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Diagnostic performance of the Idylla™ Respiratory Panel for molecular detection of Influenza A/B in patients presenting to primary care with influenza-like illness during 3 consecutive influenza seasons

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Abstract

Background: Influenza virus (IFV) is often encountered in primary care. Implementation of a rapid diagnostic test for its detection at the point-of-care would enable discrimination from other viral causes of influenza-like-illness (ILI) and might be helpful in individual patient management. In this study, the diagnostic performance of such a point-of-care platform was evaluated.

Methods: Respiratory samples (n=1490) from ILI-patients in primary care in 15 European countries were collected as part of a prospective clinical trial. Both children (n=252) and adults (n=1238) were sampled during 3 consecutive periods of high IFV endemicity. Samples were analysed in a central laboratory, after storage at -70°C, with the Idylla™ Respiratory Panel, detecting both IFV and RSV, on the Idylla™ platform. The Fast Track Diagnostics (FTD) Respiratory Pathogens 21 plus assay was used as reference. A subset of samples (n=192) was analysed both fresh and after being frozen.

Results: The reference method detected IFV-A in 42% and IFV-B in 13% of the samples. Sensitivity of the Idylla for detection of IFV-A and IFV-B was 98.2% and 92.3% and specificity 97.7% and 98.4% respectively. False negative samples contained significantly lower viral loads than true positive samples (FTD mean Ct-value 30.7 versus 26.1 for IFV-A and 30.4 versus 25.1 for IFV-B, $p<0.001$). Comparable results were obtained for Idylla analysis using fresh and frozen samples.

Conclusions: The Idylla Respiratory Panel is a promising point-of-care test for detection of IFV in ILI patients due to its excellent diagnostic performance, minimal training requirements and limited hands-on time.

1. Introduction

Influenza virus (IFV) is a highly contagious virus, causing acute respiratory illness and is often encountered in primary care. Nonspecific symptoms like fever, cough or sore throat hamper the differentiation from infection caused by other respiratory pathogens. A point-of-care test (POCT) for IFV would make it possible for general practitioners to distinguish true from other causes of influenza-like illness (ILI) and better target advice and treatment [1].

We set out to determine the performance of the Idylla™ Respiratory Panel (Idylla) for the qualitative molecular detection of IFV-A, -B and RSV in respiratory samples using a commercial multiplex PCR test as reference standard, Fast Track Diagnostics Respiratory pathogens 21 plus assay (FTD). The Idylla platform is a fully automated, real-time PCR-based diagnostics system using single-use cartridges in which extraction, amplification and detection are integrated, requiring no sample preparation and generating results within an hour. The platform has already gained currency in pathology laboratories for the detection of oncogenic mutations [2], and has the potential to impact the delivery of precision medicine in oncology due to its rapidity [3]. Considering the performance of Idylla in detecting IFV and RSV in respiratory samples, data are scarce.

Unlike other POCT platforms detecting IFV and RSV (e.g. Cobas Liat (Roche), ID Now (Abbott), GeneXpert (Cepheid)), Idylla also detects the H275Y substitution of the neuraminidase protein which is the most common mutation conferring oseltamivir resistance in IFV-A/H1N1 strains [4]. Due to the emerged resistance to adamantanes, neuraminidase inhibitors constitute the only antiviral class currently approved for treating IFV infections. Therefore, detection of this mutation might be helpful in monitoring resistance and thus evaluating the

need for novel antivirals with different viral targets [5]. Another unique feature of Idylla is the ability to subtype IFV-A positive samples into H3, H1 or 2009 H1N1.

In order to challenge the robustness of Idylla in capturing different IFV and RSV subtypes, a proficiency molecular testing panel was analyzed. Analysis was then performed on samples collected from all over Europe during periods of high influenza endemicity in 3 consecutive winter seasons. European surveillance data indicate that in the first season studied, 2015-'16, there was an almost equal distribution of IFV-A (mostly 2009 H1N1) and B (mostly Victoria lineage). The second season, 2016-'17, was dominated by IFV-A, mostly H3 subtype, and in the third season, 2017-'18, 2/3 cases were caused by IFV-B (mostly Yamagata lineage) and 1/3 by IFV-A [6]. In this study, most samples were analyzed in batch after storage at -70°C but also a subset of fresh samples were included to validate the off-site use of the platform.

2. Materials and methods

2.1 Proficiency testing samples

The 2014 Quality Control for Molecular Diagnostics (QCMD) influenza panel was tested, containing 11 samples with dilutions of different subtypes of IFV-A and -B and one negative sample.

2.2 Patient samples

Patients with ILI-symptoms presenting in primary care were enrolled in the ALIC^{4}E trial (Antivirals for influenza Like Illness? An rCt of Clinical and Cost effectiveness in primary CarE) as part of the EU funded PREPARE project (www.prepare-europe.eu) [7][8]. ILI was defined

as sudden onset of self-reported fever, with at least one respiratory symptom (cough, sore throat, running or congested nose) and one systemic symptom (headache, muscle ache, sweats or chills or tiredness) with a symptom duration of 72 hours or less. The main goal of the trial was to investigate the impact and cost effectiveness of adding antiviral agents to usual primary care of people suffering from ILI. A secondary goal was to study the epidemiology of ILI. Therefore, respiratory samples were obtained using nasal and oropharyngeal flocked swabs in 3mL Universal Transport Medium (UTM) (Copan, Brescia, Italy) for paediatric patients (<16 years) and nasopharyngeal flocked swabs for adults (≥16 years), during three consecutive seasonal influenza epidemics.

A subset of 1490 randomly selected samples collected during the ALIC^{4}E trial was used for this study. Of these, 461 (31%) were collected during the first influenza season (2015-'16), 912 (62%) during season 2 (2016-'17) and 117 (8%) during season 3 (2017-'18), both in adults (1238 (83%)) and children (252 (17%)). Samples were collected from patients presenting at 20 primary care networks in 15 European countries. Swabs were stored at -20°C (or -80°C if possible) at local laboratories, before transportation on dry ice to the central laboratory In Antwerp where all analyses were performed. A subset of samples (n=192, from the Antwerp primary care network in Belgium) was analysed both fresh, and after a freeze thaw cycle. These samples were stored and transported at 4°C and analysed within 48h after sampling.

2.3 Techniques

The Idylla™ Respiratory Panel (Janssen Pharmaceutica NV, Beerse, Belgium) was used as instructed by the manufacturer on the Idylla™ system (Biocartis NV, Mechelen, Belgium). Briefly, 200 µL of UTM from each respiratory sample was added directly into the Idylla

cartridge and then inserted into the Idylla instrument. The test processing time was approximately 1 hour. The assay provided a qualitative result for the presence (detected) or absence (not detected) of the following viruses: IFV-A, IFV-B and RSV A/B. For IFV-A positive samples, the assay could provide subtyping information for H1, H3, 2009 H1N1 and the H275Y mutation in the neuraminidase gene, if 2009 H1N1 positive.

For the FTD multiplex real-time PCR assay, nucleic acid extraction was performed on 200 µL UTM using the Specific A protocol on the NucliSENS™ EasyMAG™ (bioMérieux, Marcy l'Etoile, France) semi-automated extractor with an elution volume of 70 µL. Amplification in 6 multiplex reactions was executed on LightCycler 480 (Roche, Basel, Switzerland). Next to IFV-A (and H1N1 subtyping), IFV-B and RSV A/B, the FTD respiratory panel could also detect the following targets: human rhinovirus, coronaviruses (NL63, 229E, OC43 and HKU1), parainfluenza viruses (1-4), metapneumovirus, bocavirus, adenovirus, enterovirus, parechovirus, *Chlamydophila pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type B and *Staphylococcus aureus*. The cycle threshold (Ct) values of the assay were recorded for each target.

If discrepant results for IFV-A, -B or RSV between both tests (Idylla and FTD) occurred, samples were retested with another commercial multiplex PCR, Respifinder 2SMART (Pathofinder) using the same extraction and amplification instruments as the FTD assay. Detection is based on melting curve analysis.

2.4 Statistical analysis

MedCalc Statistical Software version 17.5.5 was used for calculation of the assay performance characteristics and SPSS statistics 21.0 software was used to analyze differences in Ct-values with Student's t-test and to create boxplots. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Proficiency testing

The 2014 IFV QCMD panel contained 6 IFV-A, 5 IFV-B and 1 negative sample (table 1). The 5 IFV-B samples, Yamagata or Victoria lineage, were all detected by Idylla as IFV-B, and the negative sample as IFV negative (Table 1). However, there were 3 discrepant results for the 6 IFV-A positive samples. IFV-A H7N7 (INFRNA14-01) could not be detected although the expected Ct-value was rather low (26.8), indicating that the assay does not target this subtype. Yet, 305 out of 314 participating laboratories could detect this subtype according to the QCMD final report. The other 2 undetected IFV-A samples had the highest expected Ct-values (INFRNA14-05: 36.3 and INFRNA14-07: 34.1), indicating that these false negative results are, most probably, due to a low concentration of IFV, possibly at the limit of detection by Idylla. The latter 2 samples were also challenging for the other participating laboratories as only 60.2 and 76.8%, for INFRNA14-05 and INFRNA14-07 respectively, could detect IFV compared to over 90% for the other samples. One of the 3 remaining IFV-A samples that were detected as IFV-A positive by Idylla could not be subtyped as H3 (INFRNA14-06, Ct 32.3), while the other 2 (IFV-A H1N1 (INFRNA14-03, Ct 30.5) and IFV-A H3N2 (INFRNA14-04, Ct 29.4)) could. The subtyping ability of Idylla most likely also correlates with the viral load in the samples.

Sample number	Sample content	Ct value QCMD testing result	Sample status	Result Idylla
INFRNA14-01	IFV-A H7N7	26.8	Frequently detected	Negative
INFRNA14-02	IFV-A & -B negative	-	Negative	Negative
INFRNA14-03	IFV-A H1N1 pdm09	30.5	Frequently detected	IFV-A H1N1
INFRNA14-04	IFV-A H3N2	29.4	Frequently detected	IFV-A H3
INFRNA14-05	IFV-A H3N2	36.3	Frequently detected	Negative
INFRNA14-06	IFV-A H3N2	32.3	Detected	IFV-A
INFRNA14-07	IFV-A H1N1 pdm09	34.1	Detected	Negative
INFRNA14-08	IFV-B Yamagata	26.9	Frequently detected	IFV-B
INFRNA14-09	IFV-B Yamagata	26.9	Frequently detected	IFV-B
INFRNA14-10	IFV-B Victoria	30.2	Detected	IFV-B
INFRNA14-11	IFV-B Yamagata	29.7	Frequently detected	IFV-B
INFRNA14-12	IFV-B Victoria	27.1	Frequently detected	IFV-B

Table 1: performance of Idylla respiratory panel on the QCMD 2014 influenza proficiency panel

3.2 Evaluation of freezing effect

A subset of 192 samples was analysed fresh and after a freeze-thaw cycle (mean storage time = 24 days, ranging from 1 to 50 days). These samples were collected during the first two seasons. IFV-A was detected in 79 (41%) fresh samples and was subtyped as 2009 H1N1 (n=14) and H3 (n=58) (table 2). Surprisingly, after a freeze-thaw cycle IFV-A was detected in 2 more samples and 2 samples were additionally subtyped as 2009 H1N1. Idylla detected IFV-B in 35 (18%) fresh samples and in 32 frozen (17%) ones. The 3 undetected IFV-B positives after freezing contained among the lowest IFV-B viral load (FTD Ct-values of 26.42, 26.51 and 28.75, compared to a mean Ct-value of 24.29, ranging from 18.66 to 29.6). RSV was detected in 3 fresh samples of which one could not be detected after a freeze-thaw cycle. This sample contained the highest FTD Ct-value (33.16) for RSV compared to the other samples (Ct 21.72 and 23.22). There were 4/192 (2%) invalid test results that were solved by retesting.

Season 1 (n=87)	Season 2 (n=105)	Total (n=192)

	fresh	frozen	fresh	frozen	fresh	frozen
IFV-A	**17 (20%)**	**17 (20%)**	**62 (59%)**	**64 (61%)**	**79 (41%)**	**81 (42%)**
H1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2009 H1N1	13 (76%)	15 (88%)	1 (2%)	1 (%)	14 (18%)	16 (20%)
H3	0 (0%)	0 (0%)	58 (94%)	58 (%)	58 (73%)	58 (72%)
no subtype	4 (24%)	2 (12%)	3 (5%)	5 (%)	7 (9%)	7 (9%)
IFV-B	**35 (40%)**	**32 (37%)**	**0 (0%)**	**0 (0%)**	**35 (18%)**	**32 (17%)**
RSV A/B	**1 (1%)**	**0 (0%)**	**2 (2%)**	**2 (2%)**	**3 (2%)**	**2 (1%)**
IFV/RSV negative	**34 (39%)**	**38 (44%)**	**41 (40%)**	**39 (37%)**	**75 (39%)**	**77 (40%)**

Table 2: results of Idylla respiratory panel on 192 fresh respiratory samples compared to the results of the same samples after a freeze-thaw cycle (frozen)

3.3 Analysis of frozen samples

The FTD reference test detected IFV-A, IFV-B and RSV in 627 (42%), 194 (13%) and 58 (4%) of the 1490 samples respectively. Of the IFV-A positives, 136 (22%) were subtyped as 2009 H1N1. H3 subtyping is not included in the FTD panel. The performance characteristics of Idylla for detection of IFV-A, IFV-A 2009 H1N1, IFV-B and RSV are shown in table 3. For IFV-A detection, 11/627 (2%) samples were missed by Idylla. The mean Ct-value of IFV-A true positives (TP) was 26.1 which is significantly lower than the mean Ct-value of 30.7 for the IFV-A false negatives (FN) ($p<0.001$), indicating that the samples with the lowest viral load were missed by Idylla (figure 1). Also for the detection of IFV-B and RSV the FNs (15/194 (8%) for IFV-B and 4/58 (7%) for RSV) had a significantly higher Ct-value than the TPs, 30.4 versus 25.1 for IFV-B ($p<0.001$, figure 2), and 35.3 versus 27.8 for RSV ($p=0.001$, figure 3).

For both IFV-A and RSV there seemed to be more FP (20 and 10 respectively) than FN results (11 and 4, respectively). All 33 initially FPs (20 IFV-A, 3 IFV-B and 10 RSV) were tested with Respifinder 2SMART. Overall, 14 (42%) of the FPs could be reclassified as TP (6/20 IFV-A, 3/3 IFV-B and 5/10 RSV), resulting in increased sensitivity (98.2% IFV-A, 92.4% IFV-B and 93.7%

RSV) and specificity (98.3% IFV-A, 100% IFV-B and 99.7% RSV) of Idylla after comparison with the combined results of both multiplex assays.

	IFV-A	IFV-A 2009 H1N1	IFV-B	RSV A/B
True positives	616	128	179	54
False negatives	11	9	15	4
True negatives	843	1348	1293	1422
False positives	20	5	3	10
Sensitivity (%)	98.2 (96.9-99.1)	93.4 (87.9-97.0)	92.3 (87.6-95.6)	93.1 (83.3-98.1)
Specificity (%)	97.7 (96.4-98.6)	99.6 (99.1-99.9)	99.8 (99.3-100.0)	99.3 (98.7-99.7)
PPV (%)	96.9 (95.2-97.9)	96.2 (91.4-98.4)	98.4 (98.1-99.5)	84.4 (74.4-91.0)
NPV (%)	98.7 (97.7-99.3)	99.3 (98.7-99.7)	98.9 (98.2-99.3)	99.7 (99.3-99.9)

Table 3: results of Idylla respiratory panel on 1490 respiratory samples with Fast Track Diagnostics Respiratory pathogens 21 plus assay as reference test

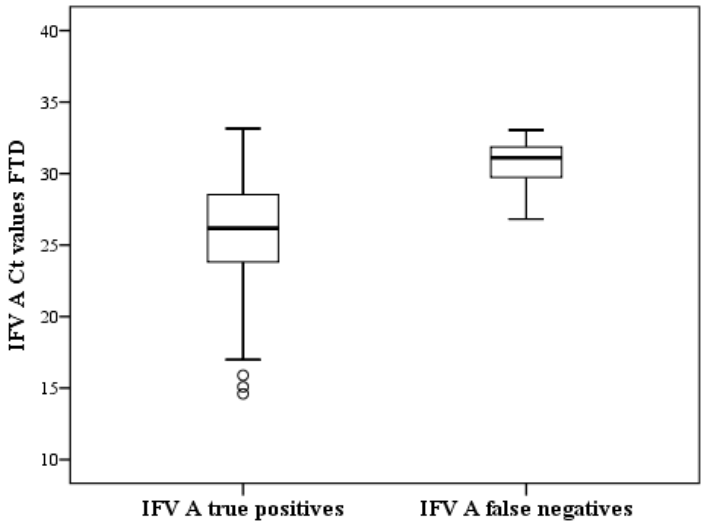

Figure 1: FTD Ct-values of Idylla IFV-A true positives (n = 616, mean Ct-value = 26.1) and false negatives (n = 11, mean Ct-value = 30.7), * p<0.001

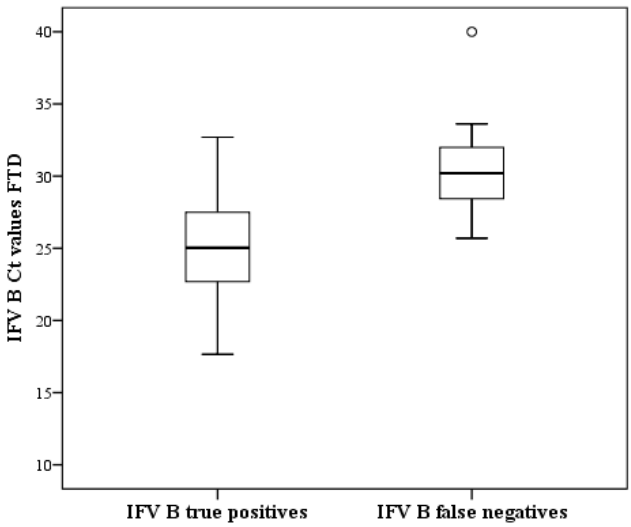

Figure 2: FTD Ct-values of Idylla IFV-B true positives (n = 179, mean Ct-value = 25.1) and false negatives (n = 15, mean Ct-value = 30.4), * p<0.001

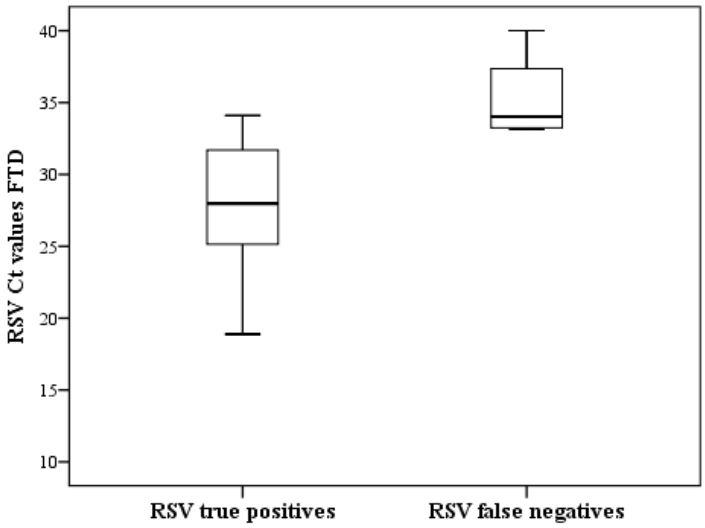

Figure 3: FTD Ct-values of Idylla RSV true positives (n = 54, mean Ct-value = 27.8) and false negatives (n = 4, mean Ct-value = 35.3), * p=0.001

3.4 Additional data from Idylla or FTD

Of the 636 IFV-A positives by Idylla, 134 (21%) were subtyped as 2009 H1N1, 484 (76%) as H3 and 19 (3%) could not be subtyped. The inability to subtype is most probably due to a low viral load in the sample and/or a false positive result as 6 unsubtypable samples were negative with FTD and for the other 13 samples the mean Ct-value of FTD was high (31.8). The

distribution of the different IFV-A subtypes and of IFV over the three different seasons highly reflects European surveillance data [6] (Table 4).

In one of the 133 IFV-A 2009 H1N1 Idylla positive samples, the oseltamivir resistance mutation H275Y was detected. This sample originated from a Norwegian patient and was collected during the first winter season 2015-'16.

Pathogens, other than IFV-A, IFV-B and RSV detected by FTD were *Staphylococcus aureus* (16%), *Streptococcus pneumoniae* (13%), coronavirus (14%), rhinovirus (9%), human metapneumovirus (5%), bocavirus (3%), RSV (2%), adenovirus (2%), *Mycoplasma pneumoniae* (1%) and enterovirus (1%).

	Season 1 (n=461)	Season 2 (n=912)	Season 3 (n=117)	Total (n=1490)
IFV-A	**121 (26%)**	**495 (54%)**	**20 (17%)**	**636 (43%)**
H1	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2009 H1N1	114 (94%)	9 (2%)	10 (50%)	133 (21%)
H3	0 (0%)	475 (96%)	10 (50%)	485 (76%)
no subtype	7 (6%)	11 (2%)	0 (0%)	18 (3%)
IFV-B	**108 (23%)**	**21 (2%)**	**53 (45%)**	**182 (12%)**
IFV negative	**232 (50%)**	**396 (43%)**	**44 (38%)**	**672 (45%)**

Table 4: results of Idylla respiratory panel over the different seasons

4. Discussion

The Idylla Respiratory Panel executed on the Idylla platform has many advantages. Firstly, the assay performs well in comparison to the commercial FTD multiplex PCR. Although results of the 2014 IFV QCMD panel were not promising, excellent sensitivity (>92%) and specificity (>98%) were obtained for clinical samples. Our study is unique as it is executed on a large number of samples, collected in 15 European countries during 3 consecutive winter seasons. Only one other group has studied the performance of Idylla using another POCT (GeneXpert

Xpert Flu/RSV, Cepheid) as comparator during 1 winter season (2015-'16) on a smaller number of samples (n=679), but also observed an excellent performance for detection of IFV [9]. The number of invalid results was also acceptable (2%) and comparable to the study above (6/679, 0.88%). Furthermore, we observed a good concordance between samples analyzed fresh and after freezing and therefore validated the use of the Idylla platform as an off-site analyzer for detection of IFV.

Secondly, the execution of the Idylla test is effortless, requiring a straightforward manual pipetting step to add sample to the cartridge, which takes less than a minute. The platform therefore overcomes the disadvantages of most molecular tests that can only be performed in a laboratory setting needing skilled technicians for their complexity and requiring sophisticated instrumentation. If more than one Idylla unit is available, the platform can also handle more samples at a time.

Another potential advantage of the Idylla panel is the detection of mutation H275Y to monitor oseltamivir resistance. In only one of the 134 IFV-A 2019 H1N1 positives the mutation was detected which is in line with a recent study indicating that resistance to neuraminidase inhibitors occurred during antiviral treatment and was not present at baseline [10]. The added value of targeting this mutation in routine diagnostics might still be rather limited due to the low current resistance rates [5], the non-targeting of common H3N2 resistance mutations, e.g. E119V and R292K [4] and the observation that resistance to neuraminidase inhibitors delayed viral clearance but had no impact on symptom resolution [10].

The main disadvantage of the Idylla platform is the turn-around time (TAT). In comparison with lab-based PCR tests, the processing time of Idylla is short. The multiplex PCR used in this study has a TAT of 6 hours and also requires a longer hands-on time. However, compared to

other available POCT systems [11] and considering its dedicated use as a near-patient analyzer, for instance in general practitioner practices, a TAT of 1 hour is rather long.

The main limitation of our study is that the Idylla test was not carried out at the point of care by general practitioners, nurses or other coworkers but in a laboratory by trained lab technicians which might bias the performance characteristics. Furthermore, the majority of the analyses was performed on frozen samples while future use of the assay will mostly be on fresh material. Nonetheless, we could determine a good correlation between both samples types for detection of both IFV-A and -B. The Idylla IFV-A H3 subtyping performance could not be validated due to the lack of a comparator test. However, the observed distribution in IFV-A H3 and 2009 H1N1 subtypes based on Idylla results (table 4) did reflect the available epidemiological data of the respective seasons [6] and good concordance with FTD for the IFV-A 2009 H1N1 subtyping was observed (table 3).

5. Conclusions

In summary, Idylla is a promising POCT for detection of IFV, requiring minimal training and hands-on time for results within an hour with excellent diagnostic performance. However, due to the current expansion of very rapid POCT platforms, the TAT of the Idylla platform should ideally be shortened, especially for near-patient testing.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee

and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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CRediT authorship contribution statement

Veerle Matheeussen: conceptualization, writing – original draft. **Katherine Loens**: conceptualization, writing – review & editing. **Mandy Kuijstermans**: data curation. **Kevin Jacobs:** data curation. **Diana Koletzki**: methodology. **Samuel Coenen:** conceptualization. **Alike W van der Velden:** project administration; writing - review & editing **Emily Bongard:** project administration. **Chris C Butler:** conceptualization, funding acquisition **Theo JM Verheij**: conceptualization, funding acquisition, writing - review & editing. **Herman Goossens**: conceptualization, funding acquisition. **Margareta Ieven**: conceptualization, supervision, writing – review & editing.

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