differences of sensitivity and specificity between the two surveillance systems and two studied age groups.

We recognize certain limitations of our study that should be addressed in future research.

Due to the limited number of participants, we could not perform a validation of certain signs and symptoms in the 0–3 months age group. Further and more extensive prospective studies would be required to elucidate the GPI case definition for this age group.

For better evaluation of sensitivity and specificity, participants with non-infectious and infectious causes which are clinically similar to pertussis, should be excluded by applying rigorous laboratory tests for diagnosing alternative cough etiologies.

CONCLUSION

The findings of our study pointed out that multiple sign and symptom combinations of the GPI pertussis case definitions were good predictors for laboratory-confirmed pertussis. Since we have found that LR+ for many proposed signs and symptoms of the GPI case definitions was above two, it is reasonable to consider the usefulness of these signs and symptoms to predict a diagnosis of pertussis. The addition of one or more signs and symptoms from the proposed case definition reduced the sensitivity but improved the specificity. Our study supported the fact that the choice of case definition in the recognition of pertussis should take into account the patient's age.

Further studies with larger samples to assess the validation of the GPI case definition for pertussis in other regions in various epidemiologic contexts are imperative.

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Евалуација дијагностичке вредности нове дефиниције случаја великог кашља – искуства из сентинелног и хоспиталног надзора над великим кашљем

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САЖЕТАК

Увод/Циљ У надзору над пертусисом у свету се користе различите дефиниције случаја великог кашља.
Циљ рада је био да се одреде оне комбинације знакова и симптома које доприносе најбољем препознавању великог кашља.

Методе У циљу евалуације знакова и симптома из дефиниција случаја великог кашља предложених од стране Глобалне пертусисне иницијативе (ГПИ) за три узрасне групе (0–3 месеца, од четири месеца до девет година и узраст ≥ 10 година), у Новом Саду је спроведена проспективна опсервациона студија у трајању од годину дана. Лабораторијска потврда инфекције изазване бактеријом *B. pertussis* је добијена употребом метода *PCR* или серолошким (*ELISA*) тестовима.

Резултати У периоду од 1. октобра 2013. до 30. септембра 2014, од укупно 319 испитаника са сумњом на велики кашаљ, код 103 (32,3%) болесника је добијена лабораторијска потврда великог кашља. Комбинација инспираторног стридора, повраћања после кашља и погоршања симптома током ноћи је имала највећи дијагностички значај (степен вероватноће позитивног резултата (*LR*+) 11,6) у доказивању пертусиса у сентинелном надзору међу болесницима узраста од четвртог месеца до девет година, док је међу хоспитализованима истог узраста најбољи показатељ позитивног резултата била апнеа (*LR*+ 13,5). У узрасту ≥ 10 година, *LR*+ за болеснике регистроване у сентинелном надзору са апнеом удруженом са повраћањем после кашља или са комбинацијом инспираторног стридора удруженог са презнојавањем између пароксизама и повраћањем после кашља био је 16,8, док је међу хоспитализованим болесницима овог узраста *LR*+ био мањи од 2,3 за све комбинације знакова/симптома.

Закључак Дефиниције случаја ГПИ имају дијагностички значај у циљу откривања оболевања од великог кашља и зато могу бити корисне у надзору над овом болешћу.

Кључне речи: велики кашаљ; пертусис; Глобална пертусисна иницијатива; дефиниција случаја; надзор