Horizon Scanning Final Report: Identification of Acute deterioration / Sepsis Technologies

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Introduction

The NIHR Innovation Observatory (IO) has completed the horizon scanning of the third of four clinical pathways for the identification of technological innovations (e.g., products/interventions) that have the potential to reduce demand for antimicrobials through infection prevention, detection and/or management intervention.

The innovation landscape presented for sepsis (including sepsis based on acute deterioration and hereinafter referred to as sepsis), aims to inform decisions by NHSE & I's AMR Programme Board, and accelerate adoption of proven innovations that will enhance appropriate antimicrobial prescribing and improve patient outcomes. This report (accompanied with the complete Excel sepsis datasets) provides important, immediately relevant data on key areas of development, to allow readers to evaluate the potential impact of these innovations and identify promising technologies for use in the NHS (or wider). To help with clarity and comprehensibility, the report has been organised and presented into three main sections:

1. Methods – Horizon scanning strategy – an overview of the search strategy devised to identify technologies related to sepsis and their related evidence

2. Results – Sepsis technology landscape – including the clinical trial, product pipeline, patent and funding landscape result sections, each containing information (including visualised data) about the global landscape of sepsis technological innovations

3. Conclusion – Summary of key themes and emerging patterns, based on the results retrieved from the scan and market intelligence

It is hoped that the visualisations and accompanying narrative presented in this report (along with the complete dataset) inform understanding and shape discussions on the availability of innovative technologies for sepsis. The report also describes some of the key providers/developers in play for the international market and offers a snapshot of current products, including those with high innovation potential. Overall, our horizon scanning activities highlight that the evolution of sepsis technology has the potential to offer significant opportunities in the NHS to deliver better outcomes.

Methods

Horizon Scanning for Sepsis Technologies

The horizon scanning methodologies developed by the IO to identify the pipeline of sepsis technologies involved the identification of information sources that detected 'signals' for sepsis technologies. The collection of primary and secondary sources were systematically scanned using a combination of traditional scanning methods (manual), automated and novel AI/machine learning techniques.

Collation of Key Terms

Specific search strategies were formulated for the scans, combining identified MeSH/key terms with Boolean operators (where applicable). A comprehensive list of keywords and concepts

was compiled by the IO's Information Specialist Team, based on the evidence reports provided by the AMR Programme Board, in addition to key, identified publications/reports. The primary concepts and terms identified related to sepsis, septicemia, pyaemias, bloodstream infection, acute deterioration, septic shock (including septicemic shock), endotoxin shock, systemic inflammatory response syndrome (SIRS), bacteremia, inflammatory mediators, gram-positive and gram-negative bacterial infection, fungal infection, viral infection, and antimicrobial resistance (AMR).

The set of systematic searches were performed in January 2022 and no date/period exclusions were applied to the searches (unless otherwise stated). Based on successive screening of sources (i.e. identification of sepsis technologies), information was extracted and imported for further data processing.

Inclusion criteria

All technological innovations included in the scan had to meet the criteria for a medical technology (e.g., device, diagnostic test, digital or a combination) and be deemed to detect or diagnose sepsis and/or provide information on antimicrobial sensitivity of the underlying causative organism. All technologies were further classified (see below) and the collated information can be found within the sepsis dataset (Excel file accompanying this report).

Classification of sepsis technologies

- Type of technology (e.g., device, diagnostic test, digital or a combination)
- Type of test (molecular, immunoassay, other)
- Pathogen target (e.g., bacterial, fungal, viral)
- Place in clinical pathway (prevention, detection, monitoring, screening)
- Care setting (e.g., primary care, secondary care, community))
- Population (e.g., neonate, child, adult, elderly)
- Biological sample type (e.g., blood, urine)
- Biomarker detected (e.g., IL-6)
- Resistance markers detected
- Turnaround time (sample to result)
- Method (e.g., RT-PCR, lateral flow immunoassay)

In addition to these fields, information relating to sensitivity/specificity and limit of detection was captured, where available, for diagnostic technologies, as well as clinical trial information and published evidence. Intelligence relating to funding/investment, development or competition awards and patents was captured, as available, under 'Additional Comments' in the sepsis dataset (accompanying Excel file).

Information sources used as part of these scans included (*inter alia*)

- OpenScan: IO's internal clinical trial database containing information from 51 registries across the globe (e.g., UK, Europe, USA)
- Regulatory agency sources (e.g., US FDA)
- Publications (including conference outputs)

- MedTech news websites (e.g., Fierce Biotech)
- Commercial websites and reports
- Academic institution webpages
- Patent databases
- NICE medical technologies guidance

Special Note: Developing optimal search strategies for detecting clinical studies

The initial trial scan (conducted with OpenScan), combined search terms for sepsis and retrieved a high volume of clinical trial records. The 6,349 retrieved trials were visualised in Carrot2, an opensource search engine software, in order to ascertain key themes across all trials. These themes highlighted a focus on sepsis biomarkers, early diagnosis of sepsis, children with sepsis, and reference to intensive care units (ICU). To achieve an appropriate balance in the number of records that could be feasibly screened within the timelines of this project, the search strategy was further refined; the combined terms for sepsis were applied only to the title field of trial records. This search strategy retrieved 202 trials, of which 59 were found to be within the scope of the project brief.

Results

The Need for Improved Technologies in Sepsis

Sepsis is a potentially life-threatening condition that occurs as a result of the body's immune reaction to infection with bacterial, viral and/or fungal pathogens. Early detection of sepsis is critical for timely administration of appropriate treatment to optimise patient outcomes. However, diagnosis of sepsis remains challenging in the early stages, as symptoms of sepsis are non-specific. Furthermore, laboratory-based culture methods can take 24 – 48 hours to yield results. Due to the limited availability of rapid and accurate diagnostics, it is recognised that there are high levels of inappropriate antibiotic use. Thus, new and emerging diagnostic solutions and clinical biomarkers have the potential to better guide antibiotic use in sepsis and to control the spread and emergence of AMR, whilst preserving positive outcomes for patients.

Product Pipeline of Sepsis Diagnostic Innovations

Our horizon scan of primary and secondary sources identified 269 technologies from across 30 countries. Whilst technological developments of sepsis innovation are occurring globally, our analysis (based on country of development) highlighted that the US (41%, 111), UK (15%, 41), Germany (6%, 15) and France (5%, 14) were the top countries for development activity (**Figure** 1). The US was found to develop a range of technologies utilising new methodologies for sepsis detection (e.g., microfluidics, biosensors) alongside existing sepsis detection methods (e.g., RT-PCR, MALDI-TOF MS, in situ hybridisation). Innovations developed in the UK primarily concentrated on utilising biomarkers to detect or monitor the progression of diagnosed or possible sepsis, and a high proportion (71%) were found to be in the earlier stages of development. Interestingly, innovation in France appears beholden to just one company, Biomerieux, as over half of their technologies (57%) were developed by that firm.

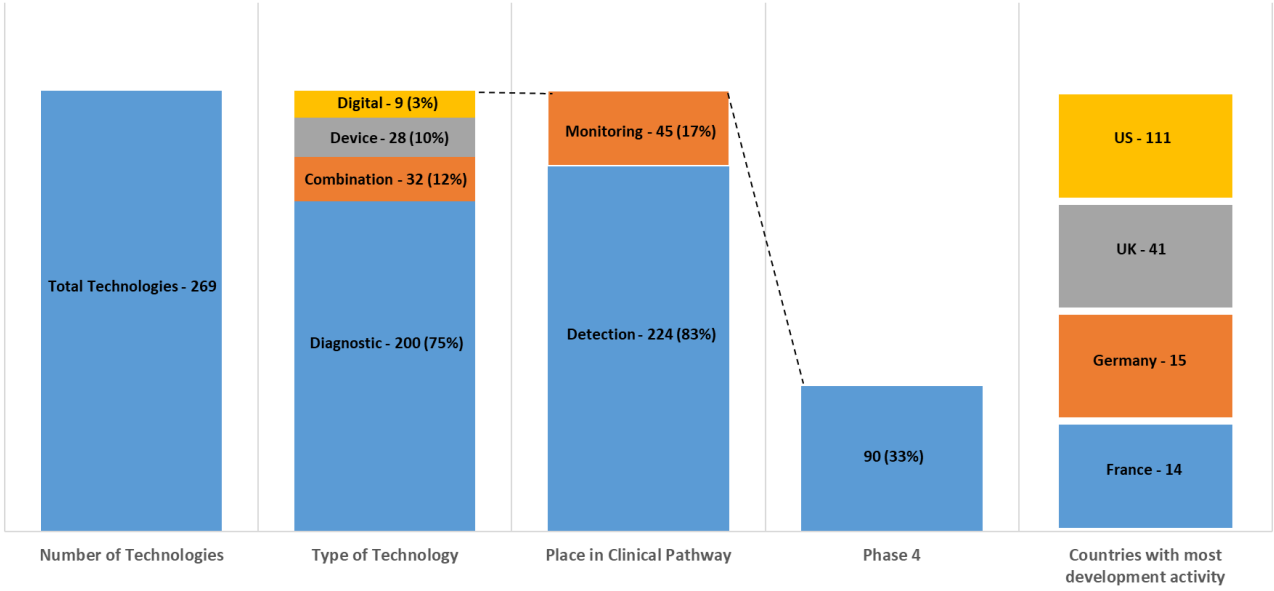

Figure 1. Insights into Sepsis Innovations.
269 sepsis technological innovations including medical devices, diagnostic tests, digital technologies (or a combination), were identified from across 30 countries. The majority of innovations were developed for the detection or diagnosis of sepsis. Development activity was largely concentrated in the US (41%) and the UK (15%), with a considerable proportion of products (33%) on the market or ready to market (Phase 4).

All technologies identified as part of this scan have been classified based on their stage of development (Phases 1-4), with Phases 3 and 4 indicative of late/mature stage of development. The majority of the devices were in the mature stage of development, i.e. on or near ready to market, as shown in **Figure** 2. Overall, 74 of the 90 products in Phase 4 (mature phase) have obtained regulatory approval in 1 or more jurisdictions, with 73% of technologies in Phase 4 awarded EU approval (CE Mark). Technologies with regulatory approval featured more traditional approaches for sepsis testing such as RT-PCR, in situ hybridisation and MALDI-TOF MS.

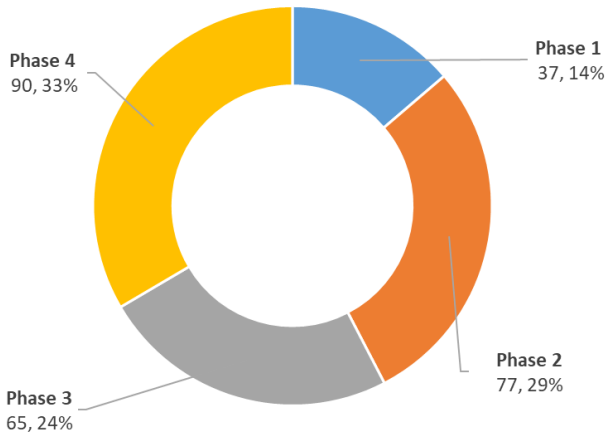

Figure 2. Doughnut chart representing the development stage of sepsis technologies.
In total, 269 sepsis technologies were identified in the Innovations Observatory's scan. The technologies have been classified by stage of development: Phase 1 (i.e. concept) – 37, 14%; Phase 2 (i.e. prototype/early-stage research including preclinical studies) – 77, 29%; Phase 3 (i.e. product validated/demonstrated in relevant environment/clinical study) – 65, 24%; Phase 4 (i.e. product ready to launch/regulatory approved) - 90, 33%.

The vast majority of identified sepsis technologies were reported in development for use only in secondary care, though 14% of solutions in the pipeline are intended for use in either primary care or multiple care settings (i.e., more than one setting of: home, primary care, secondary care or community). Although most sepsis cases are detected in hospitals, technologies outside of a secondary care setting may be useful to address a higher number of suspected sepsis cases through rapid diagnostic methods. Examples of such include Coris Bioconcept's range of lateral flow tests for multiple resistance markers (e.g RESIST-BC) across multiple care settings, and Gradientech's QuickMIC, a rapid diagnostic system utilising microfluidics, for use in primary care.

Globally, there remains a growing interest in technologies with the potential to expedite sepsis diagnosis results. Most developments to date have been targeted toward decreasing the turnaround time in line with clinical guidelines. In total we identified 117 rapid solutions which reported to provide results in 6 hours or less (sample to result). Of these, 57 had a turnaround time of <60 minutes (e.g., BioMerieux's Vidas Brahms PCT assay, Abionic's abioSCOPE PCP test); 30 reported to produce results in 1-3 hours (e.g., Mobidiag's Rapid Sepsis Diagnostic Test, BD Diagnostic's BD Max StaphSR Assay); and 30 reported to provide results in 3-6 hours (e.g., Abbott's PLEX-ID system, Molzym Molecular Diagnostic's AutoSepT). The detection strategies implemented in these rapid solutions include traditional RT-PCR as well as more novel methods, such as microfluidics, which have the potential to be developed into rapid, portable devices utilising simple techniques.

While traditional sepsis detection occurs through blood sampling, we identified 11 technologies that utilised alternative, non-invasive sampling techniques (i.e. breath, saliva or sweat). For example, the company SpotSense have developed 3 rapid solutions using saliva to monitor 3 different biomarkers related to sepsis and acute deterioration (i.e., IL-8, CRP and

PCT). Similarly, Spyras (formerly SpiraSense) use paper sensors that monitor breathing rates of hospital patients as another non-invasive means of diagnosis. It is hoped that by reducing the difficulty of collecting samples, these innovations may provide quicker and easier point of care testing (POCT).

Pipeline Insights: Biomarkers for rapid detection

The global diagnostic biomarker landscape for sepsis includes more than 170 candidates, including various cytokines, cell surface markers, receptors, complement factors, coagulation factors and acute phase reactants. Such biomarkers show great value in improving patient outcomes by improving diagnostic accuracy, reducing the time to effective treatment and limiting unnecessary tests and treatments. The identification of this diverse spectrum of biomarker profiles reflects the multitude of inflammatory mediators activated during sepsis, and thus the need for several reliable diagnostic biomarkers. A wide range of novel biomarkers (including WRS, miRNA, ADM), have been discovered and are being clinically assessed by a host of different technologies. The validity of these new and emerging biomarkers were often examined with comparison to established inflammatory biomarkers, such as CRP, PCT and IL-6.

A key difficulty in diagnosing sepsis is the availability of highly specific and sensitive biomarkers that facilitate rapid, accurate diagnosis and thereby enable timely treatment. The complex pathophysiology of sepsis explains the variety of biomarkers potentially useful to the clinical pathway, and the significance of such biomarkers was reflected in the wide array of diagnostic biomarkers we found in the development pipeline (early to late stage). These were stratified into the following categories: cell marker, organ dysfunction, receptor, coagulation, vascular endothelial damage, acute phase protein, cytokine/chemokine and other biomarkers (**Figure** 3).

The most common type of biomarker used in Phase 4 technologies were acute phase protein biomarkers, more specifically PCT. There were also a number of approved, rapid POCTs that utilised PCT as their diagnostic biomarker (e.g., VIDAS BRAHMS PCT assay, LIAISON® BRAHMS PCT® II GEN and ADVIA Centaur B·R·A·H·M·S PCT). Several of these technologies have been evaluated by NICE but with insufficient evidence to recommend routine use in the NHS[1].

In earlier stage technologies (Phase 1/Phase 2), more biomarkers tended to fall into the category of "Other biomarkers" (e.g., WRS, lactate, bilirubin). WRS, used in JW Bioscience POCT, has recently been patented as a biomarker for the use in sepsis, indicating a continued commercial interest in novel biomarkers. Additionally, biomarkers of organ dysfunction have become more prevalent in recent years with 2 technologies (bio-ADM, MR-proADM test) receiving EU CE approval for the use of adrenomedullin (ADM) as a biomarker; MR-proADM has shown improved accuracy of infection diagnosis, though NICE has noted some evidence uncertainties regarding its influence on clinical decision-making[2].

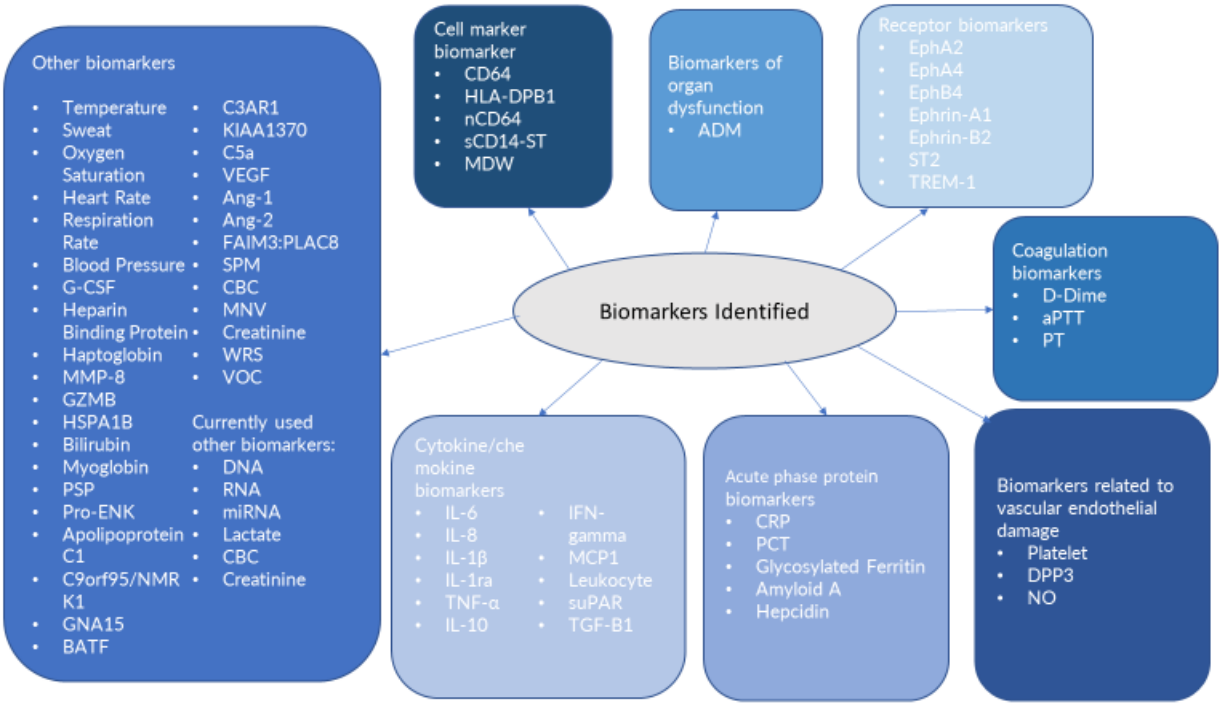

Figure 3. **Biomarkers Identified Used in Sepsis Innovations**
Each biomarker identified in the pipeline divided into relevant categories as taken from Pierrakos et al[3]. Cytokine/chemokine and acute phase protein biomarkers were the most common biomarkers utilised in sepsis technologies.

A key emerging theme identified from our global pipeline is the prevalence of multiplex biomarker panels, such as The Sepsis Metascore, PERSEVERE and HemoSpec. The lack of progress in sepsis diagnosis using a single biomarker is postulated by experts as a significant driver for the investigation of multiple 'players' present at different times during the disease. At present there is no single laboratory test that accurately diagnoses sepsis. Therefore, recent innovations utilising and investigating the performance of new biomarkers to diagnose sepsis are potentially promising. Future research on the use of panels or combinations of markers, when used alongside repeated clinical evaluation, will continue to aid in identifying reliable candidates which can detect sepsis at an early stage, assist with assessing disease severity, and indicate the need to re-evaluate ongoing therapy.

With advancing knowledge in the human genome, studies have now focused on understanding the immune response in sepsis. New methodologies, such as DNA and RNA microchips, have aided complex investigations into the significance of gene expression patterns between infectious and non-infectious etiologies. Equally, these techniques should identify specific DNA or RNA biomarkers that arise in response to sepsis and not other causes of inflammation. Technologies such as Micro-RNA Biomarker Panel, SeptiCyte® RAPID and KlotoDx are currently using such methods and attempting to reduce incorrect diagnoses by ensuring inflammation is sepsis-specific. Such innovation may push sepsis diagnosis into the field of personalised medicine.

Pipeline Insights: Technologies for pathogen identification

Our pipeline scan of technological innovations demonstrated that there were 72 technologies in development for the identification of pathogens relating to sepsis. 53% of these innovations were for the detection of only bacterial targets, which was unsurprising given that sepsis is most commonly caused by bacteria. Such bacterial targets included: *S. epidermidis; S. pyogenes; S.aureus; E.coli;* and *E. faecalis*. Of these relevant technologies, 18 applied molecular detection techniques including established methods (e.g., RT-PCR, in situ hydrbisation) as well as more novel approaches such as CRISPR and NGS. Opgen, Pathogenomix and GenomeKey are all examples of an NGS application to pathogen detection, while the use of CRISPR in the technology from Rochester Institute of Technology demonstrates a potential for rapid, low-cost detection of sepsis-causing pathogens. In addition to bacteria-only detection technologies, there was a small number (11) of innovations that detected bacterial agents plus either fungal and/or viral pathogens (e.g., SepTec, BACT/ALERT® VIRTUO, PLEX-ID).

46 pathogen detecting technologies reported to detect more than one pathogen (i.e, multiplex tests), but it is unknown what proportion of these tests provide a differential diagnosis. As with the pathogen tests mentioned above, these technologies primarily used established methods, although a small number of technologies used novel approaches such as microarrays, microfluidics or NGS. 15% of the multiplex technologies, including those such as SepTec, iDTECT Dx, and BACLIB, detect pathogens across more than one microbial type (i.e., bacterial, fungal or viral). We also note that a number of technologies (133, 49%) in the dataset lacked data relating to the pathogen identified, usually as a result of a failure to report by the developer or the early development status of the technology in question.

Pipeline Insights: Technologies for AST (with or without pathogen identification)

Antimicrobial susceptibility tests (AST) are vital for appropriate management of sepsis, yet our scan identified a minority of AST technologies (74, 28%) in development. It should be noted that over half of the technologies for AST (43, 58%) were found to identify sepsis-causing pathogens in addition to AST (e.g., VERIGENE Gram-Positive Blood Culture Test (BC-GP), OmiX-AMP, BIOFIRE® BCID2 Panel). While 56% of these technologies utilised molecular techniques, 3 developers used immunoassays, and 2 developers incorporated the use of artificial intelligence (Pattern Bioscience) or machine learning (University of California).

A number of innovations were found to detect genetic markers of resistance, often using MALDI-TOF MS or RT-PCR. Resistance markers detected were most commonly for Vancomycin-resistant Enterococcus (e.g., vanA, vanB), carbaphenom resistance (e.g., OXA-48, VIM, IMP, KPC) and methicillin resistance (e.g., mecA, mecB). However, due to the evolving nature of AMR, molecular testing for genetic markers of resistance is not always suitable for AST, and a small number of AST innovations identified in the pipeline are phenotypic resistance tests, using novel methods such as microfluidics or the use of biosensors in combination with fluorescence (e.g., Specific Diagnostics - Reveal Rapid AST System).

NGS also has the potential to be of great value to AST and pathogen identification as the method can detect across pathogen types and resistance markers. However, only 2 identified innovations (COSMOS-ID - Bacterial Isolate Sequencing, Great Ormond Street Hospital for

Children - Single diagnostic test) used this methodology for AST, suggesting the need for further validation and investment.

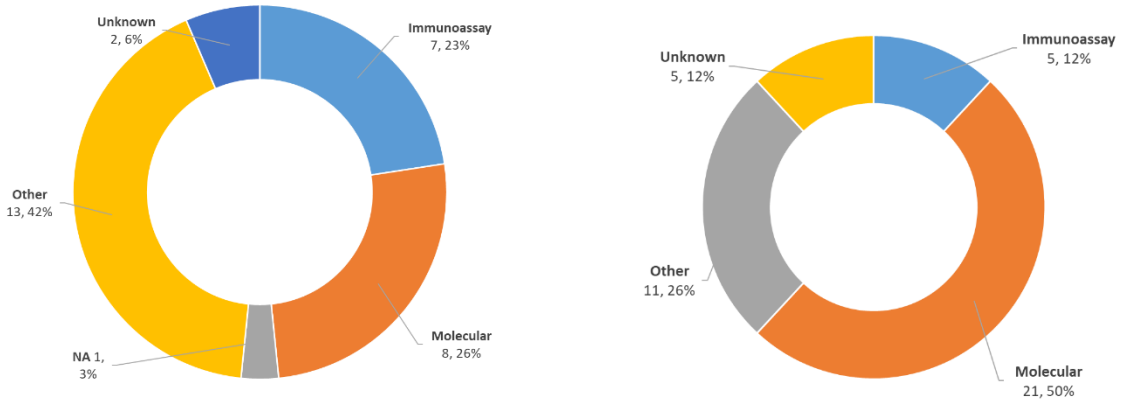

Figure 4. Type of Susceptibility Test Technology
Breakdown of type of test technology for susceptibility tests (left) and for pathogen + susceptibility tests (right). The most common category in susceptibility testing was "Other" (42%), compared to molecular testing (50%) as the most common technology type in pathogen + susceptibility.

Pipeline Insights: Innovation for Neonates

A large proportion (93%) of the identified technologies had clinical application across different age groups (e.g., for use in adult and elderly populations). Only 20 innovations in the pipeline were suitable for use in neonates, 14 of which were designed solely for that population. Given the known, low blood culture sensitivity in this population[4], it is interesting to note that 9 of these technologies require a neonate blood sample. An innovation from Lurie Childen's Hospital of Chicago, however, uses umbilical cord blood to determine levels of amyloid A, CRP and haptoglobin, thereby removing the need to obtain a blood sample from the neonate.

The methodologies in development for the neonate population include traditional approaches (e.g., RT-PCR) as well as novel methodologies such microfluidics, biosensors and digital high resolution melt (DHR-M). This latter method is in development at the University of California with funding from the NIH, and, in combination with machine learning, it offers a simple, low cost, rapid alternative to traditional blood cultures and bacterial pathogen identification. It should be noted that although the methodologies in use were distributed without any clear preference for one approach, a majority (70%) of technologies were intended for biomarker detection: 12 technologies detected biomarkers, while an additional 2 technologies used pathogen+biomarker detection. Of the 20 technologies in the pipeline for neonates, only 2 detected susceptibility.

Clinical Trial Landscape

OpenScan, the Innovation Observatory's clinical trial tool, was used to search trial data from 51 registries across the globe (including the UK, EU, USA, and China). After an initial scoping search (for more information, please see the Methods section above), we identified 59 trials

across 19 countries that met our inclusion criteria. The US (33%), China (15%), France (7%) and the UK (7%) represented those countries with the most clinical trial activity.

Figure 5 below depicts the changing clinical trial landscape covering trials registered between 2004-2024 and displays activity by trial start date and the duration of trials to completion. Ten trials were ommitted from the data visualisation, as there was insufficient information about their primary completion dates. Though the average trial lasted less than 3 years, one UK trial (ISRCTN17375399) ran from June 2006 to June 2017, and though its results are not available, it remains of interest given its joint military-funding from the UK Ministry of Defence and the US Defense Threat Reduction Agency. The length of the trial and its significant number of participants (4,385) demonstrates a larger, policy interest in sepsis that extends beyond just the scope of the NHS and other healthcare organisations.

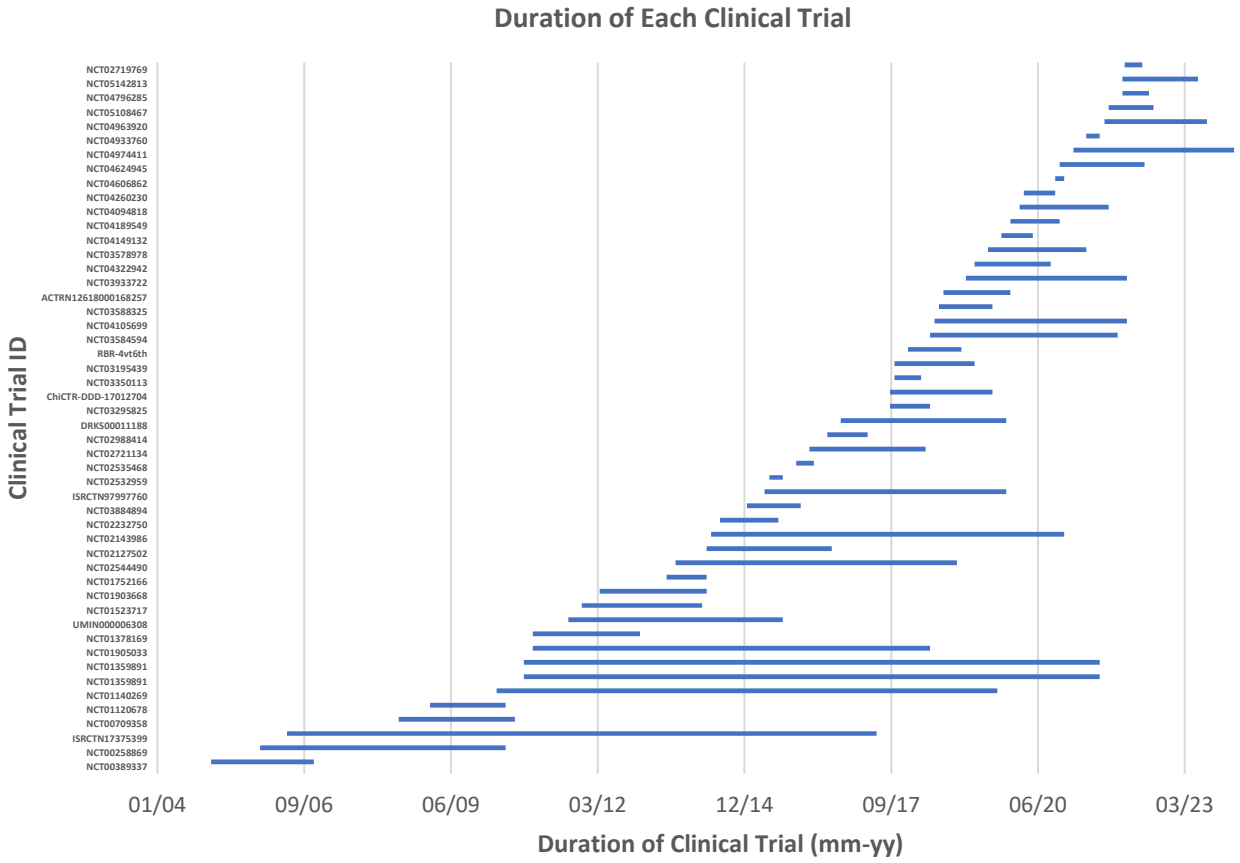

Figure 5. Evolving Clinical Trial Landscape
The clinical trial landscape (activity and duration) for sepsis technological innovations.

Within the clinical trial landscape, there was a focus on investigating molecular tests and immunoassays. Common methodologies included RT-PCR, NGS, as well as traditional ELISAs, and all of the innovations were designed for secondary care, though some were also intended for multiple care settings. Most of the technologies in clinical trials detected either biomarkers

(37%) or pathogens (28%), while a trivial number (1%) were ASTs. Pathogen-detecting innovations focused on bacterial pathogens (represented by 15 tests), while only a small number of innovations detected viral or fungal pathogens (represented by 2 tests each). One pathogen-detecting innovation of note was the Karius Test™, under investigation in over ten clinical trials including one for the prediction and diagnosis of sepsis in adults (NCT02988414). Though it claims to detect over 1000 pathogens, the results of this completed trial are not yet available.

It is a challenge to diagnose sepsis in critically ill patients, as it is often complicated by the presence of inflammation due to other underlying disease as well as the prior use of antimicrobial therapy (negatively impacting cultures). As a result, culture-independent techniques for pathogen detection and identification, such as PCR, may have an upcoming role in the sepsis diagnostic pathway. In the current scan, there were 7 trials that utilied PCR (11.5%). Additionally, though there has been discussion about the utility of less invasive sampling methods as a means to simplify POCT, nearly all the innovations in the clinical trial scan (51/59) used a blood, serum or urine sample. There was, however, one US-based trial (NCT02532959) that investigated the clinical utility of the zNose Diagnostic Breath Analysis system, which uses high-speed gas chromatography on patient exhaled breath to identify Volatile Organic Compounds (VOC) associated with sepsis.

Trial Insights: Biomarkers for Rapid Detection of Sepsis

Our trial scan identified an array of biomarkers, singularly or in combination, and these included widely used biomarkers such as CRP, PCT, IL-6 and lactate, as well as other novel biomarkers such as MDW, presepsin and pancreatic stone protein. The Beckman Coulter DxH 690T Hematology Analyzer, for example, is in a clinical trial (NCT03588325) to confirm the validity of MDW to detect the development of sepsis in adults for whom a complete blood count with differential (CBC-DIFF) had been ordered upon presentation. Given the complexities of the sepsis response, however, it is widely considered that no one biomarker will be sufficient for diagnosis[3]. Combinations of biomarkers are needed alongside new devices that can rapidly and accurately analyse such combinations, and trial NCT03588325 explicitly set out to validate MDW in a patient diagnostic pathway that also included the use of PCT or CRP. The Hemospec device, under investigation in 2 clinical trials funded by the University of Athens (NCT03350113 & NCT03306186), is another example of combined biomarker testing, featuring the use of clinical information, blood protein biomarkers, and morphology indicators of white blood cells. Although these trials completed in 2018, results have yet to be published.

We note that many of the initial trial scan results featured a study that investigated the clinical utility of novel sepsis biomarkers. Most of these trials, however, were excluded as they did not investigate a MedTech innovation, diagnostic or monitoring device. They are still worth noting, however, as it is likely that the validation of novel biomarkers will drive the development of new tests and panels in this field.

Trial Insights: Innovation for Neonates

Within the clinical trial landscape, technologies tended to focus on identifying sepsis within the adult and elderly population; these age groups accounted for 82% of trials identified. There were, however, 6 trials that included neonatal populations, and this low number may be due,

in part, to the ethical and practical limitations of any clinical trial performed in this population. Of these 6 trials, 3 investigated technologies that could be used in all age groups (neonates, children, adults and the elderly). These included: a digital biomarker prediction tool from the Chance for the Critically Ill Child Foundation; a molecular diagnostic from Inflammatrix (Insep) that uses RT-LAMP and machine learning; and an enzyme immunoassay from PHC Europe BV (PATHFAST™). The three other trials with only neonatal populations (NCT03884894, NCT01120678, NCT03578978) all came from non-commercial developers (i.e., two research institutes and one healthcare organisation) and are all intended for use in secondary care. Interestingly, despite the low blood culture sensitivity in neonates, 2 of these technologies still required a blood sample.

Patent Landscape

The data from our international patent scan revealed 4,944 patent documents in the field of sepsis technological innovation. By jurisdiction, these patent documents were led by North America (46.6%), Europe (17%), and the World Intellectual Property Organization (WIPO). Since 1988, patent applications have gradually increased, with an average of 368 annual patent applications between 2010-21. The increase in applications could be related to the driving factor of antimicrobial resistance as a global public health threat and the importance of timely diagnoses to provide appropriate treatment options[5-6]. Leading patent topics included biomarkers, molecular tests and digital solutions for risk stratification/prediction. Diagnostic-focused patents of potential interest included the University of Texas' microfluidic chip for detecting infection and inflammatory response, Gerencia Regional De Salud De Castilla Y Leon and University Valladolid's in-vitro method for differential diagnosis between septic and non-septic shock in patients, and T2 Biosystem's rapid antimicrobial susceptibility testing. Digital solutions identified from patents included Johns Hopkins University's machine learning algorithms to provide an early warning for septic shock, and Cerner Innovation's maternal-fetal digital risk assessment system.

Key Providers

The major factors for the growth of the sepsis diagnostics market include the increasing burden of sepsis, the growing burden of hospital-acquired infections, an increase in research and funding for AMR, and an increase in funding for sepsis-related research activities. High growth has been forecast in the development of sepsis diagnostic software, which is attributed to the increased adoption of innovative software platforms by healthcare providers for better diagnosis and management of sepsis. Our global scan identified 198 developers from across 30 countries. Key developers in this area include BioMerieux, Coris Bioconcept, OmiX Research and Diagnostics Laboratories, Roche Diagnostics, SpotSense, Cephied, OpGen (AdvanDx) and T2 Biosystems.

The UK has historically been at the centre of global efforts in combatting AMR and sepsis and continues to develop new and emerging diagnostics tools. A total of 36 UK-based developers were detected in our dataset, including key developers such as University of Liverpool, Kimal Plc, Sepsis Limited, Presymptom Health and University of Strathclyde. The University of Liverpool have a treatment portfolio of 3 sepsis technologies, including research collaborations with external stakeholders. The global development pipeline comprised of established

technologies (e.g., immunoassays, DNA sequencing) alongside new technologies (e.g., AI, machine learning, digital cell culture), and the clinical, financial, infrastructural, logistical, and organisational needs of such new technologies will need to be considered by the NHS (and wider).

The growth and development of sepsis diagnostic and monitoring technologies also increases the challenge of identifying those technologies with most promise. From our dataset, we have identified a small selection of technologies with high potential that may have attracted significant investment and/or have been shortlisted for development awards and competitions, along with other novel technologies that may be of interest. Technologies presented in

Table ***1*** include advances in biomarker-based POCTs for distinguishing bacterial sepsis, multiplex RT-PCR panels of bacterial pathogens, in addition to genetic markers of antibiotic resistance.

Table 1. New and emerging technologies for acute deterioration and sepsis with high potential

Developer	Technology	Product Description	Location
Immunexpress	SeptiCyte	SeptiCyte RAPID is a rapid host-response test that distinguishes sepsis from non-infectious systemic inflammation (INSI/SIRS) using host RNA signature as biomarker.	US
Cytovale	IntelliSep	IntelliSep is rapid, POCT platform using machine learning and imaging to detect sepsis causing pathogens. Validated in clinical trial (NCT04933760). Funded by US Department of Health and NSF.	US
Stanford University and Inflammatrix	Sepsis MetaScore	The Sepsis MetaScore is a mRNA assay panel of host immune response for detection of sepsis utilising a combination of biomarkers.	US
Baebies	Baebies FINDER Sepsis	Baebies FINDER Sepsis is a near-patient, rapid diagnostic in development for diagnosis of neonatal sepsis. CARB-X funded.	US
Pattern Bioscience	Digital Culture™ technology	Digital Culture™ technology for pathogen identification (ID) and antibiotic susceptibility test (AST) results together within four hours. In phase 2 of development with funding from CARB-X and the AMR Diagnostic Challenge Fund.	US
Prenosis	Prenosis Sepsis Immunoscore	Prenosis Sepsis Immunoscore uses hybrid biomarker and clinical dataset information to prioritise the sickest patients for antibiotic therapy through early risk identification. In phase 3 of development.	US
Inflammatrix	InSep	InSep is a test designed to identify the presence, type and severity of an acute infection, providing risk scores of mortality from sepsis. Validated in	US

		clinical trials (NCT04094818, NCT03744741). Funded by NIH.	
University of Liverpool; MicroLab Devices; Forsite Diagnostics	Rapid On-site Microfluidic POC Test for Sepsis	Microfluidic POCT for Sepsis is a disposable, diagnostic system combining microfluidic and lateral flow technology to measure a number of sepsis biomarkers. In phase 2 development. Funded by EPSRC.	UK
AnteoTech	Sepsis Multiplex Test	Sepsis Multiplex Test is a multiplex lateral flow assay used to monitor the biomarkers IL-6, CRP and PCT to provide a rapid, diagnostic test for sepsis. In phase 2 development.	Australia
Sepsis Limited	Point of Care Device	A point of care device for diagnosing early signs of bacterial sepsis at the patient's bedside in intensive care and emergency care services. In phase 1 development. Innovate UK funded.	UK
Stender Diagnostics	AntibioDx	AntibioDx is a diagnostic device used to provide doctors with information about the specific pathogen causing a blood stream infection and its AMR profile within 1 hour. In phase 3 development. EC funded.	Denmark
Valetude Primus	POCD Diagnostic	A point of care rapid diagnostic for rapid detection of bacterial infection and gram profiling of bacteria in a blood sample. In phase 3 development. Longitude Prize funded.	India

Other Innovations of Potential Interest

A number of innovations outside the main scope of this scan have been included in the 'Other Innovations of Interest' tab (Excel dataset), including those which target sepsis prevention, monitoring and screening.

MedTech innovations for sepsis screening and early detection of sepsis include wearable technologies, such as a wearable sticker in phase III of development by Nottingham Trent University, University of Southampton and University Hospital Southampton; and the commercially available Protocol Watch from Phillips which has some trial data in sepsis early detection. Our scan also revealed development in bedside monitoring systems such as the RespiraSense from PMD Device Solutions, Ltd., which uses a novel sensor platform to detect changes in sleep and breathing and to predict the risk of acute deterioration.

The dataset also contains several sepsis risk stratification and clinical decision support system (CDSS) tools which are designed to assess severity and prognosis in order to guide optimal treatment strategy. A CDSS in development by Hannover Medical School, described as being 'designed to solve knowledge-intensive tasks for supporting decision-making processes', has clinical trial data available in paediatric sepsis patients. The web-available qSOFA score, developed by the University of Pittsburgh, is a bedside prompt with trial data in sepsis that

may identify patients with suspected infection who are at risk of a poor outcome outside the ICU. Similarly, the University of Bristol, with funding from UKRI, is currently developing a CDSS tool which will integrate SOFA scores and patient records to guide precision antimicrobial prescribing.

Finally, we identified systems for management of sepsis via blood filtration, including: the MediSieve system by MediSieve in phase II of development; and CytoSorb by CytoSorbents Europe GmbH, which is commercially available.

Funding Landscape

A scan of funding databases identified 147 active and completed projects that fell within scope. Analysis revealed that funding for technological advancement for early diagnosis of sepsis and acute deterioration has grown, but with fluctuation, since 2001 (**Figure 6**). There was a noticeable peak in funding in 2014, with smaller periodic peaks in 2016, 2018, and 2021. Some of this fluctuation may be due, in part, to the UK Five Year Antimicrobial Resistance Strategy launched in 2013 and running until 2018[7], though with the global perspective of this landscape that would appear unlikely. It is possible that, along with the previous report on RTIs, sepsis may have received more recent funding support thanks to additional attention in AMR due to the ongoing pandemic. We also note that surveillance of AMR by the European Centre for Disease Prevention and Control (ECDC), in 2018, identified a need for investments to reinforce the best practices and aid in the reduction of AMR incidence in the EU/EEA[8].

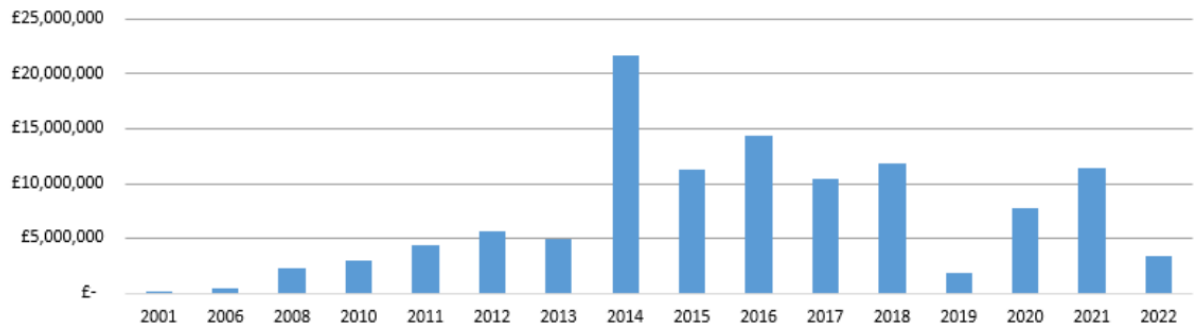

Figure 6. Global trends in the amount of funded research projects (by start year) with a focus on technological innovations for the detection of sepsis.

The majority of projects identified by the funding scan were collaborative research and development projects with a focus on technological innovations for the diagnosis and detection of pathogens that induce sepsis and acute deterioration. Various other projects such as feasibility pilot studies, research grants and funding for research infrastructure were also identified in this scan. On an international scale, the EU (56%, £70,100,990) and the US (31%, £38,361,991) awarded the highest proportion of funding to these research projects (**Figure 7**). Overall, the US funded the largest number of individual projects with a total of 67.

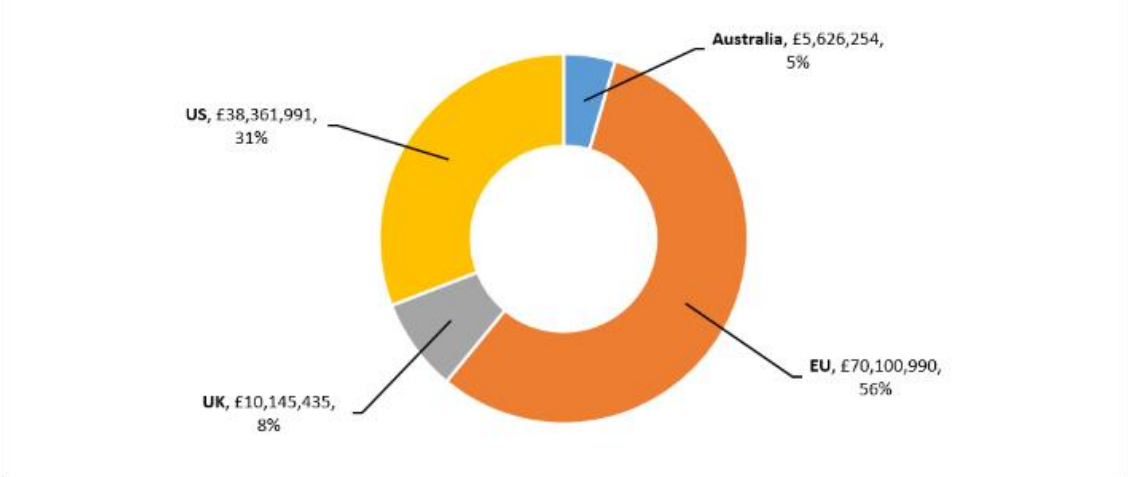

Figure 7. Doughnut chart showing the international funding landscape
Total funding identified by the Innovation Observatory across Australia (5%), EU (56%), UK (8%) and US (31%).

At our national level, the scan revealed a total of 37 research projects funded by multiple funding bodies within the UK, including: Innovate UK (58%, £5,834,677); the National Institute for Health Research (NIHR) (28%, £2,825,755); and the Medical Research Council (MRC) (10%, £1,011,750) (**Figure 8**).

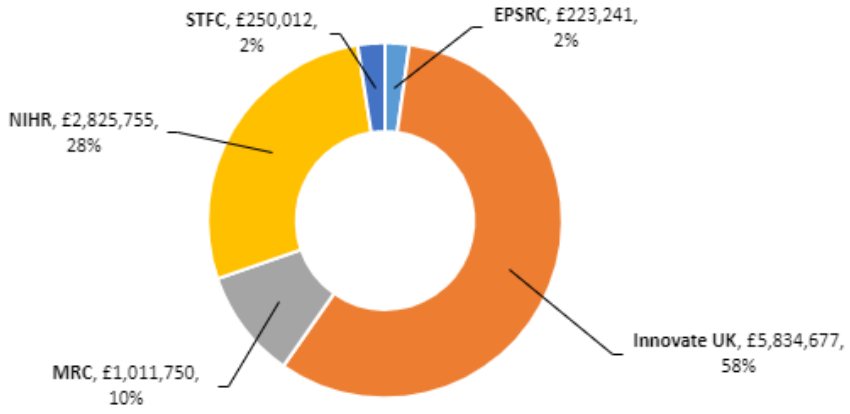

Figure 8. Doughnut chat showing the UK funding landscape
Landscape of UK funding providers, with leading funders: Innovate UK (58%), NIHR (28%), MRC (10%).

The funding landscape scan primarily constituted innovations in point of care, biosensors and machine learning. In June 2018, a smart haematology analyser, HemoScreen, received funding (€2,489,436,25) from the European Commission (EC) as part of Horizon 2020. It is a fast diagnostic test, intended for point of care, which offers multi-parametric evaluation of blood constituents, including red blood cells, white blood cells and platelets. HemoScreen is able to provide results within 6 minutes using just one drop of capillary blood, reducing sampling discomfort. Similarly, the miniaturised laser isotope ratiometer (LIR), funded by the Science and Technology Facilities Council (STFC) (£176,411), seeks to detect sepsis through non-invasive means. The device analyses changes in the ratio of naturally occurring forms of carbon dioxide

exhaled by patients, and for those intensive care patients unable to breathe own their own, the LIR can be attached to ventilators as a continuous monitoring device.

There are also a number of funding projects that focus on AST. For example, the National Science Foundation (NSF) has recently awarded Impedx Diagnostics (£539,695) for an electronic platform and system for rapid (direct from sample) phenotypic antibiotic susceptibility testing. The resulting product will allow a faster transition from broad spectrum to targeted antibiotic therapy and potentially allow for improved outcomes and a reduction in hospital stay.

We also noted an interest in MedTech innovations for the neonatal population, as reflected in the funding projects identified. The scan identified 7 projects that targeted this population. One of the innovations of interest included a fast automated multiplex analysis of neonatal sepsis markers on a centrifugal microfluidic platform which received €1,961,627 from the EC. It theoretically allows for the detection of a whole panel of neonatal sepsis pathogens and sepsis biomarkers in human serum samples, even at low bacterial loads, within four hours.

Conclusion

Despite the urgency to diagnose and treat sepsis, few rapid diagnostics or AST technologies are currently used in the clinical management of sepsis. Diagnosis remains challenging in early stages due to generalised symptoms, therefore suspicion of sepsis may only arise in later stages through clinical signs of acute deterioration (e.g., heart rate, temperature, blood pressure). Given the significant time required to determine pathogen identification and sensitivity through culture methods, patients are typically administered a broad-spectrum empirical antibiotic to ensure effective coverage, with a view to de-escalation to an appropriate narrow-spectrum antibiotic once this information becomes available.

Our global horizon scan provides NHSE/I and the AMR Programme board (and wider) with insights into the pipeline of technologies for sepsis. In particular, it reveals a number of opportunities where rapid diagnostic and AST technologies could be applied to better align sepsis management with the principles of antibiotic stewardship and control the emergence and spread of AMR:

1. There is potential to mitigate ‘defensive’ antibiotic prescribing in sepsis where rapid diagnostics can be applied to indicate risk/likelihood or rule out sepsis
2. Rapid diagnostic tests to confirm bacterial vs. viral/fungal sepsis or overlapping condition with non-infectious cause, such as systemic inflammatory response syndrome (SIRS), to ensure antibiotics are used only where effective
3. Pathogen identification and AST technologies to enable selection or de-escalation to effective narrow-spectrum antibiotic where appropriate (at limited dose and treatment duration); reserving use of broad-spectrum antibiotics for use where needed for effective coverage and in high-risk patients
4. Technologies which assess prognosis/risk in sepsis allow for optimal management, including guiding broad-spectrum antibiotic use and de-escalation of therapy

Recent research activities have enhanced understanding of the host-pathogen interaction in sepsis, and the application of omic approaches (e.g., genomic, proteomic, and metabolomic technology) to large datasets continues to change the ways in which effective biomarkers are identified and validated. On a global level, the use of traditional or novel approaches and clinical biomarkers (including combinations) will in future help improve antibiotic stewardship through optimised antibiotic use, thus increasing patient safety, reducing costs and reducing the development of antibiotic resistance.

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