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Impact of point-of-care testing for respiratory viruses on antibiotic use in adults with exacerbation of airways disease



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SUMMARY

Background: The ResPOC study demonstrated that syndromic molecular point-of-care testing (POCT) for respiratory viruses was associated with early discontinuation of unnecessary antibiotics compared to routine clinical care. Subgroup analysis suggests these changes occur predominantly in patients with exacerbation of airways disease. Use of molecular POCT for respiratory viruses is becoming widespread but there is a lack of evidence to inform the choice between multiplex syndromic panels versus POCT for influenza only.

Materials/methods: We evaluated patients from the ResPOC study with exacerbation of asthma or COPD who were treated with antibiotics. The duration of antibiotics and proportion with early discontinuation were compared between patients testing positive and negative for viruses by POCT, and controls. Patients testing positive for viruses by POCT were compared according to virus types.

Results: 118 patient with exacerbation of airways disease received antibiotics in the POCT group and 111 in the control group. In the POCT group 49/118 (42%) patients tested positive for viruses. Of those testing positive for viruses 17/49 (35%) had early discontinuation of antibiotics versus 9/69 (13%) testing negative and 7/111 (6%) of controls, $p < 0.0001$. Of those positive for viruses by POCT 10/49 (20%) were positive for influenza, 21/49 (43%) for rhinovirus and 18/49 (37%) for other viruses. The proportion with early discontinuation of antibiotics was not different between the virus types ($p = 0.34$).

Conclusions: This data suggests that syndromic molecular POCT for respiratory viruses should be favoured over POCT for influenza alone in adults with exacerbation of airways disease.

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Introduction

Antimicrobial resistance (AMR) is the arguably one of the greatest threats to global human health and is driven by the overuse of antibiotics.¹ Antibiotics are prescribed to the vast majority of patients hospitalised with acute respiratory illness (ARI), including in clinical groups where viruses are strongly implicated in their aetiology. Most asthma exacerbations are associated with respiratory virus infection, especially rhinovirus² and randomised controlled trials have failed to demonstrate any benefit from antibiotic treatment.^{3,4} Additionally, a large retrospective observational study of

nearly 20,000 patients hospitalised with an exacerbation suggests that antibiotic use does not improve outcome and is associated with higher costs.⁵ Professional societies strongly discourage the use of antibiotics in asthma exacerbation through national guidelines^{6,7} but despite this antibiotic use in adults hospitalised with exacerbation of asthma remains very common.^{8–10} Patients hospitalised with exacerbation of COPD are also routinely treated with antibiotics despite viruses being frequently implicated in their aetiology¹² and a lack of high quality evidence for benefit in patients with non-life threatening exacerbations.¹¹ Several randomised trials of biomarker-directed therapy show that antibiotics use can be safely reduced in non-critically ill hospitalised patients with exacerbation of COPD and low levels of CRP or procalcitonin^{13,14} supporting the concept that antibiotics are currently overused in this population. Diagnostic uncertainty regarding the aetiology of exacerbations of airways disease contributes to the ongoing overuse of antibiotics in these groups.

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The UK department of health commissioned report into antimicrobial resistance specifically noted the importance of rapid diagnostic tests to help combat AMR through effective antibiotic stewardship and recommended that by 2020 all prescribing of antibiotics should be informed by a diagnostic test where one exists.¹ Rapid molecular tests for respiratory viruses could potentially fulfil this need in patients hospitalised with exacerbation of airways disease.

The ResPOC study was a large pragmatic randomised controlled trial that evaluated the clinical impact of syndromic (i.e. comprehensive multiplex PCR) point-of-care testing (POCT) for respiratory viruses in adults presenting to hospital with acute respiratory illness.¹⁰ It demonstrated that syndromic POCT for respiratory viruses using the FilmArray Respiratory Panel was associated with several clinical benefits compared to routine clinical care with laboratory testing, including the earlier discontinuation of antibiotics, without any increase in adverse events. Subgroup analysis from the trial suggests that these antibiotic changes occurred predominantly in patients with exacerbation of airways disease testing positive for viruses, with little difference seen in antibiotic use in other clinical groups such as patients with community acquired pneumonia or in patients testing negative for viruses. Several observational studies support the findings of ResPOC, demonstrating a reduction in unnecessary antibiotics with rapid molecular testing for respiratory viruses in a variety of clinical setting.^{15,16} In addition a *post hoc* analysis from the trial itself suggests that the very rapid turnaround times for results seen with POCT compared to laboratory testing are critical in modifying antibiotic use in hospitalised patients.¹⁷

Several rapid molecular test platforms for respiratory viruses are now available with the potential for deployment as POCTs in clinical areas and their use in hospitals is becoming more widespread.¹⁸ However, there is a lack of evidence to inform clinicians and hospitals in the choice between multiplex syndromic panels such as the FilmArray RP, which test for a comprehensive range of respiratory viruses, and platforms that test for influenza only, or for influenza and RSV. Rapid, accurate influenza detection is clearly a priority for hospitals during periods of intense influenza transmission, to correctly and rapidly administer influenza antivirals and to efficiently utilise infection control facilities. In addition multiplex syndromic panels are more expensive than uniplex tests for influenza and it is not currently clear what additional clinical value is gained by testing for the other virus types in hospitalised patients.

In this further analysis we examine in detail the changes in antibiotic use associated with syndromic molecular POCT among patients with exacerbation of airways diseases, and determine the importance of changes in antibiotic management occurring due to the detection of non-influenza viruses.

Methods

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.¹⁰ In brief, adults presenting to the emergency department or acute medical unit with ARI were recruited at presentation and randomised 1:1 to receive POCT for respiratory viruses using the FilmArray Respiratory Panel or routine clinical care. The study was approved by the North West – Preston Regional Ethics Committee (NW/14/1467). The protocol is publically available.¹⁹

In this further analysis we evaluated patients with exacerbation of asthma or COPD who were treated with antibiotics. The duration of antibiotics and proportion treated with a single dose or short course (defined as less than 24 h) were compared between patients testing positive for viruses by POCT, those testing negative by

POCT and control patients. Patients testing positive for viruses by POCT were then compared according to the virus types detected. Kaplan–Meier curves were generated for duration of antibiotic use.

Clinical data

Early discontinuation of antibiotics was defined as receipt of less than 24 h of antibiotics before stopping (including those that only received a single dose). Where rhino/enterovirus was co-detected with influenza or RSV, they (influenza and RSV) were considered to be dominant and the patient was classified accordingly.

Statistical analysis

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). We compared duration of antibiotic use between groups using median differences and the Kruskal–Wallis test and differences in proportions using Chi Squared test or Fisher's exact test, as appropriate. Kaplan–Maier curves for the duration of antibiotics were generated and compared using the log rank test.

Results

There were 143 patients with exacerbation of airways disease in the POCT group (62 with asthma and 81 with COPD) and 118 (83%) of these received antibiotics. There were 140 patients with exacerbation of airways disease in the control group (57 with asthma and 83 with COPD) and 111 (79%) of these received antibiotics, difference in antibiotic use between POCT and control group of 4% (95%CI – 6 to 13%), $p=0.55$. In the POCT group 62/143 (43%) patients tested positive for respiratory viruses and 49/62 (79%) of these received antibiotics, 81/143 (57%) patients tested negative for viruses and 69/81 (85%) of these received antibiotics, difference in antibiotic use between POCT positive and negative patients of 6% (95%CI – 7 to 20%), $p=0.38$. Baseline characteristics of patients testing positive and negative by POCT and control patients were well matched including physiological observations and laboratory results. Only 48/140 (34%) patients in the control group were tested for respiratory viruses using laboratory PCR and the median turnaround time for results was 31.1 h compared with 1.6 h for those tested with POCT, $p<0.0001$, [Table 1](#).

Of those testing positive for viruses by POCT and who received antibiotics, 17/49 (35%) had early discontinuation of antibiotics versus 9/69 (13%) in those testing negative and 7/111 (6%) in control patients, $p<0.0001$. The median duration of antibiotic was 5.5 days in those testing positive by POCT versus 6.3 days in those testing negative by POCT and 6.4 days in the control group, $p=0.012$. The median duration of IV antibiotics was 1 h (i.e., a single dose) in those testing positive by POCT versus 6.5 in those testing negative and 26 h on the control group, $p=0.09$. Antibiotic use by POCT result and in control patients is shown in [Table 2](#). Kaplan–Meier curve analysis for duration of antibiotics is shown in [Fig. 1](#). Although the curves for the three groups (POCT positive, POCT negative and control) becomes similar after approximately 6 days from starting antibiotics, the curves show that there is a sharp reduction in antibiotic use early on for those testing positive for viruses by POCT, $p=0.034$.

Of those tested for viruses by POCT 12/143 (8%) were positive for influenza A or B, 26/143, (18%) positive for rhino/enterovirus and 24/143 (17%) positive for other viruses combined (RSV, parainfluenza 1–4, human metapneumovirus and human coronavirus), [Fig. 2](#). There were 4 co-detections; RSV with rhino/enterovirus×2, Influenza A with Human coronavirus, and RSV with hMPV and human coronavirus. In patients who received the POC test and

Table 1

Baseline characteristics and outcome of patients with exacerbation of airways disease, in patients testing positive and negative by POCT and in control patients.

	POCT group <i>n</i> = 143		Control group <i>n</i> = 140	<i>p</i> value
	POCT positive <i>n</i> = 62	POCT negative <i>n</i> = 81		
Age, years [range]	61 [19–93]	65 [18–93]	60 [19–92]	0.11
Male sex	21 (34)	47 (58)	69 (49)	0.75
White ethnicity	59 (95)	79 (98)	136 (97)	0.69
Current smoker	20 (30)	28 (35)	40 (29)	0.65
Influenza vaccine*	38 (61)	55 (68)	94 (67)	0.66
Duration of symptoms, days**	4 [3–6]	4 [2–6]	4 [2.3–5]	0.52
Pulse rate, bpm	103 [90–110]	95 [83–110]	100 [82–112]	0.1
Respiratory rate, bpm	25 [20–29]	24 [20–28]	24 [20–27]	0.13
Supplemental O ₂	16 (26)	19 (24)	21 (15)	0.13
Temperature, °C	36.7 [36.2–37.2]	36.6 [36.1–37]	36.6 [36.3–37.2]	0.45
CRP, mg/L	23 [9–65]	13 [4–53]	17 [6–50]	0.23
WCC, X10 ⁹ /L	10.8 [8.1–13.3]	10.6 [8.9–14.3]	10.4 [7.9–13.4]	0.31
CXR performed	62 (100)	80 (99)	137 (97)	0.34
Respiratory viral PCR	62 (100)	81 (100)	48 (34)	<0.0001
Turnaround time for result, hours	1.6 [1.3–3.0]	1.6 [1.3–3.0]	31.1 [25.1–49.2]	<0.0001
Length of stay, days	2.7 [0.9–5.3]	3.0 [0.9–5.2]	3.1 [1.3–6.5]	0.57
30 day mortality	0 (0)	2 (2.5)	2 (1.5)	0.46
Re-admission [‡]	3 (5)	21 (26)	25 (18)	0.0042

POCT, point-of-care test. CRP, C reactive protein. WCC, white cell count. CXR, chest X-ray. PCR, polymerase chain reaction.

* Influenza vaccine receipt for the current influenza season when recruited.

** Duration of illness prior to presentation. Data are presented a median [inter-quartile range] and number (%) except where stated otherwise.

[‡] Within 30 days of discharge.

Table 2

Antibiotic use in patients with exacerbation of airways disease testing positive and negative by POCT and in control patients, *n* = 143.

	POCT positive <i>n</i> = 62	POCT negative <i>n</i> = 81	Control <i>n</i> = 140	<i>p</i> value
Received any antibiotic	49/62 (79)	69/81 (85)	111/140 (79)	0.51
Received IV antibiotics	20/62 (32)	28/81 (35)	43/140 (31)	0.84
Duration of any antibiotic, days	5.5 [0–6.9]	6.3 [5.4–7.4]	6.4 [5.5–7.4]	0.012
Duration of IV antibiotic, hours	1 [1–48]	6.5 [1–62]	26 [1–72]	0.09
Received a single dose of antibiotics only	14/49 (29)	7/69 (10)	6/111 (5)	0.0001
Received <24 h antibiotics	17/49 (35)	9/69 (13)	7/111 (6)	<0.0001

POCT, point-of-care test. IV, intravenous. Data are presented a median [inter quartile range] and number (%) except where stated otherwise.

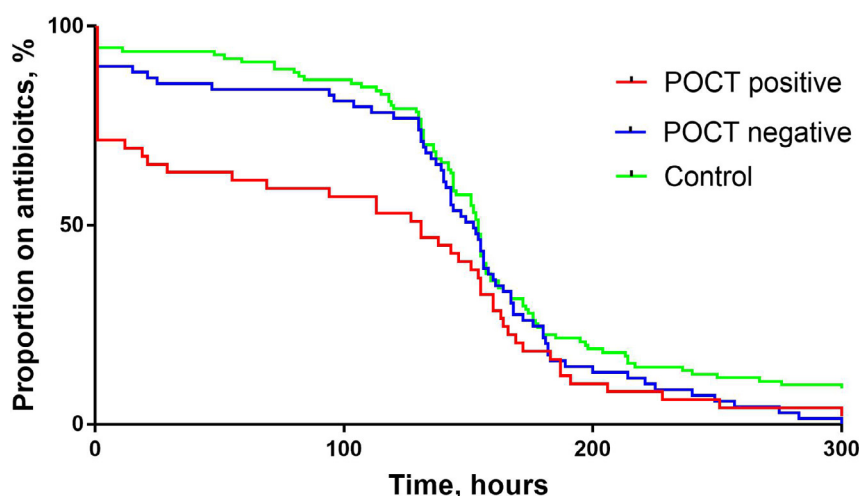


Fig. 1. Kaplan Meier curve showing antibiotic use over time in patients testing positive and negative by POCT and for control patients. Log rank test, *p* = 0.034.

had early discontinuation of antibiotics, 3/26 (11%) had influenza detected, 6/26 (23%) had rhino/enterovirus detected 8/26, (31%) had other viruses detected and 9/26 (35%) had no virus detected, Fig. 3.

Among those positive for viruses receiving antibiotics, the proportion with early discontinuation of antibiotics was not different between the virus types, 3/10 (30%) for influenza, 6/21 (29%) for

rhinovirus and 8/18 (44%) for other viruses combined, *p* = 0.54. Antibiotic use by virus type is shown in Table 3. A higher proportion of patients with influenza received IV antibiotics compared to those with rhino/enterovirus or other virus types (53% vs. 23% and 21%, *p* = 0.044) but the median duration of IV antibiotic or any antibiotic was not different between the virus types, although the small numbers of individual virus types make definitive statement

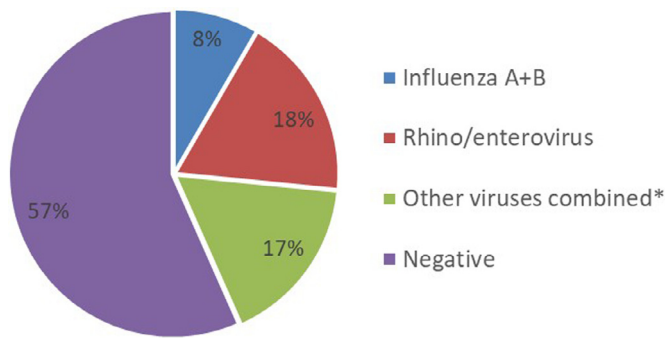


Fig. 2. Proportion of patients with viruses detected in POCT group, $n = 143$
*RSV, parainfluenza virus 1–4, human metapneumovirus, and human coronavirus.

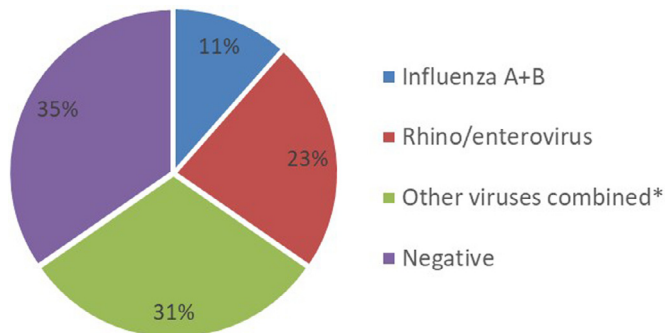


Fig. 3. Viruses detected in patients with early discontinuation of antibiotics in POCT group, $n = 26$. *RSV, parainfluenza virus 1–4, human metapneumovirus, and human coronavirus.

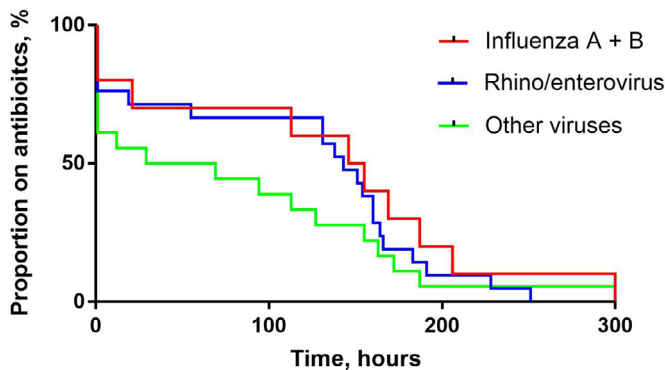


Fig. 4. Kaplan Meier curve showing antibiotic use over time for patients testing positive by POCT for influenza, rhino/enterovirus and other viruses combined (RSV, parainfluenza virus 1–4, human metapneumovirus, and human coronavirus). Log rank test, $p = 0.53$.

difficult. Survival analysis did not show any differences in early antibiotic discontinuation between virus types, $p = 0.53$, Fig. 4.

Discussion

This study shows that syndromic molecular POCT for respiratory viruses in adults presenting to hospital with exacerbation of airways disease, leads to a reduction in antibiotic use due to early discontinuation in those testing positive for viruses. Most viruses detected in these patients were non-influenza viruses with rhino/enterovirus being the most commonly detected single virus type, and there was no difference in the rate of antibiotic discontinuation between different virus types. As noted in the ResPOC study, POCT did not lead to a reduction in the proportion treated with antibiotics compared to routine clinical care however this is unsurprising as patients are started on antibiotics very early in their patient journey when admitted to hospital and this was often before the results of POCT can be made available. The reason that antibiotics are stopped early in patients with exacerbation of airways disease testing positive for viruses is unknown but is likely to be due to clinicians feeling the detection of a virus adequately explains their acute illness and giving them confidence that a bacterial infection is unlikely and no longer needs to be 'covered' with antibiotics, in combination with other data such as CRP level and radiology results.

As expected rhino/enterovirus was the most frequently detected virus in this group but the type of virus detected did not seem to influence the decision to stop antibiotics early, although as the numbers in each group were small we cannot definitively exclude a difference. This suggests that for patients with exacerbation of airways disease respiratory virus testing should be performed at the point-of-care using a comprehensive syndromic multiplex panel rather than a molecular POCT for influenza alone, which would not detect the majority of viruses associated with early antibiotic discontinuation. It could be argued that for many of the patients in the study treated with antibiotics that they should not have been treated in any case, on clinical grounds alone, given that antibiotic use in patients with asthma exacerbation is already strongly discouraged by national society guidelines. However, despite these guidelines inappropriate antibiotic use in hospitalised patients with asthma remains very common^{8–10} and diagnostic uncertainty regarding the possibility of bacterial infection, especially in the early part of hospital admission before all diagnostic information is available, is likely to be a key driver of this practice. The early provision of accurate results regarding exacerbation aetiology seems to assist in rational antibiotic decision making and is a potential alternative or complementary strategy to biomarker-directed therapy.

There are additional reasons beyond the antibiotic stewardship benefits for choosing to test using a comprehensive syndromic POCT for a range of respiratory viruses rather than with a POCT for influenza alone. Although some molecular POCT platforms for influenza have diagnostic accuracy comparable to laboratory PCR, others have demonstrated inferior sensitivity in non-industry sponsored, real world studies²⁰ potentially reducing their usefulness in the hospital setting where missed diagnoses have serious

Table 3

Antibiotic use in patients with exacerbation of airways disease testing positive by POCT, according to virus type, $n = 62$.

	Influenza A or B $n = 12$	Rhino/enterovirus $n = 26$	Other viruses Combined* $n = 24$	p value
Received any antibiotic	10/12 (83)	21/26 (81)	18/24 (75)	0.42
Received IV antibiotic	7/12 (58)	6/26 (23)	5/24 (21)	0.044
Duration of antibiotics, days	6.3 [0.7–8.0]	6.0 [0.4–6.9]	2.0 [0–6.5]	0.25
Duration of IV antibiotic, hours	1 [1–68]	30 [1–91]	1 [1–28]	0.26
Received a single dose of antibiotics only	2/10 (20)	5/21 (24)	7/18 (39)	0.46
Received <24 h antibiotics	3/10 (30)	6/21 (29)	8/18 (44)	0.55

IV, intravenous. Data are presented a median [inter quartile range] and number (%) except where stated otherwise.

* Respiratory syncytial virus (RSV), parainfluenza viruses 1–4, human metapneumovirus and human coronaviruses.

consequences including nosocomial transmission of influenza. Although influenza may represent a priority for hospital infection control teams during peak influenza season, the detection of other respiratory viruses is also important for infection control purposes as other viruses also pose a serious risk of nosocomial transmission and outbreaks, which are especially dangerous to immunocompromised patients in certain high risk areas such as haematology wards and renal units. In some hospitals a two-step testing process is adopted where a patient with a negative influenza POCT is then tested using a multiplex laboratory PCR, increasing costs and prolonging the time before result are available compared with a comprehensive syndromic POCT. Regulatory consideration are also important and rapid diagnostic platforms may not be able to be used at the POCT in certain countries due to regulatory requirements, for example the current FilmArray system is not fully CLIA waived in the US. A further significant consideration is obviously the higher cost associated with syndromic panels versus molecular POCT for influenza and there is clearly a need for health economic studies to provide evidence for the cost effectiveness of such an approach considering the incremental benefits of syndromic testing.

A lower rate of re-admission was seen in those testing positive for viruses versus those testing negative or control patients. The reason for this is not clear but it may be that non-viral exacerbations have a higher rate of subsequent exacerbations or even that clarity around the aetiology of exacerbation may reduce readmission.

Although the ResPOC study is the only published randomised controlled trial of syndromic respiratory virus testing at the point-of-care, other non-randomised, pre and post intervention studies have suggested similar benefits from rapid syndromic respiratory virus testing in terms of reducing unnecessary antibiotic use, in both paediatric and adults patients presenting to hospital.^{15,16}

The strengths of this study include the randomised nature of the parent study, the large overall cohort of patients studied and the pragmatic nature with broad generalisability to other UK and international centres. Its limitations include being a single-centre trial and the relatively small numbers of patients with asthma and COPD with each respiratory virus detected. Although it is likely to be generalisable to other centres we cannot rule out that the changes seen are dependent on the processes of care in UK hospitals. It is also currently uncertain as to how molecular POCT for respiratory viruses should be best 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 staffed by technicians and located within, or close to, acute areas.²¹

In conclusion syndromic molecular POCT for respiratory viruses in adults with exacerbation of airways disease is associated with early discontinuation of unnecessary antibiotics in those testing positive for viruses. Most viruses detected were non-influenza viruses and there was no difference in antibiotic discontinuation between different virus types. These results suggest that syndromic molecular POCT for respiratory viruses should be favoured over POCT for influenza alone in adults with exacerbation of airways disease.

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Competing interests

All authors declare that they have no conflicts of interests.

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