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

To the Editor:

Respiratory viruses are detected in around 40–50% of adults hospitalised with acute respiratory illness (ARI) [1, 2]. Routine laboratory PCR testing for respiratory viruses generally takes several hours to several days to generate results for clinicians and 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 h or less, making them potentially deployable for point-of-care testing (POCT) in clinical areas [3]. Recently, we reported on a large pragmatic randomised controlled trial (ResPOC) [4] which evaluated the impact of POCT (using the FilmArray Respiratory Panel (BioFire Diagnostics, Salt Lake City, UT, USA) which tests for a comprehensive range of viruses) in adults presenting to hospital with ARI. The study showed that POCT was associated with reductions in hospital length of stay 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 (TATs) 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 POCT TAT on clinical outcomes having previously shown significant differences between the POCT group and the control group for overall length of stay 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 patients testing positive for viruses (with those testing negative having similar outcomes to control patients) we restricted our analysis to those patients testing positive for viruses by POCT. We examined the association between POCT TAT, length of stay and antibiotic use and assessed the effect of a TAT of less than or greater than 1.6 h (the median). Statistical analyses were performed 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 r_s. We compared length of stay and antibiotic use between groups using median differences and the Mann–Whitney U-test and differences in proportions using the Chi-squared test or Fisher's exact test, as appropriate. Receiver operating characteristic (ROC) curves were generated to determine the optimal cut-off for TAT. We performed a subgroup analysis of patients who tested positive for influenza A or B and for patients who tested positive for rhinovirus.

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Of the 720 patients 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. TATs for POCT results varied from 1.1 to 6.4 h with a median (interquartile range (IQR)) of 1.6 h (1.3 to 3.1) compared to a median of 29.8 h (24.7 to 45.8) for laboratory PCR in the control group. Of the 360 patients tested for respiratory viruses by POCT, 153 (43%) were positive. Human rhinovirus (55 out of 153 patients (36%)) and Influenza A and B (53 out of 153 patients (35%)) were the most commonly detected viruses.

For patients testing positive for viruses by POCT (n=153), the median (IQR) for TAT was 1.6 h (1.3 to 3.0). Sixteen out of 153 patients (10%) 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 the ED with a TAT of ⩽1.6 h *versus* a TAT of >1.6 h (eight out of 77 patients (10%) *versus* eight out of 76 patients (11%); odds ratio (OR) 1.0 (95% CI 0.3 to 2.8); p=0.99). For those admitted (n=137), the median (IQR) length of stay was 2.3 days (1.0 to 4.0) for TATs of ⩽1.6 h *versus* 5.1 days (2.4 to 8.3) for TATs of >1.6 h (a difference of 2.8 days (95% CI 1.0 to 3.5); p<0.0001). This difference in length of stay was due to a higher proportion of patients with a TAT of ⩽1.6 h being discharged within 24 h of admission (18 out of 69 patients (26%) *versus* nine out of 68 patients (13%); OR 2.3 (95% CI 1.0 to 5.4); p=0.058; number needed to test=8) or within 48 h of admission (34 out of 69 patients (49%) *versus* 15 out of 68 patients (22%); OR 3.4 (95% CI 1.6 to 7.0); p=0.0012; number needed to test=4).

A smaller proportion of patients with a TAT of ⩽1.6 h *versus* >1.6 h were treated with antibiotics (55 out of 69 patients (80%) *versus* 63 out of 68 patients (93%); OR 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 days (0.1 to 6.9) for a TAT of ⩽1.6 h *versus* 6.5 days (2.4 to 8.5) for a TAT of >1.6 h (a difference of 3.6 days (95% CI 0.1 to 4.2; p=0.0097). This was due to a higher proportion of patients with a TAT ⩽1.6 h receiving <24 h of antibiotics (29 out of 69 patients (42%) *versus* 16 out of 68 patients (23%); OR 2.3 (95% CI 1.1 to 5.0); p=0.021; number needed to test=5) and <48 h of antibiotics (32 out of 69 patients (46%) *versus* 17 out of 68 patients (25%); OR 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 h for POCT.

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

Forty-nine out of 53 influenza positive patients (92%) were admitted to hospital, as were (excluding viral co-infections) 46 out of 51 rhinovirus positive patients (96%). Subgroup analysis for hospitalised influenza and rhinovirus positive patients showed that a rapid TAT (<1.6 h) was associated with shorter length of stay and shorter antibiotic duration for influenza positive patients but not for rhinovirus positive patients, although the numbers in the individual groups were small. Results for the main cohort and the subgroups of influenza patients and rhinovirus positive patients are shown in table 1.

This study shows that, even with the rapid TATs for results seen with molecular POCT compared to centralised laboratory PCR testing, TAT remains an important determinant of clinical decision making for respiratory virus testing. In adults with ARI, very rapid TATs are associated with higher rates of early discharge and early discontinuation of antibiotics compared to longer TATs. 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 as short as several hours in some centres, a very short TAT of under 2 h 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 addition, our findings are consistent with observational studies using rapid molecular diagnostics for respiratory viruses which show improvements in clinical outcome dependent on short TATs [6, 7]. Although the changes seen are likely to be generalisable to other centres, we cannot rule out that they 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 exclude 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 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

TABLE 1 Diagnosis and outcomes by diagnostic group for patients testing positive for viruses (n=153) with respect to point-of-care testing (POCT) turnaround time (TAT)

	Total subjects	POCT TAT		Difference (95% CI)	OR (95% CI)	p-value
		⩽1.6 h	>1.6 h			
Diagnosis (all patients)						
Subjects	153	77	76			
Exacerbation asthma/COPD	153	32/77 (42)	30/76 (39)		1.1 (0.6 to 2.1)	0.87
CAP	153	13/77 (17)	17/76 (22)		0.7 (0.3 to 1.6)	0.42
ILI/NPLRTI	153	24/77 (31)	22/76 (29)		1.1 (0.6 to 2.2)	0.86
Other	153	8/77 (10)	7/76 (9)		1.1 (0.4 to 3.0)	0.99
Severity (all patients)						
Pulse rate beats·min^{-1}	153	105 (90 to 120)	100 (88 to 110)	−5.5 (−12 to 0)		0.055
Respiratory rate breaths·min^{-1}	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^{-1}	153	37 (16 to 93)	61 (12 to 129)	24 (−10 to 24)		0.61
WCC ×10^9 per 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						
Subjects	153	77	76			
Discharged from ED	153	8/77 (10)	8/76 (11)		1.0 (0.3 to 2.8)	0.99
Admitted	153	69/77 (90)	68/76 (89)		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 h	137	18/69 (26)	9/68 (13)		2.3 (1.0 to 5.4)	0.058
Discharged within 48 h	137	34/69 (49)	15/68 (22)		3.4 (1.6 to 7.0)	**0.0012**
Treated with antibiotics	137	55/69 (80)	63/68 (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)	3.6 (0.1 to 4.2)		**0.0097**
Treated with <24 h antibiotics	137	29/69 (42)	16/68 (23)		2.3 (1.1 to 5.0)	**0.021**
Treated with <48 h antibiotics	137	32/69 (46)	17/68 (25)		2.6 (1.3 to 5.4)	**0.012**
Influenza positive only						
Subjects	49	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 h	49	7/23 (30)	4/26 (15)		2.4 (0.6 to 8.2)	0.31
Discharged within 48 h	49	12/23 (52)	7/26 (27)		3.0 (0.9 to 10.0)	0.086
Treated with antibiotics	49	18/23 (78)	25/26 (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 h antibiotics	49	11/23 (48)	6/26 (23)		3.1 (0.8 to 9.5)	0.082
Treated with <48 h antibiotics	49	12/23 (52)	6/26 (23)		3.6 (1.0 to 11.2)	**0.043**
Treated with NAIs	49	23/23 (100)	24/26 (92)		4.4 (0.2 to 97)	0.34
Rhinovirus positive only						
Subjects	46	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 h	46	7/29 (24)	4/17 (24)		1.0 (0.3 to 3.6)	1.0
Discharged within 48 h	46	13/29 (45)	5/17 (29)		2.0 (0.6 to 6.6)	0.36
Treated with antibiotics	46	23/29 (79)	15/17 (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 h antibiotics	46	11/29 (38)	4/17 (22)		2.1 (0.6 to 7.0)	0.34
Treated with <48 h antibiotics	46	12/29 (41)	4/17 (24)		2.2 (0.6 to 7.6)	0.34
Safety (all patients)[#]						
ICU admission	137	1/77 (1)	3/76 (4)		0.3 (0.1 to 2.2)	0.37
Death	153	0/77 (0)	0/76 (0)			1.0
Representation to ED	153	6/77 (8)	6/76 (8)		0.5 (0.2 to 1.5)	0.21
Readmission	138	4/77 (6)	5/76 (7)		0.8 (0.2 to 2.7)	0.72

Data is presented as n, n/n (%) or mean (interquartile range) unless otherwise stated. p-Values in bold indicate statistical significance, as defined by p⩽0.05. COPD: chronic obstructive pulmonary disease; 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 inhibitor; ED: emergency department; ICU: intensive care unit; OR: odds ratio. [#]: measured for 30 days post enrolment.

ARI, the increase in premature discharge with POCT strongly suggests that even a modestly more expensive diagnostic strategy is likely to be a 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 h 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 strategy need to be explored.

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