Data Brief

The Antimicrobial Resistance Research Landscape and Emerging Solutions

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November 2023

Executive Summary

Pathogens developing resistance to common therapeutics complicate and undermine effective responses to global health crises. While antimicrobial resistance (AMR) is often discussed as a future crisis, AMR is, in reality, already a major global health challenge. Effective policy interventions to moderate and solve AMR require an understanding of the AMR research landscape—to inform choices about funding, incentivize novel drug development, and identify gaps in existing research and policy that require further attention.

This report analyzes 211,831 AMR-related research publications from CSET's Merged Corpus that were published between 2000 and 2021, to track trends in research output, identify the leading countries and institutions publishing AMR research, major funders of this research, and patterns of international research collaboration. Our findings include:

1. The amount of both overall microbial research and AMR-specific research increased between 2000 and 2021, as did the proportion of AMR-specific research to overall microbial research.
2. Between 2000 and 2021, the U.S. produced the greatest number of AMR research publications, had some of the world's most prolific organizations, and had the most cross-country collaborations. China was a close second, having recently overtaken the U.S. in AMR publications per year.
3. Emerging technologies such as phage therapy, synthetic antimicrobial development, and therapies involving the microbiome offer promising solutions for AMR. Research related to these techniques remains a small percentage of overall AMR research, though it is increasing at a modest, steady rate and tends to be cited more often than other research.
4. About half of AMR-related research published between 2000 and 2021 discussed the pathogens that the World Health Organization (WHO) considers the most dangerous, but those papers were not cited more than other AMR-related papers.

The U.S. government can play a role in addressing the global health problems posed by AMR. Legislation could help address two main problems: the lack of market incentives for antimicrobial drug development, and the need to improve antimicrobial stewardship and surveillance for new resistant pathogens. Increasing funding for AMR research and international cooperation would also be steps in the right direction, since resistance developed anywhere in the world could cross borders and threaten the United States.

Table of Contents

Introduction

Antimicrobial Resistance is a Pressing Global Problem

Antimicrobial resistance (AMR) is often framed as a problem for the future, but in reality, it is already a major global cause of death and disease. Antimicrobial-resistant pathogens kill more people each year than HIV/AIDS or malaria.[1] In 2019, global drug-resistant bacterial infections directly killed 1.27 million people, a number that balloons to 4.95 million when counting all deaths in which antibiotic resistance played a role.[2] These statistics likely undercount global AMR deaths, since they specifically look at antibiotic-resistant bacteria and exclude deaths caused directly or in part by other resistant microbes like viruses or fungi. In the United States, AMR claims more than 35,000 lives a year, and 2.8 million people are infected annually by resistant pathogens.[3] The situation is worse for developing countries—for instance, in India, almost 60,000 newborns die each year from AMR.[4] In sub-Saharan Africa, AMR causes 24 out of every 100,000 deaths.[5] This is a worldwide problem: when a resistant pathogen arises in one country, it can spread across borders and threaten the entire world.

While AMR is already a major threat, the problem is getting worse. Data from 2022 shows an increase in life-threatening bacterial infections, with over half of such infections developing resistance.[6] The WHO calls AMR one of the "top 10 public health threats facing humanity," and predicts that drug-resistant diseases could force 24 million people into extreme poverty by 2030, cause 10 million deaths each year by 2050, and create damage to the economy as catastrophic as the 2008-2009 global financial crisis.[7]

Without robust efforts to address AMR, multi-drug resistant pathogens will spread further and render more treatments obsolete. Few novel antimicrobials are in development to replace the ones that no longer work. In fact, only 12 new antibiotics were approved between 2017 and June 2022, and 10 of these belonged to existing antimicrobial classes for which established mechanisms of AMR already exist.[8] The pipeline for antifungals and antiparasitics is similarly limited.[9] With fewer and fewer usable antimicrobials, diseases that were once easy to treat can once again threaten humanity.

What Drives Antimicrobial Resistance?

Microbes become resistant when pathogens, including bacteria, viruses, fungi, and parasites, evolve to defend themselves against common therapies used to treat them.[10]

Microbes that develop resistance are harder to treat and spread with greater ease, because they persist longer and the patient remains contagious.

Antimicrobial resistance can occur due to a variety of natural and human-caused factors, including the incorrect use of antimicrobial therapies.[11] When disease-causing microbes are exposed to antimicrobial medications, many of them will die—curing the sick patient. However, some of those microbes will naturally be better at surviving the medicine than others, and so are able to survive for longer. If antimicrobials are used incorrectly, those resistant microbes have a chance to reproduce and spread, until only microbes that have strong defenses against the antimicrobials are left.[12] When a patient gets infected by those new, stronger pathogens, the treatment that worked before becomes ineffective.

Doctors and patients can both contribute to developing AMR. When doctors overprescribe antimicrobials to patients that may not need them, they create more chances for microbes to develop resistance.[13] The same problem occurs when patients misuse or overuse antimicrobials when they are not needed.[14] AMR can affect humans, animals, and plants. Agricultural overuse of antimicrobials is a major contributing factor to the spread of AMR. When healthy livestock are overmedicated to promote growth or as a precautionary measure, their pathogens may develop resistance that can spread among other livestock or infect humans.[15] The release of AMR into the environment from agricultural runoff, and effluents from hospitals, pharmaceutical facilities, and households can also drive the emergence and spread of AMR.[16]

Microbes can be resistant to a single therapeutic, or to multiple different therapeutics. *Candida auris*, for example, is a species of fungus with emergent multi-drug resistance—meaning that the fungus has developed resistance to multiple therapeutics, making it even harder to fight.[17] Drug-resistant *C. auris* infections skyrocketed in 2021, in part as a result of COVID-19-driven hospitalizations and increased antimicrobial use.[18] Antimicrobial-resistant infections often spread rampantly at hospitals and nursing homes, where residents may already have weakened immune systems, and can put those vulnerable people at even greater risk.[19]

There are currently few drugs in development to address AMR. New therapies can take over a decade to develop and safely release to market.[20] Companies are not financially incentivized to develop new drugs for resistant pathogens.[21] Another part of the challenge is that existing therapies are not effective for long. Indeed, a robust pipeline of new therapies is needed because microbes can develop resistance to medications within 2-3 years of their deployment to the market.[22]

Global Policy Efforts

The United States is pursuing multiple avenues to combat AMR, including increasing R&D funding, engaging in international surveillance efforts, and drafting legislation.[*] A few of these efforts include:

- In 2015, the U.S. government launched the U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria, an interagency effort to accelerate AMR-related research into new therapeutics, improve international cooperation for AMR surveillance and research and development, and reduce the use of antimicrobials by asking hospitals to track and release information about their antimicrobial prescriptions.[23,†]
- In 2018, the Center for Disease Control and Prevention (CDC) and Department of Health and Human Services (HHS) launched the AMR Challenge, inviting organizations worldwide to make commitments towards prioritizing AMR.[24] In addition, the National Institutes of Health (NIH) and United States Department of Agriculture (USDA) have funded a variety of research initiatives to better understand AMR and identify new treatments.
- Most recently, in 2023, a bipartisan group of legislators reintroduced the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act to Congress, legislation which is still under discussion aimed at addressing AMR by incentivizing pharmaceutical companies to develop critical therapies, and held multiple hearings on the topic of AMR.[25]

International efforts to address AMR are ongoing. In 2006, the European Union banned the use of antibiotics for growth promotion in agriculture.[26] In 2015, the WHO developed an AMR Global Action Plan, aiming to spur and harmonize a worldwide effort against AMR.[27] Subsequently, countries like China and India have issued national policies to combat AMR, such as China's 2016 One Health National Action Plan to Contain AMR and India's 2017 National Action Plan on AMR.[28]

While these policies are steps in the right direction, the pipeline of new antimicrobials remains thin, and AMR is gaining momentum worldwide. Gaps in AMR surveillance data, particularly in lower-income regions of the world, make tracking the true impact of AMR challenging.[29] As COVID-19 revealed, the emergence of a dangerous disease in one country can very quickly spread to the rest of the globe. Appropriate antimicrobial practices in the United States can help reduce the likelihood of resistance

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[*] See Appendix G for some additional notable U.S. and international AMR policies.

[†] This plan was updated and renewed for the 2020–2025-time frame.

developing domestically, but the United States will still be vulnerable to resistant pathogens that cross borders. Additionally, developing new antimicrobial medications will help fight resistant infections whether they develop domestically or abroad.

For this reason, the United States and U.S. policymakers will benefit from understanding the state of global research on AMR. In this report, we outline the state of global research on AMR to help U.S. policymakers prepare for rising drug resistance and begin working towards solutions.

Methodology

In this report, we look at publications and trends in AMR research. Scientific research on AMR is the path to better understand how resistance happens, the foundation for new and innovative medical countermeasures, and the first step towards solving this challenge. Understanding what AMR research has taken place over the last few decades, and how that research has changed or stayed the same, will illuminate what efforts are already ongoing and identify where additional efforts might be crucial to effectively reduce AMR.

To better understand how research over the last few decades has changed in response to the growing public health threat from AMR, this report aims to:

1. Characterize the nature and scope of overall research on microbes and on antimicrobial resistance (AMR) that has taken place globally between 2000 and 2021.

2. Identify the major regional and organizational hubs for AMR research over that time frame, both within the United States and internationally.

3. Take note of trends in emerging AMR-related fields, including phage therapy and synthetic antimicrobial production.

4. Characterize funding for AMR-related research and development.

We analyzed CSET's merged academic corpus of over 260 million scientific publications to accomplish the above objectives. CSET's merged corpus of scholarly literature includes Digital Science Dimensions, Clarivate's Web of Science, Microsoft Academic Graph, China National Knowledge Infrastructure, arXiv, and Papers with Code.[30]

Our analysis searched for relevant publications in the scientific literature using keywords developed and validated by an external subject-matter expert. We first identified publications relevant to overall microbial research (see Appendix C for keywords). Within this literature, we surfaced the subset of research publications on AMR (see Appendix B). Further querying allowed examination of pathogens (Appendix

E) and emerging research topics (Appendix F). We also compared trends among AMR publications to those in the broader microbial research literature.*

Our keyword-based approach has several limitations—including our use of only English-language keywords (see Appendices for specific terms). Our reliance on English-only keywords and the English-language dominance of our merged academic corpus, which does contain translated titles and abstracts for some papers not originally published in English, may result in underestimates of total worldwide publication volume on AMR. Since publication in English is common worldwide, this analysis still provides a starting point to understand the state of global research.

In order to evaluate the robustness of our keyword-based approach, we also validated our keyword-search approach by drawing a random sample of 200 AMR publications and 100 microbial publications from the results for review by internal subject-matter experts. This yielded a false-positive rate of about 4%, meaning that 96% of the publications we surfaced for analysis were in fact relevant to AMR and microbial research generally. Some non-relevant publications therefore appear in our analysis, but not at a rate that would affect our findings. Similarly, we inevitably did not surface every publication relevant to microbial research or AMR, but the subject-matter expert review of our keywords gives us confidence that the resulting publications are sufficiently comprehensive.

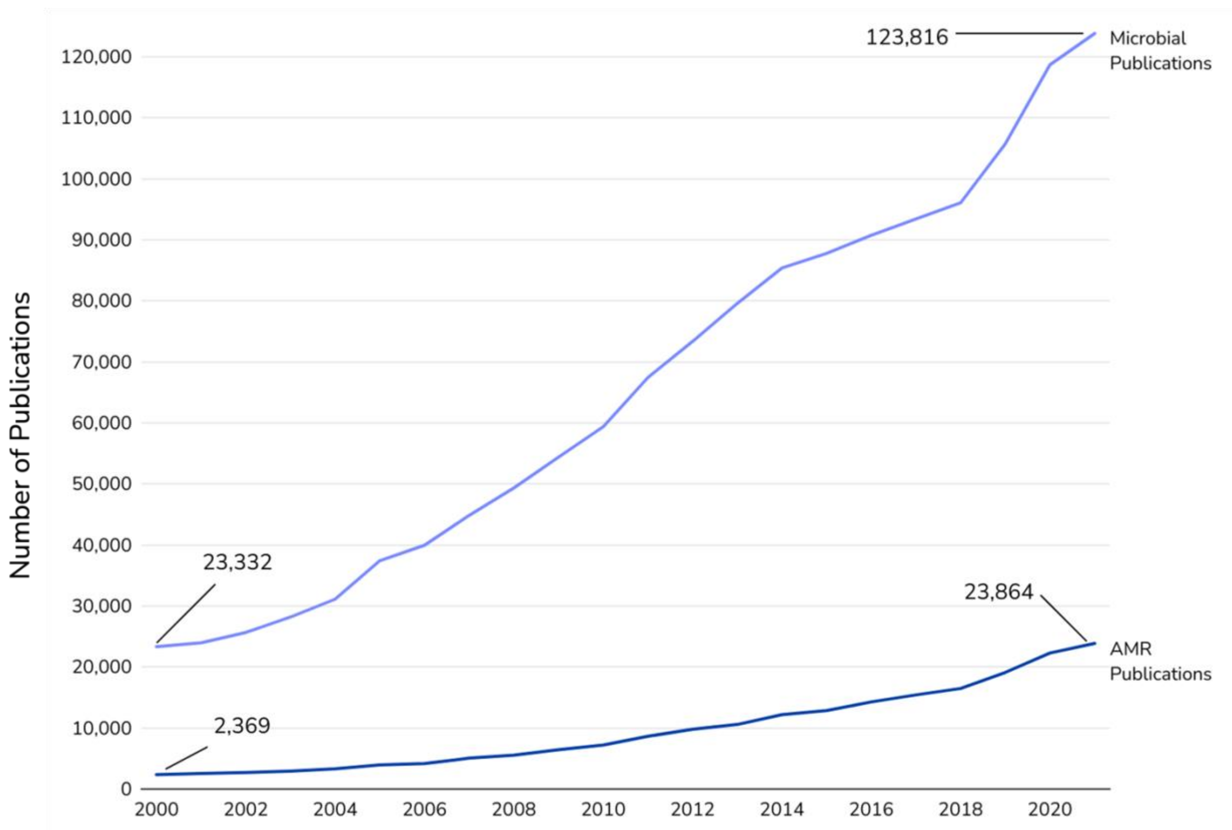
* See Appendix A for additional methodological detail.

Results

Global AMR Research: Output and Trends

We find that both overall microbial research and AMR-specific research increased between 2000 and 2021, and that the proportion of AMR-specific publications to overall microbial publications increased over that time frame. In total, we identified 211,831 antimicrobial resistance-related publications between 2000 and 2021, out of a total of about 1.4 million identified publications on microbial research through those same years (AMR-related papers made up about 15% of microbial research).

Figure 1: Microbial and AMR Publications are Increasing.



Source: CSET Merged Corpus

The U.S., China, UK, and India are Leading in AMR-related Research Output

Researchers affiliated with institutions in the United States and China were the most prolific publishers of AMR-related research in the world, together accounting for 39 percent of the global output we identified between 2000 and 2021 (Figure 2). Of the 211,831 AMR-related publications over those 21 years, the U.S. published around 20% and China published around 19%. Both the U.S. and China led over the next largest country (the UK) by a large margin, publishing over 3 times as many publications—indicating that the research outputs from the U.S. and China play an important role in shaping the world's AMR research landscape.

China and the U.S. were also the top two fastest-growing publishers of AMR-related research between 2000 and 2021.[*] In this arena, China has recently outpaced the U.S., publishing more AMR-related research per year by 2021.

However, AMR-related research publications in China made up a small percentage of overall microbial research publications—only 12% of China's microbial research was AMR-related, the second-lowest percentage amongst those countries with 1,000 or more AMR-related publications between 2000 and 2021 (ahead of only Russia). This could indicate that China's high numbers of AMR-related publications are a result of general increases in microbial research output over the last two decades, rather than due to specific concerns about AMR, despite China's high disease burden from AMR.

[*] See Appendix H

Figure 2: Top 10 Countries Publishing AMR-related Research, 2000-2021.

Country	AMR Publications	AMR Pubs as Proportion to Microbial Pubs
United States	42,346	17%
China	39,850	12%
United Kingdom	12,656	19%
India	11,865	15%
Australia	6,070	21%
Germany	5,974	13%
Iran	5,921	24%
France	5,914	15%
Canada	5,719	18%
Italy	5,465	16%

Note: Countries are sorted by overall number of AMR publications between 2000 and 2021.
Source: CSET Merged Corpus

The United Kingdom was the third-highest publisher of AMR research in the world, as shown in Figure 2. The UK government has taken action to address AMR, including appointing a Special Envoy on Antimicrobial Resistance and spearheading a global campaign to prioritize fighting AMR, and its research community has had a high output.[31] India was the fourth-highest publisher, with 11,865 papers over the past two decades. That the U.S., China, UK, and India are the world leaders in AMR research publications is not unexpected, given the large economies of those countries, advanced science and technology ecosystems, and high output of scientific publications across many disciplines.

Other regions of the world facing public health challenges from AMR are not among the top 10 publishers of AMR research. No African countries were in the top 20 of AMR publication output, despite sub-Saharan Africa having the highest number of AMR-related deaths per capita in the world.[32] South Africa and Nigeria are the only two African countries in the top 30 AMR publishers. Southeast Asia, another region impacted by AMR, has no countries in the top 20, and only one in the top 30: Thailand.[33] That said, these trends are also consistent with patterns of scientific research more broadly–these regions, with a few exceptions like South Africa, have not been prominent producers of scientific publications, largely due to economic constraints, less developed R&D ecosystems, limitations to higher education infrastructure, and a range of other socio-economic challenges.[34]

Despite relatively low general research output, we found that Iran is a leader in publishing AMR-related research. Between 2000 and 2021, Iran published the 7th highest number of AMR-related papers, the 14th most publications of overall microbial research, and had one of the top 5 highest proportions of AMR-related research to total microbial research in the world amongst countries publishing 1,000 or more AMR-related papers (24%). Unlike the other countries in the top 10, which tend to publish a lot of research across multiple subject areas, Iran does not necessarily lead in researching other emerging technology areas, like artificial intelligence.[35] Nevertheless, Iran outpaces most countries worldwide in its output of AMR-related publications, which could indicate that microbial research, and particularly AMR research, is an area of strength and a focus of Iran.

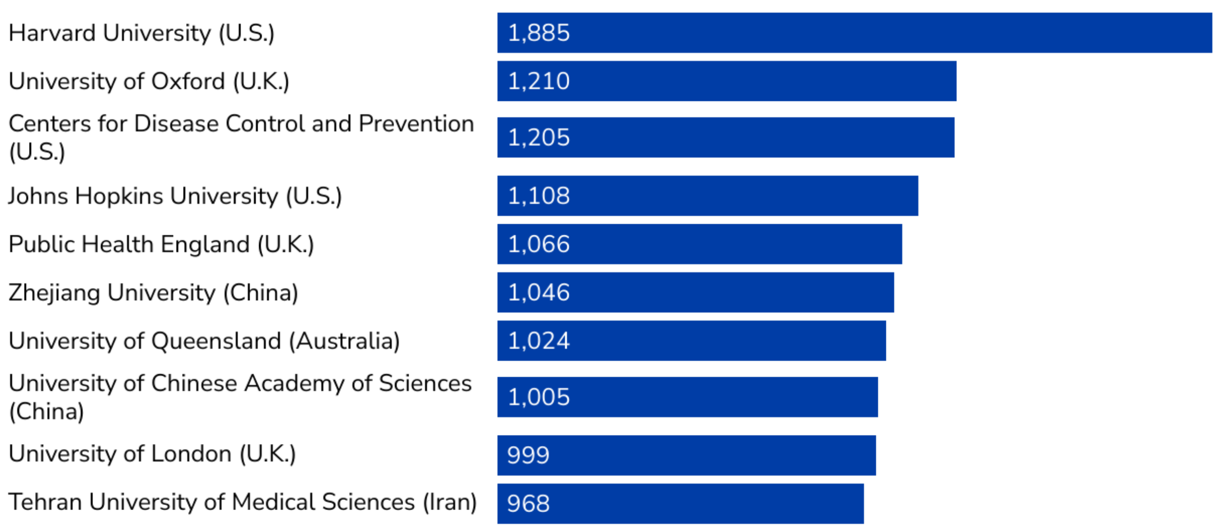
Additionally, we found that amongst the top 40 countries publishing AMR-related research (those countries with 1,000 or more publications between 2000 and 2021), countries with developing economies had some of the highest percentages of AMR-related research within their overall microbial research production. More than one-quarter (28%) of the microbial research published by scientists in Nigeria, for instance, was related to AMR. For Bangladesh, South Africa, Thailand, Malaysia, and Pakistan, the ratio of AMR-specific research publications to total microbial research publications was greater than 20%. Although these countries are not among the top producers of AMR-related research publications as a whole, the relative focus scientists from these nations are dedicating to the topic is notable, and could be a sign that some of the countries with a high disease burden from AMR are prioritizing research on that subject over other microbial research.

Other Findings

Leading Research Institutions

In addition to analyzing AMR research publication trends at the country level, we also examined the top institutions working on AMR research around the world. Three of the top 10 institutions were located in the United States, and three were located in the United Kingdom. China had two, and Australia and Iran each had one top 10 publishing organization. As Figure 3 shows, most of the highest-publishing countries on AMR research also had some of the highest-publishing institutions. However, while India has the 4th highest number of AMR publications overall, there are no Indian institutions in the top 10 (or even top 140) research organizations ranked by their AMR publication output between 2000 and 2021.

Figure 3: Top 10 Institutions Publishing AMR-related Research, 2000-2021[*,36]



Note: Institutions were determined based on listed author affiliations in relevant publications.
Source: CSET Merged Corpus

Trends in International Collaboration

Figure 4 depicts cross-country AMR research collaborations across the globe. Larger blue bubbles depict higher numbers of AMR publications in each country, and thicker pink lines indicate higher numbers of shared publications between connected countries

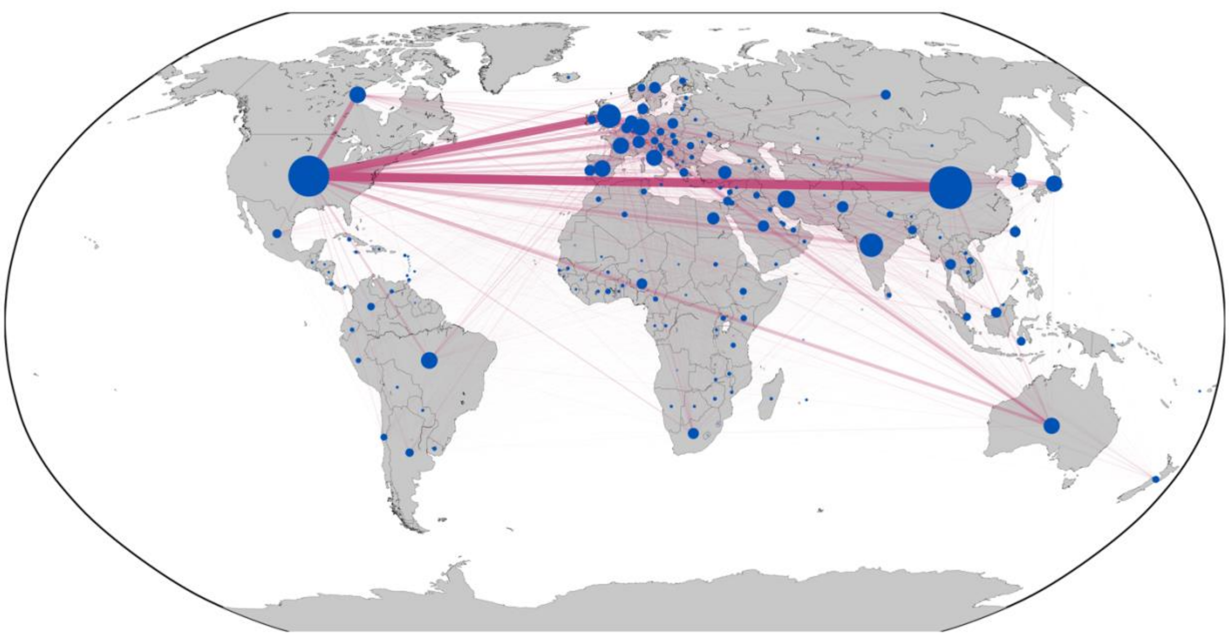
[*] Public Health England was disbanded and replaced by the UK Health Security Agency and the Office for Health Improvement and Disparities in 2021, the last year included in our analysis.

(publications with author affiliations or institutions from both countries). Overall, the United States' high number of cross-country AMR collaborations suggest that it is leveraging international partnerships and talent to enhance its AMR research.

The U.S. collaborates most frequently with China and the United Kingdom. These results are unsurprising, given the U.S. and China's high publication count and the cultural and political ties between the U.S. and UK.

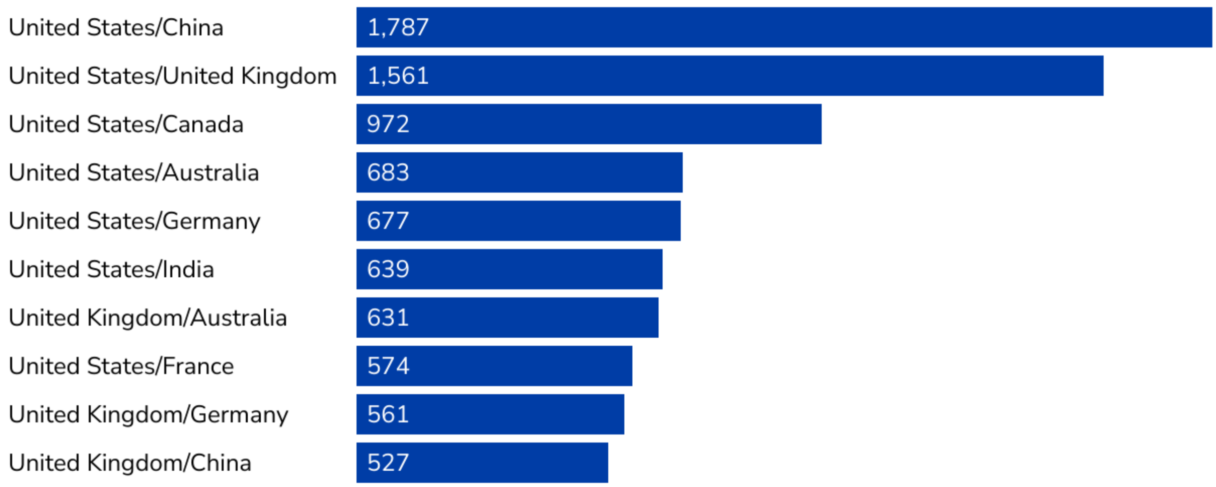
China, the UK, and India, the three highest-publishing countries of AMR-related research other than the U.S, each collaborated more often with the U.S. than any other country, including each other. For China, the UK was the second-most common collaborator on AMR-related publications, but there were over three times as many China-U.S. collaborations than there were China-UK ones. In the U.K, China was the fourth-most common collaborator, with around a third of the publications compared to the U.S. India had relatively few international collaborations with other countries, the highest number being the 639 India-U.S. publications.

Figure 4: International Collaboration on AMR-related Research, 2000-2021.



Source: CSET Merged Corpus. Larger blue bubbles depict higher numbers of AMR publications in each country, and thicker pink lines indicate higher numbers of shared publications between connected countries (publications with author affiliations or institutions from both countries).

Figure 5: Top 10 Pairs of Country Collaborators for AMR Publications, 2000-2021.

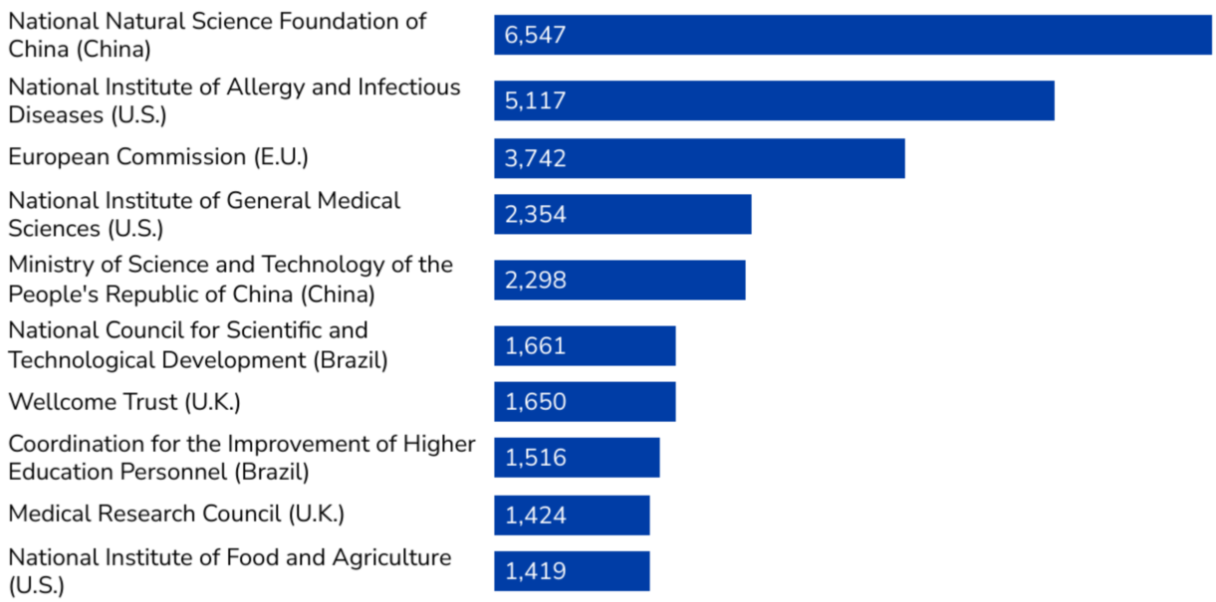


Source: CSET Merged Corpus

Leading Funders of AMR Research

Figure 6 examines the top 10 funders of AMR research around the world between 2000-2021, to identify which countries have the most top funders and analyze the relationship between the presence of leading funding organizations and the amount of AMR-related research output. Our analysis in this area was limited by incomplete data, as only around 40% of AMR-related publications we identified listed an associated funding organization. Nevertheless, this analysis provides insight into some of the most notable funding organizations for AMR-related research.

Figure 6: Number of Publications Acknowledging Funding by Leading Institutions, 2000-2021.



Source: CSET Merged Corpus

With the exception of the European Commission, a multinational institution, and the Wellcome Trust, which is a charitable organization based in the UK, most of the top 10 leading funding institutions of AMR-related research were associated with national governments. The top 10 includes entities from the U.S., China, UK, and Brazil, which could be consistent with the high publishing rates of those countries (three of which are the top-three countries publishing AMR-related research worldwide). Three of the global institutions that support AMR research most frequently were in the U.S., two of which are NIH institutes and one of which is a USDA institute (National Institute of Food and Agriculture). Two were in China—including the National Natural Science Foundation of China, which funded the most publications in the world—two were in the UK, and two were in Brazil. The leading European funder of AMR-related research was the European Commission.

Despite India's and Iran's high numbers of AMR publications, we identified relatively few top funders from India or Iran in our analysis. No Indian funders appeared in the top 10, and no Iranian funding institutions appeared near the top–the organization with the most associated publications was the Iran National Science Foundation, appearing as the 253rd funder of AMR-related research worldwide. No African or Southeast Asian funding organizations appeared in the top 30. These results identify possible disparities between the robustness of funding ecosystems for AMR research depending on countries' socioeconomic status and region, but could also indicate that having leading domestic funding institutions for AMR research is not a prerequisite for a high number of AMR publications, or that funder data from these countries is disproportionately missing.

Trends in Research on Emerging AMR Solutions

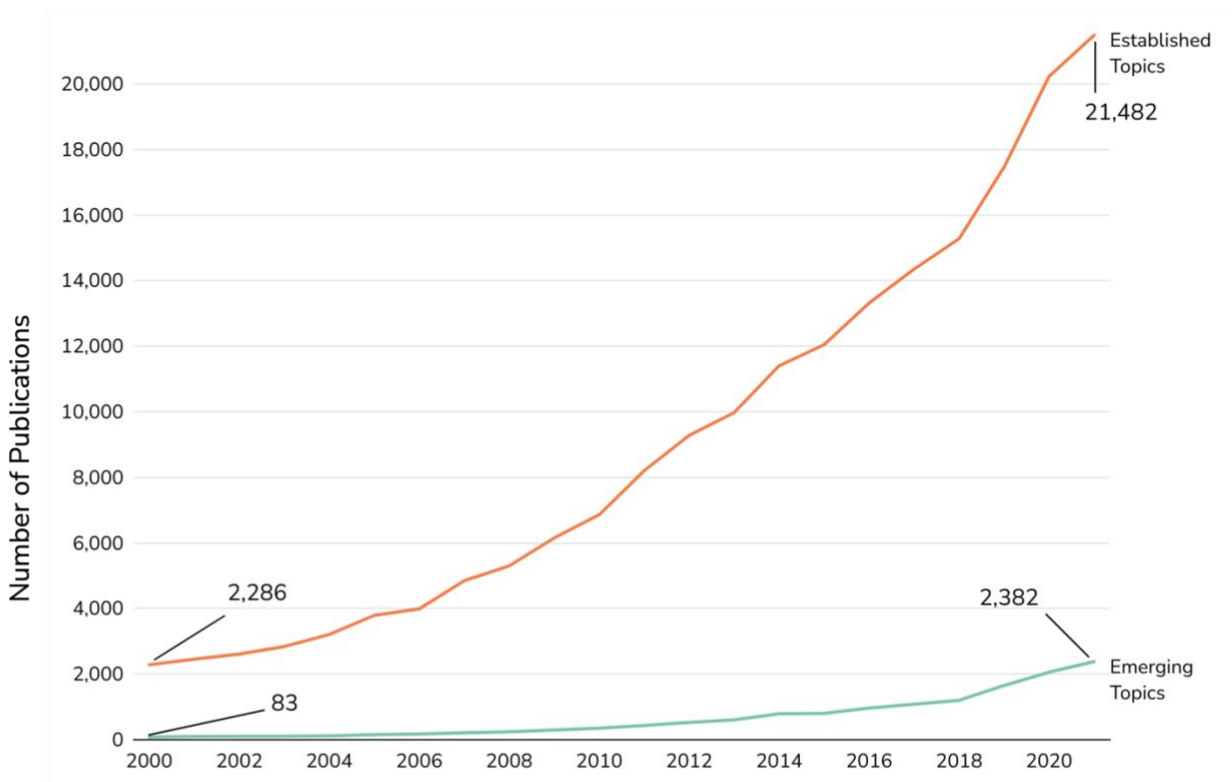
In recent years, various experts have suggested that research related to synthetic antimicrobial development, phage therapy, the microbiome, or biotechnology writ large might help researchers develop new therapies for AMR, overcome the challenges of antimicrobial drug development, and make it harder for pathogens to develop resistance.[37] These potential pathways to combat AMR include novel techniques that leverage technology, new methods of antimicrobial identification, or that focus on different aspects of the immune system. We used a set of subject matter expert-validated keywords to identify the AMR-related publications in our dataset that discussed these emerging topics (Appendix F).

Such topics include:

- Phage therapy, which involves using bacteriophages, viruses that target bacteria, to treat resistant bacterial infections.[38] Phage therapy has been in use for more than a century. However, the U.S. and other Western countries largely abandoned researching phages after the development of antibiotics, prioritizing antibiotic research, though the Soviet Union and associated countries continued to study phage therapy.[39] Due to AMR, phage therapy is experiencing a modern resurgence, which is why we are considering it an emerging field.[40]
- Synthetic antimicrobial development, which involves designing and producing antimicrobial therapies that are not found in nature and may also be a more efficient method of drug production.[41]
- The microbiome, the ecosystem of microbes that live within the human body, which has a major impact on the human immune system that scientists are just beginning to understand.[42]

Our analysis indicates that research focused on these emerging solutions makes up only 7% of the total number of AMR-related publications between 2000 and 2021 (Figure 7). This research activity has increased steadily, albeit modestly, over that 21-year period. However, even in the most recent year (2021), publications on emerging technologies made up only around 11% of total AMR-related papers. That said, we also found that research publications discussing phage therapy, synthetic antimicrobials, the microbiome, or biotechnology were cited more frequently on average than papers that did not discuss those topics. Overall, the steady increase in research publications discussing these emerging solutions as well as the citation frequency of such research over the past decade could suggest a growing interest in these topics. The relatively low number of overall publications in these areas compared to overall AMR-research output, however, suggests there is still much left to explore about these new ways to address AMR.

Figure 7: Emerging AMR Solutions Are a Small Percentage of Total AMR Research



Source: CSET Merged Corpus

WHO Priority Pathogen Research Is Large Component of AMR Research

Although any pathogen can become resistant to treatment and cause disease, the WHO in 2017 identified a list of "priority pathogens," ranked based on their mortality, healthcare burden, community burden, transmissibility, and treatability, among other factors.[*,43] The WHO selected these priority pathogens, which were all bacteria, to identify the most important research needs and spur further R&D, from discovery to

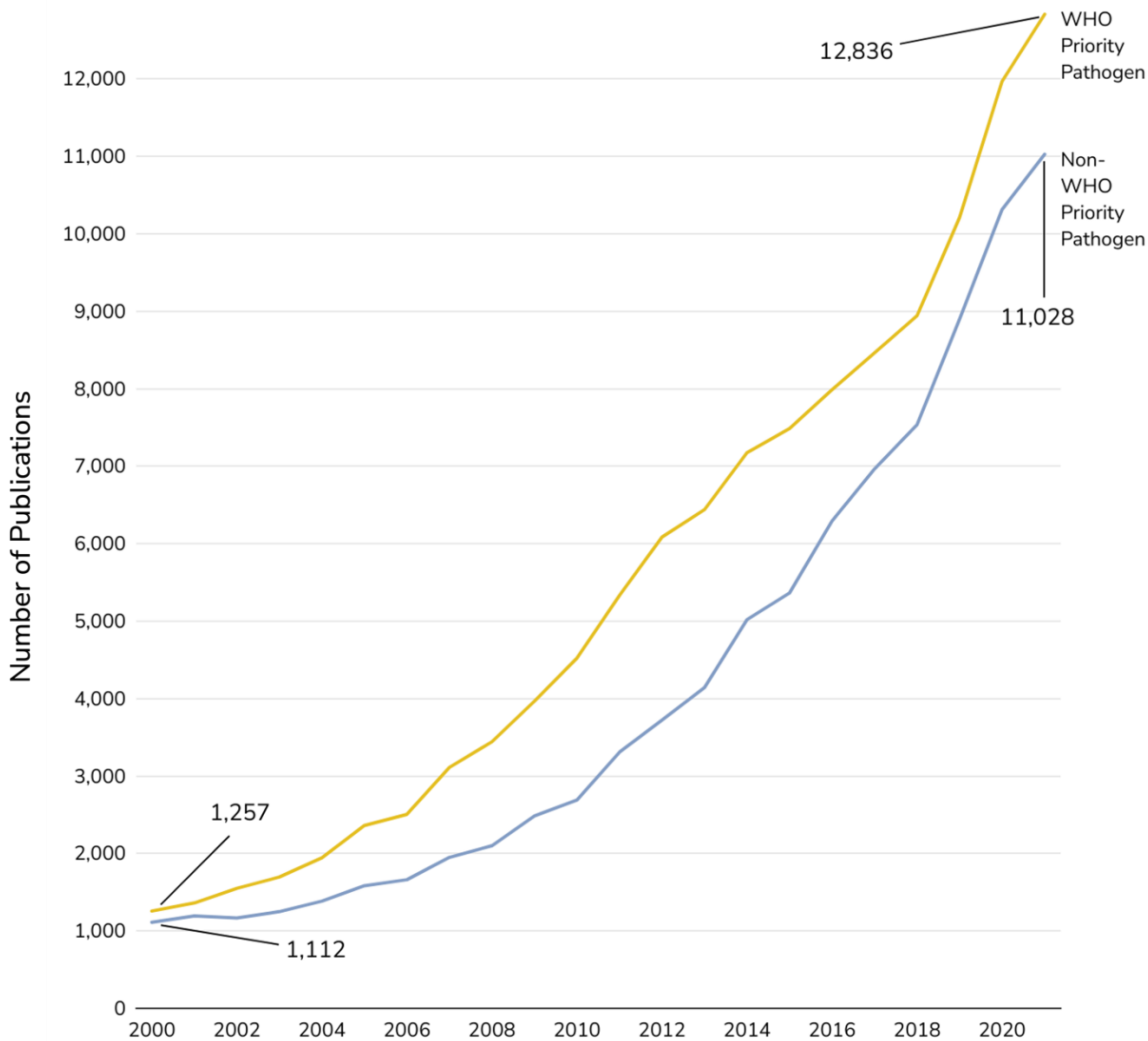
[*] See Appendix E for a list of these pathogens.

drug development.[44] We searched our set of AMR-related publications to identify whether the research landscape of publications matches the WHO's stated priorities.

We found that more than half of identified AMR publications between 2000 and 2021 discussed at least one of these priority pathogens (57%). We also found that the amount of AMR publications discussing WHO priority pathogens and the amount discussing non-priority pathogens increased at around the same rate over that time (Figure 8). We did not identify a spike in the amount of priority pathogen research publications compared to research publications on other microbes as a result of the WHO announcement, but our data only included the four years after the announcement, and the research process from funding to publication often takes longer.

We also discovered that papers discussing urgent pathogens were cited about as frequently as other papers. Overall, these findings suggest that AMR research is not ignoring these important and dangerous bacteria, but also that papers focused on the WHO pathogens are not necessarily more influential in the research community than other papers.

Figure 8: The Numbers of WHO Priority Publications and Non-Priority Publications Grow at a Similar Rate



Source: CSET Merged Corpus

Conclusion: Implications for Policymakers

Antimicrobial resistance is one of humanity's greatest and growing public health challenges. Foundational scientific research on AMR is the first step towards solving this challenge, by understanding how pathogens become resistant and discovering new therapeutic approaches. However, gaps in AMR research could slow down the global response to AMR. To effectively combat AMR, investing in diverse and innovative research could lead to more and quicker drug discovery, novel technologies, and solutions better tailored to the challenges of each region or country.

Our analysis reveals a growing AMR-related research landscape. Both AMR-specific and overall microbial research publications increased between 2000 and 2021, as did the proportion of AMR-specific research publications to overall microbial research publications. We found that the U.S., China, UK, and India are global leaders, publishing the most AMR-related papers. The U.S. produced the highest volume of AMR-related papers with international collaborators. While countries like Nigeria, South Africa, Thailand, and Malaysia do not publish a high volume of AMR papers, AMR-related research is a large percentage of their total microbial research. Iran is particularly notable, with both some of the highest publication counts and also a large (proportionately) research focus on AMR.

These findings show that the U.S. is a major contributor to global AMR research, and as a result, suggest that the U.S. has the opportunity to shape the AMR research landscape going forward, including by identifying innovative AMR solutions. Relatedly, we found that emerging topics of research make up a small, but growing and well-cited, percentage of total AMR-research publications. This area could present an opportunity for U.S. policy to support further research.

Our findings regarding the WHO priority pathogens suggest that U.S. policymakers should continue to be proactive in supporting AMR-related research, and should carefully consider its priorities. The WHO's research shows that some pathogens are particularly dangerous, and in need of greater R&D focus than other pathogens. We found that the majority of AMR-related papers between 2000 and 2021 discussed WHO priority pathogens, and the amount of research on those pathogens is increasing. This is a sign that AMR-related research is taking the most dangerous pathogens seriously, and could suggest that a drastic change in the pathogens of focus is not needed. However, our findings indicate that this increase is more likely explained by the overall increase in AMR research rather than by a shift in focus towards priority pathogens as a result of the WHO recommendations. This is unsurprising, since the research process takes years. For U.S. policy, this case shows that initiatives to change research priorities take time to come to fruition because of long research timelines. Accordingly, novel U.S. efforts to support critical AMR research should be forward-looking, starting early to ensure that important research is not playing catch-up to real-world threats. The U.S. government should carefully consider which pathogens are in need of more research when providing funding, and should provide that funding as soon as possible.

U.S. policymakers can leverage the robust scientific foundation of U.S. research to combat AMR at home and abroad by addressing research gaps, including the small percentage of publications focused on emerging AMR solutions and the low volume of AMR-related research in at-risk countries, through funding and legislation. The AMR research landscape could benefit from legislation supporting the development and sale of new therapies, additional research funding towards emerging solutions, and increased international collaboration, particularly with countries facing the brunt of resistant infections.

Legislative Proposals

The PASTEUR Act and the Strategies to Address Antimicrobial Resistance (STAAR) Act are recently proposed legislation that aim to promote AMR research and development. The PASTEUR Act aims to incentivize pharmaceutical companies to develop new antimicrobials in spite of the low potential return on investment and high risk on the market. It does so through a subscription-based model, with the U.S. government guaranteeing companies a market for their innovative antimicrobials in exchange for access to those therapies.[45] The STAAR Act, in contrast, would re-authorize the U.S. Interagency Task Force on AMR (which expired in 2006), direct the CDC to enhance AMR monitoring, support National Institute of Allergy and Infectious Disease (NIAID) efforts to establish an AMR-focused clinical trials network, provide grants to healthcare facilities to study better antimicrobial stewardship programs, and direct the NIH to build an AMR Strategic Research Plan.[46]

Addressing Research Funding Gaps

U.S. agencies involved in addressing AMR could increase the amount of research funding going towards AMR-related projects, particularly regarding emerging technologies or novel solutions, including those discussed in this brief. Various U.S. government agencies, including the National Institute of Allergy and Infectious Diseases and the National Institute of General Medical Sciences, appeared as top global funders for AMR research. These agencies could award more grants to emerging research topics, helping to identify and then implement innovative solutions more quickly. Additional legislatively-authorized funding for AMR research in general could help these agencies fund cutting-edge research without sacrificing important funding into more traditional research areas.

International Cooperation

Finally, our research has shown that some of the hardest-hit regions of the world have limited funding and limited AMR publications, despite having higher proportions of AMR research than other countries. The U.S. leads the world in AMR cross-country collaborations. Leveraging this strength further and cooperating with countries from those regions to support their antimicrobial stewardship, surveillance, and research and development, including through programs similar to the U.S./EU Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), will help prevent resistance from developing and spreading worldwide, ultimately helping keep the U.S. safe.[47]

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Acknowledgments

For feedback and assistance, we would like to thank Dr. Ivica Labuda for her subject matter expertise in evaluating the keywords used in our analysis. We are especially grateful to Yemisi Ajumobi, M.P.H., M.S. for her comprehensive review of the paper. Additionally, we are grateful to Dr. Caroline Schuerger, Dr. Stephanie Batalis, Dr. Margarita Konaev, Anna Puglisi, Dr. James Dunham, Ngor Luong, Hanna Dohmen, Ronnie Kinoshita, and Dr. Igor Mikolic-Torreira for their invaluable advice in improving the style, content, structure, and scope of this issue brief. Finally, we thank Matt Mahoney for his fact-checking of the paper.

CSET Product ID #: 20230032
Document Identifier: doi: 10.51593/20230032
Document Last Modified: 30 November 2023

Appendix A: Additional Methodological Detail

We first pulled papers that contain terms related to more general microbial research. These terms[*] do not focus on resistant pathogens. This set of publications offers insight into the level of focus and the type of research taking place to develop new therapeutics or techniques for treatment. We pulled these papers in order to compare the state of AMR research specifically to the state of microbial research generally.

Subsequently, using the above set of papers, we identified those publications that were AMR-related by using a keyword search. We refined and iterated upon our key terms three times to ensure that the publications identified by these terms were truly AMR-related. For each iteration, we manually checked a sample of publications abstracts to ensure they were relevant.[48] We further corroborated these terms with an external AMR subject matter expert, Dr. Ivica Labuda. The final key terms used for the search are listed in the Appendix B. We included some AMR-related key terms in our search that did not specifically refer to resistance, but that were closely enough related to be worth including. In particular, the term "Minimum Inhibitory Concentration" and the terms "Antimicrobial Persistence" and "Antimicrobial Tolerance" refer to resistance-adjacent concepts that we believed would help surface AMR-relevant publications and thus considered AMR-related. We also excluded papers that mentioned terms tending to yield false positive results, unrelated to AMR.

Additional AMR-relevant Keywords Used in Keyword Search:

AMR-relevant but Non-AMR-Specific Terms

- Antimicrobial Tolerance
- Antimicrobial Persistence
- Penicillin Tolerance
- Minimum Inhibitory Concentration
- Antiviral Tolerance
- Antiviral Persistence
- Antibiotic Tolerance
- Antibiotic Persistence
- Antifungal Tolerance
- Antifungal Persistence

[*] See Appendix C

Keywords Prone to Inclusion in False Positive Publications, Excluded from Keyword Search

- Asthma
- Cancer
- Leukemia
- Antitumor
- Insecticide
- Herbicide

The keywords pulled publications including the term "drug resistance," many of which were correctly identifying resistant pathogens, but some of which also referred to unrelated topics. To ensure that these publications were indeed related to antimicrobial resistance, we required that they be also contain terms related to infectious disease for inclusion in analysis.[*] Since these papers were AMR-related, we included them alongside the set of AMR-related papers discovered using the keywords in Appendix B while conducting our data analysis.

Upon completing these pulls and identifying relevant publications, we identified those publications within that set that discussed at least one of the WHO's urgent pathogens.[†] We sought to determine whether AMR research has responded to the WHO's prioritization and whether it focused on those notable pathogens. Finally, we searched for AMR publications that focused on emerging topics–including the microbiome, bacteriophages, synthetic antimicrobials, or those that generally discussed biotechnology.[‡]

[*] See Appendix D

[†] See Appendix E

[‡] See Appendix F

Appendix B: Keywords Used to Identify AMR Publications in Keyword Search

AMR Key Terms:

- Antimicrobial Resistance
- Antibiotic Resistance
- Antimicrobial Stewardship
- Phage Therapy
- Standardized Antimicrobial Administration Ratio (SAAR)
- Antimicrobial Use and Resistance (AUR)
- Drug-resistant infections
- Antibiotic-resistant infections
- Antifungal-resistant infections
- Antiviral-resistant infections
- Antimicrobial-resistant infections
- Drug-resistant pathogens
- Antibiotic-resistant pathogens
- Antifungal-resistant pathogens
- Antiviral-resistant pathogens
- Antimicrobial-resistant pathogens
- Resistance Mechanisms
- Multi-resistant bacteria
- Pan-resistant bacteria
- Antibiogram
- Intrinsic Resistance Gene
- Persister Cells
- Proto-Resistance Genes
- Resistome
- Subsistome
- Susceptibility Testing
- Antifungal Resistance
- Antiviral Resistance
- Synthetic Antimicrobials
- AMR AND microbiome
- AMR AND probiotics
- biotechnology AND AMR
- Superbug
- Antimicrobial Tolerance
- Antimicrobial Persistence
- Penicillin Tolerance
- Minimum Inhibitory Concentration
- Antiviral Tolerance
- Antiviral Persistence
- Antibiotic Tolerance
- Antibiotic Persistence
- Antifungal Tolerance
- Antifungal Persistence

Further AMR Key Terms—Resistances Developed:

- Rifampicin-resistant
- Methicillin-resistant
- Resistant to third generation
- Cephalosporins (3GC)
- Carbapenem-resistant
- Pretreatment HIVDR (PDR)
- Methicillin-resistant Staphylococcus aureus (MRSA)
- Vancomycin-Intermediate Staphylococcus aureus (VISA)
- Vancomycin-Resistant Staphylococcus aureus (VRSA)
- Penicillin-resistant Streptococcus Pneumoniae (PRSP)
- Drug-resistant HIV (HIVDR)
- Azole-Resistant Aspergillus Fumigatus
- Azole-Resistant Aspergillosis
- Antimicrobial-resistant Trichophyton indotineae
- Trichophyton rubrum resistant to terbinafine
- Oseltamivir resistance
- Vancomycin-resistant enterococcus

Appendix C: Keywords Used to Identify Microbial Publications in Keyword Search

- Antimicrobials
- Antibiotics
- Antibacterials
- Antifungals
- Antimycotics
- Fungicides
- Biofilms
- Bacteriophage
- Horizontal Gene Transfer
- Macrolides
- Narrow-Spectrum Antibiotic
- Noninferiority Clinical Trials
- Quinolones
- Superinfection
- Sulfonamides
- Cellulitis
- Antihelminth
- Antiprotozoan
- Penicillin
- Oseltamivir
- Clotrimazole
- Econazole
- Miconazole
- Terbinafine
- Fluconazole
- Ketoconazole
- Nystatin
- Amphotericin
- Acyclovir
- Ganciclovir
- Cephalosporin
- Zanamivir
- Peramivir
- Baloxavir marboxil
- Amoxicillin
- Ampicillin
- Oxacillin
- Dicloxacillin
- Erythromycin
- Tetracycline
- Doxycycline
- Metronidazole
- Clindamycin
- Aminoglycoside
- Gentamicin
- Vancomycin
- Streptomycin
- Tobramycin
- Beta lactam
- β-Lactam

Appendix D: Additional Keywords Used to Identify AMR-Related Publications, Paired with Extra Terms to Ensure Relatedness

We paired the term “Drug Resistance” with the following extra terms related to infectious disease, to ensure that the publications we identified were related to antimicrobial resistance.

- Pathogen
- Infection
- Bacteria
- Antigen
- Contagious
- Fomite
- Virus
- Outbreak
- Prokaryote
- Virulence
- Protozoa

Appendix E:[49] List of WHO Priority Pathogens[50]

As some of the WHO's Priority Pathogens were bacterial families rather than species, we used taxonomies of these families to identify the known bacterial species within them. We then applied those more granular key terms in our keyword search, to ensure that we captured papers that discussed relevant pathogens without referring to the family as a whole.

- Acinetobacter baumannii
- Campylobacter spp.
- Enterococcus faecium
- Enterobacteriaceae
- Haemophilus influenzae
- Helicobacter pylori
- Neisseria gonorrhoeae
- Salmonella
- Pseudomonas aeruginosa
- Shigella spp.
- Staphylococcus aureus
- Streptococcus pneumoniae

Appendix F: List of Keywords Related to Emerging Topics

- Bacteriophage
- Synthetic
- Microbiome
- Probiotics
- Biotechnology
- Phage Therapy

Appendix G: Notable AMR Policies

Timeline of U.S. Policies

1995 - CDC "Campaign for Appropriate Antibiotic Use in the Community" educational campaign launched (later renamed "Get Smart: Know When Antibiotics Work" in 2003)[51]

1996 - FDA, USDA, and CDC establish the National Antimicrobial Resistance Monitoring System (NARMS)[52]

1999 - FDA, CDC, and NIH/NIAID co-chair U.S. Interagency Task Force on AMR (exp. 2006)[53]

2001 - Public Health Action Plan to Combat AMR developed by the above Task Force[54]

2003 - FDA established industry guidance for assessing AMR risks as part of the drug approval process[55]

2005 - FDA includes evaluation of antimicrobial impact on human intestinal flora into pre-approval safety assessment[56]

2009 - U.S./EU Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)[57]

2010 - FDA publishes the first annual summary report of antimicrobials sold or distributed for use in food-producing animals (section 105 of the Animal Drug User Fee Amendments of 2008)[58]

2013 - CDC releases first Antibiotic Resistance Threats Report[59]

2014 - White House releases a National Strategy for Combating Antibiotic-Resistant Bacteria[60]

2015 - First National Action Plan for Combating Antibiotic Resistant Bacteria (CARB). Created a Task Force co-chaired by SecDef, Sec of Agriculture, and Sec of HHS[61]

2018 - CDC and HHS launch the AMR Challenge[62]

2020 - Federal Task Force on CARB puts forth second National Action Plan[63]

2021-2022 - PASTEUR Act and STAAR Act Introduced in Congress[64]

FY 2010 - FY 2023 - Various NIH/NIAID Research Initiatives on AMR[65]

2023 – PASTEUR Act Re-Introduced in Congress[66]

Policies Introduced Internationally

1998 - EU establishes the European Antimicrobial Resistance Surveillance System (EARSS- later EARS-Net)[67]

2006 - EU bans antibiotic use for growth promotion[68]

2013 - UK 5-Year National AMR Strategy[69]

2015 - WHO Global Action Plan on AMR[70]

2015 - WHO Global Antimicrobial Resistance and Use Surveillance System[71]

2016 - China issued a 2016-2020 One Health National Action Plan to Contain AMR[72]

2016 - Iran issued a 2016-2021 National Action Plan of the Islamic Republic of Iran for Combating Antimicrobial Resistance[73]

2017 - WHO Develops Priority Pathogens[74]

2017 - India National Action Plan on AMR[75]

2019 - Tripartite Joint Secretariat on Antimicrobial Resistance formed (FAO, OIE, and WHO)[76]

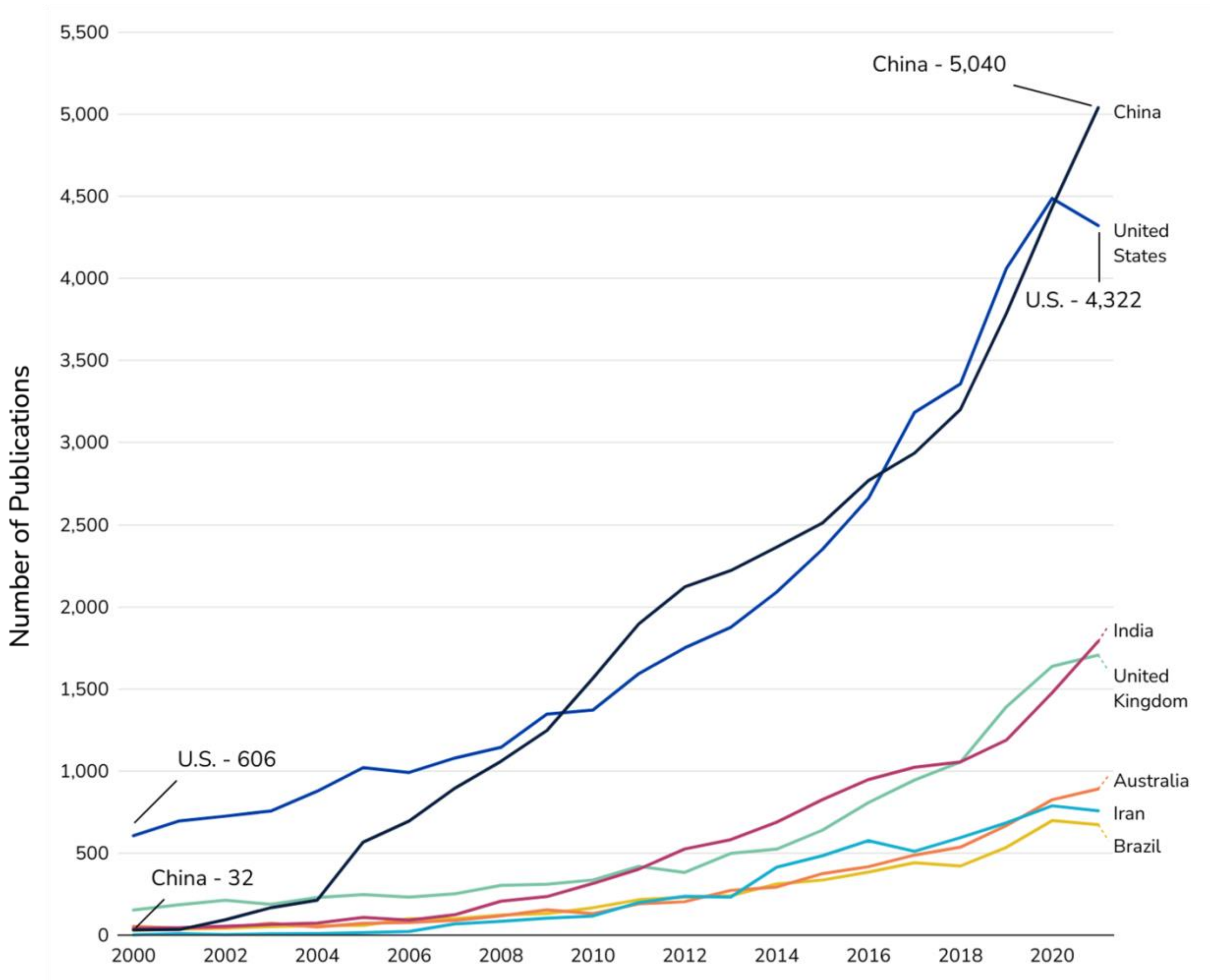
2019 - UK 5-Year National Action Plan on AMR[77]

2021 - FAO Action Plan on AMR[78]

2022 - Tripartite Joint Secretariat becomes the Quadripartite Joint Secretariat (UNEP, FAO, WHOA, and WHO)[79]

2023 - Quadripartite organizations develop the One Health Priority Research Agenda for AMR[80]

Appendix H: Countries' Increase in AMR Publications Over Time



Source: CSET Merged Corpus

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