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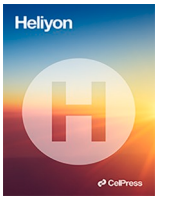

Research article

A new antigen test device for rapid influenza A and B detection

Hanan Rohana [a], Guy Marmur [b], Maya Azrad [a], Avi Peretz [a,b,*]

[a] Clinical Microbiology Laboratory, Tzafon Medical Center, Poriya, Israel
[b] Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel

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ABSTRACT

Introduction: Tests for detection of influenza must demonstrate high sensitivity and specificity, affordability, and rapidness.
Methods: This study aimed to evaluate the performance of the LabOn-Time™ Influenza A + B Rapid test device (BMT Diagnostics, Ltd), as compared to Real-time polymerase chain reaction (RT-PCR), in identifying influenza A/B among 183 nasopharyngeal samples collected between February and April 2023 from patients with Influenza-like symptoms.
Results: Out of 70 participants with a positive RT-PCR result, 53 (75.7 %) had a positive LabOn-Time result. The LabOn-Time kit had a sensitivity of 75.7 % and specificity of 100 %. The odds ratio for showing a false negative LabOn-Time result for influenza B, compared to influenza A was 5.24 (95%CI: 1.35–20.31). All false negative LabOn-Time samples had a RT-PCT cycle threshold $\geq$20. Mean time from symptom onset was significantly lower in the false negative LabOn-Time cases compared to the positive cases (36 $\pm$ 15.3 vs. 42.6 $\pm$ 10.1, respectively). The mean number of symptoms reported per patient was significantly higher in positive compared to negative LabOn-Time cases (2.5 $\pm$ 0.5 vs. 1.9 $\pm$ 0.4, $p < 0.001$).
Conclusions: The LabOn-Time device, which is very simple and intuitive to operate, could significantly contribute to early detection of influenza A/B infection.

1. Introduction

Influenza disease is primarily caused by influenza A and B viruses that typically circulate during the autumn and winter seasons [1]. Influenza can lead to life-threatening complications, including complex viral and bacterial pulmonary coinfections [2]. Every year, approximately half a million Influenza-related fatalities are reported [2]. Individuals can be contagious 1–2 days prior to symptom presentation, and remain infectious for 5–7 days thereafter [3], underscoring the need for a rapid test for early diagnosis of influenza infections.

Both viruses share morphological characteristics such as similar modes of transmission and clinical symptoms, including fever, cough, body aches and fatigue. Additionally, influenza viruses pose significant health risks to humans [4], and can lead to complications, particularly in vulnerable populations such as young childrenand individuals with comorbidities [5]. Influenza A virus is known for its ability to cause widespread epidemics and pandemics. Various hosts were reported, including both humans and animals, rendering it more prone to genetic changes and antigenic shifts [6]. Such modifications generally occur in the viral hemagglutinin (H) and neuraminidase (N) surface proteins, resulting in emergence of novel influenza A subtypes that can evade pre-existing immunity [6]. In contrast, influenza B viruses predominantly infect humans [7]. They are not classified into subtypes [8], and undergo genetic

* Corresponding author. Clinical Microbiology Laboratory, Tzafon Medical Center, Poriya, Israel.
E-mail address: aperetz@tzmc.gov.il (A. Peretz).

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changes more slowly as compared to influenza A viruses. These alterations primarily occur through a process called antigenic drift, involving gradual genetic changes in the viral surface proteins, resulting in emergence of new strains [9]. As Influenza may be prevented through vaccination, vaccine composition should be updated yearly to target new strains.

It is crucial to identify influenza viruses and distinguish them from other respiratory viruses, primarily due to the higher risk of the associated morbidity and mortality. Furthermore, Influenza can be effectively managed by specific antiviral medications [10]. However, given that, many respiratory infections induce similar respiratory and general symptoms; differential diagnosis cannot rely solely on clinical symptoms. Use of a rapid test to confirm virus identity in infected individuals will therefore enable timely intervention and assist in breaking the chain of infection [11].

The most prevalent method used worldwide to detect influenza is the reverse transcriptase-polymerase chain reaction (RT-PCR) [12], which is characterized with high sensitivity and specificity and is based on identification of identifies the viral RNA. However, the turnaround time can be several hours, depending on the assay, which delays patient management and limits outbreak control.

Additionally, it should be remembered that RT-PCR can identify the viral DNA but cannot confirm the presence of infectious virus; this can be confirmed only by viral culture. Although viral culture is highly sensitive and specific, it suffers from the longest turnaround time- 3–10 days [13].

In recent years, rapid PCR-based influenza tests have emerged as a promising alternative, offering high sensitivity and specificity while providing results within 1 h [14]. Yet, these tests are costly and require trained personnel and cannot identify influenza A subtypes. Direct and indirect immunofluorescence assays are based on detection of antibodies against inflenza. These tests' sensitivity and specificity are lower compared to cell culture and RT-PCR. In addition to the need for fluorescent microscope, which is expensive, their performance requires high sample quality and trained laboratory staff [13].

Rapid antigen tests are another recent development, which is valuable for successful outbreak control, particularly in community settings. However, so far, antigen-based rapid diagnostic tests have not reached the sensitivity of RT-PCR [15]. Therefore, new rapid and sensitive assays are required. The current study assessed the diagnostic performance of the LabOn-Time™ Influenza A + B rapid test device (LabOn-Time), in comparison with RT-PCR.

2. Materials and methods

2.1. Study population

One hundred and eighty three participants aged ≥18 years were enrolled; these participants admitted to the emergency department at the Tzafon medical center, between February and April 2023, due to Influenza-like symptoms including fever, cough, body aches and fatigue, and provided a nasophryngeal sample as part of the acceptable medical care (Fig. S1). Before enrollment, all participants signed a consent form. The institutional review board of Tzafon Medical Center site, POR-0001-23, approved study's procedures. Participants formed a random series.

2.2. Sample size calculation

For detecting influenza A/B using RT-PCR as the reference method, it was assumed that sensitivity would be around 90 %. The calculation was based on the following parameters: Expected Proportion (Sensitivity/Specificity)-90 %, Margin of Error- 5 %, Confidence Level- 95 %, and Power- 80 %. Using these inputs, the effect size (h-value) needed for the power calculation was computed using the normal quantile function to approximate the z-value at a 95 % confidence level, adjusted for the expected proportion of test accuracy. The resulting h-value used in the power calculation was approximately 0.588. The computed sample size needed to achieve this study design's goals, with 80 % power and 5 % margin of error, was approximately 23 participants.

2.3. Detection of influenza A/B by RT-PCR

Skilled personnel collected a nasopharyngeal sample from each patients using flexible nylon flocked swabs (Lingen Precision Medical Products Cp. Ltd., Shanghai, China). The swabs were placed into virus transport medium (VTM) - containing tubes. Viral inactivation was performed by mixing 200 μL of VTM with 150 μL lysis buffer (Backman Coulter, Indianapolis, USA) and incubation for 30 min at room temperature. RNA was extracted by a Biomek i7 Automated Workstation (Backman Coulter), according to the manufacturer's instructions. Then, RNA was subjected to RT-PCR using the kit TaqPath RT-PCR COVID-19, Influenza A, Influenza B, Combo Kit (Applied Biosystems™, Thermo Fisher Scientific, Waltham, MA, USA), performed with a Quanstudio5 Detection System (Applied Biosystems™, Thermo Fisher Scientific). Threshold cycle (Ct) values in the range of 0–40 were used to determine a positive result, as per kit instructions and the Israeli Ministry of Health guidelines.

2.4. Detection of influenza A/B using LabOn-Time ™ influenza A + B rapid test device

Samples were collected using the test device provided with the kit, by removing the cap and inserting the tip (swab) of the device into each nostril, and then rotating a few times. The device carrying the patient sample was then inserted into the extraction test tube and rotated at least 10 times. Results were read after 15–20 min. Appearance of one band in the test control region of the test window indicated a negative result. The result was considered positive when two or three bands appeared in the test window, i.e., the test control band (C) and either the A and/or B band, representing influenza A and B, respectively. If no band appeared in the C region, the

test was considered inconclusive and was repeated.

The minimal detection limits of the kit are $3.0*10^4$ TCID/Test for Influenza A, and $1.5*10^5$ TCID/Test.

2.5. Statistical methods

Categorical variables (presence of fever, muscle spasm, cough, diarrhea-yes/no, number of symptoms-1/2/3/4, time from symptoms onset-12/24/48 h, Ct ≤ 20/Ct > 20) are presented as absolute numbers and percentages, and continuous variables (Ct value, time from symptoms onset in hr., number of symptoms) are presented as mean and standard deviation. The Chi-squared test or Fisher Exact test were performed to analyze associations between categorical variables, and the *t*-test for independent samples was performed to analyze differences between continuous variables. For the calculation of test sensitivity, specificity, and negative and positive predictive values, RT-PCR was used as the reference method. To this end, positive specimens the RT-PCR were defined as "True Positive". Similarly, negative RT-PCR samples were considered "True Negative".

A p value < 0.05 was determined for determination of statistical significance. Statistical analyses were performed with the R program (version 4.2.1).

3. Results

3.1. LabOn-Time™ rapid test device performance

Of the 183 samples, 113 (61.7 %) tested negative by RT-PCR, while 70 (38.3 %) samples tested positive (Table 1). All the negative RT-PCR samples were also tested negative by the LabOn-Time device. Out of the 70 positive samples, 17 (24.3 %) tested negative in LabOn-Time device, while 53 (75.7 %) were positive, yielding a sensitivity of 75.7 % (53/70, 95%CI: 64.5%–84.2 %). Both the specificity and the positive predictive value (PPV) were 100 % (113/113 and 53/53, respectively, 95%CI: 94.8%–100 %). The negative predictive value (NPV) was calculated to be 86.9 % (113/130, 95%CI: 77.3%–93 %). The overall accuracy of the LabOn-Time device 90.7 % (166/183, 95%CI: 80.8%–95 %).

Significant differences in the percentage of false negative results between Influenza A and Influenza B were noted ($p = 0.011$); out of 11 samples which tested positive for Influenza B by RT-PCR, 6 (54.5 %) tested negative in the LabOn-Time device (i.e., false negative result). In contrast, of the 59 samples that tested positive for Influenza A by RT-PCT, 18.6 % (11/59) were false negative in the LabOn-Time device (Table 1). The odds ratio for having a false negative for Influenza B as compared to Influenza A was 5.24 (95 % CI: 1.35–20.31).

3.2. Comparison of Ct, symptom profile and onset between positive vs. negative samples using LabOn-Time

The mean RT-PCR Ct value of the false negative LabOn-Time cases was significantly higher compared to the positive cases (33.6 ± 2.6 vs. 25.6 ± 4.7) (Table 2). All false negative LabOn Time cases belonged to patients whose RT-PCR results had a Ct value of ≥20, whereas 81.1 % of the positive LabOn-Time cases belonged to patients whose RT-PCR results had a Ct value of ≥20 (Fig. 1, $p = 0.053$).

The mean time from symptom onset was significantly shorter in the false negative LabOn-Time cases, compared to the positive cases (36 ± 15.3 vs. 42.6 ± 10.1). Additionally, the cough rate was significantly lower in the negative (11.8 %, 2/17) compared to the positive (49.1 %, 26/53, $p = 0.006$) LabOn-Time cases. Furthermore, patients with positive LabOn-Time samples suffered from a significantly higher number of symptoms as compared to those with samples that tested negative (2.5 ± 0.5 vs. 1.9 ± 0.4, $p < 0.001$) (Table 2).

Ct values differed according to time from symptom onset as well as symptoms' number, although not statistically significant, likely due to the small sample size; samples collected within 12 h of symptom onset had the highest Ct values (mean = 34.5), compared to those collected at 24 h or 48 h (mean = 27.4 and 27.2, respectively), (Fig. 2).

An association between Ct values and number of symptoms was noted as well (Fig. 3). The highest mean Ct values were recorded for samples collected from patients with a single symptom (34.3), while samples from patients with three symptoms exhibited the lowest mean Ct value)24.92). Of note, statistical testing was not conducted due to the limited sample size.

All cases with time from symptom onset of more than 12 h, showed negative results in the LabOn-Time device (Fig. 4). Among the cases with time from symptom onset >24 h or >48 h, 25 % and 20 %, respectively tested falsely negative with the LabOn-Time device. Of note, no statistical analysis was conducted due to the limited sample size.

Table 1
PCR vs LabOn-Time test device results.

	LabOn-Time (−) (N = 17)	LabOn-Time (+) (N = 53)	*p*
RT- PCR			0.011
Influenza B (N = 11)	6 (54.5 %)	5 (45.5 %)	
Influenza A (N = 59)	11 (18.6 %)	48 (81.4 %)	

Table 2
Comparison of positive vs. negative LabOn-Time samples.

	LabOn-Time (−) (N = 17)	LabOn-Time (+) (N = 53)	*p* value
RT-PCR Ct			**< 0.001**
Mean (SD)	33.6 (2.6)	25.6 (4.7)	
Range	28.3–36.8	16.8–33.6	
RT-PCR Ct (Categorical), n (%)			0.104
≤20	0 (0)	10 (18.9)	
>20	17 (100)	43 (81.1)	
Time from symptoms' onset (h)			**0.046**
Mean (SD)	36 (15.3)	42.6 (10.1)	
Time from ' symptoms' onset (h), n (%)			**0.0020**
12	3 (17.6)	0 (0)	
24	4 (23.5)	12 (22.6)	
48	10 (58.8)	41 (77.4)	
Fever	16 (94.1)	53 (100)	0.243
Muscle spasm	15 (88.2)	47 (88.7)	0.999
Cough	2 (11.8)	26 (49.1)	**0.009**
Diarrhea	0 (0)	6 (11.3)	0.324
Number of symptoms			**< 0.001**
Mean (SD)	1.941 (0.4)	2.491 (0.5)	
Number of symptoms, n (%)			**< 0.001**
1	2 (11.8)	0 (0)	
2	14 (82.4)	28 (52.8)	
3	1 (5.9)	24 (45.3)	
4	0 (0)	1 (1.9)	

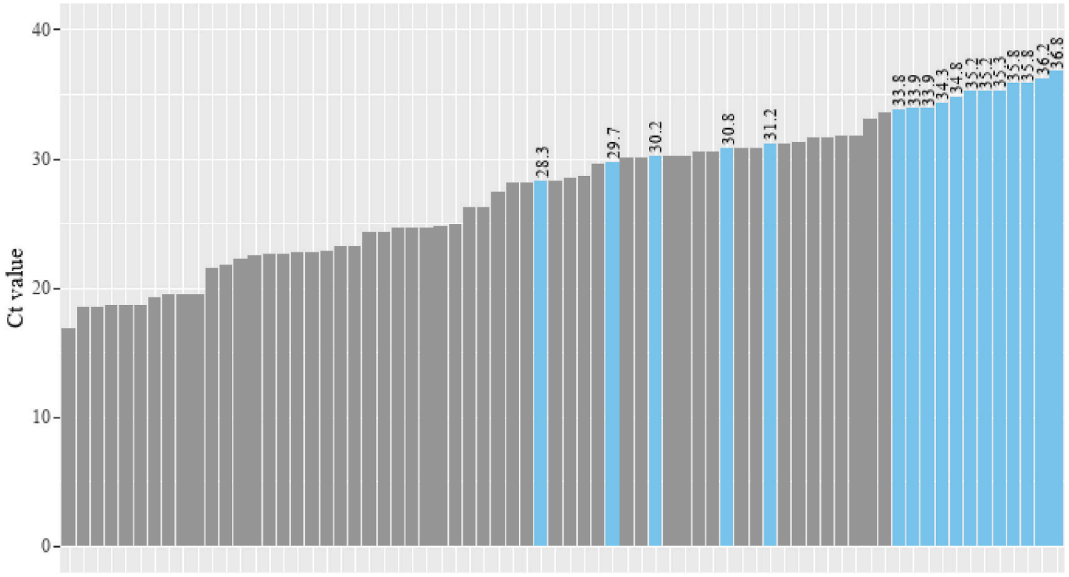

Fig. 1. Distribution of Ct values of positive samples. Grey bars represent samples of patients with positive result by both the LabOn-Time device and RT-PCR. Blue bars represent patient samples for which a negative result was shown by the LabOn-Time device; the corresponding Ct value is indicated above the bar. Bars are sorted by Ct value.

4. Discussion

Our main aim was to evaluate the clinical sensitivity and specificity of the LabOn- Time™ Influenza A + B Rapid Test device. The device had 100 % identification of negative samples and had no false-positive results (100 % specificity). It should be noted that false-positive results are a general concern as they can lead to unnecessary treatment, overburden the healthcare system and yield inaccurate surveillance data. The clinical sensitivity of the LabOn-Time device was 75.7 %. In other words, the LabOn-Time device correctly identified approximately three-quarters of the true-positive cases. Numerous studies that assessed the analytical performance of Rapid Influenza Diagnostic Tests (RIDTs), reported on broad range of sensitivities. In three meta-analyses, the pooled sensitivity ranged from 51 % to 67.5 % [16–18]. In another study, out of 144 PCR-confirmed cases, the rapid antigen-based test only detected 16, resulting in an overall sensitivity of 11.1 % [19]. In a work testing the accuracy of the QuickVue Influenza A + B antigen Test, sensitivity was found

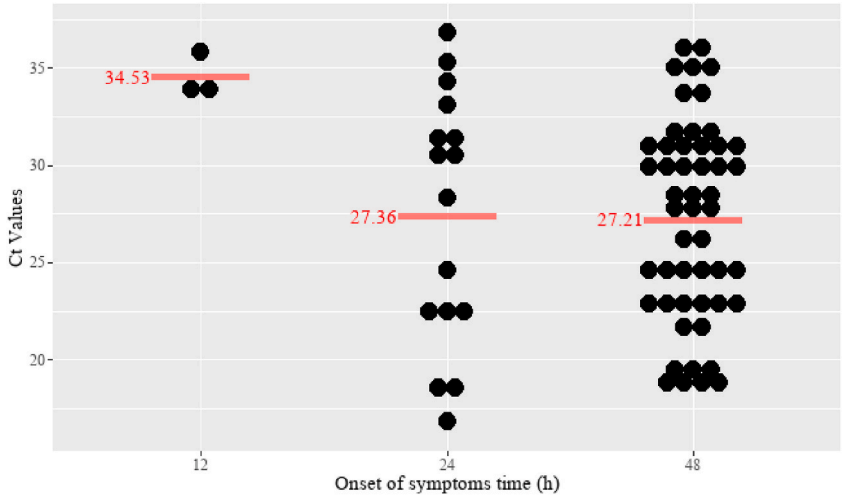

Fig. 2. Dot plot of Ct values by time from symptom onset. Red lines represent the average Ct value.

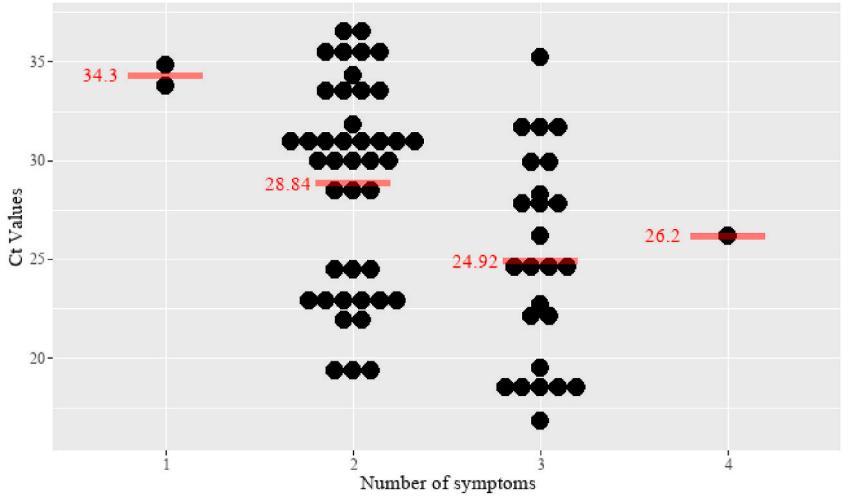

Fig. 3. Dot plot of Ct values by number of symptoms. Red lines represent the average CT value.

to be 32.3 % [13]. Taken together, the LabOn-Time device proved superior to other reported rapid antigen-detection kits.

In the current analysis, all false negative LabOn-Time results belonged to patients, whose RT-PCR results had a Ct value of ≥20, indicating a low viral load. Moreover, the mean number of symptoms reported by patients was significantly higher in positive as compared to negative LabOn-Time cases. These findings suggest that the accuracy of LabOn-Time device is increased in patients with a moderate to high viral load and in patients presenting symptoms. Hence, LabOn-Time device may be suitable for the identification of individuals who are currently infectious and should be isolated. These results are supported by a study conducted in Japan to evaluate the clinical performance of QuickNavi-Flu + COVID19 antigen test [20]. The analysis found a sensitivity below 95 % for Ct values < 20, regardless of symptoms. In asymptomatic cases, sensitivity was 46.2 % (95 % CI: 19.2–74.9) for Ct 25–29; in symptomatic cases with a Ct values ≥ 30, the sensitivity was 25.0 % (95%CI: 7.3–52.4). Thus, RIDTs performance seems to improve with increased viral load.

The time from symptom onset is also a critical factor. In this study, over 50 % of the false negative results were observed in samples from patients who experienced symptoms 48 h before sample collection, while no positive cases were detected by LabOn-Time device when symptoms appeared only 12 h prior to the test. These findings indicate that the optimal time to conduct this test is within 24 h after symptom onset. Performance of 158rapid antigen tests within this rangeresulted in sensitivity of 77 % (95 % CI 61–89 %) and specificity of 99 % (95 % CI 95–100 %) for all influenza viruses, which matches our findings [21].

Despite its high performance, which has established it as the gold-standard method for detecting Influenza A/B, RT-PCR is limited by its turnaround time and costs. Even the newer rapid PCR-based platforms, which eliminate the need for RNA extraction, still necessitate dedicated instruments that are typically not easily portable, making them relatively expensive [22].

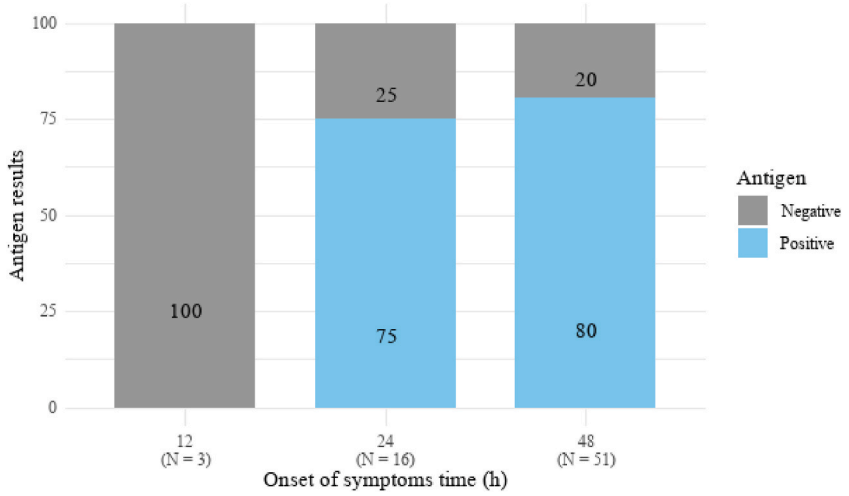

Fig. 4. Proportion of positive and negative LabOn-Time results by time from symptom onset.

The study has several limitations including being performed in one small medical center, and during one year, thus further studies should be performed to validate this study's resuts.

Due to its remarkable accuracy (90.7 %) and user-friendly nature, the LabOn-Time device proved to be a good choice for facilities seeking rapid Influenza A/B results, such as emergency rooms and intensive care units, and above all, for home-use, which is one of the manufacturer's application intended use. The use of such a device at home may decrease patient's visits at emergency rooms, resulting in reduced healthcare burden and costs and less cases of infection transmission.

The kit offers several advantages. Firstly, it has a home-use designe, facilitating self-testing without requiring expensive equipment or skilled personnel for result interpretation. Moreover, results are detected within a short timeframe of 10–15 min, making it suitable for use as a point-of-care assay. A potential drawback is the discomfort associated with nasal sample collection, but this is a common issue with other RIDTs as well. The possibility of false negative results remains the primary concern. However, the current findings indicate that false negatives were mainly observed in patients with a low viral load. Consequently, this limitation may not significantly affect the transmission of Influenza A/B.

5. Conclusions

The LabOn-Time device offers distinct advantages as a rapid, point-of-care influenza detection device, with a moderate clinical sensitivity (75.7 %) in comparison to other antigen Influenza A/B kits, and high accuracy (90.7 %) when compared to RT-PCR. Adopting this portable and affordable device may significantly contribute to early detection and play a crucial role in preventing the further spread of influenza A/B infection.

Ethics statement

The institutional review board of Tzafon Medical Center, POR-0001-23, approved all study procedures. All participants signed a consent form before enrollment.

Funding

Reagents and devices used in the study were partially provided and funded by BMT Diagnostics, Ltd.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Hanan Rohana: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Guy Marmur:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Maya Azrad:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis. **Avi Peretz:** Writing – review & editing, Writing –

original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Reagents and devices used in the current study were partially provided and funded by BMT Diagnostics, Or-Akiva, Israel, BMT Diagnostics, Ltd.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33979.

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