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Challenges and Innovations in Antimicrobial Resistance Testing

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Abstract
Antimicrobial resistance (AMR) is increasing at an alarming rate. Laboratory-based AMR surveillance programs have the crucial role of tracking AMR and reporting these data so that appropriate action may be taken. Such surveillance is essential, since AMR is not only an established cause of increased morbidity and mortality; it also contributes significantly to healthcare costs. The purpose of this review is to describe the complex nature of AMR, the laboratory-based surveillance of AMR, current and novel AMR testing methods, AMR testing guidelines and standards, and the challenges that AMR spread from food-animal isolates present to regional and international stakeholders. These topics suggest the need for a unique laboratory best practice guideline that can be utilized by laboratory stakeholders. Furthermore, testing guidelines that address the threats of spread and risk of AMR to human health, and specifically those threats that originate from the significant volume of food animals and their pathogens produced each year, are vital and should be discussed and addressed in a proposed chapter in the guidelines. Such a document could be utilized by veterinary clinical diagnostic laboratories and commercial laboratories working within the human and veterinary healthcare sectors.

1. Introduction

Microbial resistance to antimicrobials has begun to emerge, and it has affected the future of effective therapy for infectious diseases. This is particularly true in the developing world, where background diseases like malaria, HIV infection, and malnutrition have caused an increase in opportunistic infections. In the management of infections, antimicrobial testing is crucial as it indicates therapeutic use. Patients may suffer from having an ineffective drug because of the failure of therapy, while the continuation of treatment with antimicrobials almost certainly leads to the creation of microbial resistance. Unfortunately, the choice of antimicrobial agents is constrained in most cases, consequently allowing limited access to therapy in rural and urban clinics in the developing world. (Abushaheen et al.2020)

The simple test for microbes, like the beta-lactamase test, is likely to be performed at the same time that an infection is suspected. However, the results are only relevant for the range of producing organisms of the enzyme. Other tests, many of which rely on the production of carbon dioxide, necessitate the contamination of the traveler who has undertaken suitable banking facilities. Therefore, any proposed solution that does not encompass the existing government, non-government organizations, and the private sector will fail. The use of conventional ventilated and vented cabinet features has proven to be popular. A new approach to the type of antimicrobial test in a developing country is to choose a very simple endpoint that is observed and interpreted by the patient or a relative. (Salam et al.2023)

2. Understanding Antimicrobial Resistance

Antimicrobial resistance refers to a microorganism's capability to resist the action of an antimicrobial agent. It is a complex, evolving, and more serious issue than anyone had anticipated. As resistance to antibiotics and other antifungal and anti-parasitic treatments is an intrinsic and evolving characteristic of microbes, significant advancements in the efficiency of antimicrobials, including human dependency and sustainability, and their effect on human, animal, and environmental health and well-being further complicate and improve the need for

antimicrobial resistance surveillance, governance, and interventions. To develop appropriate stewardship policies, surveillance data are required. AMR interventions also require access to preventive measures such as cleaner human, animal, and environmental living and working environments, as well as enhanced preventative treatment and vaccines and enhanced systematic transmission attempts. (Coque et al.2023)

The use of resistance-testing methods for analyzing pathogen identity, quantity, and susceptibility to antimicrobials is crucial for gathering data and resolving antimicrobial management, treatment strategies, and public policy. The improvement and satisfaction of resistance-testing methods have always been important to the progress of antibiotic discovery and development, direction of use, accuracy of the determination of diagnostics, treatment effectiveness, and level of evaluation and policy-making of the antimicrobial agents and diagnostic methods offered by regulatory, scientific, veterinary, and medical laboratories. To safeguard human health and enhance patient care, it is vital that healthcare professionals have access to reliable data on organism sensitivity and are willing to use it. (Shempela et al., 2024)

2.1. Mechanisms of Resistance

The category of bacterial resistance is indeed diverse and includes intrinsic, acquired, and base level mechanisms that can be chromosomal or mobilizable. These mechanisms can be divided into more complex and detailed classifications, such as resistance genes and their variants, in addition to any mutations or modifying systems. The typical class includes those such as efflux pumps, enzymatic inactivation, modification of target enzymes, decreased permeability, and immune response inhibition. It is possible for a few of these mechanisms to be utilized by multi-drug resistant bacteria. Efflux pumps utilize the active transport of the antibiotic substance out of the bacterial cell, and enzymes inferred to break down the antibiotic. Enzymatic inactivation occurs where the aforementioned enzymes have undergone potential modification to either make the antibiotic no longer connect to its target or have an activity impairment of the enzyme that the antibiotic is supposed to inhibit. (Darby et al.2023)

Antibiotic resistance genes most frequently confer resistance to specific antibiotics. These genes are mostly linked to mobile genetic elements. Many of them can be used on a broad host range and replicate state-wide regardless of origin, and may have high rates of recombination. Transposons are a clear example of genetic mobile elements. They are made up of terminal sites with composite structures and include genes allowing their transposition to a new position in the genetic material. Although transposons refer to the so-called 'cut and paste' means—in which they are excised from their original position and inserted elsewhere—they can also follow the replicative transposition process. This last method causes two identical copies of the transposon to occur at the same time, where one is at the original position while the other targets a nearby position. On the interchangeable end, gene cassettes are present in integrons. These are also mobile gene elements and are known to have between 0 and 250 genes, with a functional expression of only one or two resistance-linked genes. (Mazhar et al.2021)

2.2. Factors Contributing to Resistance

The evolving failure of drug therapies in infections should emphasize the need for a better understanding of both the evolution of microbial resistance and the underlying predisposing factors. While resistance seems most unusual among RNA viruses, non-retroviral DNA viruses, and macroparasites, it is noted among almost all free-living microbial taxa to which any kind of drug is given. The extent of resistance is strongly influenced by the prescribing strategies used and by the ecological segregation and structure of microbial populations at relevant levels, whether within single infected hosts, within small-scale human or other populations, or between and within micro- or macro-ecological regions of operational spaces influenced by human interventions. The high-risk factors for any heavy colonization of, or severe infection by, resistant strains are the intensity and duration of locally applied antimicrobial selection pressure, together with the extent of more general host and barrier predisposition and the nature of the selective forces that operate within competing swarms at relevant locations. (Geller-McGrath et al.2023)

Commensal bacteria offer natural housing and a convenient gene-transfer service for human pathogens towards developing and improving their resistances. Generations of facultative bacteria may also cooperate and interact under adverse conditions to undergo specialized adaptive hypermutator responses. Indigenous human microbes may be preselected during long-term evolutionary relatedness or immediate colonization for inherently possessing highly efficient, clinically little advanced, resistance strategies that have not yet been widely identified and utilized by contemporary human therapies. In specific niches, stimulons contributed by eukaryotic host proteases might also help to control the infecting bacteria and limit their resisting activities. Independently evolving microbial driving forces can frequently maintain and enhance resistance despite the considerable costs that such innovative adaptations may incur, as long as the directional avoiding actions of the drugs lack sufficient delivery, local intensity, or efficiency. Microbial resistance at the community level can be increased by networks of inter-alkalizing metabolic and other relationships, and positive determinant diversity is essential for community survival. (Sariola and Gilbert, 2020)

3. Current Methods of Antimicrobial Resistance Testing

In the context of Challenges and Innovations in Antimicrobial Resistance Testing, current methods of antimicrobial resistance testing involve a variety of techniques such as phenotypic and genotypic testing. Phenotypic methods include methods like broth microdilution and disk diffusion, while genotypic methods involve detecting specific resistance genes through molecular techniques. rmacokinetic Measures in Resistance Testing Traditionally, in vitro susceptibility tests have not accounted for drug pharmacokinetics and pharmacodynamics, but pharmacokinetic measures make logical sense as causes of treatment failure. In pharmacokinetics (PK), serum or plasma drug concentrations over time allow for analysis of time-dependent measures of antimicrobial activity, such as time-dependent killing, or the time that antimicrobial drug concentrations are above the minimal inhibitory concentration (MIC), with either the time of the antibiotic plasma concentration being above the MIC for at least 40% or 50% of the dosing interval required for clinical efficacy with cell wall synthesis or protein synthesis inhibitors. Pharmacokinetic/pharmacodynamic measures of antimicrobial activity are used to predict treatment outcomes with specific doses, dosing intervals, and infection sites/disease states and may change as PK data reveal the MIC and clinical breakpoints at different infection sites. (Benkova et al.2020)

Guidance documents underscore the use of accurate MICs, based on the precise dosing regimen in combination with pharmacokinetic data, as well as how to interpret the dosing regimen relative to disease state using label or PK data from regulatory submission sites with tissue distribution of the drug. PK data limit activities that do not have clinical relevance in vivo, for instance, single exposure versus multiple doses, with most aminoglycosides, quinolones, and polymyxins. Among the factors that influence the PK measure of antimicrobial activity are drug binding to serum or tissue proteins, volume of distribution, and serum/urine pharmacokinetics in relation to creatinine clearance and dose adjustment. The requirements for information on how host cytokines and proinflammatory mediators may influence PKs from critically ill patients are becoming increasingly more apparent. Finally, daily or twice-daily dosing may cumulatively prevent rapid or complete bacterial regrowth, which would theoretically minimize the evolution or acquisition of resistance. (Wicha et al.2021)

3.1. Phenotypic Testing

Phenotypic testing for antimicrobial resistance includes tests that measure bacterial growth in the presence of specific concentrations of antibiotics. Determination of the minimum inhibitory concentration (MIC) is considered the gold standard when testing novel agents, outbreaks, or producing reliable identification for selected agents. Thus, this section will outline a few of these procedures. Originally, MIC tests determined the MIC as the lowest inhibitory concentration of chemotherapeutic agents that completely prevents the growth of organisms in the test tube over a 16-24 hour test period. These methods typically used bacteriologic growth measurements: bacterial colony formation on agar media or bacterial cloudiness in broth as endpoints. Because these measurements are cumbersome and time-consuming, they were replaced by faster and less resource-intensive methods that use decreased bacterial growth as studied by continuous cecal or turbidity monitoring endpoints. (Mahfouz et al.2020)

Another endpoint strategy provided a positive/negative result and included microdilution testing in bottled media that gave a clear match with the standard test method. The most widely used of these tests is the microbroth method, which can be purchased as a pre-prepared kit or can be made in any microbiology lab using standard broth microdilution. These manufacturing or microbiology labs can also accommodate coverage for specific antimicrobial agents, isolate dilution flexibility, and the ability to save general or unique storage use conditions and avoid unnecessary expenses of testing unnecessary isolates. Although broth microdilution has the ability to predict in vivo outcomes, these methods oversimplify antibiotic susceptibility testing. Certain benefits of these methods improve inhibition elimination by high matched special experiments or antibiotic matched disc diffusion tests. The labor, expertise, data handling, and equipment needs limit these procedures' scope to large-scale consensus gold standard validation laboratories, not the typical reference laboratory. (Kuo et al.2021)

3.2. Genotypic Testing

Genotypic testing offers a number of potential advantages in the detection of antimicrobial resistance determinants. In particular, genotypic testing provides the opportunity to screen for many different resistance determinants simultaneously, particularly for complex phenotypes such as multiresistance or for determinants that may not be associated with a recognizable phenotypic effect. The specificity of the test is increased because genotypic testing targets the elements directly responsible for the resistant phenotype, and due to the physical nature of molecular detection techniques, genotypic tests can be provided within a few hours. Molecular methods are highly sensitive and have the capacity to detect very low levels of resistance markers. This is particularly important where clinically uncharacterizable levels of resistance can still compromise antibiotic therapy. The sensitivity of PCR-based methods can make them an attractive option for the detection of low-level methicillin resistance in Coagulase Positive Staphylococci. (Kim et al.2022)

Quantitative molecular assays can be used with therapeutic drug monitoring and pharmacokinetic dosage adjustment algorithms to optimize the use of antibiotics in difficult-to-treat infections or in microbiologically complicated cases. The availability of a straightforward result that is easier to understand and less prone to

ambiguity gives molecular tests a clear advantage in the clinician-laboratorian exchange of information. The simplicity and reduced need for interpretation of molecular alerting systems allow them to be more readily integrated with guidelines for antimicrobial practice among hospitalized patients. The underlying genotypic technology can be used in forms that allow some genotype-to-phenotype correlation to be retained. Mutations leading to recognition site alteration can often be distinguished from mutations with no resistance-causing effect. Quantitative molecular assays can be highly effective at distinguishing resistant from susceptible strains in a complex heterogeneous population. Used quantitatively, molecular assays are theoretically more resistant to interference from biological diversity than other testing modalities. (Schmitz et al.2022)

4. Challenges in Antimicrobial Resistance Testing

The increasing number of gram-negative bacilli resistant to commonly used antibiotics has made the search for new and innovative therapies for infectious diseases an urgent matter. This demand has taken us to an even more advanced phase of a post-era of antibiotics such that only two or three new viable or potentially active drugs can be found. However, research for new drugs against infections is hampered not only by the urgency of public health demands but also by differences between us and the microorganisms around us, regardless of their biological simplicity and rapid reproduction. The current high prevalence of resistance is a direct result of excess or inappropriate use of drugs, due to therapeutic mistakes, self-medication practices by patients, and the use of drugs in breeding for the production of food, among other factors. These practices promote the survival of resistant microorganisms capable of transmitting their resistance genes to other non-resistant or wild microorganisms, such as S. aureus and CoNS in hospitals. (Chinemerem et al.2022)

The effective response to these challenges depends on three factors: a clear understanding of the scientific nature of drug resistance, rapid identification of patients infected with resistant isolates, and an ethical and conscientious use of available drugs. Various methods can be used for the detection of antimicrobial resistance, such as culture and specific phenotypic and molecular tests. These techniques are constantly improved and adapted according to various clinical and epidemiological needs. However, these well-defined methods and the results are not typically produced, poorly accessible, and of limited quantity and/or quality in non-recommended laboratories. In other words, traditional tests are not "ready"; hence the urgent need for the implementation of recommended detection techniques. This paper aims to describe and discuss existing methods and try to elucidate why and how we can enter a new phase in the detection of AMR either through the integration of some innovations into a single test or the development of new technologies with methods that are not only in phase with hospital and non-hospital needs.

(Chinemerem et al.2022)One of the main successes in the fight against the survival of microorganisms is the prevention of the development of resistance by encouraging the ethical and conscientious use of antibiotics. To achieve this end, we need to fast, accurately, and reliably diagnose and interpret microbial resistance. However, the current main methods for identifying isolates as resistant are underdeveloped, poorly accessible, of limited quantity or quality, and poorly adapted to the clinical and epidemiological needs of hospitals. This suggests the urgent need to promote the implementation of recommended detection techniques. Moreover, the prospect of identifying patients infected with resistant isolates harbors important implications in the context of epidemiology and infection control by reducing therapeutic failure, limiting serious nosocomial diseases, and preventing or delaying MDR infections. Treatment of infectious diseases early can prevent the dissemination of various bacteria into the hospital environment. In this context, this paper provides a critical review of phenotypic tests and molecular methods developed and recommended for the identification of antimicrobial resistance genes. This work can make it possible to integrate the merits and potential limitations of the various methods for AMR detection used outside and inside the hospital to define the bases of a single genomic test. This approach promotes a more ethical, fast, and simpler use of data and encourages the inclusion of molecular methods for the routine detection of MDR organisms, highlighting valuable findings at the clinical and epidemiological levels. (Florensa et al.2022)

4.1. Emerging Resistance Mechanisms

The World Health Organization has recently released a list of critical priority pathogens that are resistant to almost all available treatment options. There are reports that almost one out of every three infection-related deaths are caused by these resistant organisms. Such figures have alarmed the general public as well as the scientific community. Yet, resistance mechanisms are emerging or spreading without a remedy. The development of drug resistance in bacterial and fungal pathogens poses a significant risk to public health. This phenomenon affects pathogenic organisms in the community at large. In hospital environments where drug selection pressure is inherently high, the expression and spread of drug resistance affect almost all types of pathogenic and non-pathogenic microorganisms. Opportunistic pathogens are on the rise due to these reasons. Determination of drug resistance should be a priority in practice, especially in cases where hospital infections spread. (Health Organization, 2020)

There is growing concern about the resistant mechanisms present in more than one pathogenic organism with the emergence of a variety of resistant mechanisms. In particular, the resistance envelope expressed by Staphylococcus aureus and MRSA, the extended spectrum beta-lactamase production by Gram-negative

bacteria, and vanA positive Enterococcus faecium, and vancomycin ionophore producing vanB positive Enterococcus faecalis are significant. It is difficult to determine a direct role for many of these resistance determinants in the context of public health. Staphylococcus aureus, including VRSA, and Enterococcus spp. Resistance determinants to glycopeptide antibiotics are often shared within a similar genetic structure, and this genetic structure may be transmitted via transposition. It is an important public health problem that the genetic structure has spread and has been found in cases of local transfers without an exact trace of the spread. It was difficult to know how dangerous such transfers were, and the data collected did not indicate that such a transfer would be marked, but evidence of four genetic variants circulating within the hospitals gives unexpected clues that the situation may become more complex in the coming period. (Panchal et al.2020)

4.2. Limitations of Current Testing Methods

CLSI guidelines recommend methods for the detection and enumeration of most key MDR organisms and their resistance mechanisms, including plate- and non-plate-based phenotypic tests. AST is currently typically accomplished by growth-based culture and/or detection of particular resistance-associated enzymes or nucleic acids encoding them. These methods may require expensive infrastructure, microbiologic expertise, and long diagnostic times. The most common resistance detection methods—growth-based determination of minimum inhibitory concentration (MIC) and enzyme tests—can be expensive and technically challenging. MIC shows the lowest drug concentration that absolutely inhibits organisms in a specific diagnostic framework, and it has predictive value for some clinical treatment options. However, its predictive value for some types of antimicrobial therapy may be poor. Printed and diffusible antimicrobials may have lower activity than expected, and MIC results may require 12 to 48 hours of incubation for most infectious organisms. MIC testing may be time-consuming, and resistant organisms may have been both disseminated in the host and/or killed by a host immune response. The lack of growth and response to appropriate antimicrobial therapy may be explained by the ESKAPE criteria. MIC testing may not reflect the nuances of host-microbial interactions, nor may it predict treatment effectiveness in the context of particular host and microbiologic features, such as immune function, host-pathogen pharmacokinetics and pharmacodynamics, and viral coinfection. (Pierce et al.2023)

The separation of flora from potentially pathogenic organisms during clinical testing limits the accuracy of MIC for mixed specimens. Limitations may include post-analytical decision-making, drug-drug antagonism or synergism, and drug-susceptibility interactions. In this case, both the antimicrobial and the considered diagnostic specificity can develop unusual pharmacokinetic properties. The contribution of the host immune response to pathogen and antimicrobial resistance-influencing factors may also be minimized. Even discovering a causative organism in a mixed-flora specimen may be difficult. AST, when it is appropriate, must withstand the acid, neutralizing, diluting, and often cold conditions encountered during routine culture, including blood culture systems that reduce the complexity of the sample. False-negative diagnostic results may occur if the detection limits of antimicrobial resistance test methods are not achieved. To improve the gentle conditions applied using standardized safety guidelines, antimicrobial resistance-related fast, affordable, sensitive, specific, complex polymicrobial concepts will be needed. Some fast phenotypic antimicrobial susceptibility tests can be performed. To facilitate the description of culture-based detection techniques, several test methods have been combined with inexpensive dyes, test substrates, or indicators of resistance such as chromogenic enzymes, fluorophores, or calorimetric detectors. (Drane et al., 2024)

5. Innovations in Antimicrobial Resistance Testing

The strategies to control antimicrobial resistance (AMR) testing involve early detection of resistance, prudent use of antimicrobials, and optimized infection prevention programs. This chapter includes new developments in antimicrobial susceptibility testing (AST) such as real-time monitoring, whole-genome sequencing-based AST, identification of rare resistance, and cutting-edge tools to predict antibiotic resistance genes. These changes bring more opportunities to advance the efficient use of antimicrobials by providing alternative treatments. Even though clinical research on these advanced technologies is important, widespread accessibility and cost-effectiveness remain challenging. Finally, this work investigates current challenges and potential future approaches for AMR testing.

(Hassall et al.2024) High-performance detection and surveillance of antimicrobial resistance (AMR) are key aspects of managing the spread of antimicrobial resistance. Several rapid diagnostics are being developed to detect the resistance quickly so that medical professionals and patients can decide if an alternative treatment is required. These tests also have the potential to prevent overprescribing of antibiotics. (Udegbe et al.2023)

Traditional antimicrobial resistance testing ranges from disk diffusion to broth microdilution to determine minimum inhibitory concentrations. Antimicrobial susceptibility tests (ASTs) provide information about which antibiotics are effective against a specific pathogen. Therefore, this diagnostic tool has a significant role in selecting suitable antibiotics and guiding the healthcare provider's therapeutic decisions. Disk diffusion is a qualitative process and requires visual inspections, limiting its use in resistant bacteria surveillance. The MIC test is more difficult and error-prone. As a result, researchers have been concentrating on improving the speed at which antimicrobial resistance can be identified in various pathogens and implementing personalized

treatments. Implementing AMR scenarios will require more data and innovative approaches to guide decision-making more effectively. (Aljeldah, 2022)

5.1. Advances in Rapid Testing Technologies

Antimicrobial resistance is rapidly becoming one of the most serious health dilemmas facing practically all of humanity. There are various reasons for the upsurge of antibiotic resistance, and governments are rallying all their resources together to try to combat it because, in the near future, the already unprecedented resistance to known and trusted antibiotics could prove to be the undoing of modern medicine. The rapid development and implementation of genomic approaches for testing are promising to, if not eliminate drug resistance, then at least help us to negate its effects better. However, to succeed in this very ambitious goal, a number of challenges will have to be overcome, including the high cost associated with genomics. More encouraging is the development of rapid in vitro methods for testing individual organisms to help guide the choice of appropriate antimicrobials. (Velazquez-Meza et al.2022)A variety of potentially very useful new technologies are being developed, which hold the prospect of significantly reducing the time taken to identify the pathogen causing infection and hence individualizing the therapeutic approach. New diagnostic methods are incredibly important, as they would help minimize the use of broad-spectrum antibiotics used in the first instance before sensitivity tests on the infecting organisms are performed. The rapid identification facilitated by such new technologies could help contain further spread and prevent in-hospital outbreaks due to the use of more targeted or narrower spectrum antibiotic therapy. Rapid diagnostics will similarly facilitate monitoring of antimicrobial resistance and could provide important information concerning disease containment and prevention efforts on farms and production units, which in turn release associated pressure on prescribing veterinarians. (Briggs et al.2021)

5.2. Use of Artificial Intelligence and Machine Learning

Artificial intelligence and machine learning techniques, including supervised and unsupervised analyses, are becoming an integral part of the modern research approach. The use of these methods in molecular diagnostics, which must cope with the computational complexity of biological systems, is a great challenge. Over the past decades, traditional diagnostic methods, including phenotypic and genotypic methods, have enhanced our ability to identify biological agents and their components. However, they are based on complex, poorly understood interactions that are usually described only as patterns in limited numbers of variables. This complexity makes interpretation, analysis, and comparison of large amounts of molecular and biochemical data challenging, which is becoming an increasing problem due to the rapid development and spread of infectious diseases. Furthermore, the rapid development and spread of antimicrobial resistance mechanisms and the spread of multidrug-resistant microorganisms require rapid improvements in molecular diagnostics and the development and implementation of fast and reliable tests to monitor bacterial adaptation and evolution. (Aljeldah, 2022)

In many modern approaches, phenotypic properties and molecular characteristics are evaluated and analyzed in the context of artificial intelligence methods. These methods can be used for developing a variety of predictive models that rely on the evaluation of a wide range of characteristic features associated with a particular problem. To create an informative learning environment and reduce overfitting, it is important to reduce the number of features used. Many techniques and tools have been developed for this purpose and have been evaluated on various real-life applications. Integrated multi-feature selection has great potential in the development of accurate predictive models for the application in diagnostic problems, including antimicrobial resistance testing. It is the favored approach over the use of a single technique in an independent situation because of the different characteristics of the feature selection methods compared to the diverse problematic issues, such as characteristics of the given dataset, class overlap, size, class balance, and noise, associated with the available data. This requires significant consideration and adaptation of the feature selection method settings for the different diagnostic applications. (Chen et al., 2024)

conclusion

In summary, the growing public health burden of antimicrobial resistance has necessitated an increasing demand for accurate and efficient antimicrobial resistance diagnostics. Global efforts to streamline laboratory procedures and control the spread of resistant organisms will rely on high-quality, standardized resistance testing. Rapid molecular methods are increasingly becoming part of standard diagnostics despite deficiencies in some key aspects of performance. In particular, the development and regulatory acceptance of both SIS-qNAT and accurate genotypic detection methods will allow for a far greater understanding and tracking of the determinants of antibiotic resistance than currently possible. Furthermore, the development of a regulatory validated framework for accurate interpretation of molecular susceptibility data would permit these genetic analysis techniques to be used as general susceptibility tests even by inexperienced users. The growing evidence base for direct penetration of local samples may gradually begin to redefine the role of phenotypic testing and inform the appropriate selection of clinical thresholds, although it is difficult to see how this could mean the total replacement of culture-based detection methods in the foreseeable future. However, it seems easy to believe that the role of genotypic and other molecular methods would continue to grow in the years ahead in the fight against resistance.

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