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SUMMARY

Germs resistant to treatments kill roughly 35,000 Americans per year.[1] Infections caused by drug-resistant bacteria, viruses, and fungi are on the rise, and without changes in policy, could kill 12 million people annually worldwide by 2050.[2] Drug-resistant infections could reduce global GDP by 2%-3.5% by 2050, according to the World Bank.[3]

The overuse of antibiotics and poor infection control during the height of the COVID-19 pandemic may have exacerbated antimicrobial resistance (AMR).[4] AMR occurs when bacteria, viruses, fungi, and parasites evolve to no longer respond to treatments or when new pathogens that resist treatment emerge. Often referred to as "superbugs," they pose the risk of severe illness or death.

Antimicrobial resistance (AMR):

Bacteria, viruses, fungi, and parasites that have evolved where they no longer respond to medicines making infections harder to treat and increasing the risk of disease spread, severe illness and death.

Anti-microbials:

Medicines like antibiotics, antivirals, antifungals, and antiparasitics used to prevent and treat infections in humans, animals, and plants.

If science doesn't stay ahead of AMR, health care will slide backwards to the days when diseases now considered treatable — pneumonia and skin staph aureus infections — killed thousands of people each year. Yet today we're seeing the spread of deadly strains of bacteria that can cause blood infections, pneumonia, and sepsis. That's why the World Health Organization says that antimicrobial resistance is one of the top 10 global public health challenges threatening the practice of modern medicine.[5]

The U.S. needs to combat these superbugs on three fronts:

- Curtailing the overuse of antimicrobials in medicine,
- Limiting the use of antimicrobials on animals and agriculture, and
- Investing in the development of new anti-microbials to stay ahead of nature.

BACKGROUND

Prior to the discovery of penicillin in 1928, diseases such as pneumonia, skin infections, meningitis, and whooping cough were often fatal.[6] But once the use of antibiotics became mainstream in the 1940s, these infections became minor, easily treatable illnesses that no longer warranted a death sentence. The average life expectancy was extended by roughly 20 years because of the widespread use of antibiotics.[7] But almost immediately, scientists discovered that certain types of bacteria were becoming resistant to penicillin and began working on second-generation antibiotics.

Unfortunately, scientific discovery hasn't kept pace with evolutionary biology — both because superbugs evolve to evade antimicrobials and because new superbugs are also being discovered in the far reaches of the globe.

Without changes in scientific discovery and policy, AMR poses a risk to society and modern medicine. While pathogens are evolving to evade our current arsenal of drugs, scientific investment isn't keeping pace in development of new antimicrobials. When COVID-19 emerged, the response was to invest in antivirals and there were roughly 260 COVID-19 antivirals in clinical development in 2020-2021. By contrast, there are only 73 new antimicrobials in clinical development because of poor incentives and a lack of investment.[8,9]

PROBLEM STATEMENT

According to a recent study published in *The Lancet*, in 2019, 1.2 million people died directly from drug-resistant infections while AMR contributed to the deaths of 5 million additional people worldwide.[10] This means that an infection may have exacerbated existing medical conditions and contributed to death rather than being the only causal factor.

Then came the COVID-19 pandemic. The Centers for Disease Control and Prevention (CDC) data show that resistant hospital-onset infections and deaths increased at least 15% during the first year of the pandemic.[11] This could be because of an increase in hospital-acquired infection as more people were hospitalized, or because infection control languished as hospital staff were over-burdened with COVID-19 or because antibiotics were overused as people presented with ambiguous respiratory symptoms. But the fact remains that without changing how we use and develop new anti-microbials, millions more people will die, and health advances will be lost.

OVERUSE

About 80% of antibiotics used in the United States aren't used by humans, but by livestock — cows, pigs, and chickens. Many industrial-scale farms use antibiotics prophylactically — to prevent disease and to accelerate growth — which contributes to drug resistant pathogens living in the food and water supply.[12] The European Union has recently banned prophylactic antibiotic use in livestock, but the U.S. and other countries don't limit how farmers can use antibiotics.[13]

But the overuse doesn't stop there. In 2019, farmers under attack from a bacterial infection that threatened to decimate Florida citrus groves received permission from the Trump administration to use controversial bactericides on their trees. The Environmental Protection Agency allowed farmers across California, Florida, and Texas to use streptomycin and oxytetracycline — drugs typically used for syphilis, tuberculosis, and urinary tract infections — on their citrus plants.[14] Using medical-grade antimicrobials increases the risk that pathogens develop resistance to these treatments in soil, water, and eventually humans.

Finally, antibiotics are overused in the practice of medicine, which is the final key driver of antimicrobial resistance. The CDC reports that 70% of the bacteria that cause two million hospital-acquired infections annually are resistant to at least one antibiotic.[15] Although there were declines in hospital-acquired infections before the onset of the COVID-19 pandemic, hospital infections surged in recent years. This might have been because of increased antibiotics prescribed to prevent secondary lung infections brought on by a COVID hospitalization. Between March and October of 2020, 80% of hospitalized COVID patients were prescribed antibiotics.[16]

While the prescriptions may be medically necessary, increased use contributes to resistance if science can't stay ahead of AMR. Infection control efforts may have also lapsed under staff shortages and over-burdened hospitals.

Additionally, the CDC estimates that at least 30% of outpatient antibiotic prescriptions are unnecessary, most commonly prescribed for viral respiratory infections, such as viral bronchitis, otitis, and sinusitis. With millions hospitalized for respiratory problems, COVID likely exacerbated the overuse.[17]

Even necessary antimicrobial use contributes to the weakened efficacy of treatments over time. Each time pathogens are exposed to antimicrobials, they have the opportunity to adapt to evade them. But unnecessary use means that patients have no medical need for the drugs, may damage their own health from taking the drugs unnecessarily, and add to the weakening of the drugs over time.

BAD INCENTIVES

Scientists have known about AMR almost since the advent of antibiotics. Although they have worked to develop new products to stay ahead of ever-evolving pathogens, the market is not structured in a way that properly incentivizes the development and launch of new antibiotics. The new products are expected to be used sparingly to prevent pathogens from developing resistance. The prospect of limited prescribing offers drug companies little financial incentive to invest years of research and million-dollar clinical trials. As a result, the prospect of limited distribution offers drug companies little financial incentive to invest billions of dollars in research and expensive clinical trials in a new medicine intended to be used only a couple hundred times a year.

When COVID-19 first emerged, there were no tests, treatments, or vaccines for it. But within a year, we had all three. The government invested substantial resources in public-private partnerships and advanced market commitments during the pandemic, which helped reassure drug manufacturers that if they could develop a vaccine or treatment, it might be used by billions of people worldwide and lead

to large revenues. All the right incentives were in place to develop new diagnostics, treatments, and vaccines.

Developing new antimicrobial is the antithesis to developing COVID-19 treatments. Rather than being used by billions of people, new products to treat superbugs would be used for a short duration and sparingly. As a result, fewer drug companies invest in the AMR space than in other research areas.

The number of drugs in clinical development demonstrates the lack of incentives:

- Currently, there are 40 antibiotics, 21 non-traditional antibacterial products, and 12 antifungals in clinical development.[18]
- In contrast, for COVID-19, there were 1,030 drug and vaccine products investigated in 2020-2021, and 450 reached the clinical development stage.[19]
- For breast cancer, there are 160 drugs in clinical development.[20]

How can we bring to AMR the same sense of urgency which produced stunningly effective anti-COVID vaccines in record time?

RECOMMENDATIONS

Policymakers should tighten restrictions on antimicrobial use in agriculture. First, as some European nations do, the USDA should collect data on antimicrobial use.[21] Without knowing more about how they are being used, policymakers can't make informed decisions to improve the stewardship of antimicrobials. Second, we need better surveillance methods to monitor for drug resistant pathogens before they spread to humans through contaminated meat or food. Third, agricultural producers should be banned from using certain antimicrobials that are defined as "medically important" to limit the development of resistant pathogens for commonly used treatments.

To address overuse and misuse in medicine, policymakers should improve diagnostics, update stewardship guidelines, and refine quality metrics.

Diagnostics

Medical providers need easier access to advanced diagnostic tools to reduce unnecessary prescribing and ensure proper antimicrobial use. Essentially, medical labs that confirm an infection should direct providers to the best antimicrobial for the infection. Often, first-line antibiotics are cheaper than rapid diagnostic tools.[22] This encourages the overprescribing of antibiotics without testing to see what the exact infection is. Additionally, patients are hardwired to want a solution for their ailment and often push to take antibiotics "just in case," causing many people to take antibiotics for viral infections when they are ineffective.

Policymakers must direct more resources and investment toward diagnostic tools that can reduce unnecessary antibiotic use. When patients present at a doctor's office with an infection, improved and affordable diagnostics can help physicians know when they are dealing with a resistant pathogen. Doctors can prescribe the best treatment by knowing what pathogen is causing the infection. Certain antibiotics are reserved only to be used on drug resistant infections — known as last-in-line antibiotics — and they need to be used appropriately. Providers can't know when these drugs can best be used without proper diagnostics.

Overuse also results when doctors prescribe the wrong antibiotic to treat an infection. For

example, AMR is worse in middle-income countries that often don't have access to the right antibiotics for a particular infection.[23] So they use what they do have, hoping it will work. Antibiotics are broken into tiers, with the first tier having no restrictions and the final tier requiring medical necessity to use. To prevent resistance from developing, it is better to use a higher-tiered antibiotic once rather than failing on first line, second-line, and third-line drugs first.[24]

Stewardship guidelines

The CDC has an antibiotic stewardship program to help prescribers "use the right antibiotic, at the right dose, for the right duration, and at the right time, and reduce unnecessary antibiotic use."[25] The initiative is a public-private partnership to improve education and practice patterns around antibiotics. Before the onset of the COVID-19 pandemic, the CDC said it was on track to meet many of its goals, including reducing inappropriate outpatient use by 2020.[26] However, COVID-19 changed many prescribing patterns, and the CDC is now reviewing data to see if the trends hold. Pew Charitable Trusts found that even with the stewardship initiative, among two infections studied, nearly 56% of the prescriptions examined were inappropriate regarding the specific antibiotic prescribed, the duration of treatment, or the illnesses for which they were given."[27] If education and stewardship guidelines don't progress enough, policymakers should consider more direct tools — like Medicare reimbursement or quality ratings — to reduce use.

Quality metrics

Hospital-acquired infections are largely responsible for AMR-related deaths in the United States. CMS tracks these infections and penalizes hospitals with high rates of infection. As rates of hospital-acquired infections have increased in recent years, policymakers should consider if existing Medicare penalties for high infection rates are sufficient or if quality metrics need to be tweaked to reflect the latest infection trends.[28] Quality metrics and payment penalties are a more direct stewardship guidelines change how infections are addressed in health care settings.

Incentives

To encourage more investment in developing antimicrobials, policymakers should strengthen financial incentives and find new ways to pay for them:

- Offer cash prizes to companies that develop new and effective antibiotics. This would increase the incentives to develop them without encouraging overuse as drugmakers would be compensated for the innovation rather than the use of their drugs.
- Create reimbursement models based on subscription-style models which compensate antibiotic developers with an upfront payment in exchange for access to their antibiotics, encouraging innovation while decoupling reimbursement from models that encourage overuse.
- Lawmakers and NIH should also allocate funding for rapid diagnostics to make them affordable in a clinic setting
- Use government procurement to bolster and guide research. Federal agencies like the Biomedical Advanced Research and Development Authority (BARDA) and the National Strategic Stockpile should purchase antimicrobials that meet their biopreparedness mission.

CONCLUSION

AMR is not a future problem. It is already a crisis killing tens of thousands of Americans and millions worldwide. If policymakers do not act, we will quickly return to a world where any infection can be -threatening and every surgery poses the risk of death because of drug-resistant infections.

Lawmakers have introduced legislation to address the AMR crisis, including the STAAR Act (S. 3291) from Senator Sherrod Brown, D-Ohio, and the PASTEUR Act of 2021 (S. 2076), which seek to address antibiotic resistance and create incentives for new antimicrobials, respectively.[29,30] The PASTEUR Act would move toward a subscription model where antibiotic makers would be paid up front for access to novel therapies.The PASTEUR Act has now been folded into CURES 2.0, a larger package to establish a new health research agency and generally accelerate the delivery of new therapies.[31] Passing any of these bills would be an important step in the fight against AMR.

Antimicrobial resistance is a multifaceted problem and must be addressed with a multi-pronged approach. Policymakers need to consider how misuse in both agriculture and medicine contributes to resistance and recognize that the current market-based incentives we have for other therapies are not working for antimicrobials.

ABOUT THE AUTHORS

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