Adv Exp Med Biol – Clinical and Experimental Biomedicine (2018) 2: 81–91
https://doi.org/10.1007/5584_2018_240

Published online: 12 July 2018

Influenza: Underestimated in Children Below 2 Years of Age

A. Wrotek, M. Czajkowska, E. Zawłocka, and T. Jackowska

Abstract

Children under 2 years of age may receive antiviral therapy when influenza is suspected. Signs of influenza are frequently unclear and testing is indicated. The aim of the study was to assess the usefulness of clinical signs and the rapid influenza diagnostic test (RIDT) in diagnosing influenza and in choosing the appropriate treatment. In the 2015–2016 influenza season, 89 children under 2 years of age (56.7% of 157 children diagnosed with influenza) were hospitalized. There were 74 RIDT and 70 reverse transcription polymerase chain reactions (RT-PCR) performed for the purpose of diagnosis, either test per child. Eighty-three percent of children (74/89) presented with fever, 55.1% (49/89) with cough, and 39.3% (35/89) with both cough and fever. The RIDT was positive in 31.1% (23/74) of cases. The highest percentage of positive RIDT was within the first 24 h of disease, decreasing dramatically thereafter (70% vs. 13–17%, respectively). The RIDT shortened the time to diagnosis by 43.8 h/patient (an average €149 gain in treatment costs). The mean delay for RT-PCR-based diagnosis was 33.5 h/patient (an average €114 loss in treatment costs). We conclude that clinical signs have a low diagnostic sensitivity in children under 2 years of age. Likewise, RIDT is of low sensitivity, being diagnostically useful only in the first 24 h. The PCR is recommended for the diagnosis, but that requires a constant access to the method.

Keywords

Children · Diagnostics · Costs · Infants · Influenza · Rapid diagnostic test · Reverse transcription polymerase chain reaction · Sensitivity

1 Introduction

Influenza is a serious global health concern and especially younger children are at a higher risk of complications. There are various prevention strategies and treatment approaches, but the majority of them is consistent in identifying children under 2 years of age as a high-risk group as stated by the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP 2017). According to the Centers for Disease Control and Prevention (CDC 2018), antiviral treatment should be implemented, inter alia, in all children younger than 2 years with a suspicion of influenza. Polish recommendations also identify

A. Wrotek, M. Czajkowska, E. Zawłocka, and T. Jackowska (✉)
Department of Pediatrics, Center of Postgraduate Medical Education, Warsaw, Poland

Department of Pediatrics, Bielanski Hospital, Warsaw, Poland
e-mail: tjackowska@cmkp.edu.pl

children under 2 years of age as a high-risk group, in which antiviral treatment should be administered as early as possible (Jackowska 2016). It is crucial for the effectiveness of the treatment that it is implemented immediately – optimally, within the first 48 h of disease onset. A major problem is a proper diagnosis and the time limit when it should be made. From the epidemiological standpoint, "an influenza-like illness" (ILI) is defined as fever of at least 37.8 °C and sore throat or cough. Influenza, on the other hand, is defined as a disease with acute onset, high fever, cough, headache, and myalgia. Referring to these symptoms and definitions, the diagnosis may be problematic, especially in younger children who cannot verbally communicate symptoms. Thus, more sophisticated diagnostic tools are required, among which viral culture, real-time reverse transcription polymerase chain reaction (qRT-PCR) test, and antigen detection such as a rapid influenza diagnostic test (RIDT) are of increasing research and clinical interests. These methods may be performed on samples obtained from nasopharyngeal or nasal swabbing, aspirate, or lavage. A drawback of viral cultures is that it takes time to get a result, usually from 3 to 10 days. Therefore, cultures are mainly used for the epidemiological purpose or as a verification of other methods. The qRT-PCR has high sensitivity and specificity (of approx. 86–100% and 99%, respectively) (Frisbie et al. 2004) but requires more sophisticated and pricey equipment, and qualified personnel, which makes it of limited availability. In contradistinction, RIDT is inexpensive, easy to perform, and not requiring specialized equipment or highly trained personnel and gives a quick result in up to 15 min. On the downside, RIDT has suboptimal sensitivity, which is related to a higher probability of false-negative results. Sensitivity of RIDT in young children is another issue. The available studies show sensitivity of 47–70% (Eggers et al. 2015), but there are also studies that suggest that it may be as low as 23% (Koul et al. 2015). On the other hand, specificity of RIDT is satisfying, reaching 98–100% (Avril et al. 2016).

The present study seeks to assess the frequency of signs and symptoms of influenza, deemed typical, and the treatment time and costs gained/lost using the RIDT vs. RT-PCR diagnostics.

2 Methods

The study was approved by the Ethics Committee of the Medical Center for Postgraduate Education in Warsaw, Poland. The study has a retrospective character. In the 2015/2016 influenza season, 163 children at the Bielanski Hospital in Warsaw were diagnosed with influenza, including 157 hospitalizations. Out of them, 89 children (56.7%; 51 male and 38 female children) were younger than 2 years of age and were included in this study. The mean age of children was 7.4 ± 6.4(SD) months, and their number by the age groups was as follows: 9 neonates (0–1 months; 4 male and 5 female), 22 children aged 1–2 months (15 male and 7 female), 17 children aged 3–6 months (13 male and 4 female), 16 children aged 7–11 months (7 male and 9 female), and 25 children aged 12–23 months (12 male and 13 female).

When influenza was suspected, RIDT, PCR, or both were used for diagnosis. Altogether, 74 RIDT and 70 PCR were performed. In 55 patients both methods were used. In general, the PCR was performed only in case of a negative RIDT result, but in six patients, the PCR was performed after obtaining a positive RIDT result. Seventy-two patients were diagnosed with influenza type A and ten patients with influenza type B, and there were seven coinfections of type A and B. The children's parents/guardians were asked about the typical influenza signs and symptoms, including fever, cough, coryza, difficulties in breathing, apnea, seizures, headache, myalgia, chest pain, malaise, and altered mental status or anxiety.

Complications occurred in 52 patients. In most cases complications consisted of lower respiratory diseases, such as pneumonia (29 cases), bronchitis with obturation (25 cases), bronchitis without obturation (6 cases), and laryngitis (3 cases); otitis media also was a frequent complication (10 cases). One case of encephalitis was

noted as well. Some patients had several coexisting complications; each single complication was treated separately, but the patients were not further analyzed in terms of single/multiple complications.

In order to calculate the time gained or lost as a result of positive or negative RIDT test, certain assumptions need to be presented: a minimal time of 5 h or 24 h, including the time required for the transport of samples to the external laboratory cooperating with the hospital, needed to obtain the PCR result during working days (Monday to Friday). The maximum time to get the PCR results is 72 h for patients admitted to the hospital on Friday, as the first available date for the transport of samples performing PCR was Monday morning. Thus, in general, for patients who were admitted between Friday noon and Saturday, the mean time needed to obtain the PCR result was 72 h or 24 h for those admitted on Sunday. A gain in time was calculated for patients who had a true-positive result of RIDT, but when RIDT was false negative, the time needed to obtain the PCR result was treated as a loss of time. The exact admission time was omitted in the analysis, as it varied in each case, but the mean time should be around the time estimated above.

To calculate the costs generated with the use of RIDT, a simple assumption was made: the earlier the result, the faster the implementation of treatment, meaning a faster discharge and shorter hospitalization. For these calculations, we used the time gained or lost (as above outlined) and multiplied it by the officially published full medical cost of a patient-*per*-day hospitalization at the pediatric ward of the Bielanski Hospital in Warsaw, which amounted to €81.5. Since we analyzed the influence of a diagnostic method on treatment costs, false-negative RIDT results were also taken into calculations, as they may generate an additional and unnecessary cost. Both RIDT and PCR used showed positive or negative results separately for influenza type A and type B. The specific costs of tests were as follows: RIDT *ca* €9 and PCR *ca* €50.

Additionally, four theoretical diagnostic models were created, based on the study results: (1) RIDT in each child, followed by PCR in those who had a negative result (the percentage of true-positive RIDT results was extrapolated to the whole group of 89 children); (2) PCR in each child without a prior RIDT test; (3) use of PCR if it were available at the hospital's laboratory every day around the clock, with the provision, as in the first model above outlined that RIDT comes first, and when negative it would be followed by PCR; and (4) PCR in each child available every day around the clock, without a prior RIDT.

Data distribution was analyzed with the Shapiro-Wilk test, and means ±SD or medians with upper-lower centiles were given in case of normal or non-normal distribution, respectively. The independent-samples *t*-test or Mann-Whitney U test were used accordingly. A p-value of 0.05 defined the statistically differences. The evaluation was performed with a commercial statistical package Statistica v12 (Statsoft, Tulsa, OK).

3 Results

Seventy-four RIDT were performed and were positive in 25 cases, including 14 cases of influenza type A, 10 cases of influenza type B, and 1 case positive for both influenza type A and B. In six patients, initially diagnosed with influenza type A in two cases and type B in four cases, samples were further sent for a PCR diagnosis, which confirmed two cases of influenza type A infection, but among four patients diagnosed with type B, only one case was confirmed, and one turned out to be a mixed infection (type A and B), while the other two were diagnosed with the PCR as influenza type A (instead of type B). These last two cases were considered false-positive results in further analysis, although they confirmed the influenza infection as such. Finally, true-positive RIDT results were obtained only in 23/74 (31.1%) tests performed, corresponding to 25.8% of patients (23/89 children). There was a group of 15 patients in whom the RIDT was not performed and the diagnosis was based only upon the PCR.

The PCR was performed in 70 patients, including the 15 patients without the RIDT. The

diagnosis was based upon the PCR method in 66 patients (73.3%): 15 patients without a prior RIDT, 49 patients with a false-negative RIDT result, and 2 false-positive RIDT results. In one patient, the PCR helped verify the diagnosis as the RIDT was positive only for type B infection, while there turned out a mixed type A and B infection.

According to the age groups, not a single positive RIDT result was observed in neonates (0/5), 53% of positive results in children 1–2 months old (10/19), 14% in children aged 3–6 months (2/14), 36% in children aged 7–11 months (5/14), and 27% in children aged 12 months and more (6/22) (Table 1).

There was no difference between the group of patients who had the RIDT performed and those who had not in terms of age, duration of fever before hospital admission, the total feverish period, and length of hospitalization, nor the duration of signs and symptoms before hospital admission. However, the only difference observed was between the groups of patients with a true-positive RIDT result and a true-negative/false-positive RIDT result, and it was statistically significant for the duration of signs and symptoms before admission (median value 1 vs. 3 days, $p = 0.001$). This is supposedly related to a higher percentage of positive RIDT results in children who had been presenting with signs/symptoms for a shorter period of time (Table 2). For the sake of a practical purpose, the results are also shown as a growing number of patients and a growing duration of influenza signs/symptoms (Table 3). The highest percentage of positive RIDT results was observed in children who had been presenting with influenza signs/symptoms for up to 24 h (70%), and then the percentage was decreasing (from 41% in patients with symptoms lasting no more than 48 h to 31% in the whole group, including patients who had been sick for even more than 7 days). A great difference was observed between the first 24 h of disease onset and the rest of the group (70% vs.13–17%). Due to a low number of cases, the higher percentage (33%) of positive results in children who had been presenting symptoms for 121–144 h may be treated as a bias and omitted in further analysis.

The patients presented with the following signs and symptoms: the most frequent was fever in 74/89 (83.1%) children, followed by cough (49/89 children, 55.1%), coryza (46/89; 51.7%), difficulties in breathing (21/89; 23.6%), seizures (8/89; 9%), and apnea (3/89; 3.4%). Due likely to young age, no headache, myalgia, or chest pain were reported. The parents also reported malaise observed in 19 (21.3%) and altered mental state/anxiety in 14 (15.7%) cases. A typical clinical picture, i.e., fever and cough, was seen only in 35 patients (39.3%).

The performance of RIDT and PCR was a clinical practice, not belonging to theoretical models proposed above. The cost of 74 RIDTs and 70 PCRs in this study group was €4,153 with a mean of €46.7/patient. The mean hospitalization time was 9.2 days. This value was used as a reference in calculations presented below. The mean hospital treatment cost (excluding diagnostics) was €751.

In patients with a positive RIDT result, the mean time gained was 43.8 ± 21.3 h. The gain amounted to 36.4 ± 29.1 h in case of the shorter 5-h delay in obtaining the PCR result. The time gained thanks to the positive RIDT corresponded to the gain of €148.7 ± 72.2 thanks to the theoretically shorter hospitalization. In the 5-h delay model, the RIDT positive result gained €123.5 ± 99.5 (Table 4).

In patients with a negative RIDT result, when the PCR was needed to make a diagnosis, the mean time lost was 33.5 ± 20.5 h or 21.0 ± 27.2 h in the 24-h and 5-h delay models, respectively. The PCR use and the delay related to this corresponded to the loss of €113.8 ± 69.4 or €71.3 ± 92.3, respectively. The total costs of a PCR-related delay and a PCR-based diagnosis was €170.6 ± 68.4 or €128.1 ± 91.3, respectively (Table 4).

Had the RIDT been performed in each patient (not just in 74 out of the 89 patients, i.e., in 83%), then the time and money gained in the 24-h and 5-h delay models would have been 44.8 ± 23.0 h or 34.7 ± 32.2 h and €152.7 or €117.6, respectively. It needs to be underlined that there still is a low probability of a positive RIDT result (31% in the

Table 1 Rapid influenza diagnostic tests (RIDTs) performed in different age groups

Age group	No. of patients	No. of RIDT	No. of positive RIDT	% of positive RIDT
0–1 month	9	5	0	0
1–2 months	22	19	10	53
3–6 months	17	14	2	14
7–11 months	16	14	5	36
12–23 months	25	22	6	27

Table 2 Relation between the percentage of positive rapid influenza diagnostic tests (RIDT) and the length of influenza signs and symptoms

Duration of influenza signs/symptoms (hours)	No. of patients	No. of RIDT	No. of positive RIDT	% of positive RIDT
< 24	24	20	14	70
25 − 48	26	24	4	17
49–72	9	6	1	17
63–96	9	6	1	17
97–120	10	8	1	13
121–144	3	3	1	33
> 144	8	7	1	14

Table 3 Relation between the percentage of positive rapid influenza diagnostic tests (RIDTs) and the length of influenza signs and symptoms, shown as a growing number of patients and a growing duration of influenza signs/symptoms

Duration of influenza signs/symptoms (hours)	No. of patients	No. of RIDT	No. of positive RIDT	% of positive RIDT
Up to 24	24	20	14	70
Up to 48	50	44	18	41
Up to 72	59	50	19	38
Up to 96	68	56	20	36
Up to 120	78	64	21	33
Up to 144	81	67	22	33
Over 144	89	74	23	31

Table 4 Time and cost gained/lost in case of rapid influenza diagnostic test (RIDT)-based or polymerase chain reaction (PCR)-based diagnosis and in patients without RIDT

		PCR – 24-h delay	PCR – 5-h delay
Positive RIDT (n = 23)	Time gained (h)	43.8 ± 21.3	36.4 ± 29.1
	Money gained (€)	148.7 ± 72.2	123.5 ± 99.0
Negative RIDT, need for PCR (n = 51)	Time lost (h)	33.5 ± 20.5	21.0 ± 27.2
	Money lost (€)	113.8 ± 69.4	71.3 ± 92.3
	Total cost of PCR and its delay	170.6 ± 302.2	128.0 ± 99.0
RIDT in patients without RIDT* (n = 15)	Time to be gained (h)	44.8 ± 23.0	34.7 ± 32.2
	Money to be gained (€)	152.7	117.6

*Low probability of positive RIDT result (31% in the study group)

entire study group), so that the time and costs gained should be, roughly estimated, divided into three.

Theoretical models were created based on these categories. In the four theoretical models mentioned above, the estimated costs would present as follows:

First Model: RIDT in Each Child and PCR if RIDT Negative

The total cost of RIDTs in 89 children and PCRs in those with negative RIDT result (with the assumption of 31% of true-positive RIDT results, meaning that 61 patients would still require additional PCR testing) would be 16,980PLN/€3,842 (Table 5). The total mean time gained would be 43.8 h in the 24-h (1st model A) or 36.4 h in the 5-h PCR delay model (1st model B). This total time gained was used for calculating a reduction of hospital treatment costs. For the group of 28 patients with a theoretically positive RIDT, with the mean time of 1,226.4 h gained in the 24-h delay model or 1,019.2 h in the 5-h delay model, the fiscal gain would correspond to €4,162 or €3,459, respectively.

Second Model: Omission of RIDT, PCR in Each Child

The cost of 89 PCRs would be €4,430. The mean time lost was 33.5 h in the 24-h PCR delay model (2nd model A) or 21 h in the 5-h PCR delay model (2nd model B). This total time gained was used for calculating the increase of hospital treatment costs. For the whole group of 89 patients waiting for the PCR result, it would mean 2,981.5 h or 1,869 h (in the 24-h and 5-h delay models, respectively), which would correspond to hospital treatment costs being higher by €2,289 or €6,343. The lowest possible cost of diagnostics and treatment would be €712 *per* patient in the 1st model, assuming a shorter 5-h delay for the PCR result (Table 5). The cost in this case would be €63,376, which was used as a reference value for the next two models.

Third Model: RIDT in Each Child and then Rapid PCR in Those with a Negative Result

The percentage of true-positive RIDT results was extrapolated to the whole group of 89 children. The cost of RIDTs in all 89 children and 61 rapid PCRs would be €805 and 61x, where "x" stands for the unknown maximum tolerable price of a single rapid PCR testing, which is to be established (see Table 6). The total time gained, mean of 43.8 h in the 24-h PCR delay model (3rd model A) or 36.4 h in the 5-h PCR delay model (3rd model B), was used for calculating the reduction in the hospital treatment costs. The time would be gained in all patients, irrespectively, of the final diagnostic method, be it RIDT or PCR. The hospital treatment cost reduction would be €13,229 (model A) or €10,994 (model B).

Calculation of a Possibly Tolerable Rapid PCR Price (Called "x") The lowest total cost of the two models (1st and 2nd) was used as a reference value: €63,376. From this value the theoretical cost of €54,411 or €56,646 was subtracted, and then the result was divided by 61. The tolerable price range came out between €110 and €147.

Fourth Model: Rapid PCR in Each Child Without Prior Performance of RIDT

The cost of diagnostics in this model is unknown (89y, where "y" stands for the price of a single rapid PCR). When from the total cost of hospital treatment, shown in the 3rd model, the time and money gained were subtracted and the remaining part were divided by 89 rapid PCRs, the price range would emerge between €76 and €101 (Table 6).

3.1 Optimum Model

Based on the results presented above, the crucial aspects appear to be the patient's age and the time from onset of influenza symptoms to the performance of RIDT. Among the age groups, the null probability of a positive RIDT result was seen in neonates. The issue of perfect timing is also of a key importance; the shorter the disease duration, the higher the probability of a positive RIDT result. When the symptoms lasted for no longer than 24 h (in 24 patients), the probability of a

Table 5 Time and cost gained/lost in the 1st and 2nd diagnostic theoretical model

Theoretical model	No. of RIDT	Cost of RIDT (€)	No. of PCR	Cost of PCR (€)	Diagnostic cost (€)	Hospitalization cost (€)	Reduction/increase in hospital treatment costs (€)	Total cost (€)	Mean cost *per* patient (€)
1st A (24-h)	89	805	61	3,036	3,842	295,409	–4,162	66,514	747
1st B (5-h)	89	805	61	3,036	3,842	66,835	−3,459	63,376	712
2nd A (24-h)	0	0	89	4,430	4,430	66,835	10,118	76,953	865
2nd B (5-h)	0	0	89	4,430	4,430	66,835	6,343	7,3177	822

RIDT rapid influenza diagnostic test, *PCR* polymerase chain reaction. In each model, calculations were as follows: cost of RIDT = number of RIDTs multiplied by the cost of a single RIDT; cost of PCR = the cost of a single PCR multiplied by the number of PCRs needed to make a diagnosis; cost of hospitalization = number of patients (89) multiplied by 9.2 days, multiplied by the mean patient-*per*-day cost (€81.4); reduction of hospital treatment costs = 43.8 for 24-h or 36.4 for the 5-h delay model multiplied by the number of patients with positive RIDT (reduction of costs) multiplied by €3.4 (cost of patient-*per*-hour hospitalization). Reduction of costs was marked with the "–"symbol. In case of hospital treatment, the cost increase = number of patients with PCR, multiplied by the mean delay to obtain a diagnosis (33.5 h or 21.0 h in the 24-h and 5-h delay model, respectively) multiplied by €3.4 (cost of patient-*per*-hour hospitalization). The total cost was then calculated and divided by the number of patients to show the mean cost per patient

Table 6 Time and cost gained/lost in the 3rd and 4th diagnostic theoretical models

Theoretical model	No. of RIDT	Cost of RIDT (€)	No. of PCR	Cost of single rapid PCR (€)	Diagnostics cost (€)	Hospitalization cost (€)	Reduction in hospital treatment costs (€)	Total cost (€)	Mean cost *per* patient (€)
3rd A (24-h)	89	806	61	x	806 + 61x	66,835	−13,229	54,411 + 61x	x = 147
3rd B (5-h)	89	806	61	x	806 + 61x	66,835	−10,994	56,646 + 61x	x = 110
4th A (24-h)	0	0	89	y	89y	66,835	−13,229	54,411 + 89y	y = 101
4th B(5-h)	0	0	89	y	89y	66,835	−10,994	56,646 + 89y	y = 75.6

RIDT rapid influenza diagnostic test, *PCR* polymerase chain reaction. In each model, calculations were as follows: cost of RIDT = number of RIDTs multiplied by the cost of a single RIDT; cost of hospitalization = number of patients (89) multiplied by 9.22 days, multiplied by the mean patient-*per*-day cost (€81.4); reduction of hospital treatment costs = 43.8 for 24-h or 36.4 for 5-h delay model multiplied by the number of patients with positive RIDT (reduction of costs), multiplied by €3.4 (cost of patient-*per*-hour hospitalization). Reduction of costs was marked with the "–"symbol. The total cost after the reduction due to a faster diagnosis was calculated next and then divided by the required number of the rapid PCR tests to establish the PCR price

Table 7 Time and cost gained/lost in the optimum diagnostic model

Theoretical model	No. of RIDT	Cost of RIDT (€)	No. of PCR	Cost of PCR (€)	Diagnostic cost (€)	Hospitalization cost (€)	Reduction in hospital treatment costs (€)	Total cost (€)	Mean cost *per* patient (€)
Optimal A (24-h)	43	389	70	3,484	3,873	66,156	−2,824	64,010	719
Optimal B (5-h)	43	389	70	3.484	3,873	66,156	−2,347	64,488	725

RIDT rapid influenza diagnostic test, *PCR* polymerase chain reaction

positive RIDT was 70%; when they lasted for up to 48 h (in 50 patients), this probability declines to 41%. The optimum time cut-off mark seems 48 h, as it accounts for more than half of patients admitted to the hospital, and still the probability is higher than otherwise. The optimum diagnostic model would then only include patients with no more than 2-day-long disease duration, except of neonates. Hence, 50 out of the 89 patients would be eligible for RIDT. With the neonates excluded, the remaining 43 children would be eligible. In fact, 40 of them had the RIDT done, with 18 positive results (45%). Extrapolating these data, 43 RIDTs are performed and 19 patients are diagnosed. In the remaining 70 patients, the PCR would be the method of choice. The total cost of this diagnostic path would be €3,873, with an average of €43.5 *per* patient. The general cost of hospitalization would be €66,156, and after taking into account a reduced of hospital stay, the mean cost *per* patient would be in a range of €719–725 (Table 7).

4 Discussion

The American Academy of Pediatrics (AAP 2017) recommends that all children aged 6 months and older should be protected against influenza with vaccination. Moreover, all persons in the household who have contact with children younger than 5 years of age should also be vaccinated. Obviously, the preferred method of flu-fighting is vaccination, but when there is a suspicion of influenza, antiviral medications should be administered. The AAP recommendations for antiviral treatment include children hospitalized with a suspicion of influenza; children hospitalized for severe, progressive, or complicated influenza or influenza-related-disease; as well as patients from high-risk groups suspected of influenza, independently of the disease severity. Antiviral treatment should also be considered to any healthy child, especially when living at a household with other children under 6 months of age, i.e., being too small to be vaccinated. The need for prevention seems to be increasingly crucial as there are many problems with diagnosing influenza in children. Clinical signs and symptoms cannot be used in young children either to confirm or exclude influenza. The only sign that was present in a substantial percentage of children (83%) in the present study was fever, but fever as such is the most frequent sign in children hospitalized, so that it is a highly unspecific sign. Clinical findings are of little use in diagnostic utility concerning influenza (Call et al. 2005). Yet some studies suggest the opposite that experienced general practitioners may be able to correctly diagnose influenza on their judgment, from a constellation of typical symptoms, on par or even better than from the results of modern laboratory techniques (van Elden et al. 2001). The present study did not evaluate the sensitivity, specificity, and positive nor negative predictive value of the infection signs, but it shows that the signs or the lack of symptoms in children under the age of 2 years may be especially misleading. A strong emphasis should be put on keeping in mind influenza as one potential causative factor of fever in young children. That especially refers to children hospitalized.

The so-called suboptimal sensitivity of the RIDT seems to be even lower than expected in

children under 2 years of age. The percentage of true-positive results was very poor in the entire study group (31%), which is grossly in line with the surprisingly low 23% sensitivity shown in a study by Koul et al. (2015) and below the generally considered RIDT sensitivity. The most frequently mentioned factors that influence RIDT results are the age of patients, the time when RIDT was performed, and the virus type and viral load (Busson et al. 2014). Further, simple errors in obtaining specimens or test storage may cause false results. To avoid such problems, in the present study, only physicians trained in performing RIDT performed the patients' swabbing and collected samples that were stored in controlled laboratory conditions. The criteria in which patient the RIDT should be performed remain questionable, as they mainly rest on clinical decisions. The most important interfering factor was the time period between onset of infection signs and the performance of RIDT. The highest percentage of positive results (70%) noticed was too low to find it satisfying. This percentage is still considered suboptimal, and it was seen only in patients admitted within the first 24 h from onset of infection. Then, the percentage decreased dramatically. From the practical standpoint, patients are rarely referred to the hospital during the first day of influenza, which hampers the diagnostic investigation on influenza. A low number of patients with influenza type B and the lack of viral load measurements were limitations in the valuation of the present results.

Even after narrowing the eligible group of patients to those who had presented signs for no more than 48 h (neonates excluded), in our theoretical "optimal" model of diagnosis, the costs related to diagnostics and hospitalization are not much lower than those in the study group. A truly optimal diagnostic path would include PCR testing, available around the clock every day. New options are under development, and special attention is paid to expanding the availability and simplicity of molecular techniques, including multifactorial analyses of the most frequent respiratory tract pathogens (Pham et al. 2017; Malhotra et al. 2016). For the purpose of clinical practice, we presented the most tolerable price of a single PCR analysis. As of 2016/2017, the Bielanski Hospital in Warsaw, Poland, launched new diagnostic facilities with a 24 h a day availability of the rapid PCR (approx. 5 h from taking the sample to the final result) for children hospitalized, to diagnose the presence of influenza viruses and respiratory syncytial virus (RSV).

5 Conclusions

Clinical signs of influenza are often not present in children younger than 2 years of age, so there is a strong need for taking influenza into account as the possible etiological factor of an infection in the upper respiratory tract, particularly in hospitalized children. The rapid influenza diagnostic test shows low sensitivity in comparison to molecular biology techniques. Sensitivity of the test depends mostly on the time delay between onset of infection and the performance of test, reaching 70% only during the first 24 h. Neonates, in particular, are at higher risk of false-negative test results. Molecular diagnostic methods, seeking the determination of viral DNA, such as the polymerase chain reaction, are pricey and much time-consuming for the time being. The methodological advancements are underway to make these modern methods less expensive, rapid, and widely accessible.

Acknowledgements This study was supported by CMKP grant no. 501-1-20-19-17.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

References

AAP (2017) Committee on infectious diseases. Recommendations for prevention and control of influenza in children, 2017–2018. Pediatrics 140(4): e20172550

Avril E, Lacroix S, Vrignaud B, Moreau–Klein A, Coste–Burel M, Launay E, Gras–Le Guen C (2016) Variability in the diagnostic performance of a bedside rapid diagnostic influenza test over four epidemic

seasons in a pediatric emergency department. Diagn Microbiol Infect Dis 85:334–337

Busson L, Hallin M, Thomas I, De Foor M, Vandenberg O (2014) Evaluation of 3 rapid influenza diagnostic tests during the 2012–2013 epidemic: influences of subtype and viral load. Diagn Microbiol Infect Dis 80:287–291

Call S, Vollenweider M, Hornung C, Simel DL, McKinney WP (2005) Does this patent have influenza. JAMA 293:987–997

CDC (2018) Centers for disease control and prevention. https://www.cdc.gov/flu/treatment/index.html. Accessed 16 Feb 2018

Eggers M, Enders M, Terletskaina–Ladwig E (2015) Evaluation of the Becton Dickinson rapid influenza diagnostic tests in outpatients in Germany during seven influenza seasons. PLoS One:10–e0127070

Frisbie B, Tang YW, Griffin M, Poehling K, Wright PF, Holland K, Edwards KM (2004) Surveillance of childhood influenza virus infection: what is the best diagnostic method to use for archival samples? J Clin Microbiol 42:1181–1184

Jackowska T (2016) Recommendations for prevention of influenza in children, 2016–2017. Ped Pol 2016:606–616

Koul PA, Mir H, Bhat MA, Khan UH, Khan MM, Chadha MS, Lal RB (2015) Performance of rapid influenza diagnostic tests (QuickVue) for influenza A and B infection in India. Indian J Med Microbiol 33 (Suppl):26–31

Malhotra B, Swamy MA, Reddy PV, Kumar N, Tiwari JK (2016) Evaluation of custom multiplex real–time RT–PCR in comparison to fast–track diagnostics respiratory 21 pathogens kit for detection of multiple respiratory viruses. Virol J 13:91

Pham NT, Ushijima H, Thongprachum A, Trinh QD, Khamrin P, Arakawa C, Ishii W, Okitsu S, Komine–Aizawa S, Hayakawa S (2017) Multiplex PCR for the detection of 10 viruses causing encephalitis/encephalopathy and its application to clinical samples collected from Japanese children with suspected viral. Clin Lab 63:91–100

van Elden L, van Essen G, Boucher C, van Loon AM, Nijhuis M, Schipper P, Verheij TJ, Hoepelman IM (2001) Clinical diagnosis of influenza virus infection: evaluation of diagnostic tools in general practice. Brit J Gen Pract 51:630–634