MultiDrug-Resistant Organisms

Handle with care: awareness and tools to preserve antimicrobials

Better diagnostics begins with a better sample collection.

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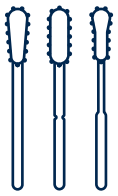
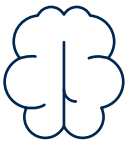


Collection

Transport

Processing



Artificial Intelligence

Our comprehensive approach to preanalytics

Background

One of the greatest threats to global health

Antimicrobial resistance (AMR) is defined as the development – by bacteria and fungi – of mechanisms able to reduce or eliminate the effectiveness of antibiotics[1].

Since the discovery of penicillin in 1928, **the rise of Multidrug-Resistant Organisms (MDRO) has become a global health concern**, reaching today more than 700,000 deaths each year. If the trend continues at its current rate, annual AMR-related deaths are expected to reach 10 million patients worldwide by 2050[2].
Since the pace of drug development is insufficient to mitigate this severe threat, promoting a deeper understanding of the reasons behind the emergence of antibiotic resistance and developing **tools to combat it are urgently needed.**

What's the Copan solution for MDRO?

- ***MDRO collection and transport***

  eSwab® - FecalSwab® - Transystem™ - SRK® - eMRSA™ - BC+™

- ***Antibiotic Susceptibility Testing***

  Radian®

How did MDRO evolve?

Natural selection and human mischief

AMR is a self-defense strategy that arose in microbes long ago, to respond to natural antibiotics produced by other microorganisms. Most antibiotics exert their functions targeting the bacteria cellular processes such as DNA/RNA synthesis, translation, and cell wall synthesis[3]. Bacteria can escape these molecules' action with two main strategies:

- ***By chromosomal mutations***
  which give an inherited resistance to subsequent generations;
- ***Via horizontal gene transfer***
  the acquisition of AMR genes from other bacteria or mobile genetic elements such as plasmids.

These mutations could counteract the antibiotic efficiency in different ways[4].

Antimicrobial use – and abuse – in healthcare and agriculture coupled with the induced proximity among humans of the last decades, **provided a fertile environment for the rapid proliferation of drug-resistant infectious diseases.**

Case study

New Delhi Enterobacterales in Tuscany, Italy

Between November 2018 and October 2019, Tuscany – a 3.7 million citizens Italian region – was hit by an **outbreak of a carbapenem-resistant strain of Enterobacteria** (NDM-CRE). The delayed identification and response led to sustained NDM-CRE transmission in the North-West area of Tuscany, with 1645 people infected.
Of these, 129 contracted a bloodstream infection – lethal in one-fourth of them[5].
Luckily, the introduction of standardized routine screening of hospitalized patients across Tuscany resulted in a progressive decrease in the bacteria diffusion within the region and its successful containment – even if a small number of NDM-CRE cases continue to be recorded today in the area.

Resistant microorganism

Eskaping bacteria

The World Health Organization has listed several pathogens that have developed high levels of resistance across the world[3]. Among these, **the pathogens part of the "ESKAPE" group** – comprising both Gram-positive and Gram-negative bacteria such as *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and Enterobacter spp.* – **are the biggest concern when talking about AMR[6]**.

In addition, the emergence of multiple-drug-resistant *Mycobacterium tuberculosis* strains seriously threaten tuberculosis control and prevention, making its global eradication an extremely challenging task[7].

- ***Methicillin-Resistant Staphylococcus aureus (MRSA)***
  Associated with healthcare settings, MRSA causes a range of infections from mild skin abscesses and post-operative wound infections to bacteremia and pneumonia. According to a 2010 metanalysis, between 13 and 74% of worldwide S. aureus infections are MRSA[8].

- ***Vancomycin-Resistant Enterococci (VRE)***
  VRE infections usually cause wound infections and bacteremia. VRE is neither more pathogenic nor more virulent than susceptible Enterococci, but treatment of VRE infection is much more problematic due to limited therapeutic options.

- ***Extended Spectrum Beta-Lactamase (ESBL)***
  ESBL is a bacterial enzyme that breaks down specific beta-lactam antibiotics. It may be produced by any Gram-negative bacteria but is most commonly produced by *E. coli.* and *K. pneumoniae.* Despite usually living unharmful in people's intestines, infected people with a weak immune system are at risk of antibiotic treatment failure.

- ***Carbapenem Resistant Enterobacteriaceae (CRE)***
  Carbapenem resistance develops by the production of carbapenem-hydrolyzing enzymes. As for ESBL, carbapenemases are most common in *E. coli* and *K. pneumonia* but can be found in almost all Enterobacteriaceae members. These organisms can cause various infections, such as wound/surgical sites, bacteremia, pneumonia, and urinary tract infections.

Economic burden

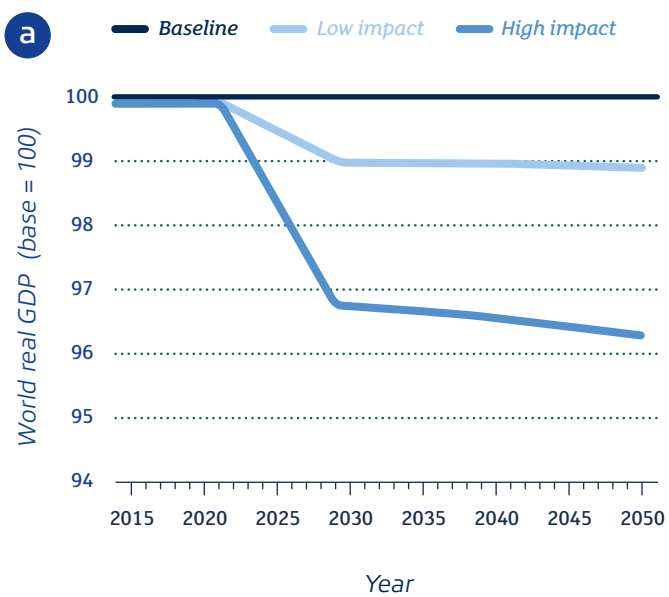
Increasingly intensive and expensive care

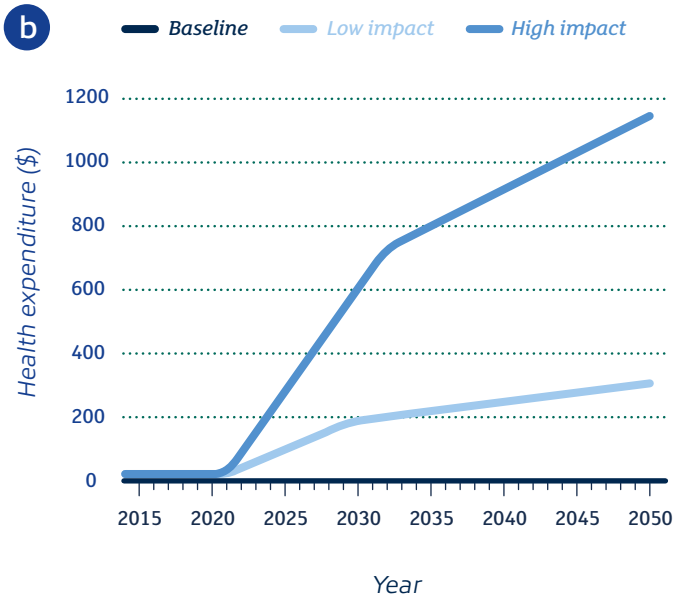
AMR's economic burden is a pan-global phenomenon that affects patients, healthcare providers, researchers, pharmaceutical organizations, and policymakers.

In the European Union, the burden of additional hospital care costs due to AMR in 2015 was estimated to be $1.6 billion[9]. **By 2050, annual global GDP is expected to fall by 1.1% in a low-impact AMR scenario and by 3.8% in a high-impact scenario** (Graph A)[9]; low-income countries would lose even more, with a 5% GDP loss in 2050 considering the worst scenario.

AMR will impact global poverty, world trade – such as livestock industries, where resistant microbes have been isolated – **and healthcare costs**, which may range from US$300 billion to more than US$1 trillion per year by 2050(Graph B)[10].

In 2017, the Organization for Economic Co-operation and Development reported that hospitals will spend on average an additional US$10/40,000 to treat each patient infected by resistant bacteria[11], leading to the risk of **long-term impoverishment, untreated morbidity, and mortality.**





Collection sites

The easiest way

MDRO can colonize and infect various body districts. No worries! **Copan's wide offer of FLOQSwabs® tips and shafts offers many options for a neat and easy collection in different sampling sites.**

- ***Throat***
- ***Nose***
- ***Skin/Wounds***
- ***Perianal/intra-anal***
- ***Rectum***
- ***Blood***
- ***Stool***






Strategies to defeat MDRO

Surveillance, awareness, and new technologies

Different strategies can be adopted to fight the rise and expansion of MDRO[12]:

Antimicrobial surveillance:

Local, global surveillance of antibiotic resistance patterns to estimate the nature and the magnitude of possible outbreaks.

Genetic engineering:

To genetically manipulate pathogen populations, eliminating resistance-carrying genetic elements.

Rapid diagnostics:

To timely detect and identify specific microbes for a fast pathogen-specific therapy.

Regulatory framework:

To stimulate vaccine and antibiotic research.

Public awareness and education.

Antibiotic stewardship.

Antimicrobial stewardship

Guiding clinicians to do better

The antimicrobial stewardship program aims to **assist and educate healthcare practitioners in giving rational and judicious antimicrobial treatment to patients, to prevent overuse/abuse of antibiotics**, reduce the exposure of the microbes to antimicrobials, and thus greaty slow down the development of AMR and its dissemination[13].
The main principles of the program are:

- ***to promote a tailored evidence-based antimicrobial use;***
- ***develop and distribute rapid diagnostic technologies;***
- ***minimize the therapy duration.***

These principles are continuously evolving, looking to increase program efficiency, reach, and implement novel approaches to patient care[14].

Some examples

Antimicrobial stewardship initiatives

Be Antibiotics Aware – CDC

Be Antibiotics Aware is the Centers for Disease Control and Prevention's national educational effort to improve antibiotic prescribing and use and combat antibiotic resistance.

ESGAP Study Group for Antimicrobial Stewardship – ESCMID

The European Study Group for Antibiotic Policies. The group promotes education and research activities on antimicrobial stewardship, sharing its knowledge and experiences through an open virtual learning community.

ATLAS Antimicrobial Testing

A fully searchable database with antibacterial surveillance data from several international programs. ATLAS is a valuable resource in the fight against antibiotic-resistant infections, enabling physicians to evaluate data and conduct complex analyses.

Antibiotic Susceptibility Testing

Driving empiric therapeutic decisions

Antibiotic Susceptibility Testing (AST) is a diagnostic assay that tests an antimicrobial agent's ability to inhibit bacterial growth in vitro and under standardized experimental conditions either on a petri dish – disk diffusion AST – or in liquid culture. AST **results are essential to driving the selection of the best antimicrobial chemotherapy for each patient, limiting antibiotic misuse**. Disk diffusion AST is flexible, cheap, and allows visibility of culture abnormalities; yet, results are available only 2-3 days after sampling. In circumstances where the appropriate antibiotic choice is crucial to prevent the emergence of multi-drug resistant bacteria and to ensure the patient's survival, this drawback is too important to be neglected.

Colibri™

WASP®

Radian®
In-line carousel

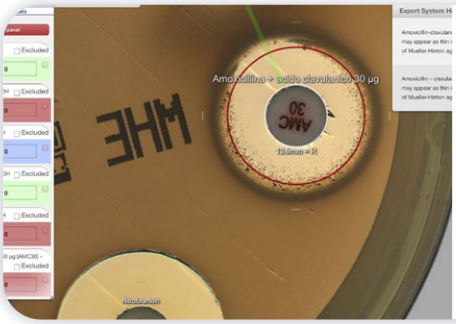
WASPLab®

Radian®
Expert System

Let's bring disk diffusion back to the future!

Radian®

Radian® - the WASP® and WASPLab® modules dedicated to the full automation and interpretation of disk diffusion AST - allows laboratories to exploit the advantages of disk diffusion while getting rid of its disadvantages. Comprised of two elements working in synergy:



Radian®
Expert system

Software module for resistence results interpretation

Radian®
In-line carousel

Hardware module for ATB disk dispensing

Radian® reduces time to result, labor, and manual activity while increasing traceability, standardization and helping clinicians make rapid therapeutic decisions. To deal with patients whose lives depend on the therapy to start as soon as possible – as sepsis patients – we also conceived a rapid direct AST (4h) compliant with the new EUCAST protocols and available on Radian® Expert System for blood cultures*.

*Available from September 2021"

MDRO collection

Collect bacteria like a pro!

We conceived many transport systems for every type of bacteria: the ones below are the best when dealing with MDRO screening and diagnosis, ensuring a neat collection for flawless diagnostics.

eSwab®

Collection And Transport Media For Traditional Bacteriology Culture

The suitability for molecular diagnostics and compatibility with WASP® processing are eSwab® main advantages when investigating resistant bacteria[15,16]. **eSwab® medium preserves the viability of aerobes, anaerobes, fastidious bacteria from swab specimens for bacterial culture purposes and can be used for the preservation of bacterial, viral or Chlamydial antigens and nucleic acids from swab specimens.[17]** In combination with Copan WASP® eSwab® reduces time to result in your lab[18].

FecalSwab®

Collection, Transport & Preservation System of Feces and Rectal Swabs for Enteric Pathogens

If you are investigating gastrointestinal tract AMR pathogens, FecalSwab® is the product to use. Compatible with both defecated stool and rectal swabs, FecalSwab® showed better preserving properties at different storage conditions than traditional media and dry containers[19,20]. Moreover, it is **validated for bacterial culture and molecular-based assays**[21], and if you are a lucky WASP® owner, you can process FecalSwab® samples with it[22].

Transystem™

Traditional Swab Collection and Transport System for Aerobic and Anaerobic Bacteria

Our Transystem™ family comprises **different media combined with various swab sizes, for the efficient and safe transport of many bacterial strains**, including resistant bacteria[23,24,25]. Choose between liquid or solid Amies and Stuart medium for aerobic culture, rapid antigen, and molecular testing; opt for gel Cary-Blair medium – with or without charcoal – for aerobic and anaerobic cultures.

SRK®

Surfaces & Equipment microbial testing devices

As antimicrobial agents became widely used, many resistant strains became endemic in hospitals. These **pathogens can survive on dry surfaces for extended periods** and are challenging to eradicate by cleaning and disinfection. Our Surface Recovery Kit line was first conceived to address **the need of hospitals for a flexible and easily processable device boosting the efficacy of environmental screenings** on surfaces and equipment. **SRK® is available in a wide range of media, volumes, and swab types** to fit any application and the main testing methods as culture and molecular assays.

eMRSA™

The enrichment broth for S. aureus spp.

We designed the eMRSA™ enrichment broth to **recover methicillin-resistant and methicillin-susceptible Staphylococcus aureus (MRSA and MSSA) in clinical specimens.** eMRSA™ contains antibiotics and other agents to inhibit the growth of non-staphylococcus isolates. Moreover, the growth of S. aureus is detected with a pH indicator that changes color from yellow to green-blue when sugars in the medium are fermented by the bacterium causing a decrease in the solution's pH.

BC+™

The positive hemoculture processing device

BC+™ is a vacuum tube designed to **transfer and transport positive blood culture for culture or microscopic analysis.** In the case of a positive hemoculture, a timely assessment of the infecting agent and possible During-resistance assessment are crucial. BC+™ allows to transport and preserve the sample for 8 hrs at room temperature and is **compatible with both manual handling and automated processing with WASP® & Radian®.**

Downstream Applications

Designed with diagnostic assays in mind

Our liquid-based media offer excellent performances for many respiratory disease downstream diagnostic assays, from traditional culture to the most advanced molecular platforms. Discover below some examples!

TEM-PCR

Target-Enriched Multiplex PCR is a highly flexible diagnostic platform capable of identifying a large spectrum of pathogens and antibiotic resistance targets in a single sample with high sensitivity and specificity. eSwab® has been used to analyze Musculoskeletal infections by TEM-PCR on infected bone areas[26].

PCR and qPCR

- Vaginal FLOQSwabs® sampling has been used to assess Mycoplasma genitalium infection using the S-DiaMGTV qPCR Kit. Moreover, positive samples were subsequently sent to a specialized laboratory to detect point mutations associated with macrolide resistance using three individual in-house nucleic acid amplification tests[27].
- Carbapenem-Resistant Enterobacteriaceae (CRE) and Vancomycin-Resistant Enterobacteriaceae (VRE) infections have been evaluated by qPCR on rectal samples collected with Transystem™ [28,29,30].
- Nasal FLOQSwabs® paired with eSwab® enabled the analysis of Hospital-Acquired Methicillin-resistant Staphylococcus aureus (MRSA) with rapid qPCR diagnostic kits[31].
- For phylogenetic typing, a selection of Escherichia coli isolates obtained by FecalSwab®-collected samples were analyzed by phylogroup-defining PCR. Group B2 E. coli were further characterized by O25:ST131-specific PCR. All phenotypically ESBL-positive isolates were tested for the presence of CTX-M, SHV, and TEM ESBL resistance genes by PCR[31].
- FecalSwab® is an accurate sampling device for CPE screening using the Xpert Carba-R v2® assay. It allows performing all eXDR screening using a single swab and repeatedly, simplifying sample collection and improving patient comfort[33].

Culture

- Pathogen viability and fecal commensal abundance were stable in FecalSwab® media at both room-temperature and refrigerated incubation conditions, resulting in a significantly increased number of well-isolated pathogen colonies than samples incubated in modified Cary-Blair media. Isolation of individual pathogen colonies was improved via WASP® planting compared to those planted using the Isoplater system. Furthermore, preincubation with Copan selenite media significantly enhanced the yield of Salmonella enterica serovar Typhimurium. Together, the automated WASP® system combined with FecalSwab® and selenite media represents a rapid and efficient approach for processing stool specimens compared to standard methods[21].
- Staphylococcus aureus is the most common pathogen involved in skin and soft tissue infections, and it is the principal cause of surgical site infections. eSwab®-collected wound samples were inoculated onto several plates to identify MRSA infections[34].
- CHROMagar MRSA/SA can be seeded with eSwab® and MSwab® aliquots starting from nasal and throat FLOQSwabs®-collected samples, facilitating efficient processing for chromogenic culture in full laboratory automation and allowing molecular testing by automated PCR systems[16].
- Vaginal specimens sampled by CLASSIQSwabs® can be used to perform disk-diffusion AST on bacterial isolates, to assess the prevalence of clinically important pathogenic antimicrobial-resistant bacteria and multidrug-resistant bacteria[34].

Scientific references

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