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Review

Rapid syndromic molecular testing in pneumonia: The current landscape and future potential

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SUMMARY

Community acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) and ventilator associated pneumonia (VAP) are all associated with significant mortality and cause huge expense to health care services around the world. Early, appropriate antimicrobial therapy is crucial for effective treatment. Syndromic diagnostic testing using novel, rapid multiplexed molecular platforms represents a new opportunity for rapidly targeted antimicrobial therapy to improve patient outcomes and facilitate antibiotic stewardship. In this article we review the currently available testing platforms and discuss the potential benefits and pitfalls of rapid testing in pneumonia.

Introduction

Lower respiratory tract infections were accountable for an estimated 2.7 million deaths in 2015, making them the third most common cause of death worldwide[1]. Community acquired pneumonia (CAP) caused nearly 30,000 deaths in England and Wales in 2015[2] and costs Europe around €10 million annually[3]. It is estimated that 25 per 10,000 adults are hospitalised with pneumonia each year[4].

Hospital acquired pneumonia (HAP) is defined as occurring >48 h after admission to a healthcare facility. It is caused by a different spectrum of more antibiotic resistant bacterial pathogens than those occurring in the community. Ventilator associated pneumonia (VAP) is defined as occurring >48 h after intubation for invasive artificial ventilation. The two entities combined (HAP and VAP) are the most common nosocomial infection in the developed world[5] with HAP complicating around 2% of hospital admissions[6].

The incidence of VAP in intubated patients is around 10%[7] and is associated with mortality of around 10%[8]. A retrospective matched cohort study by Kollef et al.[9] found patients who developed VAP were intubated for longer, spent longer on ICU, and were in hospital for a greater period of time. They estimated the additional cost of VAP from to be $40,000 per patient.

Large amounts of empirical 'broad spectrum' antibiotics are used to treat pneumonia which inadvertently promote antimicrobial resistance (AMR): a problem identified by the WHO as one of the leading threats to global health today. The O'Neill report, commissioned by the UK government in 2014, has highlighted the need for developed nations to take a lead in tackling AMR. As part of this there is a specific recommendation that all antibiotic prescriptions should be supported by diagnostic tests where available by 2020[10]. The UK government recently published a five-year action plan for tackling AMR, which emphasised the need for improved diagnostics to support antibiotic prescribing. This included a target to be able to report the percentage of antimicrobial prescriptions which are supported by a diagnostic test or decision making tool by 2024[11].

Timely administration of appropriate antibiotics is a central tenant of care for patients with pneumonia[12,13] and yet the gold-standard for microbiological diagnosis remains traditional, slow, culture based methods. These take greater than 24 h to identify an organism and often greater than 72 h to provide phenotypic antibiotic sensitivity data. Culture is insensitive, only detecting a pathogen in 23–40% of patients with clinically diagnosed pneumonia[4,14–16] and an even smaller proportion after the administration of antibiotics.

In recent years several rapid syndromic molecular tests for pneumonia have been developed. These offer the potential to revolutionise treatment by providing information to clinicians in 'real-time' on the pathogens present and their likely antibiotic

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sensitivity by also detecting genotypic markers of resistance. Multiple studies have demonstrated the superior diagnostic accuracy of PCR based platforms for detecting bacterial pathogens in the sputum compared with standard culture[16–19]. This review will discuss the commercially available syndromic molecular panels for pneumonia, their potential clinical impact and the challenges to implementing them as a 'front line' diagnostic test.

Potential clinical impact of rapid pathogen detection in pneumonia

Directed antibiotic use

The greatest potential clinical benefit of a rapid syndromic test for pneumonia is being able to better utilise antibiotics. The superior diagnostic yield of multiplex PCR means that a pathogen is detected rapidly in a much greater proportion of patients, so therapy can be quickly tailored to the responsible organism. In some situations, this will allow narrowing of antimicrobial therapy: for example, identification of *Streptococcus pneumoniae* facilitating a change of antibiotics to penicillin, in geographical areas with a low prevalence of penicillin resistant *S. pneumoniae*. In other cases, it may facilitate a change or escalation of antimicrobial therapy: for example, the identification of methicillin resistant *Staphylococcus aureus* (MRSA) which would not be covered by empirical regimens in many areas. The absence of detection is also helpful: the sensitivity when compared to culture of molecular assays is very high so can reassure clinicians that organisms are not present and so support decisions to stop unnecessary antibiotics or to deescalate antibiotics that were used empirically to cover organisms subsequently not detected.

The impact of this improved use of antibiotics are twofold: firstly, earlier appropriate antibiotics should improve clinical outcomes including mortality and length of stay. Secondly, it prevents unnecessary broad-spectrum antibiotic use, which facilitates antibiotic stewardship and reduces antibiotic related adverse events.

The aetiology of CAP and HAP/VAP are highly variable between different regions and times, and this is reflected in studies of causative microbial agents as identified by culture. Patients with underlying lung diseases, for example chronic obstructive pulmonary disease, can be colonised with microbial flora which are more typical pathogens of HAP. As a result, they may develop community acquired infections caused by these agents.

S. pneumoniae, Haemophilius influenzae, S. aureus, Moraxella catarrhalis and 'atypical' organisms including *Mycoplasma pneumoniae* and *Legionella pneumophila* are all cultured from the sputum of patients with CAP. Many of these organisms have predictable resistance patterns when interpreted with local epidemiological data. Gadsby et al. developed and internally validated their own syndromic molecular assay for pneumonia. They used this to test sputum samples of 323 adults admitted to hospital with CAP[16]. Their assay detected a pathogen in 87% of patients (as opposed to 39% of patients using only routine culture). As a result, they proposed that 77% of antibiotic prescriptions in CAP could have been deescalated based on results from multiplex PCR testing. The majority of these potential interventions involved stopping clarithromycin when atypical organisms were not detected or 'narrowing' antibiotics when a likely sensitive pathogen had been detected.

In HAP and VAP, frequently cultured bacterial pathogens include *S. aureus, Pseudomonas aeruginosa, Klebsiella* species, *Escherichia coli, Acinetobacter* species and *Enterobacter* species[20]. Empirical regimens are therefore broad spectrum and large numbers of antibiotics are consumed. The absence of certain organisms (for example *P. aeruginosa*) could facilitate a narrowing of the antimicrobial spectrum with a knock-on effect of reducing antibiotic related adverse effects and improving stewardship. Furthermore, common Gram negative isolates are increasingly resistant in pneumonia surveillance studies[21]. Rapid molecular detection of these resistance genes should facilitate earlier initiation of effective antibiotics and this should lead to better outcomes.

Treatment of other infective agents

In adults, respiratory viruses are found in approximately one third of community acquired pneumonia cases[4,22]. One study found that 36% of patients admitted to intensive care with pneumonia were positive for a respiratory virus, with a broad range of viruses detected[23]. Detection of certain viruses such as influenza and adenovirus which are known to cause pneumonia, coupled with the absence of detection of bacteria and low levels of serum biomarkers such as procalcitonin (which is elevated in patients with bacterial infection), could support decisions to stop or use an abbreviated course of antibiotics. The ResPOC trial was a pragmatic randomised controlled trial that tested patients with community acquired acute respiratory illness using the BioFire Respiratory Panel (which tests comprehensively for respiratory viruses and atypical bacteria) at the point-of-care. It found that patients who were tested with the FilmArray were significantly more likely to receive a single dose or shorter course of antibiotics[24] than those who were not. It also found a significant reduction in length of hospital stay in the intervention group along with improved use of neuraminidase inhibitors (NAI) in patients with influenza.

Currently there are no licenced antiviral agents for respiratory viruses other than influenza. The benefit from NAI treatment is greatest when they are started within 48 h of symptom onset but there is evidence in adults to suggest ongoing benefit when started beyond this time[25] and a recent study suggests that treatment earlier in admission to hospital improves outcome irrespective of overall duration of illness[26]. As such, timely identification and treatment is critical. Antiviral treatments for other respiratory viruses, including respiratory syncytial virus (RSV) are in development.

Infection control and public health

Since the 1990s infection control methods including patient source isolation and deep cleaning with targeted decolonisation have been highly successful at reducing the spread of MRSA. Enhanced infection control practices are recommended for a number of pathogens that may be present in patients with pneumonia. Early identification of these should reduce the spread of these organisms, especially in hospitalised patients. Some examples of these which are found on commercially available molecular tests are extended spectrum beta lactamases (ESBLs), carbapenemase producing enterobacteriaceae (CPEs), MRSA, Influenza and RSV.

In the UK there is a mandatory requirement to report certain infectious diseases to Public Health England, so they can be investigated. *L. pneumophilia* is associated with outbreaks from devices that aerosolize water. There were 532 cases in the UK in 2018[27], earlier sensitive detection of these would allow outbreak investigation to occur sooner and potentially stop further cases occurring.

Syndromic molecular tests for pneumonia

At the current time there are 2 FDA approved, CE marked syndromic molecular panels for pneumonia which are commercially available: the Filmarray (Biofire diagnostics LLC, Salt Lake City, Utah, US) Pneumonia panel and the Unyvero (Curetis GmbH, Holzgerlingen, Germany) Hospitalised Pneumonia (HPN) panel. Fast Track Diagnostics respiratory panel 33 (Fast Track Diagnostics SARL, Luxembourg) is another available platform with a large number of targets, but insufficient bacterial targets for it to be considered a

Table 1
Commercially available pneumonia syndromic tests.

Panel	Turn-around time (Hands on)	Targets	Comments	Refs
BioFire FilmArray Pneumonia panel[29]	75 min (5 min)	• 15 Bacterial (Semi-quantitative) • 3 Atypical bacteria • 8 Resistance genes • 8 Viruses	• CE marked, FDA approved • Potentially deployable as point-of-care test[1] • Semi-quantification (Genome copies)	[30–32,34]
Curetis Unyvero Hospitalised Pneumonia panel (HPN)[35] (formerly P55 and P50)	5 h (5 min)	• 17 Bacterial • 3 Atypical bacterial • 1 Fungal (*Pneumocystis jirovecii*) • 19 Resistance genes	• CE marked, FDA approved equivalent LRT panel (latter only validated on ET aspirates) • Very extensive range of resistance genes • No viral targets	[17,37–39,41,42,44]
FTD Respiratory Pathogens 33[43]	Platform dependant[2] (>6 h)	• 8 Bacterial • 4 Atypical bacterial • 20 Viruses • 1 Fungal (*Pneumocystis jirovecii*)	• CE marked • Laboratory based • Insufficient bacterial targets for true pneumonia panel: lacking critical Gram negative targets • Not automated • No resistance targets • Qualitative only	[18]

[1] Not CLIA wavered in the US.
[2] Validated on Applied Biosystems® 7500 and NucliSENS® easyMag®, other platforms are compatible.

true pneumonia panel so this will only be considered in brief. The commercially available platforms are summarised in Table 1.

The authors are aware of further panels in development from Mobidiag, Bruker, Accelerate and Axo Science[28] but published data is only available for the latter. There are also several research groups who have developed their own syndromic molecular pneumonia tests, most notably Gadsby et al[16].

There are a multitude of other 'respiratory pathogen' multiplex panels which have targets only for respiratory viruses, atypical bacterial targets or a very small range of typical bacteria. These are beyond the scope of this review article. We have only included assays with targets for a wide range of typical pathogens for pneumonia.

BioFire Filmarray Pneumonia panel[29]

This is an FDA approved and CE marked platform that uses nested real-time PCR to detect 34 clinically important respiratory targets (15 semi-quantitative bacterial targets, 3 qualitative atypical bacterial targets, 8 resistance genes and 8 viral targets). The semi-quantitative bacterial targets are *S. pneumoniae, H. influenzae, M. catarrhalis, S. aureus, Streptococcus pyogenes, Streptococcus agalactiae, P. aeruginosa, E. coli, Enterobacter cloacae complex, Acinetobacter calcoaceticus-baumanii complex, Klebsiella aerogenes, K. oxytoca, K. pneumoniae* group, *Proteus* species and *Serratia marcescens*. The qualitative bacterial targets are *Chlamydia pneumoniae, L. pneumophilia* and *M. pneumoniae*. Resistance gene targets are 5 carbapenemases (bla_{KPC}, bla_{NDM}, bla_{OXA-48}, bla_{VIM}, bla_{IMP}), one ESBL (bla_{CTX-M}) and two MRSA genes (*mecA/C* and *MREJ)*. The viral targets are *Influenza A, Influenza B, Rhinovirus/Enterovirus, Adenovirus, RSV, Coronavirus*, human *Metapneumovirus*, and *Parainfluenza* viruses (types 1, 2, 3 and 4). The assay is validated on several sample types; sputum (including expressed sputum), bronchoalveolar lavage fluid and endotracheal aspirates. Sample preparation takes 5 min and the test has a run time of around an hour and 15 min. A Pneumonia *plus* panel is also available which has an additional *Middle-Eastern Respiratory Syndrome Coronavirus* (MERS CoV) target.

The negative percent agreement (NPA) is the specificity of a test when compared to a non-reference standard. Some authors use this when reporting results *in lieu* of specificity as a result of the imperfect nature of current diagnostics. The NPA of bacterial detection between culture-based methods and the FA pneumonia panel varies between different organisms but is consistently very high. In the manufacturers dataset only two organisms on the panel have an NPA below 95%: *H. influenzae* (91.4% [95% CI 89.3–93.1%]) and *S. aureus* (91.2% [95% CI 89.1–93.0%])[30–32] Furthermore, the pneumonia panel detects pathogens in a much higher proportion of samples than culture. Buchan et al[31] reported that the Filmarray detected a bacterial target in 71% more specimens than routine culture, equating to over 100% increase in total bacterial detections.

The relative abundance of organism for the 15 bacterial targets is estimated based on real-time PCR relative to a material of known quantity and is grouped for reporting into bins. These represent approximately 10^4, 10^5, 10^6 and $>10^7$ genomic copies of bacterial nucleic acid per millilitre of specimen respectively. Concordance with reference molecular testing is very high[33] but as expected the overall concordance between bin and reference sputum culture (CFU/ml) concentration was lower at around 40%[29] and was highly variable between organisms. As such the manufacturer advises clinical correlation in interpretation of semi-quantitative results.

To date there have been no published prospective interventional studies evaluating the clinical impacts of using the pneumonia panel in patients with pneumonia. Observational data based on lower respiratory tract assays which preceded the final, FDA approved pneumonia panel suggested change of antibiotics could be supported in >50% of cases[31,34].

Curetis Unyvero Hospitalised Pneumonia (HPN) panel (formerly P55: LRT panel in USA)[35]

The HPN panel is CE marked and runs on the Unyvero platform which includes the Unyvero Lysator, the Unyvero Cockpit and the Unyvero analyzer. Amplicons generated by 8 parallel multiplex PCR reactions are qualitatively detected by hybridisation on arrays in a single use cartridge. It has a wide range of bacterial and resistance gene targets including 29 pathogens and 19 resistance genes. The bacterial targets are *S. pneumoniae, S. aureus, Citrobacter freundii, E. coli, E. cloacae complex, E. aerogenes, Proteus species, K. pneumoniae, K. oxytoca, K. variicola, S. marcescens,*

Morganella morganii, M. catarrhalis, P. aeruginosa, A. baumanii complex, Stenotrophomonas maltophilia, L. pneumophilia, H. influenzae, C. pneumoniae, and *M. pneumoniae*. Resistance gene targets are: bla_{KPC}, bla_{NDM}, bla_{OXA-23}, bla_{OXA-24}, bla_{OXA-48}, bla_{OXA-58}, bla_{VIM}, bla_{IMP}, bla_{CTX-M}, bla_{SHV}, bla_{TEM}, *sul1, ermB,* GyrA83 and GyrA87 for *E. coli* and *P. aeruginosa, mecA/C*. There is one fungal target (*Pneumocystis jirovecii*).

The assay is validated for use on sputum (including expectorated sputum, BAL and ET aspirate). Like the FilmArray, the Unyvero is a platform designed as a 'sample-to-answer' solution taking 5 min of low skill hands-on time with a total turnaround time of 4–5 h. An equivalent test, the lower respiratory tract panel (LRT) has FDA approval in the US but is only validated for use on tracheal aspirates.

Manufacturer reported diagnostic sensitivity for bacterial detection (when compared to reference culture and molecular detection in cases of discrepancy) is between 80 and 100% with the majority of targets >90%: the exceptions are *A. baumanii complex* (88.9%), *K. pneumoniae* (80%) and *S. marcescens* (90%). Reported specificity is 98.3%–100%. Enne et al. tested 608 surplus ICU samples and reported sensitivity of bacterial targets of between 50 and 100%: with the majority of targets >90%[36]. The most notable exceptions were *E. aerogenes* (50% [95% CI, 12–88%]) and *S. marcescens* (77.8% [95% CI, 40–97%]). Peiffer-Smadja et al. evaluated the HPN cartridge on VAP and severe HAP samples and reported a pooled sensitivity of 80% whilst only detecting 3/6[37] and 7/13[38] Gram positive isolates.

In the diagnostic performance data presented by the manufacturer, resistance marker detection aligned poorly with organism antibiogram: for example, matching in only 4/11 *mecA* detections or 9/13 quinolone resistance markers in *E. coli*. This issue was noted by Gadbsy et al[39] for the P55 assay where the sensitivity for antibiotic resistance detection was 18%.

Two predecessors to the HPN cartridge have been developed and CE marked: the earlier P50, and the later P55. The former of these was evaluated most extensively by Personne et al. who found the test to be sensitive for bacterial detection but with a run failure rate of 12.6% and extensive discrepancies with regards to sensitivity testing[40]. Furthermore, the test was unable to differentiate *S. pneumoniae* from the *S. mitis* group. Papan et al. reported that the P50 had a low sensitivity for Gram positive organisms (when evaluated on paediatric samples)[41].

The resistance panel on the P50 was broad but lacked several key emerging carbapenemase gene targets. The P55 panel rebalanced this by removing less clinically relevant resistance genes. It added targets for *S. pneumoniae* and *M. pneumoniae*. Again, the sensitivity for bacterial detection remained high when assessed by Ozongwu et al. albeit with a high overall run failure rate of 10%[17]. The targets on the panel for the HPN are the same as the P55, but the manufacturer claims it has a higher sensitivity and specificity.

To date there are no published randomised controlled trials evaluating the clinical impact of the Unyvero HPN system in patients with pneumonia. Jamal et al[42] performed a non-randomised interventional study using the P50 assay where antibiotics were adjusted based on the results and pathogens detected were compared to culture. The turnaround time for result was very quick (~4 h) compared to culture (48–96 h) and a large proportion of patients had antibiotics changed based on the P50 results, however the small number of patients studied and the lack of a comparator group make definitive conclusions impossible. Gadsby et al. retrospectively tested BAL samples with the P55 and reviewed patient notes. They reported that 53.6% of patients who had positive standard of care microbiology could potentially have had a change in antibiotics earlier based on P55 results[39]. Conversely, they reported a false negative P55 result in ~20% of those with a positive culture which could have caused harm if acted upon.

Fast track diagnostics (FTD) respiratory pathogens 33[43]

The Respiratory pathogens 33 panel differs from the first two tests discussed in that it is exclusively a laboratory centred assay. The CE marked Respiratory pathogens 33 kit can be used on several standard laboratory cyclers. As such there is no reported standard turnaround time although it is greater than 6 h. Positive signals are detected from eight multiplex real-time PCR reactions. It is not an automated process so will have a considerably longer hands-on time requiring skilled extraction and setup. The panel has 12 bacterial targets, 20 viral targets and 1 fungal target (*P. jirovecii*). The bacterial targets are: *H. influenzae (with additional specific HiB target), Bordatella* species *(excluding B. parapertussis), M. catarrhalis, Salmonella* species, *L. pneumophilia/longbeachiae, K. pneumoniae, S. aureus, S. pneumoniae, C. pneumoniae and M. pneumoniae.* The viral targets are: *Influenza (A, A(H1N1), B, C), Rhinovirus, Coronaviruses (NL63, 229E, OC43, HKU1), Parainfluenza (1–4), Metapneumoviruses A/B, Bocavirus, RSV A/B, Adenovirus, Enterovirus and Parechovirus*.

Comparing systems

There is very little published data comparing different syndromic molecular pneumonia tests. Enne et al. and the INHALE group presented data at ECCMID 2019 where they compared the Unyvero and the Filmarray on 654 surplus intensive care respiratory tract samples[36]. The Filmarray had slightly greater sensitivity for common pathogens, fewer major discordances (defined as routine culture finding 1 or more undetected organisms) and fewer machine failures. The Unyvero had slightly higher specificity and overall concordance with reference culture.

Discussion

Whilst the data presented for syndromic molecular test for pneumonia clearly demonstrates high accuracy and the detection of many more pathogens than culture, no data has yet been published showing that this translates into improved antibiotic use or clinical benefit. Other molecular diagnostics studies for blood stream infection[45] have shown improved diagnostic performance, but negligible impact on clinical outcomes when results were not provided to clinicians along with infection specialist advice. It seems likely that such a wealth of information generated will require careful interpretation by an infection specialist in consultation with the clinicians directly caring for the patient, for these benefits to be maximised.

Rapid syndromic molecular platforms have the potential to significantly improve the use of antibiotics and clinical outcomes in patient with pneumonia, but high quality randomised controlled trials are urgently required to evaluate their clinical impact. We are aware of 5 trials that are currently underway or in set up that may address this evidence gap: the SARIPOC study is a single centre randomised controlled trial (RCT) recruiting critically unwell patients with pneumonia in Southampton, UK. The INHALE study is a UK multicentre, RCT recruiting critically unwell patients with HAP and VAP. PIBCAP is a UK multicentre RCT recruiting patients with CAP. The NORCAP trial, in Norway is a single centre RCT in set up, also aiming to recruit patients with CAP. A further single centre RCT in Edinburgh is using molecular testing for broader community acquired LRTI microbial diagnosis. The first of these two studies are testing patients at the point-of-care, whereas the others use rapid laboratory-based testing.

Translating quicker tests into antibiotic savings: is antibiotic de-escalation safe?

Antibiotic de-escalation based on results is a key component of antibiotic stewardship and is widely accepted as good practice. Trials looking at the efficacy and safety of antimicrobial de-isolation based on culture results are sparse. The vast majority of published studies are observational and comparison between studies for so many variables (HAP, CAP, VAP, ICU/ non-ICU, severe sepsis etc.) are fraught with difficulties. Furthermore, due to the geographic variability in causative organisms and prescribing practices, they are often poorly transferrable between regions.

To our knowledge no interventional studies have looked at the safety or efficacy of antimicrobial de-escalation based on multiplexed PCR for pathogens of pneumonia. Studies to date have made their de-escalation intervention after at least 48 h when the patient has stabilised, and culture results are available. Both the IDSA and the National Institute for Clinical Excellence (NICE) cite an urgent need for well-run RCTs on the impact of de-escalating antimicrobial therapy[46,47].

The IDSA and the American Thoracic Society advise antibiotic de-escalation in HAP/VAP according to culture results on the basis of expert opinion, citing a high level of confidence that it 'reduces costs, burdens, and side effects, and that it is very likely that de-escalation also reduces antimicrobial resistance'[47]. There a small number of interventional studies looking at antibiotic de-escalation based upon microbiological culture results in HAP/VAP which have suggested this practice is safe[48,49]. High quality data for outcomes, including length of intensive care stay and antibiotic savings, are lacking and conflicting. A meta-analysis by Khan et al[50] of observational studies reviewing antibiotic de-escalation in pneumonia in ICU (HAP and VAP only) found no difference in mortality between those who were de-escalated according to culture result and those that weren't.

In the context of CAP, both the IDSA[51] and NICE/BTS[46] guidelines recommend organism directed therapy when a pathogen has been identified by culture. High quality data is lacking but observational data and limited interventional data suggests this is safe[52–54]. A systematic review by Paul et al[55] included studies with CAP, HAP, VAP and Blood stream infection. The reviewers found no association between de-escalation and survival with pneumonia (OR 0.97, 95% CI 0.45–2.12).

Detection of colonising flora

Concern has been raised that the high sensitivity of molecular tests will lead to excessive detection of colonising flora which may paradoxically increase unnecessary antibiotic use. This is particularly pertinent in expectorated sputa where small numbers of potentially pathogenic bacteria can be present in the absence of disease. A potential solution to this is the development of semi-quantitative molecular methods such as with the BioFire® FilmArray® Pneumonia panel. This provides a representation of the amount of bacterial DNA present which is highly concordant with reference molecular techniques.

Interpreting genotypic resistance results

As highlighted by studies using the Unyvero[17,39], molecular detection of resistance genes may correlate poorly with phenotypic sensitivity in its current form. Detection of genes from 'off panel' organisms, for example *mec*A genes in colonising coagulase negative staphylococci, may be incorrectly attributed to those organisms which are on the panel. As such, clinicians will need to be cautious in interpreting these results.

Practical issues: where to test

As well as having relatively quicker run times, syndromic multiplex molecular tests could potentially be deployed at the point-of-care. The RespPOC trial by Brendish et al., demonstrated with a respiratory viral panel that this was logistically feasible and associated with a number of clinical benefits compared to routine clinical care[24]. A *post hoc* analysis[56] of patients who tested positive for respiratory viruses in the trial highlighted an association between rapid turn-around time (defined as <1.6 h), shorter hospital admission and shorter durations of antibiotic therapy. It is our belief that point-of-care testing represents the ideal strategy for new, rapid diagnostic test platforms allowing clinicians to maximise the benefit from such accurate tests early in the decision-making process. Clearly, rigorous quality assurance is essential for any diagnostic test irrespective of the site of testing. It should also be noted that the tests described in this article are not currently CLIA waivered - a requirement for use at the point-of-care in the US.

Conclusion

Rapid syndromic molecular tests for pneumonia have improved diagnostic accuracy compared to the current gold standard of culture and can provide results in real time. In the era of widespread AMR their use has the potential to dramatically improve the rational use of antibiotics and to improve clinical outcomes in patient with pneumonia. High quality data from well conducted randomised controlled trials are now urgently needed to assess the impact of these platforms on antibiotic use and patient outcome.

Declaration of Competing Interest

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