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Evaluation of the diagnostic utility of case definitions to detect influenza virus infection in Vojvodina, Serbia

Процена дијагностичке вредности дефиниција случаја у откривању инфекција изазваних вирусом грипа у Војводини, Србија

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Evaluation of the diagnostic utility of case definitions to detect influenza virus infection in Vojvodina, Serbia

Процена дијагностичке вредности дефиниција случаја у откривању инфекција изазваних вирусом грипа у Војводини, Србија

SUMMARY

Introduction/Objective A case definition recommended by the World Health Organization is commonly used for influenza surveillance worldwide.

The aim of this study was to evaluate prognostic values of proposed case definitions of ILI (Influenza Like Illness), SARI (Severe Acute Respiratory Illness) and ARDS (Acute Respiratory Distress Syndrome) for laboratory confirmed-influenza and to compare the age distribution of influenza patients across virus types and subtypes in Vojvodina.

Methods We conducted a descriptive epidemiological study using surveillance reports and laboratory data from October 1, 2010 to May 20, 2017 (seven surveillance seasons).

Results We included 2,937 participants, 48.6% of whom were laboratory-confirmed influenza cases, and most of the confirmed cases (30.1%) were detected in February. In the 15–29 years age group, an influenza A (H3N2) was more frequent among patients with ILI (54.9% *vs.* 34.2%, p = 0.040), and less frequent in patients with SARI (39.4% *vs.* 65.8%, p= 0.009) compared with an influenza B. In patients aged 30–64 years with ARDS, an influenza B was more common than influenza A (H3N2) (13.4% vs. 6.2%, p= 0.032), but less common in comparison with an influenza A (H1N1) pdm09 (13.4% vs. 25.7%, p= 0.017).

The SARI case definition of influenza was associated with an increased likelihood of laboratory-confirmed influenza for all age groups (p<0.05). During the epidemic period, it was observed that the ILI case definition had the highest diagnostic value for influenza in the 5–14-year age group (AUC = 0.733; 95% CI: 0.704–0.764), while the SARI and ARDS case definitions were the best predictors of influenza for patients 15–29 years of age (AUC = 0.565; 95% CI: 0.504–0.615 and AUC = 0.708; 95% CI: 0.489–0.708, respectively). The case definition of ARDS had the maximum sensitivity (100%) among patients 15–29 years of age.

Conclusion The proposed case definitions of influenza appeared to be good predictors of influenza and therefore can be useful for influenza surveillance, especially in the countries with limited laboratory capacities.

Keywords: influenza virus; epidemiology; virology; case definition; surveillance

САЖЕТАК

Увод/Циљ У надзору над грипом, у свету се обично користи дефиниција случаја препоручена од стране Светске здравствене организације.

Циљ рада био је да се процени прогностички значај предложених дефиниција случаја ОСГ (обољења слична грипу), ТАРБ (тешка акутна респираторна болест) и АРДС (акутни респираторни дистресни синдром) за откривање лабораторијски потврђених случајева вируса инфлуенце и упореди узрастна дистрибуција типова/подтипова вируса грипа у Војводини.

Методе рада Спроведена је дескриптивна епидемиолошка студија употребом података из извештаја у надзору и лабораторијских података у периоду од октобра 2010. године до маја 2017. године (седам сезона надзора).

Резултати Од укупно 2937 укључених испитаника, лабораторијска потврда вируса инфлуенце добијена је код 48,6% тестираних, а већина оболелих (30,1%) је регистрована у фебруару.

У узрасту оболелих од 15 до 29 година, инфлуенца типа А (*H3N2*) чешће је детектована код пацијената са дијагнозом ОСГ (54,9% наспрам 34,2%, *p* = 0,040), али је ређе регистрована код оболелих са дијагнозом ТАРБ (39,4% наспрам 65,8%, *p* = 0,009) у поређењу са инфекцијом инфлуенце типа Б. Међу пацијентима узраста од 30 до 64 године са дијагнозом АРДС, вирус инфлуенце типа Б је био чешће регистрован него инфлуенца типа А (*H3N2*), (13,4% наспрам 6,2%, п= 0,032), али је био ређи у поређењу са вирусом инфлуенце типа А (*H1N1*) *pdm*09 (13,4% наспрам 25,7%, *p* = 0,017).

Дефиниција случаја ТАРБ је позитивно корелирала са добијањем лабораторијски потврђених случајева инфлуенце у свим добним групама (*p* < 0,05).

Посматрано током епидемијског периода, дефиниција ОСГ је имала највишу дијагностичку вредност у узрасту од 5 до 14 година (*AUC* = 0,733; 95% *CI*: 0,704–0,764), док су дефиниције случаја ТАРБ (*AUC* = 0,565; 95% *CI*: 0,504–0,615) и АРДС (*AUC* = 0,708; 95% *CI*: 0,489–0,708), биле најкориснији предиктори инфлуенце у узрасту од 15 до 29 година. У истом узрасту пацијената са дијагнозом АРДС добијена је највиша сензитивност (100%).

Закључак Предложене дефиниције случаја грипа су се показале као добри предиктори за откривање вируса инфлуенце, тако да могу бити корисне у надзора над грипом, посебно у земљама са ограниченим лабораторијским капацитетима.

Кључне речи: вирус инфлуенце; епидемиологија; вирусологија; дефиниција случаја; надзор

INTRODUCTION

The aims of existing case definitions of influenza, proposed by the Centres for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC), and the World Health Organization (WHO) are for timely detection of the start and duration of the influenza season in order to monitor changes in the antigenicity of influenza viruses and provide guidelines for influenza vaccine policies. Early detection of circulating influenza strains in terms of clinical signs/symptoms is useful for clinicians in order to support the clinical decision and improve patients' management. Due to the lack of specificity of influenza symptoms, co-infection and co-circulation of other respiratory viruses, improving the current case definitions of influenza remains a significant public health challenge [1]. The optimal case definition should be applicable every year, despite seasonal variations, in all medical settings (outpatient and inpatient medical facilities) [2].

Influenza is usually a self-limiting infection, but it can exacerbate underlying medical conditions (chronic diseases, weakened immune systems), and present with primary influenza viral pneumonia or lead to secondary bacterial pneumonia, or can occur as part of a co-infection with other pathogens [3–5]. Although all humans can be affected by an influenza virus, clinical presentation of illness differs depending on the virus type-, subtype- and strain-specific properties as well as on the immunological and physiological characteristics of patient influenced by several factors such as age, chronic medical conditions and pregnancy [6].

The main goal of this study was to analyse the utility of clinical case definition of Influenza Like Illness (ILI), Severe Acute Respiratory Illness (SARI) and Acute Respiratory Distress Syndrome (ARDS) to predict laboratory-confirmed influenza in outpatient and inpatient medical settings. Also, the comparison of the age distribution of virus types and subtypes for the seven influenza seasons was made.

METHODS

In Vojvodina – the northern region of Serbia with 1,931,809 inhabitants (26.9% of the total Serbian population according to the 2011 Census) the surveillance of influenza is coordinated by the Institute of Public Health (IPH) of Vojvodina. As described in detail previously [7, 8], data for this observational surveillance study were obtained from the sentinel (outpatients) and hospital (patients hospitalized at secondary or tertiary health care level) surveillance of influenza in Vojvodina. Data have been collected from October 1, 2010 to May 20, 2017 (seven influenza seasons) and entered into the database maintained by the Centre for Disease Control and Prevention, IPH of Vojvodina. We included participants who fulfilled the criteria for clinical case definitions of ILI and SARI [9], and those who met the American European Consensus Conference criteria [10] for ARDS. The study was done in accord with standards of the institutional committee on ethics.

Depending on the health care levels (outpatient or inpatient settings) across Vojvodina where the patients comprised, general practitioners and paediatricians as well as the specialists in general/internal medicine, infectious disease and respiratory disease interviewed the patients. Demographic, clinical, and physical examination data were obtained from patients suspected of having acute influenza through face-to-face structured interviews, using a structured questionnaire.

Virological surveillance of influenza was conducted during the whole study period, from calendar week 40 of each year to calendar week 20 of the next year. Nasal and throat swabs samples were tested in the WHO National Influenza Centre, at the Centre of Virology of the IPH of Vojvodina in Novi Sad [11]. A real-time reverse transcription polymerase chain reaction (real-time RT PCR) assays were used for the detection of influenza virus types A and B and influenza A virus subtypes A(H1N1)pdm09 and A(H3N2) [12].

Statistical analysis

For categorical data, Fisher exact test or chi-square were used where appropriate. Both univariate and multivariate analyses were stratified according to three case definitions of influenza. Differences in age, between the participants with laboratory-confirmed influenza and those without laboratory confirmation, for the three clinical case definitions, were compared by odds ratio (OR) with 95% confidence intervals (95% CI). To control for possible confounding variables, the adjusted OR was calculated using logistic regression, including sex and calendar month of symptom onset. A surveillance period was divided into an epidemic period with high influenza activity (December, January, February and March) and a period of low influenza activity (October, November, April and May).

The diagnostic value of the case definitions (ILI, SARI, ARDS) during the epidemic period was measured using sensitivity, specificity, and area under curve (AUC) with 95% confidence intervals. The sensitivity was defined as the probability of having the case definition in a case of laboratory-confirmed influenza, while the specificity was defined as the probability of not having the case definition when the patient did not have laboratory-confirmed influenza infection. The AUC, as a global measure of algorithm performance for the identification of laboratory-confirmed influenza patients, takes both sensitivity and specificity into account.

Validation of proposed case definitions during the epidemic period was stratified by age group (0–4, 5–14, 15–29, 30–64, ≥ 65 years).

A p value below 0.05 was considered significant. Statistical analysis was done using the SPSS version 21 software.

RESULTS

During the study period, a total of 2,937 specimens from patients with ILI, SARI or ARDS, were tested for influenza, and 1,427 samples were identified as influenza A or B positive (48.6%). Among study participants, 53.7% (1576/2937) were males. The median age of all cases was 43 years (IQR: 15–62 years), and decreasing to 37 years (IQR: 10–60 years) among laboratory-confirmed influenza.

Observed by clinical diagnosis, the majority of participants had the SARI clinical diagnosis (56.7%; 1665/2937). Out of total number of participants, 2477 (84.3%) cases were registered in the four-month period (from December to March), with the highest detection rate in February (30.1%; 429/1427) (Table 1).

Comparing different influenza virus types and subtypes, there were few significant differences among groups of patients with distinct clinical case definitions of influenza stratified by age. In the 15–29 years age group, influenza A (H3N2) virus was more frequently registered among patients with ILI (54.9% vs. 34.2%, p= 0.040), and less frequently in patients with SARI (39.4% vs. 65.8%, p= 0.009) compared with influenza B virus. Among patients aged from 30 to 64 years with ARDS, an influenza B was more common than influenza A (H3N2) (13.4% vs. 6.2%, p= 0.032), but less common in comparison with an influenza A (H1N1) pdm09 (13.4% vs. 25.7%, p= 0.017). No significant differences were detected among patients with different clinical case definitions of influenza regarding the frequency of influenza virus types and subtypes in the remaining age groups (Table 2).

Univariate and multivariate logistic regression analyses were performed in order to identify predictor values of proposed clinical case definitions for the entire study period. When three clinical case definitions of influenza were classified and compared with the youngest age group (0–4 years), the SARI case definition of influenza was associated with the increasing probability of having influenza for all age group, while the ILI case definition was a useful diagnostic predictor of laboratory-confirmed influenza in the 5–14 years age group ($p<0.05$). The influenza positive cases with ARDS were registered only among participants aged 15 years and older, but the ARDS case definition had a poor diagnostic value for detecting influenza virus infection ($p>0.05$) (Table 3).

When the performance of case definitions was tested only in the epidemic period, the ILI case definition had the highest accuracy in the 5–14 years age group (AUC = 0.733; 95% CI: 0.704–0.764), while the SARI and ARDS case definitions had the highest AUC values among the 15–29 year-olds (AUC = 0.565; 95% CI: 0.504–0.615 and AUC = 0.708; 95% CI: 0.489–0.708, respectively). The ILI case definition showed a high sensitivity value (above 90%) for all age groups, with the highest sensitivity among the youngest age group (95.4%). The sensitivity values of SARI case definition ranged from 81.3% to 95.2% between different age groups, with a total sensitivity value of 89.3%. During the epidemic period, the ARDS case definition had the maximum sensitivity value (100%) in patients aged 15–29 years. Total specificity values of ILI and SARI case definitions were 15.0% and 19.8%, while the ARDS had a specificity value of 43.4% (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study on the evaluation of influenza case definitions (ILI, SARI and ARDS) conducted through the sentinel and hospital-based surveillance systems in our country. As the main advantage of our study, we conducted the most comprehensive effort to determine the accuracy of three clinical case definitions of influenza for the detection of laboratory-confirmed influenza virus infection during the seven post-pandemic seasons.

Several studies reported no difference in clinical symptoms between patients with influenza A compared with influenza B viruses [1, 6]. However, different age groups may be preferentially affected by influenza during any given season depending on the pool of viruses that a

re circulating, which may result in a different disease burden [6].

By comparing the frequences of influenza A and B virus infections, we found that influenza B was more commonly detected than influenza A (H3N2) in patients with SARI aged 15–29 years, and among those with ARDS aged 30–64 years. Further, we found that influenza A (H3N2) was more frequently registered than influenza B in patients with ILI aged 15–29 years, and influenza A (H1N1) pdm09 was more often detected than influenza B virus in those with ARDS aged 30–64 years. Although the reasons for the mentioned differences are not completely clear, this result supports the results of previously reported findings [1, 4, 6], and it should be taken into consideration in future investigation. Our results are in a good agreement with the fact that the interpretation of syndromic surveillance data without information on age may be misleading [13].

Aiming to detect the maximum number of influenza cases across the three case definitions, SARI was associated with the increasing risk of laboratory-confirmed influenza in all age groups, while the case definition of ILI was positively associated with influenza in patients younger than 15 years. Further, the case definition of ARDS had no diagnostic value for the detection of influenza infection. However, when the peak of influenza activity was distinguished by months (December, January, February and March), we found that the case definition of ILI among patients aged 15–14 years and case definition of ARDS in patients aged 15–29 years, provided the most useful diagnostic value of laboratory-confirmed influenza. Although the most of the confirmed influenza cases with ARDS belonged to patients aged 60 years and older (66.4%; 75/113), the proposed case definition of ARDS is most useful for detecting of influenza among younger persons (aged 15–29 years-old) suspected of having influenza.

After examining the performance of the international case definitions of ILI commonly used for influenza surveillance among outpatients in France, Casalegno et al. [1] reported that the WHO ILI case definition (fever ≥ 38 °C with onset within the last 7 days and cough) had the highest positive AUC values in comparison with the CDC ILI (sudden onset of fever ≥ 38 °C, with absence of a known cause other than influenza, and at least one of the following symptoms: cough, and sore throat) and the ECDC ILI (sudden onset of at least one among following general symptoms: fever, feverishness, headache, malaise, myalgia, and at least one among respiratory symptoms: cough, sore throat, shortness of breath). Our results showed higher AUC value of the WHO ILI case definition than those obtained by Casalegno et al. (AUC = 0.639; 95% CI: 0.619–0.658 vs. AUC = 0.556; 95% CI: 0.547–0.566, respectively). The reason for that may be that Casalegno et al. referred to the overall period, while we estimated the AUC value only for the epidemic period. However, after comparing the results only during influenza seasonal, i.e., epidemic period, higher sensitivity values were observed (93.6% vs. 88.9%), but still lower specificity values (15.0% vs. 21.3%) than in the cited study [1]. We believe that observed differences could be explained by the fact that the median age of all participants included in the French study [1] was 9 years, while the median age of our respondents was 43 years.

As is known, the variety of other potential co-infecting pathogens among patients aged 0–4 years could be the reason for the lower performance of all case definitions in this age group [14, 15]. We found that sensitivity value of ILI case definition for patients aged 0–4 months was above 95%, similar to the values of CDC ILI or ECDC ILI case definitions (93.0%) [1]. However, in line with previously published reports [1, 16], we found a very low specificity of the proposed case definitions of ILI, which indicates that individuals without influenza infection are likely to be misclassified as false positive patients.

Further, it was observed that the SARI case definition in patients from the youngest age group had the sensitivity above 95%, and specificity about 10%. Results of the study done by Peng et al. [17], who analysed data from SARI cases in China (from 2011 to 2013), suggested the association of laboratory-confirmed influenza with increasing age of patients. Interestingly, the prevalence of laboratory-confirmed influenza among patients with SARI aged 0–4 years was only 5.2% (101/1944), whereas the prevalence of influenza cases with SARI in the same age group in our research was 18.8% (21/112). Due to the fact that two different case definitions were tested, those findings were not surprising. A similar study among hospitalized patients in India showed that sensitivity and specificity in patients with SARI were 28.0% and 84.0%, respectively [18]. Our results show that the sensitivity and specificity for all patients with SARI were 89.3% and 19.8%. Observed differences can be only interpreted as a result of the implementation of different case definitions used in two studies. For improving the specificity of SARI case definition among our patients younger than five years, it can be useful to implement a more specific case definition, similar to the research cited above [17].

The importance of the sensitivity and specificity of case definitions varies according to which of the goals have the highest priorities [1, 16, 18].

Our results show that the applied case definitions of influenza provide a high sensitivity, which supports the goal of early diagnosis and treatment and timely identification of influenza outbreaks. However, if the goal is to increase efficiency in obtaining influenza virus-positive specimens and identify circulating influenza strains while minimizing unnecessary testing, then improvement of specificity of proposed case definitions is needed [19–21].

CONCLUSION

The proposed case definitions of influenza appeared to be good predictors for laboratory-confirmed influenza, and therefore can be useful for continuous surveillance in order to predict seasonal trends and prepare for a timely response to the influenza outbreak, particularly for the purpose of surveillance in resource-poor laboratory settings.

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Conflict of Interest: None declared.

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Table 1. Influenza-positive and negative participants included in the study by sex, age distribution, case definitions, and months in Vojvodina, from 2010/11 to 2016/2017 influenza seasons

Variable	**All participants (n = 2937) n (%)**	**Influenza-positive (n = 1427) n (%)**	**Influenza-negative (n = 1510) n (%)**
Sex			
Male	1576 (53.7)	764 (53.5)	812 (53.8)
Age group (years)			
0–4	347 (11.8)	173 (12.1)	174 (11.5)
5–14	370 (12.6)	262 (18.4)	108 (7.2)
15–29	384 (13.1)	176 (12.3)	208 (13.8)
30–64	1236 (42.1)	529 (37.1)	707 (46.8)
≥ 65	600 (20.4)	287 (20.1)	313 (20.7)
Mean age (± standard deviation)	39.7 (± 25.5)	37.4 (± 26.3)	41.9 (± 24.6)
Median age (Q1–Q3 interquartile range)	43.0 (15.0–62.0)	37.0 (10.0–60.0)	46.0 (20.0–62.0)
Case definition			
ILI	956 (32.5)	595 (41.7)	361 (23.9)
SARI	1665 (56.7)	719 (50.4)	946 (62.6)
ARDS	316 (10.8)	113 (7.9)	203 (13.5)
Months of symptom onset			
October	73 (2.5)	1 (0.1)	72 (4.8)
November	84 (2.9)	1 (0.1)	83 (5.5)
December	415 (14.1)	245 (17.1)	170 (11.3)
January	557 (19.0)	243 (17.0)	314 (20.8)
February	787 (26.8)	429 (30.1)	358 (23.7)
March	718 (24.4)	379 (26.6)	339 (22.4)
April	276 (9.4)	129 (9.0)	147 (9.7)
May	27 (0.9)	0 (-)	27 (1.8)

ILI – influenza-like illness; SARI – severe acute respiratory illness; ARDS – acute respiratory distress syndrome

Table 2. Case definitions of influenza patients according to age group and influenza virus type and subtype by age groups in Vojvodina, from 2010/11 to 2016/2017 influenza seasons

Age group (years)	Influenca type/subtype	ILI	SARI	ARDS
0–4 (n[a] = 173)	B[b] n = 33 n (%)	27 (81.8)	6 (18.2)	0 (-)
	A[c] n = 140 n (%)	125 (89.3)	15 (10.7)	0 (-)
	A(H1N1) pdm09 n = 54 n (%)	48 (88.9)	6 (11.1)	0 (-)
	A(H3N2) n = 80 n (%)	73 (91.3)	7 (8.7)	0 (-)
5–14 (n[a] = 262)	B[b] n = 95 n (%)	82 (86.3)	13 (13.7)	0 (-)
	A[c] n = 167 n (%)	148 (88.6)	19 (11.4)	0 (-)
	A(H1N1) pdm09 n = 57 n (%)	52 (91.2)	5 (8.8)	0 (-)
	A(H3N2) n = 108 n (%)	94 (87.0)	14 (13.0)	0 (-)
15–29 (n[a] = 176)	B[b] n = 38 n (%)	13 (34.2)	25 (65.8)	0 (-)
	A[c] n = 138 n (%)	57 (41.3)	74 (53.6)	7 (5.1)
	A(H1N1) pdm09 n = 65 n (%)	18 (27.7)	45 (69.2)	2 (3.1)
	A(H3N2) n = 71 n (%)	39 (54.9)*	28 (39.4)*	4 (5.7)
30–64 (n[a] = 529)	B[b] n = 97 n (%)	21 (21.7)	63 (64.9)	13 (13.4)
	A[c] n = 432 n (%)	101 (23.4)	269 (62.3)	62 (14.3)
	A(H1N1) pdm09	25 (13.7)	111 (60.6)	47 (25.7)*

	n = 183 n (%)			
	A(H3N2) n = 228 n (%)	71 (31.1)	143 (62.7)	14 (6.2)*
≥ 65 **(n[a] = 287)**	B[b] n = 40 n (%)	2 (5.0)	33 (82.5)	5 (12.5)
	A[c] n = 247 n (%)	19 (7.7)	202 (81.8)	26 (10.5)
	A(H1N1) pdm09 n = 56 n (%)	5 (8.9)	43 (76.8)	8 (14.3)
	A(H3N2) n = 176 n (%)	13 (7.4)	148 (84.1)	15 (8.5)

ILI – influenza like illness; SARI – severe acute respiratory illness; ARDS – acute respiratory distress syndrome;

[a]included all influenza (A and B) cases;

[b]reference group;

[c]all influenza A cases (A(H1N1)pdm09 and A(H3N2), and those that were not subtyped/characterized)

*p-value for the comparison with influenza B patients of the same age group less than 0.05

Table 3. Case definitions of influenza associated with laboratory-confirmed influenza, stratified by age group in Vojvodina, from 2010/11 to 2016/2017 influenza seasons

Age group (years)	**ILI**				**SARI**				**ARDS**			
	Positive n = 595 n (%)	Negative n = 361 n (%)	OR (95% CI)	adj. OR[a] (95%CI)	Positive n = 719 n (%)	Negative n = 946 n (%)	OR (95% CI)	adj. OR[a] (95%CI)	Positive n = 113 n (%)	Negative n = 203 n (%)	OR (95% CI)	adj. OR[a] (95%CI)
0–4	152 (25.5)	79 (21.9)	Reference		21 (2.9)	91 (9.6)	Reference		0 (-)	4 (1.9)	NA	
5–14	230 (38.7)	81 (22.4)	1.5[b] (1.0–2.1)	1.5[b] (1.0–2.2)	32 (4.4)	26 (2.8)	5.3[b] (2.6–10.8)	5.8[b] (2.8–12.0)	0 (-)	1 (0.5)	NA	
15–29	70 (11.8)	81 (22.4)	0.5[b] (0.3–0.7)	0.5[b] (0.3–0.7)	99 (13.8)	110 (11.6)	3.9[b] (2.3–6.7)	4.5[b] (2.6–7.8)	7 (6.2)	17 (8.4)	Reference	
30–64	122 (20.5)	104 (28.8)	0.6[b] (0.4–0.9)	0.7 (0.5–1.0)	332 (46.2)	478 (50.5)	3.0[b] (1.8–4.9)	3.3[b] (2.0–5.4)	75 (66.4)	125 (61.6)	1.5 (0.6–3.7)	1.3 (0.5–3.6)
≥65	21 (3.5)	16 (4.5)	0.7 (0.3–1.4)	0.7 (0.3–1.4)	235 (32.7)	241 (25.5)	4.2[b] (2.5–7.0)	4.3[b] (2.6–7.1)	31 (27.4)	56 (27.6)	1.3 (0.5–3.6)	1.2 (0.4–3.5)

OR – odds ratio; CI – confidence interval; ILI – influenza like illness; SARI – severe acute respiratory illness; ARDS – acute respiratory distress syndrome; NA-not applicable;

[a]adjusted for the following variables: sex and months of symptom onset (influenza epidemic period and low influenza activity)

[b]statistically significant differences ($p < 0.05$)

Table 4. Sensitivity, specificity, and area under curve value of the case definitions tested for influenza confirmation during epidemic period, stratified by age group in Vojvodina, from 2010/11 to 2016/2017 influenza seasons

Age group (years)	Case definition	Se % (95 % CI)	Sp % (95 % CI)	AUC % (95% CI)
0–4	ILI	95.4 (90.7–98.1)	16.5 (9.1–26.5)	0.684 (0.644–0.716)
	SARI	95.2 (76.2–99.9)	9.9 (4.6–18.0)	0.259 (0.199–0.276)
	ARDS	NA	NA	NA
5–14	ILI	94.4 (90.5–97.0)	13.6 (7.0–23.0)	0.733 (0.704–0.764)
	SARI	81.3 (63.6–92.8)	15.4 (4.4–34.9)	0.517 (0.429–0.624)
	ARDS	NA	NA	NA
15–29	ILI	92.9 (84.1–97.6)	12.4 (6.1–21.5)	0.497 (0.443–0.537)
	SARI	85.9 (77.4–92.1)	30.0 (21.6–39.5)	0.565 (0.504–0.615)
	ARDS	100.0 (59.0–100.0)	58.8 (32.9–81.6)	0.708 (0.489–0.708)
30–64	ILI	91.0 (84.4–95.4)	18.3 (11.4–27.1)	0.575 (0.527–0.617)
	SARI	90.4 (86.7–93.3)	22.0 (18.3–26.0)	0.500 (0.475–0.521)
	ARDS	85.3 (75.3–92.4)	43.2 (34.4–52.4)	0.590 (0.526–0.638)
≥65	ILI	90.5 (69.6–98.8)	6.3 (0.2–30.2)	0.541 (0.489–0.628)
	SARI	89.8 (85.2–93.4)	14.9 (10.7–20.1)	0.519 (0.487–0.548)
	ARDS	83.9 (66.3–94.6)	41.1 (28.1–55.0)	0.563 (0.458–0.632)
All age groups	ILI	93.6 (91.3–95.4)	15.0 (11.4–19.1)	0.639 (0.619–0.658)
	SARI	89.3 (86.8–91.5)	19.8 (17.3–22.5)	0.498 (0.480–0.514)
	ARDS	85.8 (78.0–91.7)	43.4 (36.4–50.5)	0.585 (0.537–0.623)

ILI – influenza-like illness; SARI – severe acute respiratory illness; ARDS – acute respiratory distress syndrome; Se –sensitivity; Sp – specificity; AUC – area under curve; CI – confidence interval; NA – not applicable