

# Arnold Ventures

## Antimicrobial Resistance (AMR)

### Issue Brief

#### BACKGROUND

Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi and parasites change to no longer respond to medicines. These changes make infections harder to treat and increase the risk of disease, illness, and death.

As AMR increases, antibiotics and other antimicrobial medicines decrease in effectiveness, raising concern of infections that are difficult or impossible to treat. In response to this concern, the federal government – through various platforms – is trying to bring new treatments to market, with the hope that they will be better able to evade resistant bacteria.

In theory, the goal is a laudable one: invest federal funds in efforts to develop drugs for patients affected by resistant bacteria. However, the practical application of this goal has concentrated the development of new drugs on eliminating a pathogen, rather than on improving patient outcomes.<sup>1</sup> The reality is that it is rarely the case that a patient who is facing a resistant infection can be cured simply by eliminating the threat of the resistant pathogen.<sup>2</sup> That is because these patients are often complex and present with multiple comorbidities.

Moreover, whether a treatment for an infection will work for a patient depends not just on the drug's ability to eliminate the pathogen, but also how a patient's immune system reacts to the drug.<sup>3</sup> As a result, when newer antimicrobial treatments are used in patients outside the limited confines in which they are studied, patients often see no improvement in outcomes compared with currently approved "older" therapies.<sup>4,5</sup> For those patients with resistance to available drugs, the new therapies provide little to no evidence<sup>6</sup> of improvement over current care options.

#### INADEQUATE CLINICAL TRIALS

Unfortunately, there is not a direct link<sup>7</sup> between *in vitro*, or "test tube," studies of a drug's ability to eliminate a pathogen and that drug's clinical impact on patient outcomes. This fact is too often overlooked by policymakers. This is in part because the evaluation of new antimicrobial treatments is conducted through non-inferiority (NI) trials, which are supposed to evaluate whether a drug may have lesser efficacy in patients as a trade-off for better results in other areas – such as fewer adverse events. This approach is inherently incongruent<sup>8</sup> with the goal of developing new antimicrobial treatments, where lack of efficacy in patients with resistance to existing drugs is the primary problem. Additionally, NI study enrollment criteria allow for the exclusion of patients with infections resistant to older drugs.<sup>9</sup> This is the exact population of patients who will likely receive the drug in the future and for whom a more efficacious alternative is needed.

The above mechanisms for review of potential new antimicrobial treatments exist as they do today because of incentives to bring to market more and newer therapies, rather than better therapies. For example:

- The Generating Antibiotic Incentives Now (GAIN) Act of 2012: Incentives in the law require no improvement in patient outcomes and are based on whether a drug eliminates a pathogen based on a list of pathogens that are deemed to be important to public health.<sup>10</sup>
- A Centers for Medicare and Medicaid Services (CMS) rule that removed the requirement for added patient benefits for a New Technology Add-on Payment for new antibiotics.<sup>11</sup>
- As introduced, The PASTEUR Act is a manifestation of using policy to get more and newer therapies, rather than better therapies. Without meaningful improvements, this bill would award billions of taxpayer dollars to new antibiotics regardless of their clinical benefit.

### WHEN THE GOAL IS MORE NOT BETTER, PATIENTS LOSE

Policies that create monetary incentives for manufacturers to produce lower-quality, less efficacious drugs for the sake of innovating *more* drugs should be revisited. The effects of such policies can already be seen as drugs – such as cefiderocol<sup>12,13</sup> which carries a black box warning for increased mortality and plazomicin which carries a warning for increased kidney dysfunction in the patients in whom it was studied<sup>14</sup> – are approved despite significantly increased risk of patient harm. NI trials allow lower efficacy when compared to existing treatment options in patients who have effective and less expensive options.

Improving patient outcomes<sup>15</sup> should be the goal of every new therapy approved by the Food and Drug Administration. Equally important, the clinical evidence standards applied to the review of antimicrobial treatments should ensure that efficacy and safety remain the goal. Incentives to address a medical need, such as improving the ability to treat antimicrobial resistant infections, should ensure that they spur innovation that does not simply create more drugs, but creates better drugs that improve patient outcomes.

### SUPPORT POLICIES THAT PUT PATIENTS FIRST

Policies should incentivize innovation by ensuring that interventions improve patient outcomes rather than simply eliminate pathogens. Four issues should be considered when developing policies to address AMR:

1. **Patients (P):** ensure that studies enroll patients for whom currently available therapies are not effective
2. **Interventions (I):** encourage innovation by incentivizing research on a wider range of interventions beyond antibiotics, including host directed therapies.
3. **Comparators (C):** focus on evaluating how new interventions are better for patients in comparison to older therapies
4. **Outcomes (O):** evaluate patient centered outcomes, including survival, patient symptoms and day-to-day function rather than simply eliminating pathogens.

As such, the following legislative recommendations advance a PICO-oriented approach to develop clinically meaningful antimicrobial treatments:

- Require candidate antimicrobial therapies considered for subscription-based payments or advanced market commitments to demonstrate evidence from pre-approval studies on improved patient outcomes on survival, patient symptoms or patient function in their daily lives.
- Require manufacturers of novel antimicrobial therapies to study infections in patients who lack currently available, effective therapies.
- Consider other innovative biological products, such as immunomodulators, beyond antimicrobial drugs that improve patient outcomes.
- Ensure sponsors of antimicrobial therapies that receive a critical need designation appropriately use diagnostic testing for biomarkers related to diagnosing infection in patients whose benefit has been demonstrated with the drug including those due to AMR pathogens to inform the use of the drug.
- Provide guardrails to protect against “double-dipping” by requiring sponsors awarded subscription contracts to submit to the HHS Secretary annual sales volume, which may obviate the need for routine payments.
- Provide the HHS Secretary with the necessary tools and regulatory authority to expeditiously cease any payment installments under subscription contracts for sponsors that (1) do not complete a postmarket study required by the Food and Drug Administration (FDA) during the first five years of the subscription contract or (2) whose annual revenue from government programs that pay for drugs subject to a contract agreement exceeds the amount of the subscription contract paid by the HHS Secretary for that year.
- Ensure the HHS Secretary has an appropriate surveillance system in place to assess patient outcomes, and measures related to AMR, including types of patients and infections.

## Endnotes

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