**REPORT**

# DIAGNOSTICS TO ADDRESS **ANTIMICROBIAL RESISTANCE**

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# DIAGNOSTICS TO ADDRESS **ANTIMICROBIAL RESISTANCE**

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# 1. INTRODUCTION

## What is AMR?

Antimicrobials are drugs used to treat infections in humans, animals and plants caused by a range of organisms including viruses, bacteria, fungi, and parasites. Antimicrobial resistance (AMR) in these organisms can occur via naturally occurring intrinsic mechanisms, or due to resistance evolving which is caused by repeated exposure to antimicrobials.

## The scale of the challenge

AMR is recognised as a major global threat to human health. The World Health Organization (WHO) has declared AMR as "one of the top 10 global public health threats facing humanity". The misuse and overuse of antimicrobials are the key drivers in the development of resistance.[1] A recent analysis in 2017 by the World Bank indicated that in a best-case scenario the gross domestic product (GDP) shortfall due to increasing AMR will exceed 1 trillion USD annually by 2030. In the worst-case high AMR-impact scenario, the annual shortfall was predicted to be 3.4 trillion USD by 2030, and the world would lose 3.8 percent of its annual GDP by 2050. Low-income countries would suffer the largest drops in economic growth.[2] Whilst these models provide a useful estimate of the scale of the problem, there is a continued need for better and more accurate risk predictions to inform policy decisions.[3] The most recent estimates suggest that 4.95 million deaths were associated with bacterial AMR in 2019, with lower respiratory tract infections (RTIs) accounting for the largest share of these deaths (1.5 million).[4]

## What is the clinical problem?

When managing patients with an infection, clinicians need to determine what is causing their illness so that they can safely prescribe the most appropriate therapy. Their decisions over which tests to perform and what treatments to prescribe will be influenced by a variety of factors. These include: patient symptoms; type of infection; risk of severe patient illness; risks to others from pathogen transmission; stage of the disease; and availability of diagnostic tests. Currently, treatment decisions are often made without diagnostic tests, increasing the chance that an ineffective therapy could be prescribed, for example, an antibiotic to treat a viral infection, or a bacterial infection resistant to that drug.[5] In the UK, for example, 70-80% of all antibiotics are prescribed in the community and 60% are for respiratory tract infections. Twenty percent of RTI prescriptions are thought to be unnecessary or inappropriate as RTIs are often viral so antibiotics are not required.[6]

There are a variety of reasons for the lack of diagnostic test use, ranging from test availability to limitations in the utility of using a test for a particular clinical scenario. These will also vary for different clinical settings, i.e., primary care or hospital-based care. For example, in hospital care, disease can be more severe and treatment decisions often need to be made before the return of diagnostic results. As a result, broad-spectrum antimicrobials can be prescribed, which can act as a driver for the development of resistance if they are not the most appropriate treatment. In contrast, in primary care settings patients may have less severe disease, but general practitioners (GPs) may still feel under pressure to prescribe antibiotics, especially if it is unclear if the source of infection is bacterial or viral.[7]

Better availability and uptake of appropriate diagnostics, particularly those that are rapid and/or point of care, could support antimicrobial prescribing and stewardship. These will also contribute to efforts to manage and mitigate the challenges posed by AMR, including preserving the future effectiveness of antimicrobials. Antimicrobial stewardship requires an organisation and healthcare-system wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness.

The goals of antimicrobial stewardship programmes are to improve patient outcomes and safety, reduce the burden of resistance, and potentially reduce healthcare costs. However, there is no single solution that can achieve this, and a combination of approaches are needed including regulatory, policy and clinical strategies.[8-11] For example, the O'Neill *Review on Antimicrobial Resistance* states that the promotion of new, rapid diagnostics to reduce unnecessary use of antimicrobials is one of seven key interventions for better antimicrobial stewardship. Others include a global public awareness campaign and improved AMR surveillance in humans and animals.[5]

This report will investigate the use of rapid and timely diagnostics that distinguish between bacterial and viral infections—both point-of-care and laboratory tests—as an exemplar to explore the opportunities and barriers for diagnostics to support antimicrobial stewardship and the management of AMR. For the purposes of this report these will be referred to as BV diagnostics.

# 2. DIAGNOSTICS AND AMR

Diagnostic tests can be used to characterise a patient's infection to inform antimicrobial prescribing. This can support the reduction in unnecessary and/or ineffective use of antimicrobials, which in turn can help reduce the burden of AMR. Several types of diagnostic tests can be used, with varying specificities for identifying the precise cause of a patient's disease. For example, diagnostics could be used to:

- Determine the broad type of infection i.e., bacterial, viral, or fungal
- Identify the specific pathogen causing an infection
- Identify the antimicrobial susceptibility of a pathogen

These tests can be based upon a range of assays and technologies, examples include:

- Direct pathogen visualisation, e.g., through culture (microbiology) and/or microscopy
- Immunological tests/immunoassays for the presence of antibodies or antigens, or assays for other biomarkers
- Molecular diagnostics that detect pathogen nucleic acids (DNA or RNA) via methods such as polymerase chain reaction (PCR)

These assays and technologies differ in terms of their turn around times and relative cost, infrastructure, and expertise requirements. For example, molecular methods may have higher infrastructure or expertise requirements. Some assays tend to have longer turnaround times, for example tests that rely on conventional culture methods may take hours to days to return a result. Therefore, certain test characteristics will affect their suitability for use in a specific setting and the choice of a test can require a trade-off between its usability and the value of the result.

Rapid and/or point-of-care (POC) testing is an area of focus in terms of diagnostics development for infectious disease, including AMR management. The International Organization for Standardization (ISO) defines POC testing as 'testing that is performed near or at the site of a patient with the result leading to possible change in the care of the patient'. These tests should provide a faster turnaround time to enable decision making during a patient's visit to a health service. Typically, a test that provides a result within minutes to hours to inform clinical management is considered rapid. Some non-POC tests (POCTs) may still be considered rapid, for example rapid tests performed in a laboratory setting.

POCTs and other rapid tests are therefore useful in situations when diagnostic decisions must be made quickly, for example during a short patient visit to a primary care facility or in an emergency. Decisions on antimicrobial prescribing are often made in such settings, frequently during a patient's initial encounter with the health service, meaning there is a particular need for POCTs.

Using rapid diagnostics to enable a quicker and more accurate initial diagnosis can also have clinical benefits, including improved treatment adherence due to higher confidence in the decision and reductions in patient morbidity/mortality as a consequence of appropriate treatment. This may lead to cost savings from reduced unnecessary treatment, further diagnostic tests, and further visits to healthcare facilities or hospitalisation. The settings requiring POCTs often lack specialist laboratory equipment and staff, meaning that to be useful, POCTs often require certain characteristics in addition to faster turnaround times. These include:

- Ease of data interpretation and integration of that information into clinical records
- Ease of use, with minimal training requirement
- Stable and robust technology with minimal or no maintenance needed
- Low infrastructure requirements and/or portability
- Simple to integrate testing into clinical pathways

There are a range of technologies that can be used to deliver POCTs, including:

- Lateral flow tests and test strips
- Cartridge or cassette-based tests
- Microarray/chip technology
- Biosensor or biowire

## Rapid diagnostics to distinguish between bacterial and viral infections

Rapid BV diagnostics will be most suitable for clinical scenarios when it is unclear what type of infection the patient has, and a decision is required over whether to prescribe antibiotics or not. In some cases, BV diagnostics may perform additional functions, for example, identifying specific pathogens or prediction of antimicrobial susceptibility. The utility of rapid BV diagnostics is likely to be highest in those situations when patient numbers are higher, there may be limited time to perform time-consuming diagnostics assays, and the rates of inappropriate prescribing of antibiotics are known to be higher.[12]

## Types of tests used in rapid BV diagnostics

Tests to distinguish between bacterial and viral infections can use two approaches: detecting the host response or detecting a pathogen signature. Described below are some of the main types of tests belonging to each category that are currently in use. Key resources with further details of specific tests are summarised in Appendix 1.

### Host response tests

These tests are based on assays that detect proteins or other biomarkers such as RNA signatures in the blood that are associated with the host immune response to bacterial or viral pathogens, either singly or in combination. Tests can be designed to:

**1. Indicate presence of bacterial infection**
These tests are typically single biomarker-based tests that measure host inflammatory biomarkers which increase in level during bacterial infection. Measuring the amount of the biomarker can therefore be used to indicate if bacterial infection is likely present or not, which can then be used to guide antibiotic use. Theoretically a similar test could be developed to detect only viral infection, but none appear to be commercially available. Procalcitonin (PCT) and C-reactive protein (CRP) are two of the main biomarkers used.

**C-reactive protein (CRP)**

CRP is a protein released by the liver during inflammation, which can then be detected in the blood. It can be used as a host response biomarker to determine the likely type of pathogen causing respiratory infection, when levels are typically much higher for bacterial infections compared to viral. The concentration of CRP is used to guide clinical decision making (section 4).

**Example:** *The Afinion™ CRP test by Abbott detects the inflammatory biomarker CRP in the blood to indicate if a bacterial infection is likely. It is an immunochemical assay where a membrane coated with anti-CRP antibodies react with the CRP in the sample. An Afinion analyser measures the colour intensity of the membrane which is proportional to the amount of CRP in the sample. The test is designed for POC and has a turnaround time of four minutes.*

**2. Detect presence of bacterial and viral infections**

These tests work in the same way as bacterial-only tests but can be used to identify the presence of both bacterial and viral infections by measuring biomarkers associated with each. These multi-biomarker tests can have the advantage of increasing confidence in the test result compared to bacterial infection only tests, as by identifying both pathogen types the test is typically more sensitive and specific.

**Example:** *The FebriDx® test by Lumos Diagnostics detects the presence of two biomarkers, CRP (bacterial) and MxA (viral) in the blood that can be used to indicate if bacterial or viral infection is likely. It consists of a single lateral-flow test strip containing monoclonal anti-MxA and anti-CRP antibodies, which react with the CRP and MxA in the sample The test is designed for POC and has a turnaround time of 10 minutes.*

**Example:** *The LIAISON® test by MeMed BV® detects the presence of three biomarkers: TRAIL and IP-10 (viral) and CRP (bacterial) in the blood. It is chemiluminescent test where the sample is placed in a tube containing anti-CRP, anti-TRAIL and anti IP-10 antibodies which react with the corresponding biomarkers in the sample. A LIAISON analyser measures the amount of chemiluminescence in the sample and integrates the results with a machine learning algorithm to differentiate between bacterial and viral infections. The test is designed for POC and has a turnaround time of 35 minutes.*

## Pathogen signature tests

These tests are based on assays that detect antigens or nucleic acids belonging to one or more pathogens, in order to identify potential pathogens causing an infection. They therefore rely on being able to detect the pathogen in order to determine if the infection is bacterial or viral. Tests can be designed to:

**1. Identify pre-defined pathogens**

These tests are used to identify one or more specific pathogens typically using PCR to amplify and detect pathogen specific genomic regions or immunoassay methods to detect pathogen specific antigens. They are most commonly used for identifying viruses though they can also be used for certain bacteria. Other rapid tests in development identify specific pathogens through characteristics, such as their growth rate under specific conditions (described further in section 3).

**Example:** *The FilmArray® Respiratory 2.1 Panel is a multiplex PCR test for the detection of 18 viruses and four bacteria that can cause respiratory infection. It uses a nasopharyngeal swab sample analysed in a BioFire device and has a turnaround time of around 45 minutes.*

**Example:** *The mariPOC® Respi+ test by ArcDia is a pathogen specific immunoassay for the detection of 10 viruses and one bacterium responsible for causing respiratory illness with influenza and COVID-19-like symptoms. It uses a nasopharyngeal swab sample analysed in a mariPOC® device. The test has a maximum turnaround time of two hours, though it claims 80% of positive viral results will be reported within 20 minutes.*

**2. Identify all pathogens present in a sample**

In theory, metagenomic or other sequencing tests could be used to identify all known pathogens present in a sample, thus distinguishing between bacterial and viral infections. There are two main approaches: tests sequence all the genomic

material present in a sample, or conserved regions found across the entire pathogen class—particularly bacterial and fungal species—can be amplified and sequenced to allow pathogen identification. In practice, however, these more complex methods are unlikely to be used for the primary purpose of distinguishing between bacterial and viral infections.

**Example:** *The Sepsitest™-UMD by Molzym uses 16S and 18S gene PCR amplification followed by Sanger sequencing to identify all known bacterial and fungal species present in a sample. The test is stated to have a turnaround time of approximately one working day and can be used on a range of clinical specimens. It can identify sepsis causing pathogens but can also be applied to other clinical scenarios.*

**3. Detect likelihood of AMR resistance**
Detection of specific characteristics that can be used to predict sensitivity or resistance, e.g., genetic markers associated with resistance. This information is not likely to be used for distinguishing between bacterial and viral infections but is most useful once the causative pathogen is known. AMR resistance prediction can be incorporated into some of the pathogen specific tests described above.

# 3. RAPID BV DIAGNOSTIC PRODUCTS/ APPROACHES IN RESEARCH & DEVELOPMENT

Research and development needs will differ depending on the intended purpose and context of use of the rapid BV test. There is a drive towards the use of POCTs for use in primary care and emergency facilities, where primary care needs in terms of testing are diagnostic accuracy, quick turnaround time and suitability for use in non-specialist facilities.

In situations where patients are already hospitalised, there is a need for more rapid alternatives to conventional culture-based antimicrobial diagnostics to confirm initial diagnoses and guide further decision making.

Some of the main products and approaches in development capable of addressing these different needs for BV tests are:

**1. Multi-host response biomarker POCTs for distinguishing bacterial from viral infections**
Use of existing single biomarker POCTs based on CRP has demonstrated likely utility in improving antibiotic prescribing for RTIs in various healthcare settings, whilst the biomarker procalcitonin has also been explored with less success.[6, 13-15] However, doubts remain over the specificity of these biomarkers for identifying bacterial infections, as their levels can increase for various reasons, including some viral infections. This can impact on the willingness of clinicians to act on test results when prescribing antibiotics, especially at intermediate test result levels. Tests that use multiple host biomarkers are being developed that can identity both viral and bacterial infections with increased sensitivity and specificity.[16] For example, an increase in diagnostic accuracy and confidence in comparison to bacteria-only biomarker tests was stated as an advantage of using FebriDx® in the UK's National Institute for Health and Care Excellence (NICE) Medtech Innovation Briefing.[17] These tests may also perform well for indications other than of respiratory disease, for example populations with fever.[18]

**2. New materials for more rapid and versatile POCTs**
There is a continued need for POCTs that deliver results faster with minimal training required, and which are stable and able to be used in multiple settings.[19] Cost is also an important factor, particularly in low- and middle-income countries. These devices are often designed to be used as a first line test applied to high numbers of patients with a potential infection. Therefore, POCTs should be relatively low-cost if their implementation is to be affordable. For example,

one research group have developed a paper-based colorimetric assay for growth based detection and antibacterial resistance testing of *E. coli*.[20] Other rapid and affordable approaches in development make use of nanotechnologies to deliver optical or electrochemical based pathogen detection.[21,22]

**3. Direct from sample sequencing-based tests for pathogen identification**

Next-generation sequencing (NGS) based tests that can perform pathogen sequencing directly from a clinical sample could be a useful rapid alternative to culture and PCR based methods for quicker pathogen identification in some specific, mostly hospital based, clinical scenarios. For example, this is a particular area of interest for the management of sepsis, when a variety of pathogens could be responsible for the infection and there is a need for critically ill patients to receive the most appropriate treatment as soon as possible. NGS is also being explored for use in respiratory infections. Pathogen agnostic methods, such as metagenomics or sequencing of conserved genes across species, are being designed for use as a rapid test, in some cases suitable for use outside laboratory settings.[23-25]

**4. Novel nucleic acid amplification technologies**

New methods for amplification based molecular identification of pathogens continue to be developed which are simpler, cost effective and/or more rapid than conventional PCR techniques. These include isothermal methods such as loop-mediated isothermal amplification (LAMP), which remove the need for specific equipment to amplify DNA and instead can be performed at room temperature, often with comparable or greater sensitivity to PCR.[26] Another example of a recent technology is CRISPR-based LAMP systems for highly specific and sensitive detection of pathogen RNA and DNA.[27]

## Who is developing tests?

BV diagnostics is an active commercial sector with significant interest from industry, academia, and government agencies.[28] Funding initiatives, for example the Longitude Prize, fund innovation to develop diagnostics for the prevention and management of AMR. A trend analysis of patent filings found that most patents for POC tests for antibiotic resistant bacteria or important infectious diseases were filed in the USA (25%), Patent Cooperation Treaty (PCT) (21%), European Patent Convention (12%), China (8%), Japan (6%) and Canada (5%). However, the number of patent filings appears to have declined over time.

The process of developing and implementing tests is very challenging and bottlenecks currently hinder both investment in development and implementation of existing technologies. There is a significant gap between the perceived needs of frontline clinicians and industry professionals on what constitutes the ideal POCT. There is also quite limited evidence when establishing the value of diagnostics and, given that the process of developing diagnostics is costly, there is concern around investor return.[29]

# 4. BV DIAGNOSTIC USE IN HIGHER INCOME COUNTRIES

The landscape of BV diagnostic use in high-income countries is varied and complex and data comparing use of BV diagnostics across and between countries are limited.

The International Society of Antimicrobial Chemotherapy (ISAC) undertook a global survey of the use of rapid diagnostics for infectious disease in clinical practice in 2019.[30] While this survey does not comment on the test methods used, it reports their use for different diseases. Therefore, whilst it cannot be used directly to assess the use of BV diagnostics specifically, it can be used to help understand the use of rapid pathogen diagnostics more generally, and priority areas for different countries. Thirty-one countries responded and of the respondents who disclosed their nationality, 92% were from very highly developed or highly developed nations, according to the United Nations Human Development Index. Tests for influenza were the most frequently used by very highly developed countries with over 70% reporting use. In highly developed countries the most commonly used tests were for hepatitis B and hepatitis C. Ninety-one percent of those using rapid diagnostic tests reported them to be carried out in a laboratory setting, with 28% reporting use in an emergency setting. Only 5% and 7% recorded using tests in clinics and wards respectively.

One of the most common uses for BV diagnostics is for RTIs. A recent audit of GP practices across Europe evaluated antimicrobial prescribing decisions and use of diagnostic tests for RTIs.[31] There was significant variability in the extent of use of diagnostic testing between countries, as well as the types of diagnostic tests used. The audit collected information on POC and laboratory test use, as well as on which biomarkers were tested for. POCTs were used the most in Norway and Denmark (in 77.3% and 67.9% of cases respectively). POCTs were not used at all by Moldova, Croatia, and Romania, and for less than 10% of patients in over half the countries surveyed. Of the types of POC testing performed, CRP was by far the most frequently used in those countries where POC testing was also the highest: Norway (73.9%), Denmark (49.7%) and the Netherlands (30.7%). Other countries typically used CRP testing less, if not POC then testing was often performed in laboratories. Use of other tests varied widely, e.g., Influenza POC testing was only used in seven countries, ranging from 0.3% of patients in Denmark to 2.8% in Norway, though it was used more frequently and in more countries as a laboratory-based test. The different types of tests used by each country are summarised in Table 1, adapted from the original paper.

**Table 1.** Percentage of patients presenting to GP practices for RTIs assessed using different types of diagnostic test, presented by country, adapted from.[31]

| Country* | Diagnostic testing all types | POC (All) | Lab (All) | Strep A POC | Strep A Lab | CRP POC | CRP lab | Flu POC | Flu lab | Multiplex PCR lab | RSV lab | WBC lab | Chest x ray lab |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NO | 79.1 | 77.3 | 17.5 | 12.8 | 0 | 73.9 | 0 | 2.8 | 10.9 | 10.9 | 5.2 | 0.5 | 2.4 |
| DK | 71.4 | 67.9 | 11.5 | 23 | 0.5 | 49.7 | 0.5 | 0.3 | 3.8 | 1.3 | 1.3 | 0.5 | 1.5 |
| MD | 55 | 0 | 55 | 0 | 0 | 0 | 10.8 | 0 | 0.8 | 0 | 0 | 52.5 | 15.8 |
| GE | 43.3 | 16.7 | 32.5 | 0.8 | 0 | 2.1 | 12.5 | 0 | 0 | 0 | 0 | 9.6 | 18.3 |
| GR | 37.4 | 1.7 | 36.1 | 0 | 4.6 | 0 | 8 | 0 | 1.7 | 0 | 0.4 | 26.1 | 29.8 |
| NL | 35.4 | 33.5 | 2.8 | 0.3 | 0 | 30.7 | 1.6 | 0 | 0 | 0 | 0 | 0.9 | 0.9 |
| AM | 34.6 | 6.8 | 28.5 | 1.4 | 9 | 0.3 | 0.6 | 2.3 | 7 | 0 | 3.7 | 4.2 | 4.8 |
| UA | 30.8 | 12.6 | 19.8 | 1.6 | 1.2 | 0 | 1.2 | 1.6 | 0.8 | 0 | 0 | 17.4 | 5.7 |
| HR | 30 | 0 | 30 | 0 | 0.4 | 0 | 28.1 | 0 | 2.2 | 0 | 0 | 28.5 | 6.3 |
| FR | 22.5 | 13.4 | 9.9 | 13.4 | 0 | 0 | 6.5 | 0 | 2.3 | 0 | 1.1 | 6.1 | 5 |
| DE | 16.6 | 9.5 | 7.1 | 0 | 0 | 8.7 | 5 | 0 | 1.7 | 0 | 0 | 2.1 | 0.4 |
| HU | 12.3 | 10.6 | 1.7 | 0 | 0 | 7 | 1.7 | 2.3 | 0 | 0 | 0 | 0.7 | 0 |
| PL | 12 | 7.9 | 4.6 | 2.5 | 0 | 3.3 | 2.9 | 0.8 | 0 | 0 | 0 | 0.8 | 1.2 |
| IE | 9.3 | 1 | 8.2 | 0 | 0 | 0 | 1.4 | 0 | 0 | 0 | 0.3 | 1.7 | 6.5 |
| UK | 8.8 | 3.6 | 5.2 | 0 | 0 | 1.9 | 1 | 1.6 | 0.3 | 0 | 0.3 | 1 | 2.3 |
| BE | 8.7 | 1 | 8 | 0 | 0 | 0 | 6.2 | 0 | 0 | 0.7 | 0 | 6.9 | 0.7 |
| ES | 8.6 | 7.6 | 1 | 5.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| RO | 6.1 | 0 | 6.1 | 0 | 1.6 | 0 | 0.4 | 0 | 1.6 | 0 | 0 | 0.4 | 2.4 |

*Countries are presented in order of extent of diagnostic testing of all types performed. For specific tests, only those which could be useful for distinguishing between bacterial and viral infections are included (not all may necessarily be considered 'rapid tests' e.g., x ray and WBC – white blood cell count differential). Full results can be seen in supplementary table 2 of the paper. AM = Armenia. BE = Belgium. DE = Germany. DK = Denmark. ES = Spain. FR = France. GE = Georgia. GR = Greece. HR = Croatia. HU = Hungary. IE = Ireland. MD = Moldova. NL = the Netherlands. NO = Norway. PL= Poland. RO = Romania. UA = Ukraine. UK = United Kingdom.

## Case study: C-reactive protein POC testing for respiratory tract infections

Tests that measure CRP levels can support clinical management of patients with RTIs. For example, in the UK, NICE clinical guidelines for the diagnosis and management of pneumonia suggest that antibiotics should be withheld if the concentration is less than 20mg/L, a delayed prescription considered if between 20-100mg/L, and antibiotics offered if greater than 100mg/L.[40] Whilst many BV tests were only made commercially available relatively recently or are still in development, CRP tests for both POC and laboratory use have been available and in use by some countries for many years.[32] This makes using CRP POC tests for RTIs a useful example by which to examine the current use of a widely available BV test in higher income countries. This analysis is restricted to Europe, which has the most complete and comparable data available.

### What CRP tests are available?

In 2019, The European Network for Health Technology Assessment undertook a review of CRP POCTs to guide antibiotic prescribing in primary care settings for acute RTIs.[15] Fifteen CE-marked CRP POCT systems were identified, broadly classified into quantitative (using an analyser to provide a quantitative CRP measurement) and semi-quantitative devices (using strips, dipsticks, or single-use disposable tests). All tests were designed for measurement of CRP in human whole blood, serum or plasma and intended for use by healthcare professionals.

### What is the evidence of utility of CRP POC testing?

A 2018 systematic review assessed the impact of CRP POC testing in patients presenting to ambulatory care services with respiratory infections.[33] It found that for acute infections a CRP POCT accompanied by clinical guidance can reduce antibiotic prescription in adults and children. If not accompanied by clinical guidance, it is only effective in reducing antibiotic prescriptions in adults. There was no significant evidence found on effects of testing beyond reducing antibiotic use, e.g., the effect of testing on clinical recovery, re-consultation, and subsequent management decisions. The review also noted that guidance on test use is important for it to be used effectively in practice to reduce AMR prescribing. Another study carried out modelling of the potential implementation of CRP POCT in Dutch primary care for community-acquired acute RTIs. While the modelling predicted that use of testing would likely increase the cost per consultation, it also predicted that antibiotic consumption, and consequently the risk of AMR developing, would decrease.[34]

### Differential use of CRP tests in Europe

Despite the availability of CRP tests and the evidence supporting their use, there are large differences between the use of CRP tests between countries (Table 1). The European Network for Health Technology Assessment 2019 review identified that the use of CRP POCT in patients with suspected lower respiratory tract infections was available in multiple countries. It was specifically included in guidelines in the UK, Norway, Sweden, the Netherlands, Germany, Switzerland, Czech Republic and Estonia, to determine the severity of infection and to guide antimicrobial prescribing.[15] All countries where reimbursement status was available had made positive recommendations for reimbursement (this is despite several of these countries not having specific clinical guidelines). A more recent audit (2022) of the GP practices described above and shown in Table 1 found that the use of CRP POCT for RTIs across European GP practices remains variable.

# 5. FACTORS INFLUENCING DIFFERENCES IN THE USE OF BV DIAGNOSTICS

There are a variety of factors that contribute to the differences and variability of the use of available BV diagnostics between countries. These include:

**Support for diagnostic development.** There are challenges around adequate funding and investment for developing tests and gathering the information needed to validate tests and meet regulatory requirements. For example, a 2018 Longitude Prize Patent report stated that "Longitude Prize teams are struggling to attract adequate funding and investment to ready their tests for market and gather adequate data to validate tests and reach regulatory standards. The reasons for this are two-fold. Investors are concerned that price expectations are too low to assure return on investment and are not convinced that financing will be available either from health systems or funders to help create this new market. This is a warning to policy makers that initially there will likely be a need to ring-fence funds to assure that products are purchased and new norms are created whereby biological testing before antibiotic prescribing becomes the norm."[28]

Funding is not only a barrier for diagnostic test development, but also for their use within clinical pathways. For example, in the UK, GPs do not receive additional funding to purchase or maintain easy, quick, POCTs that could be used to inform prescribing decisions.[35] The 2019 global ISAC survey of the use of rapid diagnostics for infectious disease in clinical practice, reported that 64% of those surveyed (mostly in very high or highly developed countries) said the lack of money was the major barrier to introducing rapid diagnostic tests.[30]

**Reimbursement of diagnostics: Denmark**

One study found that in 2013 GPs were carrying out POC testing before 44% of all antibiotic prescriptions, an increase from 28% in 2004.[36] This high rate of POCT use may be aided by GPs having in-house laboratory facilities, as well as reimbursement by the Danish health service. Young, female GPs were more likely to test than older, male GPs. It was suggested that older GPs had more confidence in their clinical judgement and some GPs were concerned about the consequences of over reliance on test results. However, GPs also think that diagnostics are helpful in cases of diagnostic uncertainty. This suggests other factors beyond reimbursement affect the decision to test.

**Laboratory infrastructure.** Coordination and arrangement of laboratories differs significantly between countries. For example, in France, there is a push to reduce the number of centralised laboratories and the resulting diagnostic gap in service provision is likely to result in increased demand for POC testing.[37] In Denmark, a high rate of POCT use may be aided by GPs having in-house laboratory facilities.[36]

Antimicrobial stewardship programmes highlight diagnostics as a key tool to reduce prescribing, currently, diagnostics are often insufficiently embedded within clinical pathways. Laboratory infrastructure is one dimension, but this needs to be supported by effective guidance and training to improve access and embedding diagnostics in clinical pathways to support responsible prescribing decisions.

**Laboratory support for implementation: Norway**

A 2013 article highlighted the role of NOKLUS, a quality improvement scheme introduced in 1992 for laboratory services in primary care.[38] Nearly all (99%) of GPs take part in the voluntary scheme, which provides training on how to carry out tests and interpret results. Central laboratories have overall responsibility for training personnel, quality assurance and ensuring that the instruments used by GPs are of high quality. NOKLUS is expanding to other settings where POCTs could be used, for example nursing homes and military institutions.

**Clinical practice.** Diagnostics can be used to change clinical practice. In a qualitative study of UK general practice staff, healthcare practitioners reported that CRP testing could increase diagnostic certainty for acute cough, inform appropriate management, manage patient expectations for antibiotics, support patient education and improve appropriate antibiotic prescribing.[19] However, there are some practical challenges to implementation. Reported barriers to implementation include: CRP test cost; time-to-result; easy access to the POCT machine; and consequence for the clinical workflow. There was a better uptake of CRP tests in situations where there was a dedicated staff member who would test patients with respiratory symptoms using a machine located in their consultation room.

Prescribing is often based on clinical judgement, and clinicians can 'act on the safe side' even if a test suggests that antibiotics should be delayed or not given. A prospective audit of antibiotic prescribing, diagnostics and prescribing confidence found that in nearly 90% of consultations, GPs were confident in their antibiotic prescribing decisions.[31] Diagnostics on their own may be insufficient to drive a change in prescribing practice, however when used within a comprehensive antimicrobial stewardship programme, they can be used to facilitate patient-clinician decision making and improve prescribing practice.

**Patient perceptions.** Patient attitudes towards CRP testing have been found to be largely positive.[6] An assessment of patient views as part of a pan-European randomised controlled trial (RCT) (GRACE INTRO), where antibiotic prescriptions were made on the basis of a CRP POCT, found that most patients were satisfied with the test.[39] CRP POC testing was also found to support discussion with patients about AMR, overprescribing and unnecessary antibiotic use. As a result, diagnostic tests have the potential to improve patient confidence in the decision to withhold antibiotics.

**Demonstration of clinical utility.** Determining the clinical utility of diagnostics for antibiotic prescribing is challenging but it is a key consideration when determining if implementation of these tests is appropriate. A major challenge is how to measure and establish overprescribing.

A systematic review of POCTs to distinguish bacterial and viral RTIs found evidence for clinical utility for both single and combination biomarkers. These include CRP and PCT, interleukin, interferon, and other host proteins/immune system markers.[16] It is not clear what level of reduced antimicrobial prescribing is sufficient or what other characteristics of a test (i.e., portability, usability, speed, etc) are required for the tests to be considered to have clinical utility. Different countries will have different evidence requirements and therefore broad assessments of feasibility, costs and benefits are needed, including impact assessments, to enable these evaluations.

**Guidance for implementation**. This includes guidance on diagnostic test use and for which clinical indications, as well as training in the use of diagnostics to support prescribing. Important details include when should a test be considered, the appropriate type of test, interpreting results and relevance for clinical decision making, guidance for patients if antimicrobials are withheld, when to seek further medical intervention and service provision/ reimbursement arrangements.

The PACE study for CRP-guided prescribing of antibiotics for exacerbations of COPD in primary care found that a lower percentage of patients reported antibiotic use and received antibiotic prescriptions from clinicians, with no evidence of harm.[40] Evidence-based specific guidelines for the use of diagnostic tests are needed for high-risk populations (i.e., COPD, elderly populations, immunocompromised populations).

# 6. EVIDENCE OF COST EFFECTIVENESS

Cost effectiveness of diagnostic tests for antibiotic prescribing is often promised, but it is not clear how best to quantify these benefits. Theoretically, the use of such tests should result in reduced repeat appointments, prescribing and adverse events, resulting in some cost-savings.[41] In practice, these tests will have some additional cost in terms of the test and staff time, and it is unclear if these savings would be sufficient to justify their use. The value of diagnostics for antibiotics is multifaceted, with individual, population, and health system benefits, as well as short-, medium- and long-term benefits from reduced antimicrobial resistance and more appropriate prescribing. Therefore, the evaluation process needs to capture a wide range of outcomes to inform the analysis of cost-effectiveness. Frequently studies only consider direct costs related to the assay.[12]

Evidence for cost-effectiveness of POC BV tests has been mixed. One cost-modelling study found that the hypothetical implementation of the FebriDx® test in GP and emergency care settings could be cost-saving.[41] However, this modelling study simplified both costs and benefits and may not reflect true cost-effectiveness of BV tests and their impact on health systems. Another modelling study of CRP POC testing found cost-effectiveness was unclear because there is variation in the use and implementation of these tests in clinical practice.[42] Further RCTs are needed to address the uncertainty of cost-effectiveness of these tests.[43]

When evaluating cost-effectiveness, it is important to link the use of diagnostic tests to the goals of AMR stewardship. In the UK, NICE and National Health Service (NHS) England have established a new health technology evaluation process and new payment model for antimicrobials.[44] Typically, reimbursement of antimicrobials is based on the volume used by the NHS. Under this new payment model, suppliers of two new antimicrobials received payments determined by the value of this new antimicrobial to the NHS and not linked to the volumes purchased by the NHS. This separation ensures the value of AMR stewardship of these antimicrobials is recognised, whilst providing reasonable remuneration to manufacturers whose financial returns are not now directly linked to prescribing levels of the antimicrobial.

Extending this approach to diagnostics, it could be possible to determine the value to the health system of diagnostic test for antibiotic prescribing. Ultimately, these tests have a key role in antimicrobial stewardship, to improve clinical decision making and reduce the volume of antimicrobials used in healthcare. Uncertainty around the types of evidence sought to evaluate cost-effectiveness and to determine acceptable reimbursement of diagnostics may contribute to the challenge of incentivising investment in diagnostics development.

There are ongoing efforts to build the evidence to support cost-effectiveness evaluation of specific diagnostic tests for antimicrobial prescribing. One study has attempted to better quantify the true cost of antibiotics capturing the relative costs of AMR for each unit of antibiotic consumed.[45] In addition, a systematic review of cost-effectiveness studies of AMR interventions is underway, and this will provide key insights into this complex landscape.[46]

# 7. RECOMMENDATIONS

| | |
|---|---|
| **INVESTMENT** | Support for diagnostic test development and validation. In particular, there is a need to bridge the gap between research and developing the evidence for implementation into clinical practice. |
| **ACCESS** | Measures are required to improve access to testing addressing existing diagnostic laboratory (or other) infrastructure. A focus on flexible point of care technologies will improve access in areas of health systems with limited or no access to laboratory services. |
| **IMPLEMENTATION** | The COVID-19 pandemic has raised awareness of the clinical utility of rapid and easy to use diagnostics and created familiarity with their regular use. This increased awareness of and familiarity with rapid diagnostics could boost adoption of these tests to support prescribing. Novel test funding structures could incentivise implementation as well as support for healthcare providers to use diagnostic tests for example appropriate professional guidance for the use of diagnostics for prescribing specific antimicrobials. |
| **AWARENESS** | Increasing knowledge and understanding of AMR in patients and healthcare providers, and how diagnostics could help to ensure that patients receive the optimal drug for their illness, will support antimicrobial stewardship. |

# 8. CONCLUSIONS

For health systems to manage the challenge of AMR and enhance antimicrobial stewardship, the development of more accurate and rapid diagnostics for a range of clinical indications remains a priority. For maximum impact, this will include not only BV diagnostics but also POC tests that can identify the type of pathogen causing the infection and its antimicrobial susceptibility profile. Some of the diagnostic technologies described in this report aim to identify pathogens in a more rapid manner than conventional culture-based tests, but their turnaround times and cost may still prevent their use in primary care settings. Looking ahead, there is a need to generate evidence of clinical utility in the appropriate setting for the intended test use and new funding approaches should be considered to ensure implementation of proven novel diagnostics. As such, there is a great opportunity to support the development and implementation of these types of tests, and to contribute to tackling one of the great global healthcare challenges of the 21st century whilst preserving valuable antimicrobial resources for the years to come.

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# Appendix 1. AMR Diagnostics: key resources



**Point of Care Testing for Infectious Disease in Europe: A Scoping Review and Survey Study – ECDC scoping review[37]**

- A scoping review of the literature on point of care tests for infectious diseases in EU/EEA countries as of November 2019, and a survey of key stakeholders
- ECDC report of the scoping review[47], the mapping exercise[48] and publication of results[37]
- This scoping review provides details on the infectious disease POCT landscape in Europe, available pathogen tests, test characteristics and performance, and further questions around country use of POCT

**Point-of-care testing, antibiotic prescribing, and prescribing confidence for respiratory tract infections in primary care: a prospective audit in 18 European countries – POCT Europe review[31]**

- A prospective audit of European GPs to describe between-country differences in respiratory tract management, focused on diagnostics testing and antibiotic prescribing; investigate factors related to antibiotic prescribing and prescribing confidence
- Breakdown of country use of diagnostic testing with a focus on C-reactive protein and group A streptococcal [strep A] infection and setting in which diagnostics were used (i.e., laboratory vs. POC)
- Most comprehensive data identified describing differences in the use of BV diagnostics in Europe

**Rapid tests to distinguish bacterial from viral infections: a review of the evidence[16,49]**

- A systematic review of diagnostic accuracy studies reporting on POC and rapid diagnostic tests to identify bacterial or viral aetiology
- Discusses papers identified, details of bacterial and viral test performance. Evidence suggests that combining biomarkers has potential clinical utility for discriminating the aetiology of RTIs
- The current evidence base is limited, precluding firm conclusions and future research needs to be in primary care and evaluate patient outcomes and cost-effectiveness

**Innovation in AMR: patent trends for novel diagnostics[28]**

- Patent trends of novel diagnostics for AMR
- Key trends in data, technology transfer between academia and industry, pathogen specific developments, technologies and technology characteristics, and appraisal of the innovation-to-marketisation gap
- This report provides evidence for significant innovation in the diagnostic space and also the difficulties of encouraging development of AMR diagnostics for use

**Implications of Using Host Response-Based Molecular Diagnostics on the Management of Bacterial and Viral Infections: A Review[50]**

- A review of host immune response and immune based diagnostics for infectious diseases
- Provides evidence for the utility of host-response signatures to develop AMR diagnostics and novel techniques
- Discussion of the implications of host-based diagnostics on healthcare costs and public health measures

**An Overview of Emerging Point-of-Care Tests for Differentiating Bacterial and Viral Infections**[12]

- Overview of information related to POCT for differentiating bacterial and viral infections and a summary of considerations for implementation of the technology, procedure and intervention
- Describes types of POCTs, examples of available BV tests, available evidence for these tests, impact on prescribing, evidence for key parameters of use (i.e., cost-effectiveness and feasibility) and wider issues to consider
- This report provides valuable information relevant to the healthcare stakeholders to inform understanding of BV diagnostics

**Rapid diagnostic tests for infectious diseases in the emergency department**[51]

- Non-exhaustive list of commercially available FDA- and CE-approved assays for clinical syndromes: pharyngitis and upper respiratory tract infection, lower respiratory tract infection, gastrointestinal infection, meningitis and encephalitis, fever in returning travellers and sexually transmitted infection, including HIV.
- Describes test performance and impact on clinical outcomes focused on use explored in emergency departments
- Provides information on how diagnostics may be used to inform clinical decision making as well as the ended for additional clinical studies to evaluate clinical effectiveness and cost-effectiveness

**Rapid Methods for Antimicrobial Resistance Diagnostics**[22]

- A summary of rapid methods for AMR diagnostics
- Describes broad categories of technologies available for AMR diagnostics and an overview of commercially available technologies for antimicrobial susceptibility testing (determining if a pathogen is sensitive or resistant to an antimicrobial)
- Provides a useful summary of the types of technologies which may be used for AMR diagnostics and some considerations for use

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