ERJ Express. Published on June 25, 2018 as doi: 10.1183/13993003.00555-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

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Please cite this article as: Brendish NJ, Malachira AK, Beard KR, *et al*. Impact of turnaround time on outcome with point-of-care testing for respiratory viruses: a *post hoc* analysis from a randomised controlled trial. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.00555-2018).

Impact of turnaround time on outcome with point-of-care testing for respiratory viruses: a *post hoc* analysis from a randomised controlled trial

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Take home message

As very rapid turnaround times lead to better outcomes, respiratory virus diagnostics should be performed at the point-of-care

International Standard Randomised Controlled Trial Number (ISRCTN): 90211642

To the Editor

Respiratory viruses are detected in around 40-50% of adults hospitalised with acute respiratory illness (ARI) [1, 2]. Routine laboratory polymerase chain reaction (PCR) testing generally takes several hours to several days to generate results to clinicians so cannot be used to inform decision making in real-time. Decisions about hospitalisation, antibiotics, antivirals and side room isolation therefore need to be made presumptively and reviewed when results are available. Newer rapid molecular test platforms are accurate, easy to use, and generate a result in 1 hour or less, making them potentially deployable as point-of-care tests (POCT) in clinical areas [3]. Recently, we reported on a large pragmatic randomised controlled trial (ResPOC) which evaluated the impact of POCT using the FilmArray Respiratory Panel (which tests for a comprehensive range of viruses) in adults presenting to hospital with ARI [4]. The study showed that POCT was associated with reductions in hospital length of stay (LOS) overall and reductions in antibiotics use in patients with exacerbation of airways disease. Although this evidence would suggest that rapid molecular testing needs to be performed within clinical areas for these improved clinical outcomes, it has been suggested that rapid molecular test platforms used within centralised laboratories might also be associated with these clinical benefits, although the turnaround times (TAT) are likely to be much longer. In this follow-on study we evaluate the impact of POCT TAT on clinical outcomes with a view to determining how rapid molecular testing for respiratory viruses should be best implemented in clinical practice.

The study design, inclusion and exclusion criteria, outcome measures and baseline population characteristics of the ResPOC study have been previously described in the original report of this trial [4]. The study was approved by the North West – Preston Regional Ethics Committee (NW/14/1467). The protocol is published and freely available [5].

A *post hoc* analysis was performed to explore the impact of the TAT of POCT on clinical outcomes having previously shown significant differences between the POCT group and control group for overall LOS and antibiotic use. TAT is defined as the time from a patient being recruited to the results being communicated to clinicians. As our previous study demonstrated that the improved outcomes seen with POCT occur only in patient testing positive for viruses (with those testing negative having similar outcome to control patients) we restricted our analysis to those patients testing positive for viruses by POCT. We examined the association between POCT TAT, LOS and antibiotic use and assessed the effect of a TAT of less than or greater than 1.6 hours (the median). Statistical analyses were done using Prism version 7.0 (Graphpad software; La Jolla, CA, USA) and Stata version 13.1 (StataCorp; College Station, TX, USA). Correlation was assessed using Spearman's rank correlation coefficient (r_s). We compared LOS and antibiotic use between groups using median differences and the Mann-Whitney U test and differences in proportions using Chi squared or Fisher's exact test, as appropriate. ROC curves were generated to determine the optimal cut off for TAT. We performed a subgroup analysis of patient positive for influenza A or B and for patient positive for rhinovirus

Of the 720 patents recruited in the parent randomised controlled trial, 360 allocated to the intervention (POCT) group and 354 allocated to the control (routine clinical care) group were included in the original analysis. TAT for POCT results varied from 1.1 to 6.4 hours with a median [IQR] of 1.6 [1.3 to 3.1] hours compared to a median of 29.8 [24.7 to 45.8] hours for laboratory PCR, in the control group. Of the 360 patients tested for respiratory viruses by POCT, 153 (43%) were positive. Human rhinovirus (55 [36%] of 153) and Influenza A and B (53 [35%] of 153) were the most commonly detected viruses.

For patient testing positive for viruses by POCT (n=153), the median [IQR] TAT was 1.6 hours [1.3 to 3.0]. 16 (10%) of 153 patients were discharged directly from the emergency department (ED). For

patients admitted to hospital (n=137), TAT was positively correlated with length of hospital stay (r_s = 0.24 [95% CI 0.07 to 0.39]; p=0.0051) and duration of antibiotics (r_s = 0.22 [95% CI 0.05 to 0.38; p=0.0096].

There was no difference in the proportions discharged directly from ED with a TAT of ≤1.6 hours vs >1.6 hours, 8 (10%) of 77 vs 8 (10%) of 76, Odds ratio 0.99 (95%CI 0.3 to 2.8), p=1.0. For those admitted (n=137), the median [IQR] LOS was 2.3 [1.0 to 4.0] days for TAT of ≤1.6 hours vs 5.1 [2.4 to 8.3] days for TAT of ≥1.6 hours, difference of 2.8 (95%CI 1.0 to 3.5) days, p<0.0001. This difference in LOS was due to a higher proportion of patients with a TAT of ≤1.6 hours being discharged within 24 hours of admission, 18 (26%) of 69 vs 9 (13%) of 68 , Odds ratio 2.3 (95%CI 1.0 to 5.4), p=0.058 [number needed to test = 8] or within 48 hours of admission, 34 (49%) of 69 vs 15 (22%) of 68, Odds ratio 3.4 (95%CI 1.6 to 7.0), p=0.0012 [number needed to test =4].

A smaller proportion of patient with a TAT of ≤1.6 hours vs >1.6 hours were treated with antibiotics, 55 (80%) of 69 vs 63 (93%) of 68, Odds ratio 0.3 (95%CI 0.1 to 0.9), p=0.029 [number needed to test = 8]. The median [IQR] duration of antibiotics was 2.9 [0.1 to 6.9] days for a TAT of ≤1.6 days vs 6.5 [2.4 to 8.5] days for a TAT of >1.6 days, difference of 2.3 (95%CI 0 to 2.8) days; p=0.0097. This was due to a higher proportion of patients with a TAT ≤1.6 hours receiving <24 hour and <48 hours of antibiotics, 29 (42%) of 69 vs 16 (23%) of 68, Odds ratio of 2.3 (95%CI 1.1 to 5.0), p= 0.021 [number needed to test = 5] and 32 (46%) 69 of vs 17 (25%) of 68, Odds ratio 2.6 (95%CI 1.3 to 5.4); p=0.012 [number needed to test = 5], compared to those with a TAT of >1.6 hours for POCT testing.

ROC curve analysis showed that a TAT cut off of <1.6 hours had optimal sensitivity and specificity for association with early discharge, 48% (95%CI 32 to 56) and 77% (95%CI 65 to 87%), AUC of 0.68, p=0.0002, and early discontinuation of antibiotics, 45% (95%CI 33 to 57) and 74% (95%CI 23 to 84), AUC of 0.61, p=0.021.

49 (92%) of 53 influenza positive patients were admitted to hospital. Excluding viral co-infections, 49 (96%) of 51 rhinovirus positive patients were admitted to hospital. Subgroup analysis for hospitalised influenza and rhinovirus positive patients showed that rapid TAT (<1.6 hours) was associated with shorter length of stay and antibiotic duration for influenza positive patients but not for rhinovirus positive patients, although the numbers in the individual groups were small.

This study shows that even with the rapid turnaround times for results seen with molecular POCT compared to centralised laboratory PCR testing, TAT for results remains an important determinant of clinical outcome for respiratory virus testing. Very rapid turnaround times are associated with higher rates of early discharge and early discontinuation of antibiotics compared to longer TATs in adults with acute respiratory illness. This suggests that there is a brief and early 'window period' for the results of respiratory virus testing to alter patient management after admission to hospital. Although the TAT of laboratory PCR testing is variable across different institutions, and may be a short as several hours in some centres, a very short TAT of under 2 hours is unlikely to be achievable within centralised laboratories and so rapid molecular viral diagnostics should be performed in clinical areas at the point-of-care in order to realise these clinical benefits.

Although this study is a *post hoc* analysis its strengths include the randomised nature of the parent study, the large cohort of patients studied and its pragmatic nature. In additional our findings are consistent with observational studies using rapid molecular diagnostics for respiratory viruses and showing improvements in clinical outcome, dependent on short TATs [6, 7]. Although it is likely to generalisable to other centres we cannot rule out that the changes seen are dependent on the processes of care in UK hospitals. Although there was no measured increase in adverse events in the group associated with premature discharge and reduced antibiotic use, we cannot exude a subsequent increase in primary care visits post discharge, as this data was not available to us.

The cost effectiveness of a routine molecular POCT testing strategy for respiratory viruses in hospitalised adults is currently unknown. As length of hospital stay is the key determinant of cost for patients hospitalised with ARI, the increase in premature discharge with POCT strongly suggests that even a modestly more expensive diagnostic strategy is likely to be cost saving compared to routine clinical care. It is currently uncertain as to how molecular POCT for respiratory viruses could be implemented within the NHS and other health systems. Potential models include training clinical staff to perform the testing or the development of dedicated point-of-care testing laboratories within or close to acute areas.

In summary POCT with a TAT of <1.6 hours was associated with higher rates of early hospital discharge and early discontinuation of antibiotics, compared to longer TATs. As these very rapid TATs are unlikely to be achievable with centralised laboratory testing, viral diagnostics should be performed at the point-of-care and models for the implementation of this need strategy to be explored.

Table 1. Diagnostic group and outcomes by turnaround time, for patients testing positive for viruses, n=153.

		Turnaround time for POCT		Difference (95%CI)	Odds ratio (95%CI)	p value
		≤1.6 hours	>1.6 hours			
	n	77	76			
Diagnosis (all patients)						
Exacerbation Asthma/COPD	153	32 (42)	30 (39)	-	1.1 (0.6 to 2.1)	0.87
CAP	153	13 (17)	17 (22)	-	0.7 (0.3 to 1.6)	0.42
ILI /NPLRTI	153	24 (31)	22 (29)	-	1.1 (0.6 to 2.2)	0.86
Other	153	8 (10)	7 (9)	-	1.1 (0.4 to 3.0)	0.99
Severity (all patients)						
Pulse rate (bpm)	153	105 [90 to 120]	100 [88 to 110]	-5.5 (-12 to 0)	-	0.055
Respiratory rate (bpm)	153	25 [20 to 28]	20 [18 to 26]	-5 (-5 to -1)	-	**0.0012**
Systolic BP (mmHg)	153	134 [118 to 153]	132 [117 to 150]	-2 (-9 to 6)	-	0.74
Saturations (%)	153	96 [93 to 98]	96 [93 to 98]	0 (-1 to 1)	-	0.76
CRP (mg/L)	153	37 [16 to 93]	61 [12 to 129]	24 (-10 to 24)	-	0.61
WCC ($x10^9$/L)	153	10.8 [7.6 to 15.2]	10.2 [7.9 to 13.2]	-0.6 (-2 to 0.9)	-	0.47
Outcomes (all patients)						
Discharged from ED	153	8 (10)	8 (10)	-	1.0 (0.3 to 2.8)	0.99
Admitted	153	69 (90)	68 (90)	-	1.0 (0.4 to 2.9)	0.99
Length of hospital stay (days)	137	2.3 [1.0 to 4.0]	5.1 [2.4 to 8.3]	2.8 (1.0 to 3.5)	-	**<0.0001**
Discharged within 24 hours	137	18 (26)	9 (13)	-	2.3 (1.0 to 5.4)	0.058
Discharged within 48 hours	137	34 (49)	15 (22)	-	3.4 (1.6 to 7.0)	**0.0012**
Treated with antibiotics	137	55 (80)	63 (93)	-	0.3 (0.1 to 0.9)	**0.029**
Duration of antibiotics, days	137	2.9 [0.1 to 6.9]	6.5 [2.4 to 8.5]	2.3 (0 to 2.8)	-	**0.0097**
Treated with <24 hours antibiotics	137	29 (42)	16 (23)	-	2.3 (1.1 to 5.0)	**0.021**

Treated with <48 hours antibiotics	137	32 (46)	17 (25)	-	2.6 (1.3 to 5.4)	**0.012**
Influenza positive only		23	26			
Length of hospital stay (days)	49	2.0 [0.9 to 3.7]	5.1 [1.8 to 7.1]	3.1 (0.3 to 4.2)	-	**0.023**
Discharged within 24 hours	49	7 (30)	4 (15)	-	2.4 (0.6 to 8.2)	0.31
Discharged within 48 hours	49	12 (52)	7 (27)	-	3.0 (0.9 to 10.0)	0.086
Treated with antibiotics	49	18 (78)	25 (96)	-	0.1 (0.1 to 1.3)	0.086
Duration of antibiotics, days	49	1.1 [0.1 to 6.9]	7.0 [3.8 to 8.9]	5.9 (0.3 to 6.1)	-	**0.0048**
Treated with <24 hours antibiotics	49	11 (42)	6 (23)	-	3.1 (0.8 to 9.5)	0.082
Treated with <48 hours antibiotics	49	12 (52)	6 (23)	-	3.6 (1.0 to 11.2)	**0.043**
Treated with NAIs	49	23 (100)	24 (92)	-	4.4 (0.2 to 97)	0.34
Rhinovirus positive only		29	17			
Length of hospital stay (days)	46	2.4 [1.0 to 4.5]	2.6 [1.0 to 8.5]	0.2 (-1.0 to 2.3)	-	0.44
Discharged within 24 hours	46	7 (24)	4 (24)	-	1.0 (0.3 to 3.6)	1.0
Discharged within 48 hours	46	13 (45)	5 (29)	-	2.0 (0.6 to 6.6)	0.36
Treated with antibiotics	46	23 (79)	15 (88)	-	0.5 (0.1 to 2.6)	0.69
Duration of antibiotics, days	46	6.0 [0.1 to 7.5]	6.4 [3.1 to 8.6]	0.4 (-0.7 to 5.4)	-	0.44
Treated with <24 hours antibiotics	46	11 (38)	4 (22)	-	2.1 (0.6 to 7.0)	0.34
Treated with <48 hours antibiotics	46	12 (41)	4 (22)	-	2.2 (0.6 to 7.6)	0.34
Safety (all patients)						
ICU admission*	137	1(1)	3(4)	-	0.3 (0.1 to 2.2)	0.37
Death*	153	0 (0)	0 (0)	-	-	1.0
Representation to ED*	153	6 (8)	11 (14)	-	0.5 (0.2 to 1.5)	0.21
Readmission*	138	4 (6)	5 (7)	-	0.8 (0.2 to 2.7)	0.72

POCT, point-of-care testing. CI, confidence interval. CAP, community acquired pneumonia. ILI, influenza-like illness. NPLRTI, non-pneumonic lower respiratory tract infection. BP, blood pressure. CRP, C reactive protein. WCC, white cell count. NAI, neuraminidase inhibitors. ED, emergency department. ICI, intensive care unit. *Measured for 30 days post enrolment.

Funding

University of Southampton. The manufactures of the molecular test platform (Biofire, Salt Lake City, Utah, US) had no role in the study conception, design, data analysis or manuscript preparation. The corresponding author had full access to all of the data and the final responsibility to submit for publication. This report is independent research supported by the National Institute for Health Research (NIHR Post Doctorial Fellowship, Dr Tristan Clark, PDF 2016-09-061). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Competing interests

All authors declare that they have no conflicts of interests.

Acknowledgements

We thank all of the patients and clinical staff at the Southampton General Hospital including; clinicians, nurses, and laboratory technicians. We thank the directors, research nurses, data managers, clinical trials assistants and laboratory staff at the NIHR Southampton Clinical Research Facility and the NIHR Southampton Biomedical Research Centre. We thank the staff at the R&D department, University Hospital Southampton NHS Foundation Trust and the NIHR Clinical Research Network, Wessex for their support throughout the trial.

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