Sepsis and AMR:
how diagnostic solutions empower clinicians tackling the coupled threat

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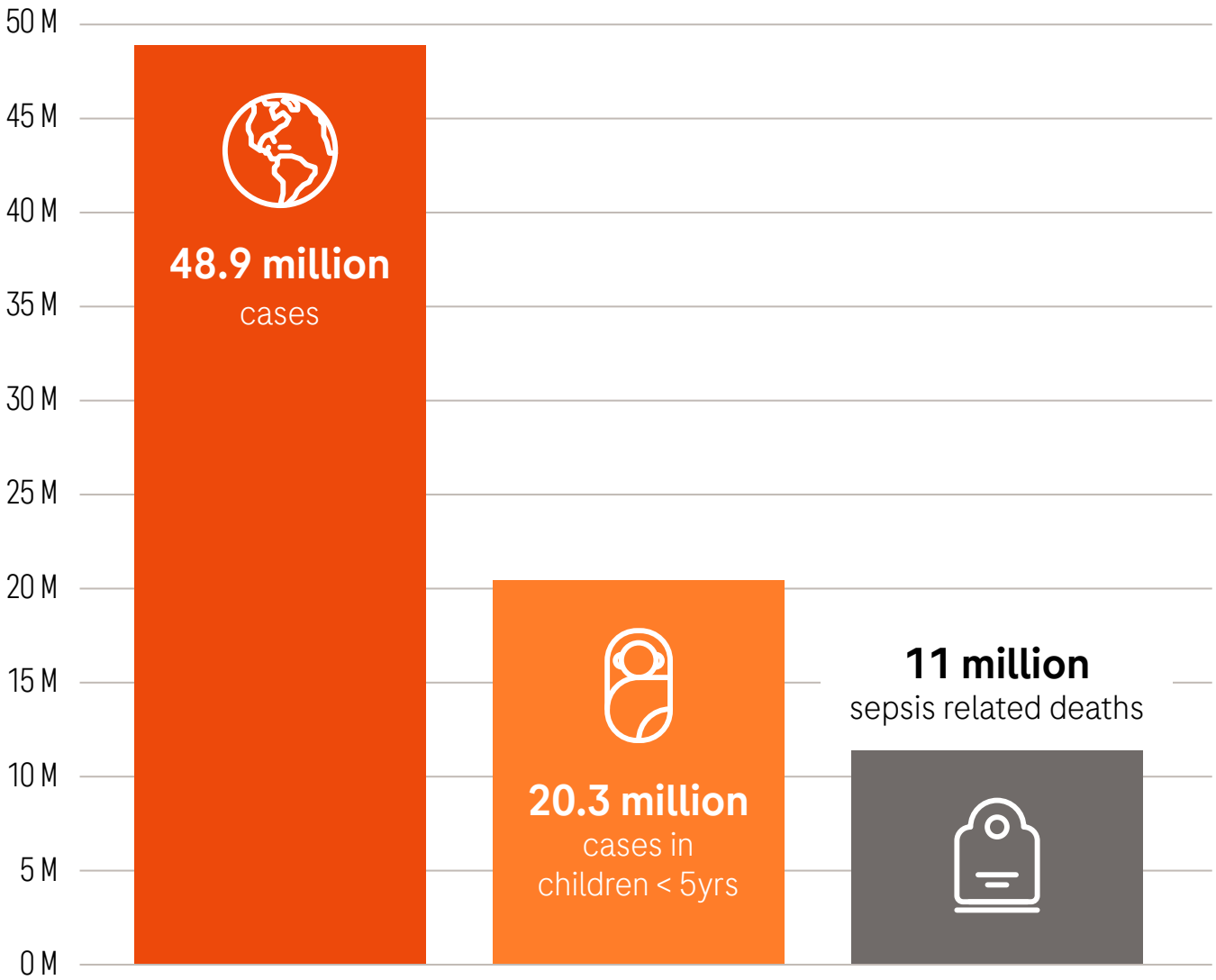
Sepsis: a leading cause of preventable death

Sepsis is a preventable but life-threatening condition, caused by a dysregulated host response to infection.[1] Despite an abundance of awareness campaigns and cross-disciplinary efforts to alleviate the global burden, sepsis continues to increase in prevalence.[2] With limited time to intervene and challenges impeding timely diagnosis and treatment, sepsis is a leading cause of mortality, associated with 1 in 5 deaths worldwide.[3]

Global disease burden[3]

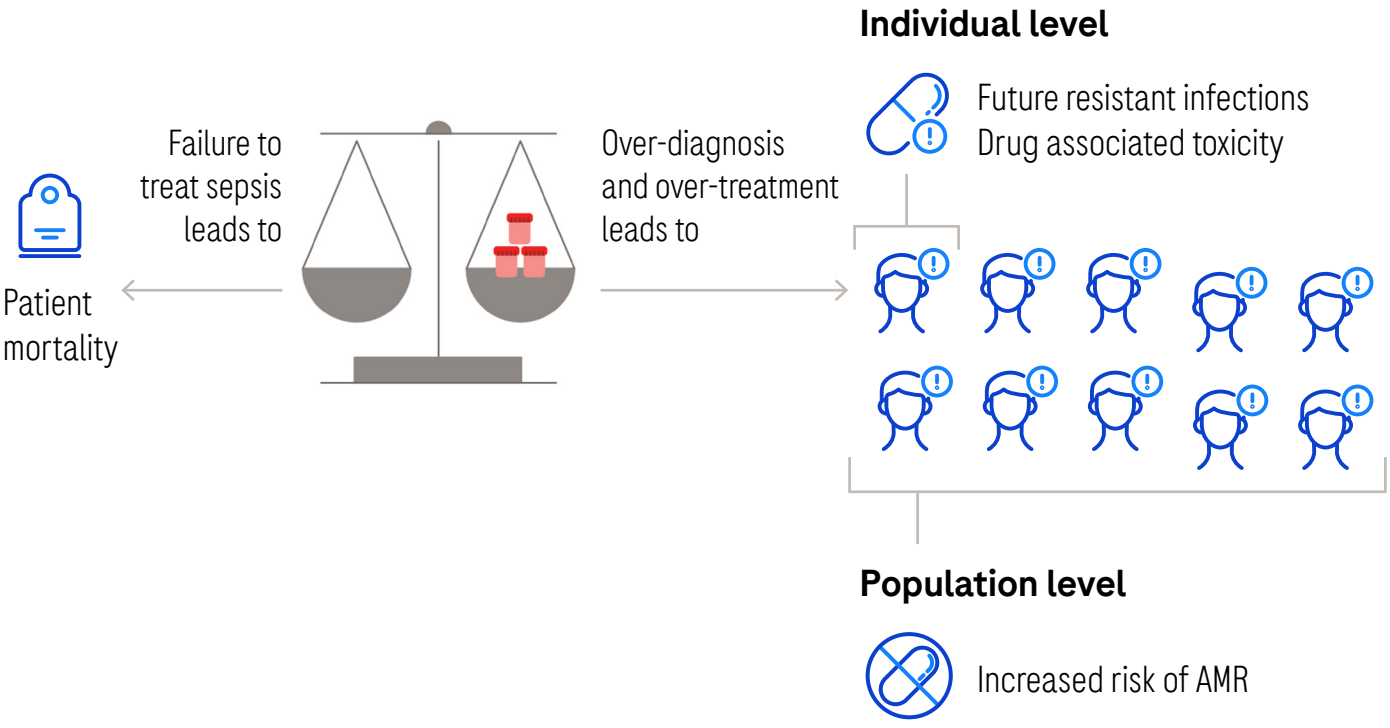


Treatment tightrope: the coupled threats of sepsis and AMR

Sepsis is a medical emergency with a narrow window for therapeutic intervention.[4] Administration of empiric broad-spectrum antimicrobials is the mainstay treatment, with many guidelines outlining a 1-hour to treatment goal.[5] These immense efficiency pressures result in clinicians administering antimicrobials to patients, often without a clear diagnosis.[6] Alongside antimicrobials being administered to patients who don't need them, physicians also need to decide on the appropriate dose and duration of therapy in order to avoid overtreatment. The overtreatment and the less-than judicious use of antimicrobials for not only sepsis, but also other infectious syndromes has compromised their long term effectiveness.[7]

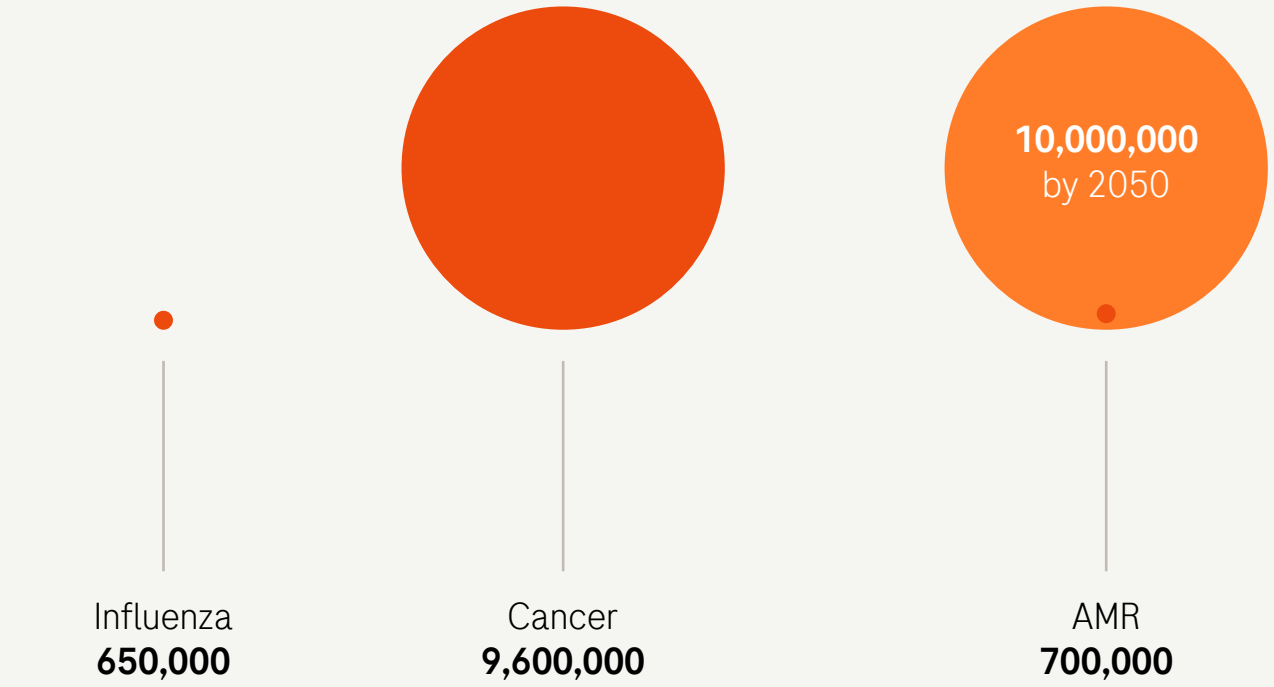
Microorganisms, including bacteria, fungi, viruses and parasites evolve mechanisms to withstand the effects of antimicrobial drugs designed to eliminate them, known as antimicrobial resistance (AMR).[8] The reduced efficacy of antimicrobials results in an inability to eradicate the infection, leading to further prescription of alternative antimicrobials, which in turn increases the risk of future, multi-drug resistant infections.

For every hour of delayed therapy, the chance of survival decreases by 7.6%.[5] Without diagnostic certainty, clinicians must weigh up the risks to act fast:



Antimicrobial overuse accelerates the evolution of AMR, rendering empiric treatments increasingly ineffective and fuelling a harmful cycle that ultimately results in more sepsis-related deaths.[2] With increasing rates of drug-resistant infections expected to claim more than 39 million lives by 2050, there is an urgent need for increased access to diagnostics tools, as well as novel solutions to promote antimicrobial stewardship (AMS). AMS is defined as an 'organisational or healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness'.[9] AMS aims to strike a balance between promptly managing suspected sepsis cases and avoiding antimicrobial misuse and overuse.[10]

Without intervention, AMR will be the leading cause of global death by 2050:[11-14]

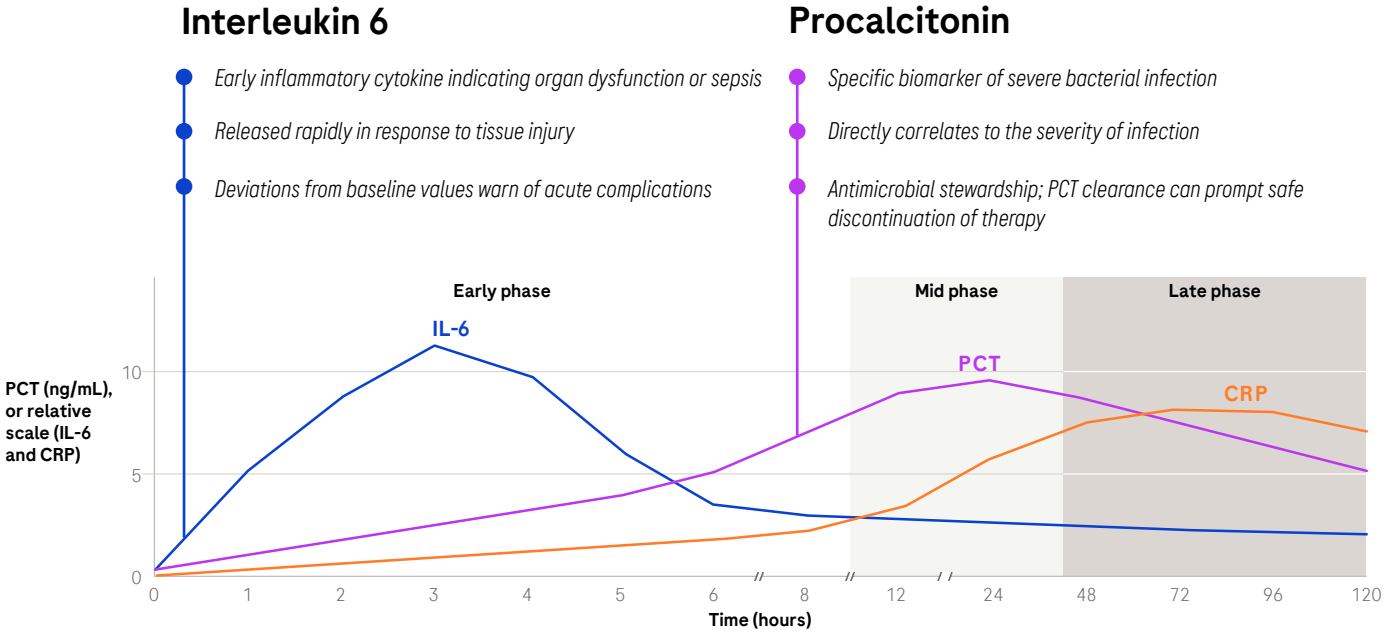


Challenges contribute to antimicrobial overuse

With a complex aetiology and high heterogeneity across individuals, there are several challenges which hinder the early diagnosis of sepsis. The initial identification of patients with sepsis is in itself a challenge, with many patients presenting with non-specific symptoms until their condition rapidly deteriorates.[15] Even in earlier stages of infection, current laboratory tests lack sensitivity and specificity, and routine diagnostic tools such as blood cultures fail to return results that meet the time-to-treatment target of 1 hour.[6,16,17] The shortcomings of current diagnostics are further compounded by long hospital waiting times and workforce shortages, which has led to the prioritisation of early sepsis treatment at the expense of long-term antimicrobial efficiency.[2] Physicians will also need to carefully consider when it is appropriate to discontinue antimicrobials; prematurely discontinuing treatment can have serious consequences, including treatment failure and patient mortality. The possibility of these adverse outcomes may trigger antimicrobial overuse through extended therapy duration.

Roche's PCT and IL-6: enabling the right response at the right time

The coupled threats of AMR and sepsis are a major global health security challenge. Roche understands the significant burden of disease and has identified unmet needs across the patient pathway, to develop cross-technology solutions that tackle the disease end-to-end. With earlier diagnosis of sepsis imperative for helping improve patient outcomes, at the heart of Roche's strategy are two complementary biomarker assays for procalcitonin (PCT) and interleukin 6 (IL-6), that are available on a fully automated platform and are tools that support clinicians in their decisions. Infection biomarkers are a prime opportunity to close the diagnostic gap, providing a more complete clinical picture sooner whilst stewarding clinical decisions around antimicrobial use.[18,19]



Levels of **IL-6** and **PCT** rise early, at the onset of infection, aiding in **early-stage diagnosis.**

IL-6, a proinflammatory cytokine produced by monocytes and macrophages, is an early and sensitive biomarker of sepsis.[20] IL-6 levels rise within an hour of inflammatory insult, with the magnitude of IL-6 elevation directly correlating with infection severity.[21,22] IL-6 enables the reliable identification of patients at high risk of developing sepsis, and is particularly valuable for diagnosing neonatal sepsis, where symptoms may be subtle and time to intervene limited.[23,24] In the context of neonatal infection, IL-6 is an earlier and more potent indicator of sepsis onset than other sepsis biomarkers, such as PCT and C-reactive protein (CRP).[25] One study including over 1,500 neonates found serum IL-6 to detect sepsis with high accuracy and negative predictive value for this patient group, and defined distinct serum IL-6 cut off values for diagnosis dependent on chronological age (day of life).[24] One of the most significant challenges impeding neonatal diagnosis via blood culture is the low obtainable blood volume in low birth-weight infants.[5,24] This challenge is overcome by IL-6 being available on automated platforms with sample volumes as low as 18 µl.[23,24]

PCT, the precursor to the hormone calcitonin, is another inflammatory serum biomarker for sepsis.[25] PCT plays a pivotal role in distinguishing clinically relevant bacterial infections from viral or non-infectious causes, to determine whether a patient specifically requires antibiotic therapy. Undetectable in healthy individuals, PCT levels increase approximately 4-hr post-exposure to bacterial endotoxins and other mediators, and directly correlate with the extent and severity of infection. Monitoring PCT kinetics enables the evaluation of antibiotic efficacy, as a sustained decline in PCT levels reflects bacterial clearance and can guide timely discontinuation of therapy.[26] The ADAPT-Sepsis trial investigated the clinical effectiveness of daily PCT-guided treatment protocols for hospitalised adult patients receiving IV antibiotics.[27] The multicentre trial found after 28 days that daily PCT-guided protocols cause a safe, significant reduction in antibiotic days of treatment (DOT) when administered, whilst CRP-guided protocols did not. These results support PCT as an earlier sepsis biomarker and more responsive to treatment than CRP, with PCT levels normalising more rapidly following antibiotics. With these precise diagnostic insights clinicians are empowered to make confident care decisions; evaluating the need for already initiated treatment to optimise therapy regimens or ensure their safe discontinuation.[27,28]

Greater access to diagnostics supports more effective antimicrobial stewardship

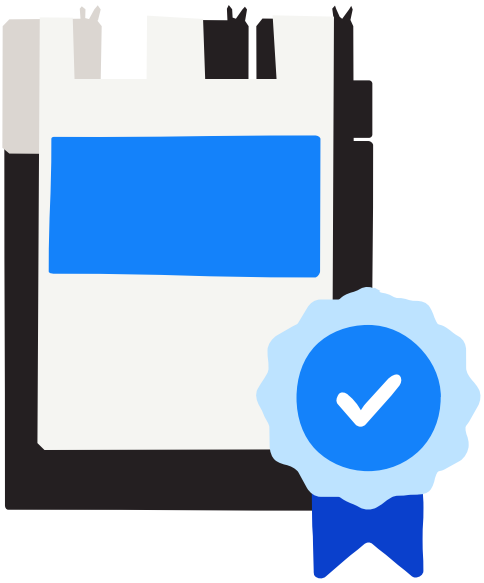
Clinicians and laboratories face significant efficiency pressures when diagnosing and treating sepsis, often exacerbated by staffing and budget constraints. It is imperative to ensure appropriate funding and reimbursement of these IVDs, given their clinical utility in improving care delivery and tackling AMR, and their potential cost-saving benefits. This can be challenging at times given the complexity of health systems. Health economic studies demonstrate that PCT-guided antibiotic protocols offer substantial cost savings and clinical benefits when compared to standard of care (SOC) in intensive care units (ICUs) and hospital settings, and these benefits are observed across diverse healthcare systems. A key driver of the significant cost reduction is the shortening of hospital stays, with savings representing the largest component of incremental cost reduction per person. Fortunately, there are numerous current initiatives aimed at addressing the funding and reimbursement gaps. Global organizations and foundations are actively investing in research and development for AMR diagnostics and novel antimicrobial therapies.[29-33] The aim of these initiatives is to foster a balance between prompt sepsis management and avoiding antimicrobial misuse, thereby promoting AMS. The push for automated processes in emergency and intensive care settings, which allow for rapid measurement of biomarkers like PCT and IL-6 within 20 minutes, also highlights the need for reimbursement models that support the adoption of such efficient diagnostic solutions. These efforts collectively aim to drive the integration of advanced diagnostic solutions into routine clinical practice, ultimately supporting better patient outcomes and mitigating the global threat of AMR.

Excellent clinical performance[23,34]

Available on a fully automated platform (only 18 min to result)[23,34]

Only 18 µL sample volume required[23,34]

Long onboard reagent stability[23,34]



Roche's commitment: transforming diagnostics and shaping the future of care

With the continuing widespread use of antimicrobials, the AMR crisis has intensified and remains an ever-present threat to global health. Nowhere is this more evident than in the management of sepsis, with AMR diminishing the efficacy of antimicrobials and increasing patient mortality rates. Diagnostics have an integral role in AMS. As a global leader in in vitro diagnostics (IVD), Roche provides innovative molecular technologies that enable laboratories to detect sepsis swiftly and simply. Alongside PCT and IL-6, syndromic blood culture identification (BCID) panels rapidly identify pathogens and their resistance genes, helping clinicians assess effective treatment options. Mass spectrometry can further enhance diagnostic capabilities, with automated Mass Spec instrumentation enabling TDM for safer, more tailored therapeutic strategies. Altogether, these accurate and actionable results can help support better patient outcomes, whilst mitigating against the AMR crisis.

Roche offers a comprehensive portfolio that supports patients and clinicians through every stage (treatment initiation through optimization and discontinuation) and care setting of the sepsis patient journey. As the threat of AMR continues to grow, Roche is uniquely placed with the complementary strengths of Roche Pharma and Roche Diagnostics reinforcing their commitment to the AMR space. Roche is continuously monitoring the global disease landscape to identify strategies to combat and control the spread of resistant pathogens. Amongst many larger pharmaceutical companies retracting investment in the development of novel antibiotics, Roche is one of the few still investing significantly in in-house research and academic collaborations to bolster their antibiotic pipeline. Roche is a perennial partner to global health systems, providing world-class solutions to this worldwide challenge.

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