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# Rethinking "Antimicrobial Resistance": Focusing on Patients instead of Pathogenic Organisms

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## ABSTRACT

Antimicrobial resistance (AMR) has received widespread attention in the press and considerable resources from governments and global organizations, and that has resulted in many new drugs but not in better outcomes for patients. To achieve better outcomes, researchers and regulators should focus more on a drug's meaningful clinical benefit to patients and less on the *in vitro* study of the drug's ability to inhibit the growth of pathogenic organisms. That requires putting resistance in the context of overall infections and the impact of the human immune response to develop medical interventions that improve the lives of patients.

## Introduction

Antimicrobial resistance (AMR) has received widespread attention in the press and considerable resources from governments and global organizations.[1] The focus has been on pathogenic organisms' ability to resist inhibition of growth by drugs *in vitro*. Missing from this equation are patients and patient outcomes.[2] Although AMR's importance is based on the association between *in vitro* resistance and worse patient outcomes, it is essential to define resistance in ways that are meaningful for patients and clinicians. That requires putting resistance in the context of overall infections and the impact of the human immune response to develop medical interventions that improve the lives of patients.

Research shows that attempts to address AMR have centered on "bugs and drugs" – developing many new drugs with *in vitro* biological activity against organisms, without evaluating or demonstrating whether those same drugs improve patient outcomes.[3,4] That is why new drugs have not improved survival for patients in the United States (US) and many other countries. Here we discuss current issues with AMR and suggest how to move forward to develop evidence and interventions to save and improve patients' lives.

## The Focus on Pathogens Instead of Patients

The definitions and evaluations of resistance often are based on assumptions related to *in vitro* growth inhibition and pharmacokinetics, rather than randomized assessments of patient outcomes in clinical trials.[2,5] Preclinical data do not consider the human immune system's effect on patient outcomes.[6] Case reports of poor outcomes in patients infected with "resistant" pathogens cannot show that those outcomes are due to resistance. Patients infected with resistant organisms are often older and sicker, and poor outcomes may be due to these factors, not resistance.[2] One study showed that when controlling for other diseases and severity of illness, there was no difference in deaths for patients infected with methicillin-susceptible and methicillin-resistant Staphylococcus aureus (MRSA).[7]

In the US, the 21st Century Cures law of 2016 allowed regulators to use definitions of resistance developed by outside groups that accept money from pharmaceutical corporations.[8] These groups have recently suggested changes in definitions that make older drugs seem less effective,[9] although the definitions often have not aligned with patient outcomes.[10] Instead, the suggested new definitions encourage clinicians to use newer, more expensive drugs that are not proven to improve patient outcomes compared to older drugs.

Research shows that most deaths are from infections in patients who receive a drug to which the infecting organisms are "susceptible" *in vitro*. A study of nearly 50,000 patients in 173 US hospitals showed approximately 99% of patients had infections with gram-negative bacteria to which at least one susceptible drug remained.[11] Similarly, in a global study from the US Department of Defense Military Health System, 99% of all bloodstream infections (both gram positive and gram-negative organisms) and 94% of deaths were in patients for whom a drug exists that is able to inhibit growth of the bacteria in the test tube.[12] The proportion of patients who died from a resistant bacteria was only one of every 17 infections, indicating that most patients who died with infections had "susceptible bacteria." And yet, the needs of those patients are not considered in AMR discussions because they are not infected with a "priority pathogen." This calls into question the definition of "resistance" that relies solely on *in vitro* results. A focus on patient outcomes would define "resistance" as infections in which patients do not get better regardless of the results of *in vitro* testing.

## Exaggerating the Impact of Antimicrobial Resistance

Resistance is often defined by how many drugs or classes of drugs lack *in vitro* biological activity. For example, the US Centers for Disease Control and

Prevention (CDC) defines "multi-drug resistance" as organisms "resistant to one or more classes of antibiotics."[13] However, focusing on which drugs might *not* work is less clinically useful to patients than focusing on how many potentially effective drugs remain for treatment. Studies using this more clinically relevant definition termed "difficult to treat resistance" (DTR) show a better correlation with patient survival.[11,14] As noted above, patients infected with organisms resistant *in vitro* are on average older, sicker, have more co-morbid diseases, and received more prior antibiotics than patients with "susceptible" infections.[15] For this reason, many patients die with, not from, resistant organisms. One study measured the attributable mortality – deaths due to the infection – as 25%, meaning that 3 of 4 patients infected with resistant organisms do not die from the infection but rather die from weakened immunity and/or other underlying diseases.[16] Another study using US data showed attributable mortality in infections from gram negative bacteria in various diseases as approximately 7.5% to 12.6% (1 in 8 to 1 in 13 deaths due to resistant infection), depending on the disease and the drugs used for comparisons.[17]

A widely reported alarming prediction of 39 million deaths and "more deaths than cancer by 2050"[16] are not based on evidence; on the contrary, rates of *in vitro* resistance in the US and in other countries have remained stable or decreased over the last decade. This and previous frightening predictions are from modeling based on assumptions. As was amply demonstrated during the COVID-19 pandemic, models can be largely inaccurate at predicting numbers of infections, deaths, and the impact of medical interventions.[18] The models regarding AMR assume a continued and large increase in "resistance," which as we noted above is defined by how many drugs lack *in vitro* activity rather than how many potentially effective drugs remain.[19-22] Unfortunately, the focus on future predictions shifts attention away from the current patients who need more effective treatments now, not in 2050.

## Impact on Drug and Device Development

The focus on pathogens has resulted in development of medical interventions that focus on *in vitro* biological activity instead of improving patient outcomes.[3,4] For several decades, government regulators have allowed studies to enroll patients who already have effective options for what regulators define as serious and life-threatening diseases. Equally problematic, standards for approval allow the new drug to be up to 20% less effective for the types of patients enrolled – the oddly named "non-inferiority" trials – exposing patients in clinical trials to potential harm while potentially offering no benefit to any patients.[23] These studies did not focus on whether the new drugs decreased adverse effects to offset the potential decrease in efficacy.[24,25]

Regulators and drug companies have claimed that approving drugs studied in patients who already have effective options will provide "new options" for future patients when the older drugs to which the new drugs were compared might decrease in efficacy.[26] This claim lacks a scientific foundation, since infectious diseases are caused by the presence of pathogenic organisms *and* a response from the host's immune system, which can often clear common bacteria before a disease develops.[27,28,] Different types of patients have different immune responses, which is why COVID-19 had different effects in older persons and those with underlying diseases compared to younger, healthier people.[15]

Moreover, at least a dozen drugs with *in vitro* activity have been shown to be harmful for patients in clinical trials.[27] One notable example is the antibiotic cefiderocol (Fetroja). This drug demonstrated "similarity" in efficacy to an older effective drug in patients who already had effective options for complicated urinary tract infections. However, in a randomized trial the drug increased deaths by 16% in patients who were infected with resistant organisms compared to older drugs whose efficacy were also considered questionable.[30]

Regulators in the US have approved a dozen drugs over the last ten years for infections due to

methicillin-resistant *Staphylococcus aureus* (MRSA drugs).[31,32] None of these drugs decreased deaths in clinical trials; moreover, in clinical practice, mortality in bloodstream infections in the large global US military health system did not change over a decade, despite these new drugs.[12] Since no patients with MRSA over that decade had resistance to all current drugs, poor outcomes must be due to factors other than *in vitro* resistance. Despite this evidence, regulators continue to approve drugs based on a single trial plus "confirmatory evidence" that are often from *in vitro* data or data from animal models.[33] However, confirmatory trials are supposed to provide evidence that a drug improves patients' lives, not to confirm how a drug might work in pre-clinical studies. In fact, legal precedent from the 1970s that was the genesis of current FDA standards for drug approval pointed out the lack of correlation between *in vitro* data, animal models, and patient outcomes in disease.[34]

Due to all these shortcomings in how current drugs are studied for most bacterial and fungal infections, it is not possible for patients and clinicians to know which drugs are likely to be better for which patients. Since it is impossible to show statistically that two drugs are exactly equal, non-inferiority trials are intended to allow some loss of efficacy as long as the new drug has some added benefit in terms of fewer or less severe adverse effects, improved convenience, or less cost, and does not result in irreparable patient harm.[35] Patients with effective options need fewer or less serious adverse effects, whereas patients who lack effective options need treatments with better efficacy. Therefore, studies in these different types of patients should differ in their research questions.

Unfortunately, research on the protocols of infectious disease trials shows that this trade-off is not evaluated in most studies.[24] Consent forms also fail to explain that the goal for study participants and the future approval of the drug is non-inferiority compared to existing treatments, raising ethical as well as scientific issues. The loss of efficacy allowed by regulators in non-inferiority trials has steadily increased in recent years from 10% to 20%.[23,31] That means that a new drug can be approved despite being 70% effective when the older drug it is compared to is 90% effective. Few patients would sign up for a trial or treatment where as many as 1 in 5 patients (20%) might do worse with the new drug compared to an older available approved drug; In fact, in a recent survey most patients said they would decline to join a study with a potential loss of efficacy of 10% regardless of other potential benefits.[25] Moreover, if drug B is approved based on potentially 20% less efficacy than drug A, and drug C is allowed to be approved if 20% worse than drug B, there can be a slippery slope called "biocreep" resulting in less and less efficacy for each newly approved drug.[36] Equally problematic, the outcomes in these trials are often laboratory tests or subjective clinician judgments rather than objective measurements of patients' health such as survival, symptoms and function in patients' lives.[31]

## Solutions

The approach to infections needs to focus more on patients and patient outcomes, and that means we need drug approval policies that require better evidence. If government policies are needed to provide incentives for new treatments, those policies should focus on prioritizing interventions that improve patient outcomes in terms of helping them live longer or better, rather than focusing on just changing laboratory tests. For example, the Get Antibiotic Incentives Now (GAIN) Act of 2012 allowed FDA to grant priority review to shorten the review time for "life-threatening diseases" if the drug had *in vitro* activity against a list of organisms that includes almost every human pathogen, even some to which resistance has not yet developed.[37] The law did not require improved patient outcomes as a criterion for priority review; As a result, since the passage of this law, there has been an increase in the number of antimicrobials approved in the US, but none of them have demonstrated improved patient outcomes.[31,32,38].

For example, sulopenem recently gained extended exclusivity under the GAIN Act for uncomplicated urinary tract infections – a disease with short-term reversible morbidity-- despite a lack of evidence of improved patient outcomes and unknown risks compared to older drugs. Therefore, the law should be amended to provide priority review only to interventions that have direct evidence of improving patient outcomes in diseases with high mortality. Similarly, the recent change by the US Center for Medicare and Medicaid Services that allows higher payments for antibiotics in the absence of evidence of improved patient outcomes should be reversed to increase payments only for interventions that improve the lives of patients.[39] Any new legislative efforts to provide incentives for drug companies to develop new antimicrobials, such as the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act introduced in the US, should provide such incentives only to drugs that provide direct evidence that they improve patient outcomes.[5]

There is also a need to improve the evidence from clinical trials in infectious diseases to justify clinical use in practice, and to justify government coverage for payment. The following suggestions would improve the evidence and therefore benefit patients:

1. Studies should enroll patients for whom current therapies have suboptimal effectiveness. This would help ensure that interventions focus on patients who most need them, thus justifying the potential harm of new interventions. In addition, patients should be enrolled based on patient characteristics, rather than infecting organisms alone.

2. In addition to small molecule antimicrobials, more research is needed to evaluate interventions that focus on the patients' microbiome, immune system, and personal protective equipment such as gowns and masks. For example, steroids given to patients with severe pneumonia have recently been shown to improve survival. Better diagnostic devices which are evaluated to show their benefits on patient outcomes (not just accuracy of tests) would be helpful in applying new interventions appropriately.

3. Trials should be designed to evaluate superiority in effectiveness. Non-inferiority trials should be reserved only for interventions where the new treatment is likely to have decreased adverse effects, improved convenience, or less cost, and only in diseases where lesser efficacy does not result in increased harm for patients. This is consistent with the Declaration of Helsinki, which states that potential research participants should not be randomized to any drug less effective than the best available one if they would be subject to irreparable harm.

4. The outcomes used as endpoints in clinical trials should be direct measures of survival, patient symptoms, and function in their daily lives. These are more meaningful than indirect measures such as culture results or clinicians' decisions and make more sense when studying acute diseases where the direct impact on patients' lives can be measured in a short period of time. Any studies using indirect measures should show how they reflect direct benefits to patients.

5. Researchers should enroll sufficient numbers of male and female participants of varying ages and health status and use appropriate inferential statistical analyses (not descriptive statistics only) so that the results are relevant to clinical practice.

How do we know these strategies will work? The vast improvements in the lives of patients living with HIV/AIDS were achieved by following the precepts above. First, effective therapies were developed, then those with fewer adverse effects and finally those with greater convenience. Evaluating interventions for diagnosis, prevention

and treatment of bacterial, fungal and other viral diseases should follow this same model. We have tried it the "usual way" for decades and the result has been a greater quantity of costly drugs without evidence that they improve patients' lives. Focusing on patients and improving patient outcomes would help patients infected with resistant organisms as well as the greater numbers of patients who experience poor outcomes with "susceptible" bacteria.

## Conclusions

For several decades, the focus of infectious diseases research and policy has centered on pathogens and resistance to the biological effects of growth inhibition by drugs *in vitro* and misleadingly framed as a world crisis. While AMR is a serious issue, it should be put into the context of overall patient outcomes regardless of infecting pathogens. A patient-centered view shows that resistance to all first line antimicrobials is uncommon in developed countries and has not increased (or has decreased) over time. This is in part due to stewardship efforts to use drugs more appropriately. Historically, infection mortality decreased before the first antibiotic was discovered, showing the importance of infection control, clean water and food, particularly in developing countries – challenges that will not be addressed by new drugs. The focus on "bugs and drugs" has resulted in more new drugs on the market and increased prices, but not improved patient outcomes. This result is not surprising as current government policies do not place the incentive on improving patient outcomes. Policy interventions should focus on patients and improving patient outcomes for all those who experience poor outcomes with infections, not only those infected with specific types of pathogens. The evidence shows that patients with "susceptible" infections who still have unmet needs outnumber those with AMR. Focusing on improving outcomes could expand the types of interventions and help all those with infections including susceptible as well as resistant infections.

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The authors have no conflicts of interest to disclose.

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