DTI
Drug Target Insights 2022; 16: 69-70
ISSN 1177-3928 | DOI: 10.33393/dti.2022.2545
EDITORIAL

Focus on Antimicrobial Resistance (AMR)
Open Access

AMR research: a perspective from personal experience

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Antimicrobial resistance (AMR) has been well recognized as a global health issue. It is a 'slow pandemic' with huge socioeconomic impact. With around 15 years of experience of working with antibiotic-resistant pathogenic bacteria and anti-pathogenic natural products, I believe I have developed some insight into the issue, and I consider it worth sharing with the readers the variety of experiences I had while working in the AMR field. The views expressed are not claimed to be free from personal beliefs and bias, and are likely to be more relevant to researchers in the Low- and Middle-Income Countries (LMIC). Some of the points discussed are not exclusively relevant to AMR, non-AMR researchers may also correlate their experience with them, and of course, many may disagree with my observations as this is a non-diplomatic personal account!

1. Finding a critical mass of people working on similar aspects of AMR can be a challenge! With AMR getting quite a bit of attention in scientific circles as well as the media, this statement may sound strange, but this is a reality at least for certain geographic area. When you do not have sufficient number of AMR labs in your city/state, it may be difficult to find people with whom you can exchange ideas, resistant strains, protocols, etc. Even finding people with most relevant expertise to act as members of Research Progress Committees/Thesis Evaluation Committees of your PhD students becomes difficult when you do not have many of them in your near vicinity. Though online meetings with experts anywhere in the world are possible, this in my opinion is never as effective as offline face-to-face interactions.
2. Oversimplified perception of AMR research in certain circles of scientific community: While you are presenting before grant review committees, often the committee will comprise a mix of expertise, with few of them not directly involved in wet-lab AMR work. They may perceive AMR research too simplistically as if it is all about determining the minimum inhibitory concentration (MIC)/minimum bactericidal concentration (MBC) of test compounds, that is, screening molecules/natural extracts for bactericidal activity through broth dilution assay. In my personal experience, many of these committee members are not updated with the most recent trends in AMR research, for example, use of alternative model organisms (*Caenorhabditis elegans* and Zebrafish) for the study of host-pathogen interactions, and for screening a library of natural/synthetic compounds for preliminary detection of *in vivo* anti-pathogenic activity. Such model systems also provide an excellent opportunity for detecting anti-virulence activity in test compounds and extracts (1). Recently while presenting a grant proposal involving use of *C. elegans* as a model host, and implementing whole-transcriptome analysis of bacterial pathogen treated with certain anti-pathogenic herbal formulation for novel target identification, I had to face these naughty comments from the grant-reviewing panel:
   A. "Instead of working with *C. elegans*, do experiments directly with higher animals": Despite arguing that use of simpler organisms like *C. elegans* at an early stage can reduce animal sacrifice at later stages, and informing the committee of few hundred papers citing *C. elegans* as a valid and useful model for AMR research, I failed to convince the committee (or the committee failed to understand the value of *C. elegans* in AMR research).
   B. "Since whole genome sequence of most of the pathogenic bacteria is available, we already have sufficient targets known"!!!: While dearth of validated novel antimicrobial targets is widely accepted as one of the major hurdles in discovering new antibiotics (2), one of the committee members *educated* me that full-genome sequencing of pathogens has already solved that problem, and he claimed that we need to focus more on antimicrobial surveillance. I again failed to make the committee understand that surveillance at best tells us which resistant phenotypes are more prevalent in the given geographic area, but it cannot solve the problem of finding novel targets and antibiotics.

The point is that oversimplification of the AMR research reducing it to simple antibacterial growth inhibition assay can do many harms. If people with such exaggerated simplistic perception of AMR research happen to head some academic institute, they may do even more harm by indirectly dissuading brilliant young minds to join AMR labs.

Received: December 12, 2022
Accepted: December 12, 2022
Published online: December 23, 2022

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3. AMR surveillance vs. antibiotic discovery: While many countries have floated their national action plans to combat AMR, most applicant labs are inclined towards AMR surveillance. While AMR surveillance is an important area of investigation, it contributes largely towards characterization of the problem and helps in identifying the priority pathogens, but the solution is arrived at only from discovery and development of novel antimicrobial compounds and formulations. Inherently AMR surveillance projects are guaranteed to generate some visible output because irrespective of where you source the sample from (soil, water, or clinical samples), almost all samples can be shown to contain AMR genes to a more or less extent through metagenomics. On the other hand, labs pursuing identification of novel targets and/or new antibiotics cannot be sure of a visible output as the probability of negative results is quite high. I personally feel that while AMR surveillance should actively be pursued by public health organizations, academic labs and university-industry partnerships should be funded more for antibiotic discovery programmes.
4. Exploring natural products for anti-pathogenic activity can be tricky: While traditional medicine (TM) can offer potent leads against various diseases including antibiotic-resistant infections, the wholistic philosophy of TM largely mismatches with the reductionist approach of modern drug discovery programmes (3). Concepts like hormesis (non-linear dose-response patterns) and 'multiplicity of targets' have to be understood by the researcher dealing with polyherbal formulations or multicomponent plant extracts. Unfortunately, not many people can claim familiarity with both modern science as well as TM. When you present your research to an audience largely comprising either TM practitioners or modern scientists trained in reductionist approach, it is difficult to be appreciated. Most TM formulations do not exert outright bactericidal effect at low concentrations, instead they may exert anti-virulence effect by simultaneously affecting multiple cellular and molecular targets in susceptible pathogens. To identify such polyphasic effect, simple growth inhibition assay can never be sufficient. Such widespread effects can only be grasped through 'omics' approach. Novel antimicrobial mechanisms can be identified through novel types of assays only. Training of the next generation of microbiologists needs to go beyond conventional MIC determination assays.
5. AMR among non-bacterial pathogens needs more attention: While resistant infections caused by bacterial pathogens are responsible for considerable morbidity and mortality, infection burden owing to fungal, protozoan, viral, and helminth infection is also heavy. For a variety of reasons, most AMR research has revolved around pathogenic bacteria, and AMR in non-bacterial pathogens could not get sufficient attention. Since meeting the criteria of 'selective toxicity' is even more difficult with potential new antimicrobials against eukaryotic and viral agent of diseases, building human resource skilled in investigating such non-bacterial pathogens is urgently required. Graduate courses in microbiology should be reframed to put more emphasis on eukaryotic microorganisms in theory as well as lab component of syllabus (4).

Finally, I thank all the contributing authors whose articles appear in this special issue, and the reviewers who devoted their precious time in the peer-review process. I enjoyed support from the publisher, particularly Lucia Steele, for always being responsive.

Happy reading to all readers!

Disclosures

Conflict of interest: The author declares no conflict of interest.
Financial support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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