# TITLE PAGE

**Title**: UK clinicians' attitudes towards the application of molecular diagnostics to guide antibiotic use in ICU patients with pneumonias: A quantitative study

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## SYNOPSIS

**Background**: Molecular diagnostic tests may improve antibiotic prescribing by enabling earlier tailoring of antimicrobial therapy. However, clinicians' trust and acceptance of these tests will determine their application in practice.

**Objectives**: To examine ICU prescribers' views on the application of molecular diagnostics in patients with suspected hospital-acquired and ventilator-associated pneumonias (HAP/VAP).

**Methods**: Sixty-three ICU clinicians from 5 UK hospitals completed a cross-sectional questionnaire between May-July 2020 assessing attitudes towards using molecular diagnostics to inform initial agent choice and to help stop broad-spectrum antibiotics early.

**Results**: Attitudes towards using molecular diagnostics to inform initial treatment choices and to stop broad-spectrum antibiotics early were nuanced. Most (83%) were positive about molecular diagnostics, agreeing that using results to inform broad-spectrum antibiotics prescribing is good practice. However, many (58%) believed sick patients are often too unstable to risk stopping broad-spectrum antibiotics based on a negative result.

**Conclusions**: Positive attitudes towards the application of molecular diagnostics to improve antibiotic stewardship were juxta-positioned against the perceived need to initiate and maintain broad-spectrum antibiotics to protect unstable patients.

**Abstract word coun**t: 170/250

## INTRODUCTION

Rapid molecular diagnostic tests, such as the FilmArray Pneumonia Plus Panel (bioMérieux) ('Pneumonia Panel')[1] might support clinicians' antibiotic prescribing and promote stewardship by enabling earlier tailoring of patients' antimicrobial therapy. These tests can accurately detect multiple respiratory pathogens and antimicrobial resistance genes directly from respiratory secretions, with results in 1-6hrs compared with the current, culture-based, turnaround of 48-72hrs.[2,3]

Antibiotic prescribing in ICU is complex, where antibiotic decisions are often made under diagnostic uncertainty with high-stake consequences. Poor laboratory sensitivity in terms of pathogen recovery and a *circa* 48-72hr delay between specimen receipt and result exacerbate these challenges.[2] One recent qualitative study highlighted that ICU clinicians often face two competing, and sometimes contradictory, imperatives: at the personal level, the need to protect the patient and the prescriber against the consequences of not prescribing, versus at the societal level, concerns about antimicrobial resistance.[4] Clinical uncertainty complicated these decisions, whereby clinicians often defaulted to prescribing broad-spectrum antibiotics 'just in case' of infection, to 'err on the side of caution'.

Although molecular diagnostic platforms could support clinicians with complex prescribing decision-making, little is known about clinicians' perceptions of these tests, and the drivers and barriers towards their application particularly around two key behaviours: i) the initial choosing of an antibiotic, and ii) stopping a broad-spectrum antibiotic early. Emerging research suggests clinicians' views about these tests are complex and that although clinicians were open to using molecular diagnostic technology as a prescribing decision aid, trust and acceptance of these tests can be low.[5]

The UK Department of Health and Social Care identified a 'lack of engagement to understand frontline needs' as a potential barrier to the clinical adoption of molecular tests.[6]

This study seeks to address this by assessing: What are clinicians' attitudes towards using rapid molecular diagnostics as an antibiotic prescribing decision aid for suspected hospital-acquired and ventilator-associated pneumonias (HAP/VAP) ICU patients?

## MATERIALS AND METHODS

This research is part of the INHALE research programme (ISRCTN16483855), investigating the utility of molecular diagnostics to improve antimicrobial prescribing for ICU patients with suspected HAP/VAP (see trial protocol[7]). The INHALE RCT was paused during the COVID-19 pandemic's first wave, and a microbiological sub-study was conducted at five INHALE sites examining the utility of the FilmArray Pneumonia Plus Panel ('Pneumonia Panel') test for investigating possible secondary infection in ICU patients with COVID-19. See Table S1 for organisms detected by the 'Pneumonia Panel'.

### Sample and setting

All five ICUs participating in INHALE's COVID-19 microbiological sub-study were included; four National Health Service (NHS) teaching hospitals, and one NHS general hospital; all in England. Intensivists and microbiologists involved in the treatment of ICU patients with suspected HAP/VAP and COVID-19 were eligible to participate. Research nurses administered the questionnaire to clinicians at opportune times (e.g., end of shift). Data collection occurred between May and July 2020.

### Questionnaire design

Clinicians completed a questionnaire capturing demographic data and their views about the application of rapid molecular diagnostics for ICU patients with HAP/VAP ('Pneumonia Panel') both as a tool to *i) inform the initial choice of agent* (reliability $\alpha$=.64; 5 items: e.g., "I prefer NOT to run a molecular diagnostic test on all patients before prescribing a broad-spectrum antibiotic"), and *ii) to stop broad-spectrum antibiotics early* (reliability

$\alpha$=.85; 5 items: e.g., "It is too risky to stop a broad-spectrum antibiotic based on a negative molecular diagnostic result").

One item was included to probe a practical limitation of the diagnostic: "Lack of sputum often prevents rapid molecular diagnostic tests, where these are clinically indicated".

**Data analysis**

To assess clinicians' views about using molecular diagnostics for ICU, frequency counts and percentages for each scale item were calculated for patient cases with and without COVID-19. Mean scores were calculated for attitudes towards applying molecular diagnostics ('Pneumonia Panel') as a tool to *i) inform the initial choice of agent* and ii) *stop broad-spectrum antibiotics early*. Differences between clinicians' views about the application of molecular diagnostics for patients in ICU with and without COVID-19 infection were compared using McNemar's tests and paired samples t-tests.

## RESULTS

63/197 questionnaires were completed (32% response rate). Participants were ICU consultants (*n*=31, 49.2%); middle-grade ICU trainees (*n*=9, 14.3%), early-grade ICU trainees (*n*=7, 11.1%), consultant clinical microbiologists (*n*=8, 12.7%), other clinicians (*n*=6, 9.5%,), and two clinicians who did not specify their hospital, grade and specialty (3.2%). See Table S2 for an overview of participant characteristics, and Table S3 for additional demographic data.

### Attitudes towards the application of rapid molecular diagnostics ('Pneumonia Panel') as an aid to prescribing broad-spectrum antibiotics in ICU (Table 1, Figure 1)

i) *Attitudes towards the application of the 'Pneumonia Panel' as a tool to inform the initial choice of antibiotic*

Most clinicians endorsed the value of molecular diagnostics, however, many were hesitant about using them to inform the initial choice of antibiotic (Table 1). For example, 40.4%, (*N*=21) agreed it was "NOT too risky to wait more than 24 hours for a test result".

*Attitudes towards the application of the 'Pneumonia Panel' as a tool to stop broad-spectrum antibiotics early*

Clinicians' attitudes towards using the 'Pneumonia Panel' test to guide the early stopping of broad-spectrum antibiotics were nuanced. As can be seen from Table 1, over half believed that "sick patients are often too unstable to risk stopping broad-spectrum antibiotics based on a negative rapid molecular diagnostic result" (66.0%, *N*=35), and that "it is too risky to stop a broad-spectrum antibiotic, based on a negative molecular diagnostic result, if the patient is still clinically unwell" (63.3%, *N*=31).

Clinicians' views about applying molecular diagnostics did not significantly differ at the scale- or individual-level (all $p>.05$) for patients with and without COVID-19.

## DISCUSSION

Attitudes towards using molecular diagnostics in ICU were nuanced. Most clinicians saw potential in molecular diagnostics, perceiving their value in aiding the selection of early antibiotics – consistent with previous research suggesting this technology might assist the optimisation of antimicrobial therapy.[3,5] However, many were hesitant to use them to help inform the initial choice of antibiotics. Our findings identified an apparent tension between ideas about best practice and the clinical application of these tests to inform treatment of ICU patients. Most clinicians had concerns about their application to stop broad-spectrum antibiotics early, deeming it too risky. These findings corroborate and reinforce the findings of qualitative studies showing that initiating and continuing broad-spectrum antibiotic prescriptions often reflect a desire to protect both patent and clinician by *erring on the side of caution*.[4]

Findings suggest there is uncertainty about the place of these tests in practice. Prior research has identified a number of factors that may affect the uptake of molecular diagnostics, such as misapprehensions and uncertainty about test capabilities, leading to a lack of trust in this technology.[5] Uncertainties around the nature (e.g., viral, bacterial, non-microbial) and primary focus (e.g., lung, central line, abdominal) of the pathology driving a patient's 'septic state'[8] may also undermine clinicians' confidence in molecular tests performed on one sample site.

### Limitations

Study recruitment was challenging given clinical pressures during the COVID-19 pandemic. Given 5/10 adult sites were able to participate and only 1/3 of eligible clinicians at these sites completed questionnaires, it is possible our sample was not representative. Further, survey responses may reflect what clinicians thought 'ought to be done' rather than their actual prescribing practice.

## Study implications

The varied nature of clinicians' views identified in this study emphasises the clinical complexity of ICU and prescribing decisions. Molecular diagnostic technologies offer the potential for improving prescribing practices. However, our findings illustrate the unique challenges facing the adoption of these tests into ICU settings, with unanswered questions regarding the place and suitability of these tests in clinical practice.

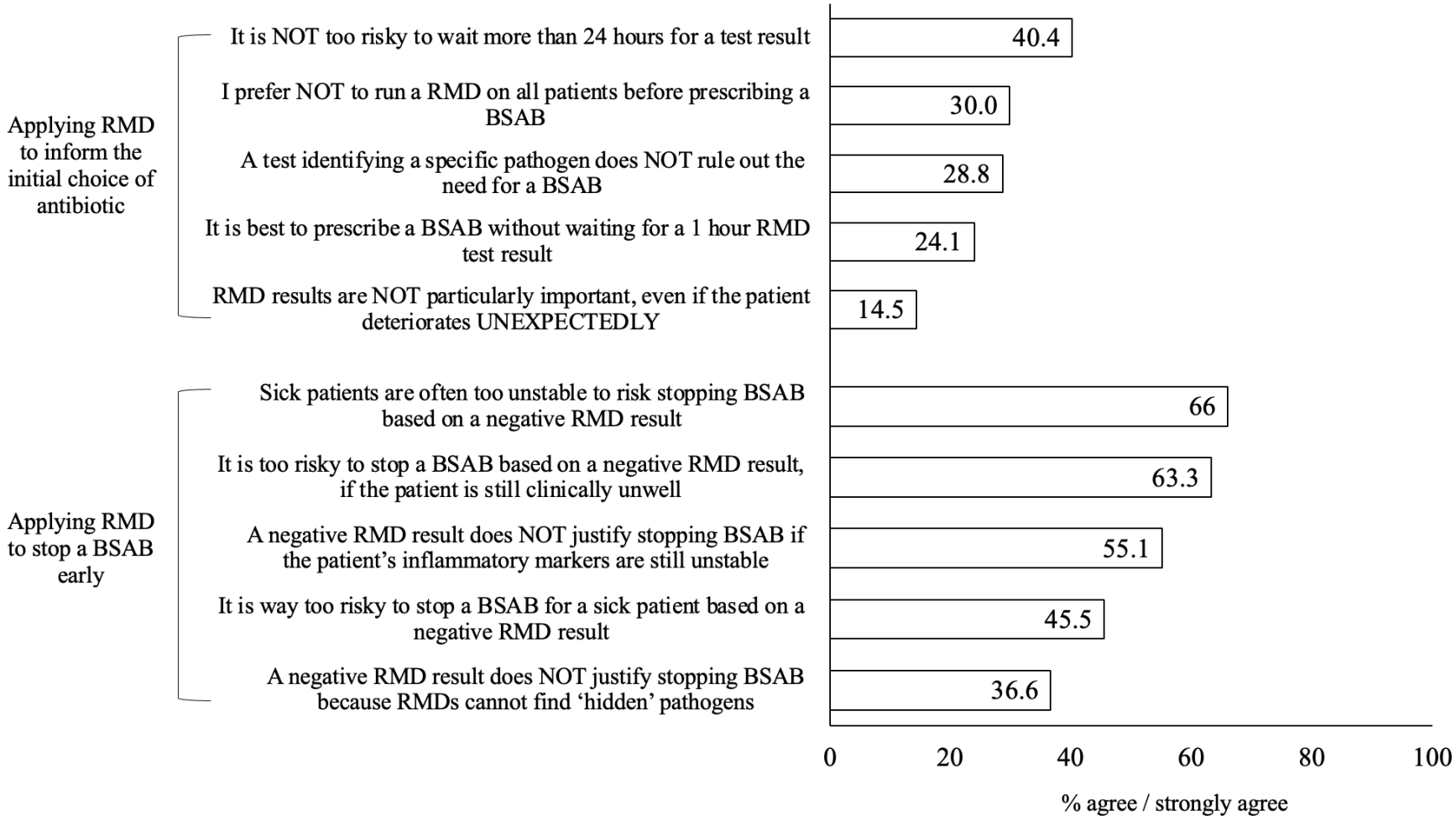
Findings suggest a disconnect between theory and practice. Most clinicians agreed that molecular diagnostics have the potential to improve patient care and antibiotic stewardship, in principle. However, their application in practice was more nuanced. Here, many clinicians perceived the value of molecular diagnostics in informing the initiation of antibiotics, and continuation was juxta positioned against the perceived need to prescribe broad-spectrum antibiotics early and continue with treatment, even when test results supported curtailment. Often, the perceived need to continue was linked to the belief that it would be too risky to stop broad-spectrum antibiotics if the patient remained clinically unwell or appeared unstable. These clinicians appeared to be balancing the technological information against their instincts derived from clinical experience: an apparent conflict between the science and the art of medicine.

## Conclusion

Clinicians' views about using molecular diagnostics to support antibiotic prescribing decisions for ICU patients with HAP/VAP were nuanced. Positive attitudes towards the application of molecular diagnostics to improve antibiotic stewardship were juxta-positioned against the perceived need to initiate and maintain broad-spectrum antibiotics to protect unstable patients.

**Figure 1.**

*Clinicians' agreement with attitudes towards the application of rapid molecular diagnostics (RMD; 'Pneumonia Panel') as a tool to inform the initial choice of antibiotic and to stop a broad-spectrum antibiotic (BSAB) early*



206 **Table 1.**

207 *Clinicians' attitudes towards the application of rapid molecular diagnostics (RMD; 'Pneumonia Panel')*

| | ***Yes*** | ***No*** | ***Don't know*** |
|---|---|---|---|
| **Attitudes towards applying rapid molecular diagnostics (RMD) as a tool to guide the initial choice of antibiotic** | | | |
| It is NOT too risky to wait more than 24 hours for a RMD test result | 21 (40.4%) | 30 (57.7%) | 1 (1.9%) |
| I prefer NOT to run a RMD on all patients before prescribing a BSAB | 15 (30%) | 33 (66%) | 2 (4%) |
| A test identifying a specific pathogen does NOT rule out the need for a BSAB | 15 (28.8%) | 33 (63.5%) | 4 (7.7%) |
| It is best to prescribe a BSAB without waiting for a 1-hour RMD test result | 13 (24.1%) | 40 (74.1%) | 1 (1.9%) |
| RMD results are NOT particularly important, even if the patient deteriorates UNEXPECTEDLY | 8 (14.5%) | 45 (81.8%) | 2 (3.6%) |
| **Attitudes towards using RMD as a tool to stop BSAB early** | | | |
| Sick patients are often too unstable to risk stopping BSAB based on a negative RMD result | 35 (66%) | 18 (34%) | 0 |
| It is too risky to stop a BSAB, based on a negative RMD result, if the patient is still clinically unwell | 31 (63.3%) | 16 (32.7%) | 2 (4.1%) |
| A negative RMD result does NOT justify stopping BSAB if the patient's inflammatory markers are still unstable | 27 (55.1%) | 20 (40.8%) | 2 (4.1%) |
| It is way too risky to stop a BSAB for a sick patient based on a negative RMD result | 20 (45.5%) | 20 (45.5%) | 4 (9.1%) |
| A negative RMD result does NOT justify stopping BSAB because RMD cannot find 'hidden' pathogens | 15 (36.6%) | 21 (51.2%) | 5 (12.2%) |
| **Practical limitations with applying RMD** | | | |
| Lack of sputum often prevents RMD tests where these are clinically indicated | 27 (60%) | 16 (35.6%) | 2 (4.4%) |

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209 *Note*. Clinicians responded to the above statements for patient cases both with and without COVID-19. There were no significant differences
210 between clinicians' beliefs for COVID-19 and non-COVID-19 cases (all $p>.05$), so responses for non-COVID-19 cases are reported here.
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**Transparency declaration**

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UCL-Business company (Spoonful of Sugar Ltd) providing consultancy on treatment engagement and patient support programmes to healthcare policy makers, providers and pharmaceutical industry.

ZM has undertaken paid work for UCL-Business company Spoonful of Sugar Ltd.

DML reports personal fees from Accelerate, Allecra, Antabio, Astellas, Beckman Coulter, bioMérieux, Cepheid, Centauri, Entasis, Johnson & Johnson, Meiji, Melinta, Menarini, Mutabilis, Nordic, ParaPharm, QPEX, Roche, Shionogi, Tetraphase, Wockhardt, 471 Zambon, Cardiome, and Eumedica. He also reports grants and personal fees from VenatoRx; personal fees and other (shareholder) from GlaxoSmithKline; personal fees and other (stock options) from T.A.Z.; grants, personal fees, and other (shareholder) from Merck/MSD and Pfizer; other (shareholder) from Perkin Elmer and Dechra. He also has nominated holdings in Avacta, Byotrol, Destiny, Diaceutics, Evgen, Faron, Fusion Antibodies, Genedrive, Hardide, Renalytics, Scancell and Synairgen (all of which have research/products pertinent to medical and diagnostic innovation) through Enterprise Investment Schemes but has no authority to trade these shares directly. All are outside the submitted work.

VG reports receiving speaking honoraria from bioMérieux and support for conference attendances from Merck/MSD and Gilead, outside the submitted work.

Other authors have no potential conflicts of interest.

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

## Ethics approval

This research received ethical approval from the London - Brighton & Sussex Research Ethics Committee (19/LO/0400). This research used implied informed consent to minimise clinical disruption.

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