Bolstering Public Health Preparedness by Investing in Post-Market Incentives for Novel Antibiotics

healthpolicy@duke.edu

October 23, 2023

Duke | MARGOLIS CENTER *for* Health Policy

DUKE-MARGOLIS AUTHORS

Nicholas R. Harrison

Marianne Hamilton Lopez

KEY POINTS

- Investments in post-market incentives for novel antibiotics represent investments in public health preparedness.
- Until proposals to prevent viral pandemics and bolster public health preparedness are aligned with related efforts to combat antibiotic resistant bacteria, the United States will remain at risk.
- Policymakers can support pharmaceutical manufacturing and supply chains, surveillance systems, post-market evidence development infrastructure, and diagnostic capabilities in a manner that reduces post-market costs for the smaller novel antibiotic developers who conduct the majority of current antibiotic research and development.

Novel Antibiotics and the Threat of Rising Antimicrobial Resistance & Drug-Resistant Infections

Access to innovative, novel antibiotics is critical to prepare for health emergencies and protect economic and national security. Without a reliable pipeline of novel antibiotics, rising antimicrobial resistance (AMR) could lead to a world where effective, modern medicine—including routine surgeries and chemotherapy—frequently lead to dangerous antibiotic resistant infections.[1] And without effective antibiotics, secondary bacterial infections following viral outbreaks, natural disasters, or the intentional or accidental release of infectious agents could wreak havoc on global public health and economic prosperity.[2,3,4]

While difficult-to-treat antibiotic resistant infections are expected to increase as bacteria become less susceptible to existing antibiotics, novel antibiotic development has slowed because of a challenging market and limited profitability. In many parts of the world, antibiotic resistant infections are rare, and the number of patients expected to receive novel antibiotics is limited. And antibiotic stewardship efforts—which are well-intended and necessary to limit infectious bacterias' exposure to selective pressure from antibiotics—further limit the prescription of novel antibiotics. As a result, novel antibiotics cannot generate self-sustaining revenue based on sales volumes. And despite the need to combat antibiotic resistance with novel life-saving antibiotics, the availability of inexpensive and typically curative generic antibiotics limits the demand for novel antibiotics and suppresses the price health care systems expect to pay for all antibiotics.

In recent years, policymakers working to reinvigorate investments in novel antibiotic research and development have primarily focused on establishing push incentives (support provided prior to regulatory approval). Programs like BARDA's DRIVe and CARB-X have provided critical and substantial funding that has sustained novel antibiotic research and development.[5,6] But to prepare for an uncertain future where global prosperity depends on global public health and a shared capacity to address emerging infectious diseases, novel antibiotic developers need additional support.

> ***"Our investments in combating AMR can be foundations for preparedness. We know that the infrastructure and capacities that we need to address AMR align well with the capacities that we need to address pandemics."***
>
> - Jose Fernandez, Acting Director, Pandemics and Emerging Threats, Office of Global Affairs, HHS
> *September 2022 PACCARB Meeting*[15]

Accordingly, the G7 and G20 are coordinating global efforts to address rising AMR and encouraging member countries to implement pull incentives (support provided after regulatory approval) aligned toward common goals.[11,12] In 2022, the G7 health ministers acknowledged that AMR is "an urgent public health and socio-economic problem that has a profound effect on the world" and that it is "essential to ensure a sustainable market for existing as well as new antibiotics". Furthermore, the G7 health ministers agreed to "explore a range of market incentive options, with a particular emphasis on supporting relevant pull incentives".[11] Their proposed approach is prudent, as globally-coordinated pull incentives to sustain investment in novel antibiotics are expected to create an additive impact and increase the likelihood that developers reinvest in the novel antibiotics market.[13,14] Finally, because no single incentive or market entry reward is a complete solution, policymakers can consider a range of incentives that create cost-savings and bolster public health preparedness.

Progress Toward Pull Incentives

Policymakers in the U.S. and among other countries are contemplating substantial pull incentives that aim to encourage large drug developers to reallocate research and development investments toward novel antibiotics.

In the U.S., the proposed PASTEUR Act would award qualifying novel antibiotic developers with 5 to 10-year subscription-like contracts worth between $750 million and $3 billion per antibiotic, depending on several favored characteristics that reflect the antibiotic's clinical and public health value.[7] In the United Kingdom, NHS England is already expanding subscription-like contracts for lifesaving novel antibiotics.[8] And smaller incentives providing limited additional reimbursement for novel antibiotics are being implemented in Sweden and Germany.[9,10]

Despite these initial efforts, experts anticipate that additional countries will need to design and implement substantial pull incentives to adequately encourage additional investments in antibiotic research and development.

Designing Pull Incentives that Bolster Public Health Preparedness and Help Sustain Novel Antibiotic Development

Several proposed pull incentives aim to directly reward novel antibiotic developers for bringing critical antibiotic products to market, but because post-market costs required to manufacture and commercialize novel antibiotics in the United States and around the world substantially limit return on investment, additional incentives to sustain the market for novel antibiotics are necessary. Experts have estimated that for a novel antibiotic approved with a single indication and an excellent safety profile, the first five years following approval generate manufacturing costs of $150 million, post-market requirement (PMR) costs of $25 million, diagnostic development costs of $7 million (to provide antibiotic susceptibility testing), and surveillance/pharmacovigilance costs of $5 million.[16] These costs are estimated based on lean company operations, reflecting the fact that small- and medium-sized companies conducting novel antibiotic research and development operate on extremely limited budgets and with zero or little revenue.

Policymakers can also encourage a sustainable market for novel antibiotics by designing pull incentives that create efficiencies and post-market cost-savings. This brief describes opportunities for policymakers to establish incentives that can:

- Reduce the risk and cost of supply disruptions by supporting domestic antibiotic manufacturing capacity and advanced manufacturing technologies that ensure domestic supply chain resilience.
- Reduce costs by providing subsidized access to surveillance capabilities or clinical trial networks that help antibiotic developers meet post-market requirements (PMRs).
- Provide support for diagnostic test development and antibiotic stewardship programs that utilize diagnostic tests to guide novel antibiotic prescribing and mitigate the emergence of antibiotic resistance.

Pull incentives such as these can advance the entire bioindustrial base, improve the efficiency of medical countermeasure development, and bolster public and private sector capacity to detect and respond to viral and bacterial threats.

Estimating Post-Market Costs

More specific analysis of post-market costs for novel antibiotic developers might better guide policymaking and the design of incentives that target these post-market costs. Robust data characterizing the post-market costs that impact novel antibiotic developers is limited, and existing estimates are based on generalized circumstances which may not apply to future novel antibiotics.[17] For instance, although a novel antibiotic might achieve FDA approval with a single indication, subsequent label expansion or frequent off-label prescribing might warrant additional post-market studies, pharmacovigilance activities, and AST development. A rigorous effort to research and characterize how different approval scenarios and prescribing patterns impact post-market costs would advance policymakers' understanding of existing market challenges. With additional information regarding post-market costs, policymakers might better tailor new or enhanced pull incentives for novel antibiotics.

As policymakers consider bolstering public health preparedness through pull incentives for novel antibiotics, prioritizing support to cover or reduce certain post-market costs might have outsized impacts for two reasons. First, investments in domestic pharmaceutical manufacturing, surveillance capabilities, evidence development infrastructure (like clinical trial networks), and diagnostic development (specifically, antibiotic susceptibility test (AST) development) may be able to benefit multiple novel antibiotic developers. And second, investments in these capabilities can bolster the broader bioindustrial base, expanding domestic capacity to surge drug and diagnostic manufacturing, as well as surveillance and evidence development capabilities to quickly detect and counter viral and bacterial threats.

Sustaining Novel Antibiotic Development Bolsters Public Health Preparedness

The COVID-19 pandemic focused policymakers' attention on the nation's public health preparedness and many policymakers are interested preparing the nation to counter future health threats. In late 2021, the Biden-Harris Administration initiated a whole-of-government review of national bio-preparedness policies and published a detailed set of goals. The goals focus on improving medical defenses, monitoring and detecting threats, modernizing public health infrastructure, and adding defensive and operational capabilities.[18] Likewise, the recently elevated Administration for Strategic Preparedness and Response (ASPR) is working with the National Biodefense Science Board (NBSB) to consider next steps. Recommendations from the NBSB include steps to improve command and coordination, human resources for health emergency response, essential medicine supply chains, and public health and health care data interoperability and integration.[19]

Until proposals to bolster public health preparedness are aligned with related efforts to combat antibiotic resistant bacteria and drug-resistant infections, the United States will remain at risk. Fortunately, efforts to bolster public health preparedness by investing in medical countermeasures, domestic manufacturing capacity, surveillance capabilities, and diagnostics can improve preparedness against both viral and bacterial threats. As an example, the Biden administration proposed developing the capability to respond to an emerging viral threat by developing an effective vaccine within 100 days of detecting the virus.[24] While developing vaccines for bacterial threats can be more challenging, a similarly rapid response to counter bacterial threats might involve early detection through local antibiotic resistance surveillance, rapid diagnostic development, and rapid, reliable antibiotic manufacturing and distribution. The ASPR and BARDA are at the center of some of these efforts. The BARDA's 2022 – 2026 Strategic Plan recognizes antibiotic resistance as a top global health threat and calls for the BARDA to establish the next iteration of its accelerator program to combat antibiotic resistant bacteria (CARB-X) and to continue to incentivize novel antibiotic development through Project BioShield.[25] But efforts to prepare for bacterial threats ought to involve a broader range of pull incentives.

Legislative Proposals

Congress has likewise reviewed the nation's public health preparedness and introduced several bills designed to prevent and prepare for future public health threats.

The *PREVENT Pandemics Act,* parts of which became law in late 2022, proposed to better coordinate public health agencies and improve medical countermeasure research, medical countermeasure supply chains, surveillance of emerging infectious diseases, diagnostic test development, the public health workforce, and other preparedness and response capabilities.[20]

The *MADE in America Act* proposed a program to expedite the validation of domestic advanced manufacturing for drugs and biologics and a similar proposal became law in late 2022.[21]

The *Onshoring Essential Antibiotics Act,* parts of which became law in late 2022, proposed to provide substantial grants for the manufacture of essential generic antimicrobial drugs and fund an analysis of foreign supply chain vulnerabilities most likely to impact access to essential medicines.[22,23]

U.S. National Action Plan

The U.S. National Action Plan to Combat Antibiotic Resistant Bacteria (NAP) proposes a range of objectives that policymakers can adopt to help sustain the market for antibiotics, several of which reflect opportunities outlined in this issue brief.[26] Policymakers can adopt the following NAP objectives and align them with broader efforts to prevent pandemics and bolster public health preparedness:

- Secure U.S.-based manufacturing capacity for antibiotics
- Purchase novel antibiotics through BARDA
- Explore how to increase antibiotic resistance and antibiotic use reporting to the National Healthcare Safety Network (NHSN) through CDC and CMS
- Establish and support clinical trial networks for novel antibiotic development
- Support projects to develop or enhance bacterial diagnostics for antibiotic resistant infections through ASPR, CDC, FDA, and NIH
- Consider additional changes the CMS new technology add-on payment (NTAP) program for novel antibiotics

BOX 1. Outcome-Based & Lego-Regulatory Pull Incentives for Novel Antibiotics

Policymakers can consider pull incentives in two categories—outcome-based incentives and lego-regulatory incentives. Outcome-based incentives provide direct monetary rewards while lego-regulatory incentives indirectly increase financial returns. In the context of pull incentives for novel antibiotics, the proposed PASTEUR Act represents an outcome-based incentive because the PASTEUR Act would establish subscription-like contracts that provide guaranteed revenue for novel antibiotic developers.[27] While the GAIN Act—which created the FDA's qualifying infectious disease product (QIDP) designation—is a lego-regulatory incentive because FDA-approved QIDPs are eligible for five years of additional marketing exclusivity, which indirectly increases financial returns for antibiotic developers. Both outcome-based and lego-regulatory pull incentives can effectively augment antibiotic development and commercialization, and policymakers interested in bolstering public health preparedness by sustaining markets for medical countermeasures, including novel antibiotics, can consider either approach.

No matter the type of pull incentive, pull incentives ought to be appropriately tailored so they are politically and administratively feasible. And appropriately tailored pull incentives may be easier to design through legislative approaches as opposed to administrative or regulatory approaches.[28] Although administrative and regulatory agencies have various authorities and expertise, legislators have substantially more flexibility that enables them to design appropriately tailored and impactful pull incentives. This is important because policy researchers and advocates for novel antibiotics have called for pull incentives that encourage the development and appropriate use of genuinely innovative antibiotics for which there are unmet medical needs. Because tailoring a pull incentive to reward innovation can be challenging and existing administrative frameworks may be too broad or too narrow, legislators may be better equipped to specify how qualification criteria operate. Moreover, legislators can strike balanced policy approaches. For example, legislators might seek to limit novel antibiotic pricing, thereby limiting revenue, while at the same time providing access to valuable subscription-like contracts that serve federal antibiotic purchasers, thereby increasing revenue. Ultimately, legislative, administrative, and regulatory approaches may be suited to designing appropriately tailored outcome-based and lego-regulatory pull incentives.

Aligning Public Health Preparedness and Pull Incentives for Novel Antibiotics

Manufacturing Antibiotics to Prepare for Bacterial and Viral Threats

Policymakers ought to include a focus on antibiotics in strategies to prevent shortages of critical medicines brought on by natural disasters, health emergencies, and geopolitical conflicts. Currently, policymakers are considering strategies to prevent shortages of critical medicines and medical supplies by supporting additional domestic pharmaceutical manufacturing capacity, advanced manufacturing technologies, and more resilient supply chains.[22, 29,30,31] These proposals are being explored to improve the domestic bioindustrial base and to mitigate the risk that natural disasters or foreign adversaries unexpectedly restrict access to critical medicines and medical supplies. Although policymakers are focused primarily on critical medicines to prepare for viral outbreaks, a sufficient and reliable supply of antibiotics is likewise necessary to bolster preparedness against both bacterial and viral threats—owing to potential outbreaks of antibiotic resistant bacteria and surges in secondary bacterial infections that occur during viral outbreaks. While it is difficult to predict whether future bacterial or viral threats are likely to create demand shocks for generic antibiotics or novel antibiotics, global antibiotic supply chains for both generic and novel antibiotics are fragmented and at risk of collapse.[32] Accordingly, there are opportunities to design policies that support pharmaceutical manufacturing and supply chain reliability that both bolster preparedness against bacterial and viral threats, and serve as pull incentives for novel antibiotics. Policies that subsidize domestic antibiotic manufacturing capacity, mitigate supply chain disruptions, fund advanced manufacturing technologies, and enable advance purchase agreements represent sensible options and might function as follows.

First, policies that reduce the cost of manufacturing antibiotics can improve the odds of commercial viability for novel antibiotic developers. Manufacturing represents the most expensive post-market cost novel antibiotic developers face and revenue from novel antibiotic sales has generally been insufficient to offset initial manufacturing costs. Manufacturing a novel antibiotic during its first five years on the market has been estimated to cost between $150 million and $400 million and requires developers to commit substantial time and money to secure supplies of raw materials, active pharmaceutical ingredients (APIs), manufacturing capacity, and fill-finish capacity.[16] Unlike multinational pharmaceutical developers, who may own and control their own manufacturing capacity, most of today's novel antibiotic developers are smaller companies developing a single product. These smaller antibiotic developers are unable to leverage economies of scale and invest in their own manufacturing capacity. Instead, smaller antibiotic developers depend entirely on contract manufacturers to sustain supplies of their product, and in doing so, face additional technical and operational risks. And because antibiotics are relatively complex molecules, manufacturing antibiotics often requires longer lead times as compared to other kinds of small molecule drugs. For these reasons, policymakers ought to consider how to reduce domestic antibiotic manufacturing costs—potentially by subsidizing domestic antibiotic manufacturing capacity and requiring quality assurances—as they enact policies to prevent shortages of critical medicines and increase the overall availability of domestic pharmaceutical manufacturing capacity.[33]

Second, policies that mitigate supply chain disruptions can help novel antibiotic developers meet demand for high quality antibiotics, avoid sudden revenue losses, and surge production during demand shocks to counter bacterial and viral threats. Sustaining reliable antibiotic supply chains and manufacturing capacity is critical because several antibiotic classes, including tetracyclines and cephalosporins, are critical for routine health care and preparedness against bacterial and viral threats. Recent analyses indicate that antibiotic manufacturing, particularly API and intermediate manufacturing, is highly concentrated in Asia, representing a risk to the domestic supply of antibiotics during global health threats or geopolitical conflicts. Sixty-five percent of manufacturing sites producing four key antibiotic intermediates are located in China, and among a representative set of antibiotic APIs, around seventy percent are manufactured in either India or China (35 percent and 34 percent, respectively).[34] By enacting policies to mitigate supply chain disruptions, potentially by funding the onshoring, ally-shoring, or nearshoring of antibiotic supply chains, policymakers

may be able to reduce costs for certain novel antibiotic developers (as recommended above) and mitigate the risk of antibiotic shortages. Doing so can help ensure that the United States has access to a reliable, high-quality supply of generic and novel antibiotics for routine clinical care and to prepare for bacterial and viral threats.

Policymakers are beginning to recognize the potential benefit of these approaches and provisions from the *Onshoring Essential Antibiotics Act* that fund domestic antibiotic manufacturing through grants were included in the *Consolidated Appropriations Act, 2023.*[33] This new law enables the Department of Health and Human Services in collaboration with the ASPR and the FDA to award contracts to increase domestic capacity to manufacture and stockpile critical antibiotics (see section 2411). This additional domestic antibiotic manufacturing capacity might mitigate shortages of both critical generic antibiotics and future novel antibiotics. And although generic antibiotics are used in substantially higher quantities, there may be instances where the domestic availability of particular APIs and manufacturing processes might serve as a means to enhance the supply chain redundancy of novel antibiotic manufacturing. This is particularly true in the context of the proposed *PASTEUR Act,* which would require eligible novel antibiotic developers to ensure a reliable drug supply chain—where any interruption to domestic drug access would not last for more than 60 days—as a condition of the developer's contract.[35]

Third, investments in advanced manufacturing technologies can reduce supply chain risks and potentially lower the cost of domestic antibiotic manufacturing.[36,37] Advanced manufacturing technologies are expected to improve the agility and flexibility of high-quality pharmaceutical manufacturing. For smaller developers producing limited quantities of novel antibiotics, subsidized access to advanced manufacturing technologies might allow them to more easily establish a reliable domestic supply chain, reducing the risk of shortages and ensuring their compliance with reliability requirements related to incentives like the proposed *PASTEUR Act.* Ultimately, multiple drug developers and regulatory agencies need to invest in leveraging advanced manufacturing technologies to mitigate manufacturing and supply chain risks, and policymakers and developers are taking early steps to do so. The Austrian federal government and Sandoz have partnered to invest more than EUR 250 million to develop innovative manufacturing technology for both APIs and finished dosage forms of penicillin products.[38] Although inexpensive penicillin products are available globally, and particularly from China, this investment will help to sustain the last remaining integrated production site for antibiotics among western nations. Policymakers ought to consider making similar investments to rekindle critical antibiotic manufacturing in the U.S., strengthening fragile antibiotic supply chains and preserving antibiotic manufacturing knowledge and expertise among domestic pharmaceutical developers. Although the *Consolidated Appropriations Act, 2023* includes a new Advanced Manufacturing Technologies Designation Program to expedite the development and review of drugs, biological products, or APIs made with advanced manufacturing technology (see section 3213), additional direct investment in such technology may be warranted.[33]

Fourth, policymakers can bolster fragile antibiotic supply chains and help ensure the market for critical antibiotics by committing to advanced purchase agreements. The U.S. Strategic National Stockpile can purchase antibiotics that target drug-resistant infections and secondary bacterial infections with the potential to surge during viral pandemics or other health emergencies.[39] Because policies that fund or subsidize domestic antibiotic manufacturing capacity would take time to strengthen supply chains, policymakers can leverage the ASPR to immediately invest in secure supplies of high-impact novel antibiotics to bolster preparedness and help stabilize the market for novel antibiotics. Currently, the ASPR secures supplies of medical countermeasures with biothreat indications according to the Public Health Emergency Medical Countermeasures Enterprise's (PHEMCE) procurement strategy. However, policymakers ought to expand PHEMCE's procurement strategy to include high-impact novel antibiotics effective against drug-resistant infections and infections with the potential to surge during viral pandemics or other health emergencies.[40] Providing novel antibiotic developers with PHEMCE procurement contracts would both improve preparedness against bacterial and viral threats, and help to stabilize the market for high-impact novel antibiotics.

Prioritizing Data Reporting and Surveillance Strategies to Prepare for Health Emergencies and Monitor Antibiotic Resistance

Responding to health emergencies and protecting public health depends on surveillance strategies that allow public health agencies to monitor a range of existing and emerging threats, including both bacterial and viral threats. The ongoing COVID-19 pandemic and more recent monkeypox outbreak revealed challenges federal and state governments encountered while working to quickly implement effective data reporting and surveillance strategies. Accordingly, throughout 2022 policymakers and their partners proposed efforts to better leverage and integrate new and existing surveillance capabilities among government agencies and private health care organizations (including health systems, health insurers, and clinical laboratories), some of which were included in the *Consolidated Appropriations Act, 2023* (see chapter 2, sections 2211 – 2216).[20,33] A standardized health care data reporting system for rapid analysis, resource allocation, and forecasting during health emergencies has also been recommended.[41] And while various surveillance and data reporting efforts are promising, some policymakers have primarily focused on surveilling viral threats, despite the clear and present threat of antibiotic resistant bacteria. As these efforts are implemented, policymakers ought to incorporate surveillance and data reporting strategies that bolster public health preparedness by monitoring bacterial and viral threats, including antibiotic resistance. Whether for routine or emergency threat surveillance and response, future efforts must recognize that effective surveillance and data reporting relies on a well-trained workforce, modern data infrastructure (with integrated data systems and data exchange standards), laboratory and genomic testing, and environmental surveillance like wastewater testing.[41,42,43,44,45]

Improved surveillance capabilities can bolster public health preparedness and facilitate data capture that helps antibiotic developers conduct FDA-required post-market surveillance programs. As a condition of FDA approval, novel antibiotic developers are required to monitor antibiotic resistance that impacts their antibiotic products.[46] And the proposed PASTEUR Act would go further, requiring eligible antibiotic developers to identify, track, and publicly report antibiotic resistance data and trends.[35] To fulfill existing requirements, antibiotic developers pay for systems and staff that monitor and track antibiotic resistance. These systems and staff are required to submit quarterly and annual drug safety update reports and surveillance reports to the FDA and other regulatory authorities around the world.[16] In addition to these industry-sponsored surveillance activities, there are several public and private organizations that monitor and track antibiotic resistance with a variety of methods and data sources (and many of these organizations surveil a wider range of bacteria, infections, and geographic regions). Both industry-sponsored surveillance activities and those operated by other organizations require similar capabilities. Accordingly, policymakers have an opportunity to support a more efficient surveillance infrastructure that serves both antibiotic developers and other stakeholders who monitor and track antibiotic resistance.[47]

Policymakers ought to encourage cooperation among stakeholders to consolidate surveillance activities under a centralized, well-funded entity, such as a public-private partnership, third-party contractor, or public health agency. Doing so could reduce the financial and administrative burden on smaller antibiotic developers, health care organizations, and public health agencies, all while improving access to integrated bacterial and viral surveillance data. Existing proposals that focus on the CDC and the agency's role in combating AMR are an important starting point. The proposed STAAR Act would strengthen capacity for antibiotic resistance surveillance activities among the CDC and its partners.[48,49,50] And in 2022, the House and Senate Appropriations Committees proposed an additional $20 – $30 million in annual funding for the CDC's programs to monitor and combat antibiotic resistance (ultimately increasing annual funding by $15 million to $197 million).[51,52,53,54,55,56] Relatedly, the same committees proposed an additional $10 million in annual funding for the CDC's National Healthcare Safety Network, which tracks safety-related measures including antibiotic use and antibiotic resistance among hospitals and other facilities (ultimately increasing annual funding by just $3 million to $24 million).[53,55,56] These investments are timely, but as policymakers advance CDC-based surveillance systems the capabilities of these systems ought to be integrated with each other and aligned toward multiple purposes,

including FDA-required post-market surveillance of antibiotic resistance. An approach that leverages standardized health care data and reduces reporting burden may be appropriate. To do so, a centralized data reporting system can be implemented by federal agencies, but hosted and guided by a public-private collaboration determining which data elements ought to be reported to serve the purposes of multiple stakeholders (including health care systems, the CDC, the FDA, and antibiotic developers). This centralized data reporting system ought to increase routine surveillance capabilities and reduce the cost of FDA-required post-market surveillance, acting as a pull incentive for novel antibiotic development.

Building Evidence Development Infrastructure and Clinical Trial Networks to Counter Bacterial and Viral Threats

Policymakers can bolster public health preparedness by supporting evidence development infrastructure focused on responding to health emergencies, investigating infectious diseases, and evaluating antimicrobial therapies (including antibiotics and antivirals). Supporting evidence development infrastructure can improve the cost-effectiveness of clinical trials and streamline comparative effectiveness research, and recommendations to establish a domestic "warm base" research network have been proposed.[57,58,59] As an example, during the COVID-19 pandemic the RECOVERY trial became well-known for identifying the first existing therapy shown to reduce the risk of dying from COVID-19.[60] The RECOVERY trial took place in the United Kingdom and relied on the country's integrated health care system to rapidly enroll tens of thousands of trial participants. While the integrated data infrastructure that enabled the RECOVERY trial is less available in the United States, clinical trial networks with capabilities similar to those that enabled the RECOVERY trial have been established in the United States. The National Institutes of Health (NIH) funds several clinical trial networks (including the ACTG, CTSN, NCTN, and PETAL), each of which designs and conducts collaborative clinical trials and can onboard trial sites and enroll patients more efficiently than traditional clinical trials.[61,62,63,64] The investigators running these clinical trial networks have experience designing and executing master protocol studies that simultaneously evaluate more than one investigational drug or more than one disease or infection. Accordingly, policymakers ought to support efforts like the proposed STAAR Act, which would establish a Clinical Trials Network on Antibacterial Resistance within the National Institute of Allergy and Infectious Diseases (NIAID).[50] Clinical trial networks focused on infectious diseases could enable rapid trial enrollment to counter bacterial and viral threats, evaluate multiple interventions simultaneously, and report results more quickly than traditional clinical trials.[57,65] Eventually, an even broader "warm base" research network involving partnerships between larger academic medical centers and community-based care sites, and point-of-care approaches that leverage data from routine clinical practice, could provide critical and timely research capacity during a health emergency.[58]

New clinical trial networks focused on infectious diseases might facilitate a variety of studies, including FDA-required studies and PMRs that evaluate the clinical impact of novel antibiotics. Clinical trial networks could act as a pull incentive for novel antibiotic development, reducing post-market costs while also facilitating evidence development that improves antibiotic prescribing and antibiotic stewardship. In part because every novel antibiotic developer must fulfill PMRs that include pediatric studies and safety studies among special adult populations if safety signals arise during initial clinical trials (special adult populations often include obese adults or adults with renal impairment). Fulfilling these PMRs can cost novel antibiotic developers tens of millions of dollars and discourages developers from pursuing multiple indications for novel antibiotics. For example, for a novel antibiotic with two indications and for which limited safety signals were detected during initial clinical trials, additional studies in special adult populations might cost around $3 million.[16] These costs discourage

the development of antibiotics for unmet medical needs—including antibiotic resistance—and create a perverse incentive for developers to pursue singular, less developmentally challenging indications such as chronic urinary tract infection (cUTI). And when antibiotic developers do pursue multiple indications for a novel antibiotic, the additional market share and revenue that results from a novel antibiotic approval with multiple indications may not outweigh the time and money antibiotic developers commit to fulfilling additional PMRs. Furthermore, the substantial cost of fulfilling PMRs impacts novel antibiotic developers as they simultaneously spend on capabilities related to manufacturing and supply chains, pharmacovigilance and surveillance, and other necessities, all while revenue is extremely limited or non-existent.

Clinical trial networks might also facilitate expensive and challenging FDA-required pediatric safety studies. As in the example above, for a novel antibiotic with two indications and for which limited safety signals were detected during initial clinical trials, FDA-required pediatric studies might cost around $50 million.[16] And beyond costs, recruiting and enrolling pediatric trial participants into antibiotic clinical trials is typically challenging, slowing trial progression and sometimes jeopardizing trial completion.[66,67] Enrollment proceeds slowly in part because the parents of pediatric trial participants are asked to allow their children to undergo multiple assessments, blood draws, and invasive procedures.[67] And although clinical investigators are committed to the safety and wellbeing of pediatric trial participants, parents are naturally cautious and concerned about additional factors like potential side effects, harm, and lack of benefit.

Accordingly, support for evidence development infrastructure like new clinical trial networks focused on infectious diseases and critical antimicrobials can offer efficiencies and mitigate post-market costs. The centralized infrastructure, standardization, data sharing, and patient recruitment reach of a clinical trial network can reduce costs, minimize duplicative efforts, increase the generalizability of results, and engage a broader patient pool. Existing policy research supports the formation of pediatric clinical trial networks and policymakers can establish a pediatric clinical trial network focused on antimicrobials, including novel antibiotics, much like GARDP has committed to supporting for pediatric studies of the novel antibiotic cefepime-taniborbactam.[68,69,70] Another example includes the I-ACT for Children's global site network, which was established to accelerate pediatric drug development and improve health outcomes in children.[71] However, the I-ACT network is not specific to any particular therapeutic area and pediatric studies of antibiotics may need targeted support, as pediatric studies of antibiotics made up less than one percent of all pediatric studies registered with ClinicalTrials.gov between 2007 and 2015.[68] Ultimately, mitigating the cost and challenge of FDA-required pediatric studies for antibiotics could serve as a pull incentive for novel antibiotic development and advance the evidence available to clinicians prescribing novel antibiotics among pediatric populations.

Advancing Bacterial Diagnostics to Counter Bacterial Threats and Guide Appropriate Antibiotic Prescribing

Clinicians and public health agencies can combat the spread of infectious diseases more rapidly when health systems are equipped with rapid and reliable viral and bacterial diagnostics. The COVID-19 pandemic illustrated how delayed access to rapid and reliable diagnostic tests can cripple early responses to emerging infectious diseases.[72] At the same time, the COVID-19 pandemic led to a surge in antibiotic resistant infections owing to the additional strain on limited resources for infection prevention and control.[2,73] Circumstances such as these threaten domestic and global health security, and policymakers ought to ensure that public health agencies and health systems are equipped with reliable viral and bacterial diagnostics. Only then can public health agencies and health systems identify viral and bacterial threats and respond with the appropriate countermeasures, including generic and novel antibiotics as appropriate.

Policymakers ought to consider the importance of both bacterial diagnostics and viral diagnostics and can support the development of bacterial diagnostics and antibiotic susceptibility tests (ASTs) by establishing public-private partnerships. During the COVID-19 pandemic, the NIH's RADx network facilitated cooperation between diagnostic developers, academic investigators, and federal agencies to ensure rapid diagnostics for COVID-19 were developed quickly and efficiently. The RADx network enabled stakeholders to cooperatively assess and conduct studies, prepare data for regulatory review, and accelerate diagnostic test availability.[74] Policymakers can apply this model to mitigate the challenges and costs of developing and implementing bacterial diagnostics, including diagnostics that distinguish viral infections from bacterial infections, and diagnostics that identify bacterial species and their genetic features, and diagnostics that determine antibiotic susceptibilities (ASTs). Such a model might leverage and advance the work of organizations like the Antibiotic Resistance Leadership Group (ARLG), which design master protocol studies that streamline randomized controlled trials of bacterial diagnostics. With access to improved bacterial diagnostics, health systems are better prepared to address bacterial threats and secondary bacterial infections during viral pandemics or other health emergencies, inform clinical decision-making, and monitor antibiotic resistance.

Beyond bolstering preparedness, equipping public-private partnerships to advance bacterial diagnostics and ASTs might mitigate developmental costs that are otherwise paid by novel antibiotic developers. Currently, novel antibiotic developers subsidize AST development, committing financial and technical support to diagnostic developers willing to include novel antibiotics on their existing diagnostic platforms. The developmental process is limited by the availability of funding and human resources, and may not result in an AST until years following the approval of a novel antibiotic. Funding the development of an AST has been estimated to cost novel antibiotic developers around $7 million and involves considerable technical and regulatory risk.[16,75] Moreover, AST development depends on the availability of bacterial isolates for comparative studies between new AST devices and standard reference methods. And in the case of novel antibiotics that address antibiotic resistant bacteria, the appropriate antibiotic resistant bacterial isolates may be rare and can be challenging to source from clinical sites. Despite these hurdles, ASTs are an important component of antibiotic stewardship, helping inform clinicians who treat challenging infections about whether a generic or novel antibiotic is most appropriate. For these reasons, public-private partnerships between public health agencies, novel antibiotic developers, diagnostic developers, and health systems can streamline bacterial diagnostic and AST development by supporting access to bacterial isolates, developmental and clinical resources, and regulatory expertise. Such an approach might facilitate efficiencies and reduce post-market costs for novel antibiotic developers who typically fund AST development, thereby serving as a pull incentive for novel antibiotic development.

Policy Recommendations and Final Thoughts

Bolstering public health preparedness requires focusing on both viral and bacterial threats, including threats posed by drug-resistant infections and AMR. Accordingly, policymakers ought to consider opportunities to advance the bioindustrial base that serve to mitigate the threat of drug-resistant infections. By focusing on opportunities across key domains, policymakers can establish subsidies and cost-cutting post-market incentives for companies developing novel antibiotics while pursuing a broader strategy to bolster public health preparedness. The following specific actions will prepare the United States for an uncertain future where national security depends on actions to address emerging infectious diseases, with a specific focus on threatening drug-resistant infections and AMR.

Manufacturing & Supply Chains

Policymakers are considering opportunities to support additional domestic pharmaceutical manufacturing capacity, advanced manufacturing technologies, and more resilient supply chains. The following specific recommendations combine opportunities to bolster public health preparedness and advance manufacturing and supply chains for novel and generic antibiotics.

I. The ASPR and the BARDA, in collaboration with the PACCARB and existing domestic antibiotic manufacturers, ought to collaborate toward opportunities to reduce domestic antibiotic manufacturing costs, potentially by leveraging project Bioshield to subsidize domestic antibiotic manufacturing capacity, similar to what has been done to secure penicillin production in Europe.[38]

II. The Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) is collaborating to improve financial incentives and the development of antimicrobial drugs and plans to discuss and examine incentives for antibiotic innovation and access.[76] Toward this aim, the BARDA, HHS Office of Global Affairs, and other TATFAR partners ought to consider how to mitigate antibiotic supply chain disruptions, potentially by advocating for the onshoring, ally-shoring, or nearshoring antibiotic supply chains.

III. HHS and the FDA ought to task the future National Centers of Excellence in Advanced and Continuous Pharmaceutical Manufacturing with researching how government agencies and private sector partners might leverage advanced manufacturing technologies to produce antibiotic APIs and finished dosage forms.[33]

IV. Through the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), the ASPR ought to update its procurement strategy to include high-impact novel antibiotics.

Threat Surveillance & Data Reporting

Policymakers are considering opportunities to monitor a range of existing and emerging threats. The following specific recommendations combine opportunities to capture and report standardized health care data with efforts to advance surveillance strategies that monitor bacterial and viral threats, including antibiotic resistance.

I. HHS, the CDC, the NIH and their federal, state, and local partners ought to incorporate surveillance strategies focused on monitoring both bacterial and viral threats, including surveillance of antibiotic resistance, as they advance health data systems, genomic pathogen surveillance, and data sharing as part of Title II, Subtitle B, Chapter 2 of the *Consolidated Appropriations Act, 2023*—"Improving State, Local, and Tribal Public Health Data".[33]

II. The PACCARB, CDC, and FDA ought to convene stakeholders engaged in variety of both viral and antibiotic resistance surveillance—whether primarily for public health, clinical care, or regulatory purposes—including the ARM Register, and consider potential approaches to consolidate data capture and surveillance activities under a centralized, adequately-funded entity such as a public-private partnership, third-party contractor, or public health agency.[77]

III. HHS—with expert input from the CDC and the FDA—novel antibiotic developers, and professional societies focused on infectious diseases and epidemiology ought to convene and propose approaches to align the capabilities of current and emerging surveillance systems (including the CDC's AR Lab Network and the NHSN) such that these systems facilitate FDA-required post-market surveillance of novel antibiotics.

IV. HHS, the CDC, the CMS, and other federal agencies along with state and private stakeholders ought to identify use cases where a standardized health care data reporting system can address core public health needs during an emergency such as an outbreak of antibiotic resistant bacteria, and pre-specify what data elements would be required for an effective response.

Evidence Development Infrastructure

Policymakers are considering opportunities to support evidence development infrastructure like research networks that generate regulatory grade clinical evidence and can respond during health emergencies. The following specific recommendations combine opportunities to bolster evidence development capacity with valuable, but challenging post-market evidence development for novel antibiotics.

I. Policymakers within Congress and the NIH ought to support efforts to establish a clinical trial network focused on investigating treatments for drug-resistant infections, as well as a distinct pediatric clinical trial network focused on antimicrobials, including novel antibiotics, potentially in collaboration with I-ACT for Children.[71] Such clinical trial networks could facilitate the completion of FDA-required studies and PMRs that evaluate the clinical impacts of novel antibiotics and provide clinicians with valuable evidence about novel antibiotic use among varied patient populations.

II. Policymakers within Congress, the OSTP, the FDA, and among other federal agencies ought to support efforts to develop a "warm-base" research network that can function as an emergency clinical trial network in response to emergent health threats, like outbreaks of drug-resistant infections.

Diagnostic Capabilities

Policymakers are considering opportunities to equip health systems with rapid and reliable diagnostics, particularly during public health emergencies to combat infectious diseases. The following specific recommendations combine opportunities to bolster public health preparedness and advance the availability and stewardship of bacterial diagnostics that enable appropriate antibiotic prescribing.

I. Policymakers at HHS, the FDA, the CDC, and the Centers for Medicare and Medicaid Services (CMS) ought to develop an interagency strategy addressing how to ensure that public health agencies and health systems are equipped with (or have rapid access to) reliable viral and bacterial diagnostics when novel or emerging threats are detected through surveillance, with a specific focus on bacterial diagnostics that enable rapid microbial identification and antibiotic susceptibility testing.

II. HHS, the FDA, and the CDC ought to consider supporting a public-private partnership between public health agencies, novel antibiotic developers, diagnostic developers, and health systems in order to streamline bacterial diagnostic and AST development by supporting access to bacterial isolates, developmental and clinical resources, and regulatory expertise.

No single incentive is a solution for the entire bioindustrial base needed to prevent and counter viral and bacterial threats, especially drug-resistant infections. Thankfully, policymakers have multiple opportunities to align steps they are already considering to bolster public health preparedness with efforts to combat antibiotic resistance and drug-resistant infections. Policymakers must now implement strategies to combat emerging infectious diseases and protect public health that ensure the United States has access to today's life-saving antibiotics, and tomorrow's next-generation novel antibiotics.

Acknowledgements

The authors thank John H. Rex, Christina Silcox, Gerrit Hamre, Trevan Locke, Stephen Covill, and Thomas Roades for their review of the manuscript, Derick Repista for substantial contributions to the bibliography, Patty Green for communications support, and Laura Hughes for the graphic design of this paper.

References

[1] World Health Organization. "Antimicrobial Resistance." November 17, 2021. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.

[2] U.S. Centers for Disease Control and Prevention. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022. Atlanta, GA. U.S. Department of Health and Human Services, CDC; 2022. https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf.

[3] Yu P, Zaleski A, Li Q, et al. Elevated Levels of Pathogenic Indicator Bacteria and Antibiotic Resistance Genes after Hurricane Harvey's Flooding in Houston. *Environmental Science & Technology Letters.* 2018;5(8):481-486. doi:https://doi.org/10.1021/acs.estlett.8b00329.

[4] Sepsis Alliance. "Natural Disasters | Sepsis Alliance." Updated November 7, 2022. https://www.sepsis.org/sepsisand/natural-disasters/.

[5] U.S Department of Health and Human Services , Administration for Strategic Preparedness and Response, Biomedical Advanced Research and Development Authority. "BARDA VENTURES." https://drive.hhs.gov/ventures.html.

[6] Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). "CARB-X." https://carb-x.org/.

[7] Office of Senator Michael Bennet. "Bennet, Young, Doyle, Ferguson Introduce PASTEUR Act to Fight Antimicrobial Resistance." Press Release. June 16, 2021. https://www.bennet.senate.gov/public/index.cfm/2021/6/bennet-young-doyle-ferguson-introduce-pasteur-act-to-fight-antimicrobial-resistance.

[8] NHS England. "NHS steps up battle against life-threatening infections following successful world-first pilot." Press Release. July 11, 2023. https://www.england.nhs.uk/2023/07/nhs-steps-up-battle-against-life-threatening-infections-following-successful-world-first-pilot/.

[9] Folkhälsomyndigheten. "Availability to antibiotics of particular importance – A Swedish pilot study of an alternative reimbursement model". February 17, 2023. https://www.folkhalsomyndigheten.se/publikationer-och-material/publikationsarkiv/a/availability-to-antibiotics-of-particular-importance/.

[10] G7 Finance Ministers. "Annex A – G7 Finance Ministers' Statement on Actions to Support Antibiotic Development". December 13, 2021. https://www.gov.uk/government/publications/g7-finance-ministers-statement-on-actions-to-support-antibiotic-development.

[11] G7 Health Ministers. "G7 Health Ministers' Communiqué." May 20, 2022. https://www.g7germany.de/resource/blob/974430/2042058/5651daa321517b089cdccfaffd1e37a1/2022-05-20-g7-health-ministers-communique-data.pdf?download=1.

[12] G20 Health Ministers. "Statement | G20 Health Minister's Declaration." November 19, 2020. http://www.g20.utoronto.ca/2020/G20_Health_Ministers_Declaration_EN_%2020201119.pdf.

[13] The Review on Antimicrobial Resistance Chaired by O'Neill, Jim. *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations.* May 2016. https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf.

[14] Schneider, Monika, Harrison, Nicholas R., and McClellan, Mark B. *Recommended Post-Market Incentive Strategies to Support the Development of Innovative Antibiotics.* Duke-Margolis Center for Health Policy. September 2020. https://healthpolicy.duke.edu/sites/default/files/2020-09/Recommendations%20Report%20Sept%202020.pdf.

[15] Fernandez, Jose. "Pandemic Response from a Global Perspective." Presentation at the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB) Public Meeting; September 12 – 13, 2022: Washington, D.C. https://www.hhs.gov/ash/advisory-committees/paccarb/meetings/upcoming-meetings/september-12-2022-public-meeting/index.html.

[16] Krause, Kevin. "The Post-Approval Challenges of Antimicrobial Development." Presentation at The National Academies of Sciences, Engineering, and Medicine. Examining the Long-term Health and Economic Effects of Antimicrobial Resistance in the United States: Meeting #3, Virtual. January 5, 2021. https://www.nationalacademies.org/documents/embed/link/LF2255DA3DD1C41C0A42D3BEF0989ACAECE3053A6A9B/file/D24089DFF83828A2B92B04B52128EC8F4FFB467C8826?noSaveAs=1.

[17] Outterson K. Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. Health Aff. 2021;40(11):1758-21. doi:https://doi.org/10.1377/hlthaff.2021.00688.

[18] The White House Office of Science and Technology Policy and the National Security Council. *American Pandemic Preparedness: Transforming Our Capabilities.* September 2021. https://www.whitehouse.gov/wp-content/uploads/2021/09/American-Pandemic-Preparedness-Transforming-Our-Capabilities-Final-For-Web.pdf.

[19] National Biodefense Science Board. *NBSB Recommendations for the 2023-2026 National Health Security Strategy.* December 16, 2021. https://aspr.hhs.gov/AboutASPR/WorkingwithASPR/BoardsandCommittees/Documents/NBSB-2023to2026-Recommendations-for-NHSS-16Dec2021-508.pdf.

[20] U.S. Congress. Senate. Prepare for and Respond to Existing Viruses, Emerging New Threats, and Pandemics (PREVENT Pandemics) Act of 2021. S 3799. Introduced in Senate March 10, 2022. https://www.congress.gov/bill/117th-congress/senate-bill/3799/text.

[21] U.S. Congress. Senate. Manufacturing API, Drugs, and Excipients (MADE) in America Act of 2021. S 2082. 117th Cong. Introduced in Senate June 16, 2021. https://www.congress.gov/bill/117th-congress/senate-bill/2082?s=1&r=14.

[22] Office of Senator Bill Cassidy. "Cassidy, Smith Introduce Bipartisan Legislation to Improve U.S. Supply Chain for Critical Antibiotics." Press Release. April 26, 2021. https://www.cassidy.senate.gov/newsroom/press-releases/cassidy-smith-introduce-bipartisan-legislation-to-improve-us-supply-chain-for-critical-antibiotics.

[23] Senator Tina Smith. "U.S. senator Tina Smith's bills to reduce the cost of prescription drugs and expand access to health care signed into law." Press Release. January 13, 2023. https://www.smith.senate.gov/u-s-senator-tina-smiths-bills-to-reduce-the-cost-of-prescription-drugs-and-expand-access-to-health-care-signed-into-law/.

[24] The White House Office of Science and Technology Policy and the National Security Council. *American Pandemic Preparedness: Transforming Our Capabilities.* September 2021. https://www.whitehouse.gov/wp-content/uploads/2021/09/American-Pandemic-Preparedness-Transforming-Our-Capabilities-Final-For-Web.pdf.

[25] U.S Department of Health and Human Services, Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority. *BARDA Strategic Plan 2022-2026.* May 2022. https://www.medicalcountermeasures.gov/media/38717/barda-strategic-plan-2022-2026.pdf.

[26] U.S. Department of Health and Human Services. *National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020 – 2025.* October 2020. https://www.hhs.gov/sites/default/files/carb-national-action-plan-2020-2025.pdf.

[27] U.S. Department of Health and Human Services. *Generating Antibiotic Incentives Now: Required by Section 805 of the Food and Drug Administration Safety and Innovation Act.* https://www.fda.gov/media/110982/download.

[28] Gottlieb, Scott. Opening remarks presented at: Combating Rising Antimicrobial Resistance: Advancing Public Health Preparedness, Antibiotics, & Innovation Webinar; May 12, 2021: Washington, D.C. https://healthpolicy.duke.edu/events/combating-rising-antimicrobial-resistance-advancing-public-health-preparedness-antibiotics.

[29] Office of Senator Tim Scott. "Scott, Colleagues Reintroduce Bill to Encourage America's Pharmaceutical Independence." Press Release. June 16, 2021. https://www.scott.senate.gov/media-center/press-releases/scott-colleagues-reintroduce-bill-to-encourage-americas-pharmaceutical-independence.

[30] The White House. "FACT SHEET: President Biden to Launch a National Biotechnology and Biomanufacturing Initiative." September 12, 2022. https://www.whitehouse.gov/briefing-room/statements-releases/2022/09/12/fact-sheet-president-biden-to-launch-a-national-biotechnology-and-biomanufacturing-initiative/.

[31] U.S. Department of Health and Human Services. Administration for Strategic Preparedness & Response. *Public Health Supply Chain and Industrial Base One-Year Report In Response to Executive Order 14017.* February 2022. https://aspr.hhs.gov/MCM/IBx/2022Report/Pages/default.aspx.

[32] Cogan, Deidre, Karrar, Karrar, and Jayasree K. Lyer. *Shortages, stockouts, and scarcity | The issues facing the security of antibiotic supply and the role for pharmaceutical companies.* Access to Medicine Foundation. May 31, 2018. https://accesstomedicinefoundation.org/resource/shortages-stockouts-and-scarcity-the-issues-facing-the-security-of-antibiotic-supply-and-the-role-for-pharmaceutical-companies.

[33] U.S. Congress. House. Consolidated Appropriations Act of 2023. HR 2617. 117th Cong. Became law December 29, 2022. https://www.congress.gov/bill/117th-congress/house-bill/2617.

[34] Boston Consulting Group and the Wellcome Trust. *Understanding the antibiotic manufacturing ecosystem | A view of global supply chains, pressure points, and implications for antimicrobial resistance response.* April 2022. https://cms.wellcome.org/sites/default/files/2022-04/understanding-the-antibiotic-manufacturing-ecosystem-2022.pdf.

[35] U.S. Congress. House. The Pioneering Antimicrobial Subscriptions To End Up surging Resistance (PASTEUR) Act of 2021. HR 3932. 117th Cong. Introduced in House June 16, 2021. https://www.congress.gov/bill/117th-congress/house-bill/3932.

[36] U.S Department of Health and Human Services, Food and Drug Administration. *FDA's Work to Combat the Covid—19 Pandemic.* July 2022. https://www.fda.gov/media/160998/download.

[37] The National Academies of Sciences, Engineering, and Medicine 2021. *Innovations in Pharmaceutical Manufacturing on the Horizon: Technical Challenges, Regulatory Issues, and Recommendations.* Washington, DC: The National Academies Press, 2021. https://www.ncbi.nlm.nih.gov/books/NBK570308/pdf/Bookshelf_NBK570308.pdf.

[38] Sandoz. "Sandoz Announces Further Investment in Key Manufacturing Facility in Austria, to Support Increased Global Demand for Essential Antibiotics." Press Release. GlobeNewswire News Room. November 7, 2022. https://www.globenewswire.com/news-release/2022/11/07/2549379/0/en/Sandoz-announces-further-investment-in-key-manufacturing-facility-in-Austria-to-support-increased-global-demand-for-essential-antibiotics.html.

[39] The Pew Charitable Trusts. *Recommendations Related to Antibiotic Resistance.* February 2022. https://www.pewtrusts.org/-/media/assets/2022/02/pew-offers-senate-suggestions-to-prepare-for-future-pandemics.pdf.

[40] Boyer, Beth, Canter, Brian, Colvill, Stephen, Harrison, Nicholas R., McStay, Frank, Roades, Thoman, Silcox, Christina, Romine, Morgan, McClellan, Mark B.. "Comment Letter on Pandemic and All-Hazards Preparedness Act (PAHPA) Reauthorization". Duke-Margolis Center for Health Policy, Washington, D.C. March 29, 2023. https://healthpolicy.duke.edu/publications/comment-letter-pandemic-and-all-hazards-preparedness-act-pahpa-reauthorization.

[41] Silcox, Christina, Campbell, Hilary, Roades, Thomas, Harvey, Melissa, Lurie, Nicole, McClellan, Mark B. Informing Local Emergency Response Through Standard Health Care Data Reporting. Duke-Margolis Center for Health Policy, Washington, D.C. May 17, 2023. https://healthpolicy.duke.edu/publications/informing-local-emergency-response-through-standard-health-care-data-reporting.

[42] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Office of Public Health Scientific Services. Public Health Surveillance Preparing for the Future. September 2018. https://www.cdc.gov/surveillance/pdfs/Surveillance-Series-Bookleth.pdf.

[43] World Health Organization. *Global genomic surveillance strategy for pathogens with pandemic and epidemic potential,* 2022–2032. March 2022. https://www.who.int/publications/i/item/9789240046979.

[44] U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. "National Wastewater Surveillance System (NWSS)." Updated March 14, 2023. https://www.cdc.gov/nwss/wastewater-surveillance/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fhealthywater%2Fsurveillance%2Fwastewater-surveillance%2Fwastewater-surveillance.html.

[45] LaFee, Scott and Scripps Research Communications. "UC San Diego Researchers Add Monkeypox to Wastewater Surveillance." Press Release. UC San Diego Health. August 10, 2022. https://health.ucsd.edu/news/releases/Pages/2022-08-10-uc-san-diego-researchers-add-monkeypox-to-wastewater-surveillance.aspx.

[46] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Microbiology Data for Systemic Antibacterial Drugs — Development, Analysis, and Presentation Guidance for Industry.* February 2018. https://www.fda.gov/media/77442/download.

[47] Sader HS, Rhomberg PR, Fuhrmeister AS, Mendes RE, Flamm RK, Jones RN. Antimicrobial Resistance Surveillance and New Drug Development. *Open Forum Infectious Diseases.* 2019;6(Supplement_1):S5-S13. doi:10.1093/ofid/ofy345.

[48] Office of Senator Sherrod Brown. "Brown Introduces Legislation to Combat Threat of Antibiotic Resistant 'Superbugs'." Press Release. December 1, 2021. https://www.brown.senate.gov/newsroom/press/release/brown-combat-antibiotic-resistant-superbugs.

[49] U.S. Congress. Senate. Strategies To Address Antibiotic Resistance Act (STARR) Act of 2021. S 3291. 117th Cong. Introduced in Senate December 1, 2021. https://www.congress.gov/bill/117th-congress/senate-bill/3291.

[50] Office of Senator Sherrod Brown. "Strategies To Address Antibiotic Resistance (STAAR) Act Section-By-Section Summary." Accessed February 7, 2023. https://www.brown.senate.gov/imo/media/doc/staar_act_section_by_section.pdf.

[51] U.S. Congress. House, Committee on Appropriations. "Appropriations Committee Releases Reports for Labor, Health and Human Services, Education, and Related Agencies and Transportation, and Housing and Urban Development, and Related Agencies Bills, Revised Fiscal Year 2023 Subcommittee Allocations." Press Release. June 29, 2022. https://democrats-appropriations.house.gov/news/press-releases/appropriations-committee-releases-reports-for-labor-health-and-human-services-0.

[52] U.S. Congress, House, Committee on Appropriations. "House Passes 2023 Government Funding Legislation." Press Release. December 23, 2022. https://democrats-appropriations.house.gov/news/press-releases/house-passes-2023-government-funding-legislation.

[53] U.S. Congress, House, Committee on Appropriations. Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Bill, 2023 Report. 117th Cong., 2d sess., 2023. S.Rep. 117-XX. Page 74-75. https://docs.house.gov/meetings/AP/AP00/20220630/114968/HMKP-117-AP00-20220630-SD003.PDF.

[54] U.S. Congress, Senate, Committee on Appropriations. "Chairman Leahy Releases Fiscal Year 2023 Senate Appropriations Bills." Press Release. July 28, 2022. https://www.appropriations.senate.gov/news/majority/breaking-chairman-leahy-releases-fiscal-year-2023-senate-appropriations-bills.

[55] U.S. Congress, Senate, Committee on Appropriations. Explanatory Statement for Departments Of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Bill, 2023. 117th Cong., 2d sess., 2023. S.Rep. 117-403. Page 76, 78. https://www.appropriations.senate.gov/imo/media/doc/LHHSFY23REPT.pdf.

[56] U.S. Congress, Senate, Committee on Appropriations. Division H-Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2023. 117th Cong., 2d sess., 2023. S.Rep. 117-403. Page 26-27. https://www.appropriations.senate.gov/imo/media/doc/Division%20H%20-%20LHHS%20Statement%20FY23.pdf.

[57] LaVange L, Adam SJ, Currier JS, et al. Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV): Designing Master Protocols for Evaluation of Candidate COVID-19 Therapeutics. *Annals of Internal Medicine.* 2021/09/21 2021;174(9):1293-1300. doi:10.7326/M21-1269.

[58] Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials. Fed. Reg. 87 FR 64821. October 26, 2022. https://www.federalregister.gov/documents/2022/10/26/2022-23110/request-for-information-clinical-research-infrastructure-and-emergency-clinical-trials.

[59] Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB). "Preparing for the Next Pandemic in The Era of Antimicrobial Resistance: A Report with Recommendations." March 24, 2023. https://www.hhs.gov/sites/default/files/paccarb-pandemic-preparedness-report.pdf.

[60] The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *New England Journal of Medicine.* 2021/02/25 2020;384(8):693-704. doi:10.1056/NEJMoa2021436.

[61] National Institutes of Health, National Institute of Allergy and Infectious Diseases. "AIDS Clinical Trails Group (ACTG)." Updated September 3,2021. https://www.niaid.nih.gov/research/aids-clinical-trials-group.

[62] Cardiothoracic Surgical Trials Network. "Cardiothoracic Surgical Trials Network." http://www.ctsurgerynet.org/index.html.

[63] National Institutes of Health, National Cancer Institute. "NCTN: NCI's National Clinical Trials Network." Accessed February 13, 2023. https://www.cancer.gov/research/infrastructure/clinical-trials/nctn.

[64] PETAL Network Prevention & Early Treatment of Acute Lung Injury. "PETAL Network Prevention & Early Treatment of Acute Lung Injury." https://petalnet.org/.

[65] Yajima R, More AF, Garvan C, Harper C, Grimes KV. A US clinical trial network is needed for the next pandemic. Nat Med. 2022;28(7):1330-1331. doi:10.1038/s41591-022-01831-1.

[66] Noel, Gary and Johnson & Johnson. "Industry Perspectives." Presentation at the Clinical Trials Transformation Initiative (CTTI) Improving Pediatric Trials in Antibacterial Drug Development No Sick Child Left Behind Meeting, Silver Spring, MD, April 5, 2016. https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_ABDD_Peds_Trials_Meeting_Industry_Perspectives_Gnoel.pdf.

[67] Bradley, John, Benjamin, Jr, Daniel, Corneli, Amy, et al. "Pediatric Trials in Antibacterial Drug Development: Findings from the Clinical Trials Transformation Project." Poster Presentation at the North American Cystic Fibrosis Conference, Orlando, FL, October 2016. https://ctti-clinicaltrials.org/wp-content/uploads/2021/06/CTTI_Poster_NACF_2016.pdf.

[68] Critical Path Institute. "Critical Path Institute Establishes The Global Pediatric Clinical Trials Network Pre-Launch Consortium." Press Release. July 22, 2015. https://c-path.org/critical-path-institute-establishes-the-global-pediatric-clinical-trials-network-pre-launch-consortium/.

[69] Corneli A, Wheeler C, Bradley J, et al. Facilitators and barriers to the successful implementation of pediatric antibacterial drug trials: Findings from CTTI's survey of investigators. *Contemporary Clinical Trials Communications.* 2018/03/01/ 2018;9:115-120. doi:https://doi.org/10.1016/j.conctc.2018.01.003.

[70] VenatorX Pharmaceuticals. "Venatorx Pharmaceuticals and GARDP Partner to Develop New Antibiotic for Hospital Acquired Infections with Limited Treatment Options." Press Release. April 29, 2020. https://www.venatorx.com/press-releases/venatorx-pharmaceuticals-and-gardp-partner-to-develop-new-antibiotic-for-hospital-acquired-infections-with-limited-treatment-options/.

[71] Institute for Advancing Clinical Trials for Children. "Mission, Vision, and Values." https://www.iactc.org/about-us/mission-vision-values/.

[72] Cohen, Jon. The United States badly bungled coronavirus testing—but things may soon improve. AAAS Articles DO Group. March 29, 2021. doi:10.1126/science.abb5152.

[73] U.S Department of Health and Human Services, Centers for Disease Control and Prevention. "COVID-19 Reverses Progress in Fight Against Antimicrobial Resistance in U.S." Press Release. July 12, 2022. https://www.cdc.gov/media/releases/2022/s0712-Antimicrobial-Resistance.html.

[74] National Institutes of Health. "Rapid Acceleration of Diagnostics (RADX)." https://www.nih.gov/research-training/medical-research-initiatives/radx.

[75] Duke-Margolis Center for Health Policy. "Advancing Bacterial Diagnostic Development." Webinar at the Duke-Margolis Center for Health Policy, Washington, DC. September 15, 2022. https://healthpolicy.duke.edu/events/advancing-bacterial-diagnostic-development.

[76] U.S Department of Health and Human Services, Centers for Disease Control and Prevention. "Actions | TATFAR | CDC," February 22, 2023. https://www.cdc.gov/drugresistance/tatfar/tatfar-recommendations.html.

[77] Vivli. "AMR Register." https://amr.vivli.org/.