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The Economics of Antibiotic Resistance

Anthony McDonnell, Ranil Dissanayake, Katherine Klemperer, Flavio Toxvaerd, and Michael Sharland

Abstract

Antibiotic resistance (ABR) is a major challenge that already contributes to almost five million deaths per year. Without action, this number will likely rise substantially. In this paper, we provide the first comprehensive assessment of the economic drivers of ABR, arguing that ABR in large part arises from extensive unresolved market (and regulatory) failures on both the supply and demand side. Each of these failures is well-understood from other contexts in economics. Specifically, ABR is a common pool problem that arises from too-rapid depletion of the stock of working antibiotics and insufficient replenishment with new antibiotics. We identify specific unresolved failures in the market for antibiotic innovation, in pricing structures that undermine its insurance function and in the production of known antibiotics on the supply side. We also identify failures on the demand side, including an underinvestment in preventative action, mismatch problems in the market for human antibiotic use and un-internalised negative externalities in pharmaceutical production and agriculture. We conclude by briefly considering how to resolve these market failures.

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Introduction

Antibiotic resistance (ABR) already directly causes 1.27 million deaths every year and contributes to a further 3.7 million; without action, it will likely become substantially more damaging over time (Murray et al., 2022; Review on Antimicrobial Resistance, 2014). Antibiotic resistance is a global public 'bad'—something that affects all countries (though its costs may vary by country). Understanding both why ABR arises and why existing public policy responses have so far been ineffective in combating it is of first-order importance. This paper is a comprehensive treatment of the economics underlying the problem of ABR, specifically focusing on the market failures that lead to ABR and that make collective action to address ABR more difficult, as well as drawing on the economics literature on these problems to propose effective solutions.

As Table 1 outlines, the burden of ABR falls particularly heavily on LMICs, where a much higher percentage of deaths comes from resistance, and where the demographic of people dying is far younger, losing more of their lives due to resistance. Addressing ABR thus has both direct development benefits in poorer countries and global public good characteristics.

TABLE 1. Annual burden of antibiotic resistance

	Total Direct Deaths from ABR		Direct Deaths from ABR Among Children Under Five		
Country Group	Number	Percentage of Deaths from all Causes	Number	Per 100,000 Children Under Five	Average Number of Life Years Lost Per ABR Death
High-income countries	141,000	1.1	893	1.4	17
Low- and middle-income countries	1,129,000	2.7	252,833	40.8	40
Sub-Saharan Africa	317,500	2.4	128,900	75	60

Sources: (McDonnell & Klemperer, 2022a; Murray et al., 2022).

The rest of this paper proceeds as follows. First, we provide a general overview of the problem of antibiotic resistance. We then consider the market (and regulatory) failures on the supply and demand side in the market for antibiotics that lead to the problem of ABR. We end by examining proposed solutions to the problems we have identified. In the appendix we include definitions for a list of useful medical and economic terms that might help some readers better understand the concepts discussed in this paper.

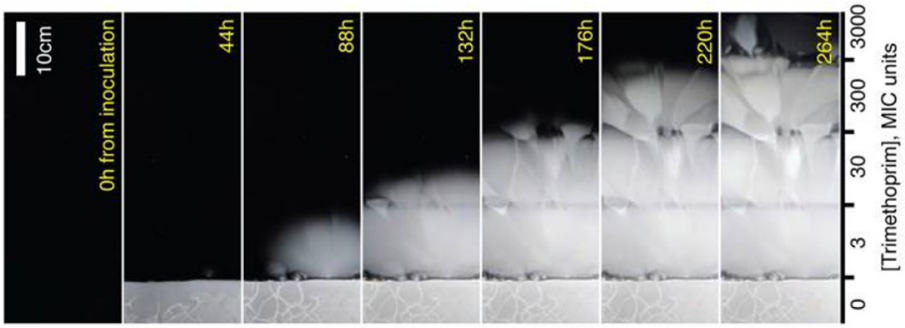
The changing landscape of infectious disease mortality

Infectious diseases have long been a major cause of mortality, killing 797 people in the United States (US) per 100,000 in 1900. Infection control and vaccines greatly reduced this

burden in the first half of the twentieth century, with deaths from infectious disease falling to 283 per 100,000 by the late 1930s. But it was the discovery of penicillin by Alexander Fleming in 1928, first used in humans in 1941, that drastically turned things around. By 1980, infectious diseases caused just 36 deaths per 100,000 in the US (Armstrong et al., 1999). Antibiotics[1] underpin much of modern medicine. For example, many surgeries rely on the availability of effective antibiotics for treating complications; and cancer patients rely on antibiotics to enable them to use treatments that compromise their immune systems, knowing that antibiotics can treat any infections they contract.

However, over time, genetic mutations and the consolidation of genes that enable bacteria to evade antibiotics have created bacteria resistant to their effects. Any bacteria that are better able to withstand an antibiotic—however slight this advantage—are more likely to survive and reproduce in an environment where this antibiotic is present, meaning that the next generation will contain an increased fraction of these bacteria's genes. The use of antibiotic drugs increases the rate of this process by giving resistant bacteria a stronger comparative advantage against other bacteria—i.e., providing a stronger selective pressure for resistance. The development of resistance can happen very quickly in these circumstances. For example, as Figure 1 shows, bacteria exposed to gradated concentrations of the antibiotic trimethoprim rapidly evolved resistance, and within 264 hours were able to survive in environments which contained 3000 times the concentration previously required to kill them (Baym et al., 2016).

FIGURE 1. Evolution of antibiotic resistance in E. coli



Note: MIC is the minimum inhibiting concentration, the smallest amount of an antibiotic needed to be effective.
Source: Kishony Lab, Harvard and Technion-Israel Institute of Technology. From Baym et al., "Spatiotemporal microbial evolution on antibiotic landscapes." *Science* 353, 1147–1151(2016). DOI:10.1126/science.aag0822. Reprinted with permission from AAAS.

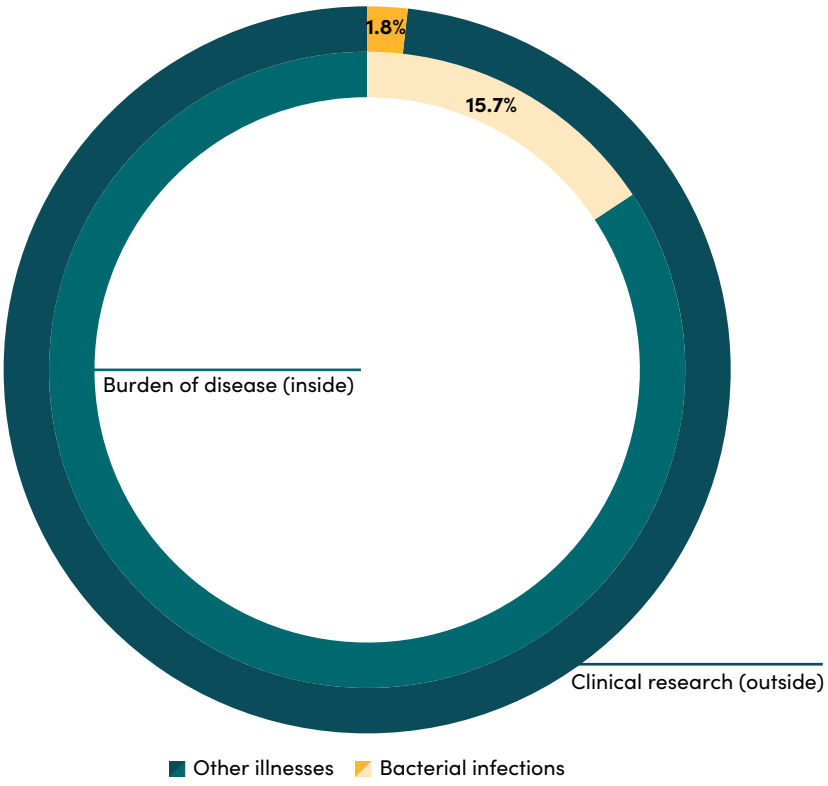
Without concerted action, it is estimated that Antimicrobial Resistance (AMR) could cause an additional 10 million deaths a year by 2050, including 7.5million from antibiotic resistance (Review on Antimicrobial Resistance, 2014). It could also greatly undermine much of modern health care,

1 Antibiotics are part of the wider category of "antimicrobials" which also includes antifungals, antivirals, and antiparasitics. For this paper, we focus on antibiotics—however, it should be noted that drug resistance can form in all antimicrobials. Antifungals, in particular, are plagued by similar economic issues around a lack of innovation and the need to reduce unnecessary use and environmental and agricultural pollution.

trade, and travel, wiping trillions off the global economy (IMF, 2022). COVID-19 highlighted just how devastating the costs of an infectious disease can be when there is no effective treatment.

Despite this threat, our pool of effective antibiotics is diminishing. We have not been successful enough in finding new drugs.[2] As outlined in Figure 2, fewer than 1.8 percent of the 13,605 Phase II and Phase III clinical trials recruiting patients as of August 21, 2023 relate to bacterial infections (as tracked on clinicaltrials.gov), even though 15.7 percent of global deaths are from bacterial infections, of which one-half to two-thirds of which are linked to resistance (Murray et al., 2022). However, the problem isn't just the number of new products, but also their quality. In 2020, there were 60 antibiotic agents in development, most of which offered little benefit over existing drugs, and very few of which targeted the most critical resistant bacteria. Such is the deficiency of the current pipeline of new antibiotics, that the WHO stated the lack of innovation is "undermining efforts to combat drug-resistant infections" (World Health Organization, 2020).

FIGURE 2. Bacterial infections are responsible for a much larger share of the global burden of disease than clinical research



Notes: The number of Phase II and III clinical trials related to bacterial infections was assessed by inserting the search term bacterial into the condition or disease search box on clinicaltrials.gov and applying four filters to the search: "Phase II" OR "Phase III," "intervention," and "recruiting." The total number of Phase II and III trials was found using the same search terms, without any condition or disease indicated. Searches were conducted August 21, 2023.
Source: McDonnell et al., 2023.

2 Drugs in development are often presented as having great promise, but given that 90% of drugs that go into human trials are not approved, these statements should be taken with a pinch of salt.

Understanding why action to contain ABR is so difficult to sustain is therefore of substantial public policy importance. Economics provides a ready set of analytical tools that are well suited to the problem and can shed light on its genesis and its potential solution. Indeed, some papers have considered one, or some, of the economic concepts of externalities, principal-agent problems, or global public goods, and how they relate to ABR (Broughton, 2017; Institute of Medicine (US) Forum on Emerging Infections, 2003; Roope et al., 2019). Other publications that have attempted to set out the broad causes of—and solutions to—ABR have also looked at the some of the economic problems (Hall et al., 2018; Review on Antimicrobial Resistance, 2016a). However, these generally focus on solutions rather than the economic drivers of resistance and have a broader focus than just economics. To the best of our knowledge,[3] there has been no assessment of ABR which comprehensively identifies and explains each of the economic problems underlying it. We attempt to provide a thorough end-to-end analysis of all the economic problems which underly ABR.

The economics of antibiotic resistance

As with most normal goods, the marginal cost of antibiotic production increases with quantity produced and the marginal benefit of each unit consumed declines. Under perfect market conditions, these dynamics would create an equilibrium under which antibiotics are consumed to the socially[4] optimal level—where the benefits and costs are in equilibrium, including some socially-acceptable sustainable level of resistance generation. However, the market for antibiotics is riddled with failures that create the conditions for unnecessarily high levels of resistance through over-consumption[5] of existing antibiotics and under-production of new antibiotics. Many aspects of the supply and demand for antibiotics and the growth of ABR are amenable to analytic tools and ideas well-known to economists from other contexts, such as the management of natural resources, collective action problems, and industry regulation.

The common pool problem

The global supply and effectiveness of antibiotics is undermined by what economists call a 'common pool' problem (Lloyd, 1980; Ostrom, 2015). Common pool problems arise when a finite collective resource (the common pool resource) is available for use by all members of the collective, without any

3 We searched google scholar using various search terms including "economics of AMR", "economics of antibiotic resistance", "economics of antimicrobial resistance", "economic problems of antibiotics resistance", "economic basis of AMR". Most results discussed the economic impacts of antimicrobial resistance. A few considered parts of the underlying economic problems but did not provide a full comprehensive analysis.

4 In practice what is 'socially optimal' in economic terms can differ slightly from what is 'clinically optimal'. Socially optimal consumption occurs when the benefit to society of consuming one more unit of a good or service is equal to its costs, accounting for all relevant costs and benefits to society. The term 'clinically optimal' refers to the act of making the best decision for a patient based on available resources.

5 As discussed later, many LMICs underutilise antimicrobials. While the evidence on optimal use level is limited, the large disparities between the amounts of antibiotics different countries use should raise questions.

effective mechanism to moderate each member's use.[6] Though unfettered use by all members runs the pool dry too quickly, no individual member has any incentive to marshal their consumption, given their beliefs about how others will act. In such cases, individuals end up using too much of the common pool resource in equilibrium, leading to its depletion.

An arsenal of viable antibiotics with manageable resistance is such a common pool resource. A healthy pool of antibiotics would entail the antibiotics in our arsenal to be able to effectively treat all infections where they are needed, without being unduly undermined by resistance. However, viable antibiotics are a finite resource: use of antibiotics increases the prevalence of resistance in the population, and faster, less well-managed use increases the pace at which resistance increases and the pool is diminished.[7] The pool's replenishment rate depends on our ability to discover or engineer new antibiotics which are not undermined by resistance.

As it currently stands, our pool of antibiotics is insufficient to meet expected needs—its level of depletion is already too great for comfort. Figure 3 visualises the causes of this insufficiency. On the input side, the pipeline of new antibiotics is inadequate because of inadequate funding, challenges with research, and limited markets. On the output side, we're losing antibiotics too quickly to resistance due to misuse and overuse in treatment and agriculture, and through environmental pollution.

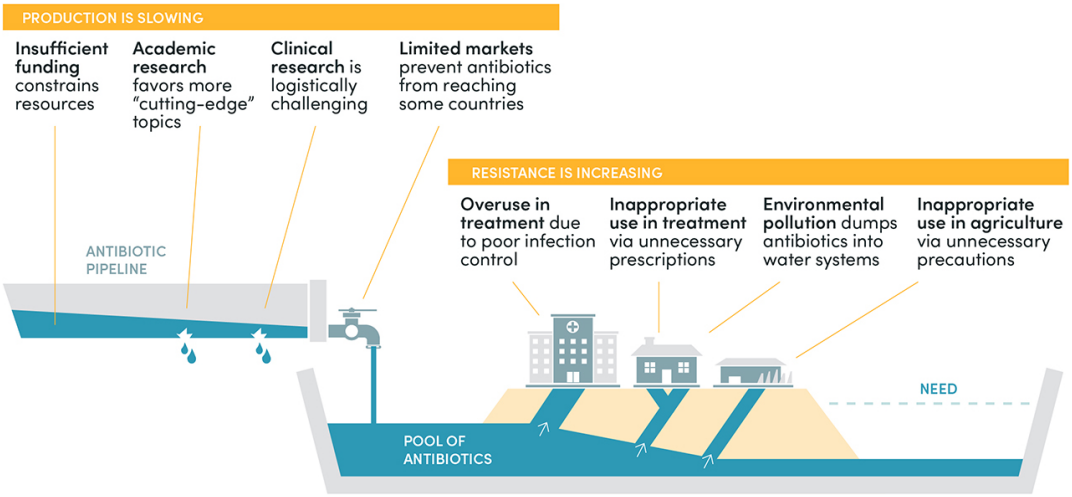
Whilst there is no good metric comparing this pool of antibiotics over time, there is wide consensus that we have been losing antibiotics far more quickly than we've found new ones (Ventola, 2015). And as long as the outflow from the pool continues to be greater than the inflow, deaths from resistance will likely increase.

The next section looks at the failures that underpin each of these problems in turn.

6 Prices would normally fulfil this function. As supply dries up, prices would rise, causing a moderation in demand. For pharmaceuticals, price performs this function poorly. A number of factors prevent the price acting as an effective signal of social costs and benefits of medicine use, which much of this paper goes on to explain. These factors include both positive and negative externalities and market power in production, for example. These issues are exacerbated by a mismatch problem: it is not simply the level of consumption of antibiotics that matters for AMR but the appropriateness of their use. To minimize AMR, we would ideally want some consumers to use more antibiotics and others to use less. Prices solve this matching function poorly because in an environment with very poor information, willingness to pay and appropriateness of use are poorly correlated. Price rises can serve a useful function: they signal to innovators that the return on investing in new antibiotics is increasing; but, again, imperfections and interventions in the market distort this signal.

7 The rate at which resistance increases differs between antibiotics, so this is not a straightforward relationship. Nonetheless, the general trend across antibiotics is an increased rate of resistance development with increased inappropriate use.

FIGURE 3. The causes of the pool of effective antibiotics drying up



The economics of antibiotic supply failures

Pharmaceutical research is expensive. Kevin Outterson estimates that an incentive for new antibiotics needs to pay around 3.1 billion USD, which could be paid out over a decade at a rate of $310 million a year (Outterson, 2021).

This alone does not imply any market failure, as many expensive things are built and sold privately; indeed, this is not even particularly expensive for pharmaceuticals. The global revenue of the pharmaceutical industry was $1,420 billion in 2021 (Mikulic, 2023). All of the 200 top selling drugs that year, as tracked by Pharmalive, earn significantly more than the proposed incentive needed for a new antibiotic. Indeed, 48 products had greater revenue in 2021 alone than the proposed lifetime incentive for a new antibiotic, and the 200th best-selling product in 2021 (Takhzyro) earnt $870 million—2.8 times the annual revenue it was suggested that a new antibiotic needs (Humphreys, 2022). The 90 (disproportionately wealthy) countries tracked by IQVIA's MIDAS project, spent a combined $34 billion on antibiotics, of which $8 billion went to patented antibiotics (Madden & Outterson, 2023). It is possible for antibiotics to privately generate sufficient returns to incentivise the research necessary for their development.

However, novel antibiotics are underprovided relative to their social value.[8] Products generated by antibiotic research are extremely valuable to society. It is very difficult for researchers (and those who fund them) to realise the full value of the innovations they produce. The market failures that make this the case contribute to a sluggish pipeline of new antibiotics and are elaborated below.

8 As we will discuss, this problem (common to most medicines and medical technologies) is particularly acute in the case of antimicrobials.

Public good characteristics of antibiotic innovations

It traditionally takes 10 to 15 years to come up with a new antibiotic (Review on Antimicrobial Resistance, 2015c), more than five years of which is spent in pre-clinical research. Whilst COVID-19 highlighted that it was possible to speed these timelines up, this was partly by adapting existing products which meant the pre-clinical research stage was very short. Because resistant bacteria are, by definition, able to avoid the treatments we have, there may not be products that can be easily adapted to treat them. Innovation is required urgently. Additionally, the clinical trial process for COVID was partly so fast because large sums were paid to speed it up—something that would not have been good value for money had it not been so important to find a solution quickly (Wellcome, 2021). There may be a time when similar steps are needed to expedite antibiotic research, but this would be more expensive and only make sense when there are large societal costs due to the lack of an effective treatment.

But pure innovation (that is, the idea behind a new product or service) has public good characteristics that make it prone to under-provision in the private market (Romer, 1990). These characteristics are particularly acute in the case of antibiotic research. The idea behind an innovation (that is the blueprint, concept, or instructions for producing a new product, or implementation of a process or provision of a service) is non-rivalrous: any number of people can use it simultaneously, without degrading or reducing the quantity of the idea available. At the same time, it is only imperfectly excludable: patents and secrecy can make it more difficult for others to use the idea, but do not make it impossible. Together, these characteristics make it difficult to recoup the costs or realise the full benefits of investing in the research and development that drives innovation.[9]

For antibiotic development, excludability is artificially created by the use of time-limited patents or legally backed exclusivity of production. This confers a (temporary) monopoly on the production of a new product, which allows innovators to charge a higher price for it, facilitating the recoupment of the high up-front costs of innovation. (Though the logic of patent protection is simple, the economics of how they work in practice are more complicated; see Boldrin & Levine, 2013).

However, in the case of antibiotics, this solution has many imperfections due to further market failures. The private value of a newly developed antibiotic is primarily determined by the monopoly price and quantity sold of the antibiotic under its patent or exclusive license period. To maximise the private incentive to develop new antibiotics, the simplest policy would be to allow private firms to charge a higher price for longer. However, the conditions under which the social benefits to an antibiotic are maximised are very different.

9 There is a second public good characteristic, which we come to below: the existence of antibiotics which do not suffer from resistance problems is a public good since they allow the pursuit of various risky activities safe in the knowledge that infections can be treated. This insurance value of working antibiotic existence is neither excludable nor rival. This is particularly true of antibiotics developed for reserve use.

First, the socially optimal distribution of antibiotic use is unlikely to be determined by willingness- or ability-to-pay, but by some combination of value to improve health outcomes and need to restrict use to prevent widespread resistance. Optimal global health policy would involve a combination of increasing use in the lowest-use places with the highest unmet clinical need, while simultaneously reducing unnecessary use. The former is appropriate in places where infections kill many people and are allowed to linger and develop mutations that may confer resistance: in such places, antibiotic use has a positive externality. Unnecessary use confers relatively little benefit to patients but nevertheless provides the selective pressure that leads to resistant strains thriving, meaning this use has a particularly large negative externality, as discussed further below.[10]

Secondly, under some circumstances, antibiotic use has an additional substantial—but difficult to value—positive externality that is, again, not reflected in the private cost. Specifically, appropriate early use of antibiotics can slow the proliferation of dangerous pathogens before they become widespread (Rex, 2020). However, this potential to prevent the spread of resistant strains is difficult to quantify, because our understanding of what causes a specific resistant bacterium to emerge or spread is often very limited, meaning we cannot identify the impact of specific drugs (Colson et al., 2021; Niewiadomska et al., 2019); if used appropriately, the costs of widespread infection are reduced. The observed value of antibiotic use is modest (the health of the individuals it is used to treat), but its value relative to a counterfactual of wide-spread infection is very large.[11]

In any case, the patented period is usually short relative to the effective lifespan of an antibiotic: antibiotics treating susceptible infections remain very efficacious, so these drugs remain societally useful for far longer than drugs in most areas of medicine. Antibiotic treatments from the 1940s–50s (for example penicillin) are still widely used today, meaning that the period of protected sales is a less effective means for innovators and producers to capture the value that society gets from at least some antibiotics than it is for other areas of medicine or innovation, though there is some variation on this. Whilst there are other areas of medicine where we still rely on technology that is very old, antimicrobials, such as antibiotics, are unusual in that old treatments are both were both very effective and yet innovation remains a priority, because resistance causes antimicrobials to become less effective over time.

Market failures in the production of knowledge

Antibiotic research, often conducted in academic settings, is misaligned with the social value of creating new antibiotics due to prevailing incentive structures. By publishing in prestigious journals, academics seek status, promotion, and funding—a goal misaligned with antibiotic research since this is often

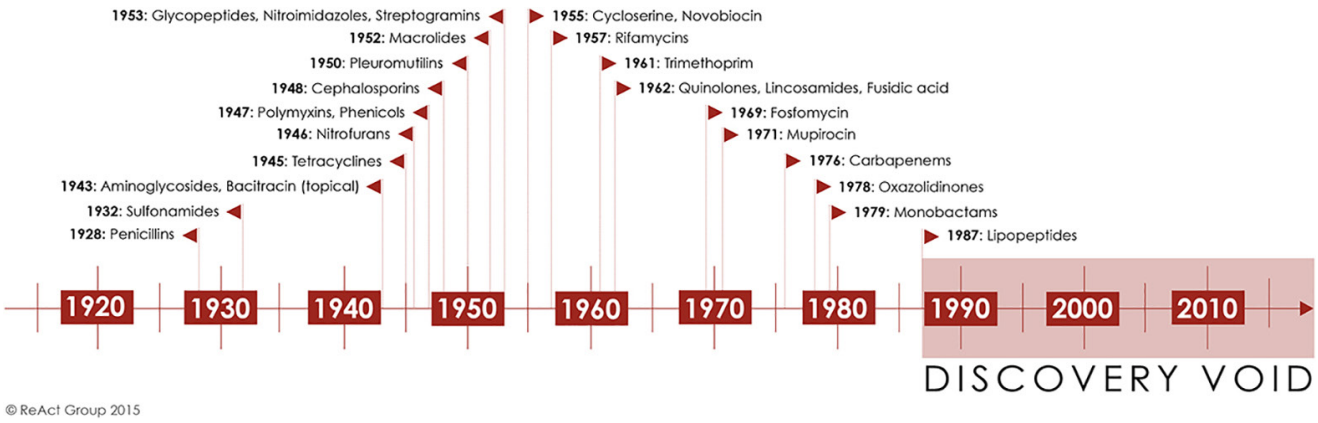
10 'Particularly large' because all antibiotic use has a negative externality to the extent that it always contributes to resistance.

11 Much like a fire extinguisher that can put out a fire long before it becomes a catastrophe. As an (extreme) example, if the first person infected with COVID-19 was effectively treated in a way that prevented the infection from spreading, this would have stopped millions of people dying and avoided trillions in economic losses.

underfunded and garners fewer citations. This misalignment limits resources, leads to fewer staff and equipment, and impacts the quantity of essential research activities, and is a particular problem for antibiotics as the only area where very effective treatments needs to be replaced. Consequently, the pipeline of antibiotic research is weakened, resulting in fewer early-stage clinical trials for antibiotics compared to other medical research areas (Review on Antimicrobial Resistance, 2015d).

In part, these failures reflect that the private benefits of antibiotic research fall particularly far short of the social benefits. Antibiotic research is becoming more challenging, with sharply increasing marginal costs: the effort required to find new drugs is increasing, and since antibiotics become less efficacious over time, ever-increasing efforts are required simply to maintain current treatment standards. Most antibiotics are natural compounds, and it seems likely that a large portion of natural antibiotic compounds have already been discovered (Brown & Wright, 2016). This may be because it is difficult to kill bacteria without harming the individuals they infect—and we have found limited ways to do so. Broadly, all antibiotics to date rely on one of just five modes of action (Walsh & Wencewicz, 2016), and resistance to one of these approaches often carries through to other drugs using the same mechanism (Reygaert, 2018), so we might simply be running out of new ways to treat infections. Figure 4, below, outlines the number of new classes of antibiotics approved per year.

FIGURE 4. Timeline of discovery of different classes of antibiotics



Source: ReAct, 2015.

The social benefits of finding new drugs are very high (given how important antibiotics are to modern medicine) but with costs of search increasing and the academic and private returns modest, there is a particular undersupply of research effort.

Regulatory failures exacerbate market failures

The market failures that undermine antibiotic research are exacerbated by government failures, specifically a complex regulatory framework. More pre-clinical research is needed to find products for drugs to be approved. Only around 10 percent of drugs that enter human trials are approved

(Mullard, 2016), and whilst the majority of the 90 percent of products discarded are done so for sound scientific reasons, commercial and economic challenges might be leading to perfectly good drugs being excluded. Specifically, the regulatory hurdles that are designed to prevent medicines that don't work or are harmful from being approved (so-called 'type 1' or false positive errors) can instead lead to an unacceptably high number of medicines that do work being filtered out by an overly burdensome regulatory process (called 'type 2' errors, the false negative problem) (Eichler et al., 2008).

This is particularly problematic in the development of new antibiotics. Conducting randomised controlled trials for antibiotics is challenging due to the need for quick treatment and the difficulty of finding centres of excellence for resistant infections[12] (Luepke et al., 2017). Proving the superiority of new antibiotics is also challenging as existing antibiotics are generally effective for susceptible infections, and so superiority can only be demonstrated in patients with resistant infections. These patients are difficult to find as we do not have effective ways of rapidly diagnosing a patient with resistant infections, and whenever a cluster of resistance arises in one place, hospitals are, rightly, keen to eliminate it (Rex & Outterson, 2016). What this means is that antibiotic trials in patients with multi-drug resistant (MDR) infections are usually underpowered—they do not have enough participants to satisfy the stringent criteria set by regulators. Achieving large enough trials in MDR infections is not just expensive, but challenging to design and conduct at any price. There is therefore a mismatch between regulatory regimes, the capacity of private research and pharmaceutical institutions to meet them and the socially optimal rate of drug discovery.

There has been a lot of movement to reduce the evidence base needed to approve new antibiotics in recent years. Whilst this has been successful, it has created a separate problem; there is now often insufficient information on drugs being approved to know if they are clinically much more effective than already existing treatments. The balancing act required is difficult to achieve.

New antibiotics are usually licensed after clinical trials have been conducted according to regulatory standards, usually both the FDA and the EMA. These trials are most commonly performed in low-risk populations with less severe clinical infections such as Urinary Tract Infections, and include few patients with multidrug resistant (MDR) pathogens. Over the last 20 years, only small trials of new Reserve antibiotics in the sickest patients with carbapenem-resistant severe infections have been conducted by the pharmaceutical industry (Huttner et al., 2023). There is an urgent need for public health focussed strategic trials comparing efficacy between different new and existing antibiotics, including toxicity, health economics, and selection of resistance outcomes. Countries, therefore, have no data to inform technology appraisals to determine their public health utility. The WHO EML

12 Centres of excellence for bacterial infections are rare, partly because moving patients with highly resistant infections to such centres would increase the chance that their infection would be passed on, and also because hospitals worry that patients with other illnesses would be reluctant to visit healthcare facilities associated with housing many infectious patients.

AWaRe Book[13] in 2022 could not identify sufficient data to provide evidence-based guidance for the use of any Reserve antibiotic.

The (unpriced) insurance value of antibiotics

New antibiotics to which bacteria have evolved limited resistance provide insurance value which is not rewarded under most payment systems. While it is very difficult to predict when resistance to existing drugs may surge, it is evident that drug resistance can develop rapidly, within months (Laxminarayan et al., 2013). For this reason, there is a value in having different treatments against resistance ready in case it emerges. If new antibiotics have limited resistance, their social value is maximised by sparing use in cases where first-line antibiotics are ineffective. In most of the world, there are protections against the unnecessary use of antibiotics through stewardship programs, though these are often very weak or not enforced at all. They are most likely to be enforced, and most stringently, for newer antibiotics—which are much more likely to be held on Reserve lists—meaning sales can be low during the patented period of a drug (Outterson et al., 2022). Thus, unless resistance emerges, there is no private return to innovators under conventional purchasing systems.

Due to the public good characteristics of antibiotic innovation, the matching problem in their use (elaborated below), the long lifespan of many antibiotics, and the insurance value of new ones, the conventional solution for spurring innovation (patent protection) is a particularly poor fit for maximising the social benefit of the pool of antibiotics. Lengthening the patent period for antibiotics is not an efficient solution, partly because of the mismatch between willingness-to-pay and the optimal distribution of use and partly because the pharmaceutical industry has a very high discount rate. This is due to high costs of capital, which in turn is due to the fact that the pharmaceutical industry lacks long term assets or predictable revenue streams, with patents for their drugs expiring about 10 years after drugs reach the market. And since drug-resistant infections occur at a higher rate in developing countries (Murray et al., 2022) with lower ability and willingness to pay for new antibiotics for insurance purposes, socially valuable innovation is further underprovided. In other low-volume sectors such as orphan drugs, governments have intervened to adjust the rules and promote innovation (Mikami, 2019). A similar approach may be necessary to encourage the development and availability of new antibiotics.

The benefits of these drugs are realised by society as a whole rather than the individual patients, which further complicates their valuation. Healthcare systems often prioritise the benefits to the individual patient rather than the broader societal implications, leading to an undervaluation of new treatments (Laxminarayan & Klugman, 2011).

13 A World Health Organisation publication written to provide concise, evidence-based guidance on the choice of antibiotic, dose, route of administration, and duration of treatment for more than 30 of the most common clinical infections.

Market failures in access

Exacerbating these problems, the supply of available antibiotics can also be unreliable. Due to commercial reasons, and difficulties in running clinical trials, a larger portion of antibiotics are removed from market compared to other drugs (Luepke et al., 2017). Companies are even deciding not to maintain registration of drugs in the European Union (EU)—the world's second largest pharma market—as the costs of maintaining registrations is greater than their sales (European Medicines Agency, 2020).

With older off-patent antibiotics there can also be significant supply chain issues: this is particularly true of amoxicillin. This partly arises from amoxicillin being a generic drug that is widely available and very inexpensive, which in turn means lower financial incentives for manufacturers. The limited profitability can result in reduced investment in its production infrastructure, and in some instances, manufacturers may exit the market for more profitable alternative antibiotics, or other drugs. Consequently, this narrows the number of suppliers, thus making the supply chain more vulnerable to disruptions. The demand for amoxicillin can also fluctuate, due to changing disease patterns, public health crises, or shifts in prescribing patterns. This introduces another layer of complexity to the supply chain (Chigome et al., 2019; Cohen et al., 2023).

Though this is not a market failure per se, given the difficulty of exactly anticipating demand and calibrating supply to match, there are sometimes highly socially costly shortages of basic antibiotics, with little market incentive to create resilience to such shortages. In a market with already very thin margins, overproduction can lead to significant financial losses which fall on the producers. While they cannot restrict supply to raise prices (since market entry is nearly free for generic drugs), each producer has a strong incentive not to over-produce, since any periods for which supply is too high can drive prices below what is economically viable. On the other hand, the costs of underproduction are largely borne by the public and the state. When surges in demand result in shortages, patient care suffers, and the social costs of illness and disease increase. These costs are borne by society at large, but private producers prefer occasional shortages and responding to price signals by increasing production to maintaining a 'buffer' in supply which would prevent shortages but result in lower prices in normal times. Therefore, they tend to only produce doses where they are confident they can sell, with little inventory to meet fluctuations in demand. Yet the social cost of undersupply in the event of a demand surge is much larger than the private costs of maintaining higher supply at all times.

The key problem is regular stockouts of generic antibiotics, where there are few suppliers of specific antibiotics, despite the high global volume overall. Stockouts can be caused by fragility in the production of the Active Pharmaceutical Ingredient (API), which are mostly manufactured in China (Nishino, 2022). Recent stockouts have highlighted the insufficient number of plants making API for important generic antibiotics such as piperacillin-tazobactam or penicillin (Cogan et al., 2018; Shafiq et al., 2021). These acute shortages can lead to people going without treatment, or more often being treated with broader-spectrum Watch or Reserve antibiotics which are more likely to generate resistance. Essentially, supply

chain fragilities, while privately optimal given market incentives, can carry very large social costs when shortages occur either due to demand or supply shocks.

The economics of antibiotic demand failures

On the demand and use side, the central problem of antibiotic use is that willingness (ability) to pay for antibiotics is poorly aligned with their social value. That is, some people cannot pay for antibiotics when it would be highly socially valuable for them to be used (usually because antibiotics are expensive or impossible to access when use would be highly efficacious), while others are willing to pay for them when use is of little value (either because of poor information about their appropriate use, or because they are used for non-medical activities with relatively low social value). This is both inequitable and inefficient. But this is not the only market failure that contributes to resistance: market failures in infection prevention mean that the use of antibiotics (and thus resistance) is more widespread than it would otherwise be, and the failure to correctly internalise the cost of environmental pollution from the production of medication also leads to sub-optimally high resistance.

Aligning use with social value is particularly important in the case of antibiotics, since bacteria evolve resistance when exposed to antibiotics. Use always has some negative externality, and inappropriate use has particularly large negative externalities since not all uses contribute to resistance equally. The private benefits and costs to antibiotic use are thus particularly poorly aligned with social benefit and cost. Indeed, a large portion of current antibiotic use is unnecessary, taken for mild infections caused by viruses. What's more, we also fail to take adequate steps to prevent bacterial illnesses, which means that even some necessary use is avoidable.

There are four primary routes to resistance generation and spread: poor infection control, inappropriate use of antibiotics in humans, unnecessary use in agriculture, and environmental pollution.

External benefits and public good aspects of infection control

Infection control in hospitals can be effective in reducing the number of people acquiring MDR pathogens, and thus reduce the need for broad spectrum antibiotics. It is often simple: a significant proportion of hospital-acquired infections in the US could be averted if health workers washed their hands properly (Kampf et al., 2009). With fewer infections, there could be less antibiotic use, and thus less resistance selection. But the costs of better infection control are typically private; the benefits are at least partly social (that is, the costs accrue to the individual undertaking better infection control, but some of the benefits are enjoyed by others and in particular people in the future). Since the social benefit of infection control is larger than the private benefit, individuals invest too little in it (Pigou, 2002).[14]

14 Note that in practice there is evidence to suggest that knowledge of positive externalities in healthcare practices may increase, rather than decrease, take-up of medicines or health-practices, since most people care at least a little about the people around them. See, for example, Derksen et al., 2022.

Even if this has a small effect on infection rates, it can have a large impact on the total number of people infected, since a lack of infection control means that not only is resistance generated, but it also spreads between patients. With better infection control, each individual contracting a resistant infection would pass it on to fewer other people. This is quantified by epidemiologists by a disease's basic reproduction number (R0) which is the average number of people who contract an infection for each person who is sick. If R0 is kept below one, then any pathogen will eventually die out. Infection control is the best way to keep R0 low for bacterial infections.

But infection control is not only a problem of misaligned private and social benefits and costs. The infrastructure required to promote infection control, such as building a sewage system or water infrastructure for each house, is both beyond the means of most individuals and, being most effective when applied or available to all houses or establishments within a geographical area, has public good characteristics. Providing such infrastructure requires solving collective action problems and is thus typically best provided by governments.

But the political benefits to such infrastructure projects are typically realised in the distant future (and thus beyond the expected political lifetime of the owner of the policy) and are intangible and so have less immediate political return. ('Infections avoided' are less visible to a population than 'infections experienced but cured efficiently'). This leads to under provision (Yamasaki, 2020). Furthermore, sanitation is rarely a high political priority—possibly because it predominantly impacts the less well-off, and discussing or being associated with sewage and faeces might not be a vote winner (Sinharoy et al., 2019). Humans' natural disgust at the thought of faeces might be an evolved defensive measure—but one that is counterproductive in the modern world (Curtis & Biran, 2001).

Misallocation and mismatch problems in human use

Resistant bacteria have selective advantages if their host receives treatments that are less effective against them than against other bacteria, and so they can out-survive their susceptible counterparts. The vast majority of drug-resistant infections are still susceptible to something: by getting a working treatment to a patient quickly, we can reduce, or even remove any evolutionary advantage that that pathogen holds. However, small market sizes, difficulties with registration, and concern over misuse mean that pharmaceutical companies have little incentive to ensure that antibiotics are easily available worldwide (Klemperer et al., forthcoming). Some people for whom the use of antibiotics yields particularly high social value do not get them.

Problems of access, however, work both ways: though some people for whom antibiotic use has high social value lack access to them, others for whom use of antibiotics has negative social value have too much access. Up to 50 percent of antibiotics are unnecessarily or inappropriately prescribed (Milani et al., 2019), varying by country and by setting. This problem is driven by two well-known economic problems. Firstly, externalities: most of the costs of unnecessary use are borne by society, so patients often take antibiotics even when the personal benefits are low (that is, the private price

of an antibiotic tends to be trivial relative to the external cost of promoting resistance). Secondly, the principal-agent problem. This occurs when there is a conflict in priorities between the principal (in this case, the patient) and the agent (the healthcare provider); since the agent here is incentivised to increase profit, they may unnecessarily prescribe antibiotics. Principal-agent problems arise when incentives are misaligned and there is an information asymmetry whereby one party in a transaction has more information than the other—in this case, the patient likely has less medical knowledge than the healthcare provider (Li et al., 2012; Stacherl et al., 2023). This may work in two ways. First, healthcare providers may prescribe inappropriate use of antibiotics, and in some health systems doctors are incentivised to prescribe antibiotics, and this can lead to more prescriptions (Li et al., 2012; Stacherl et al., 2023). Second, patients may demand their use (based on faulty understanding of medicine) and pressure the doctor to provide them. Patients often see antibiotics as a cure-all, and so demand them even in cases where their use is not justified (Stivers, 2021).

The typical solution for a mismatch between the social and private benefit of a good is to tax or subsidise it until the two match. This can be applied for overuse (taxation or regulation, both ways of increasing the cost of overuse), underuse (subsidy), and use in reserve (public purchase of production for reserve), but since there is simultaneously over- and under-use of antibiotics, and willingness-to-pay is poorly correlated to social value, it is particularly difficult to design a tax and subsidy regime that suits antibiotic use.

This is a mismatching problem—a situation where supply and demand need to be matched in such a way as to maximise social utility, and where the price mechanism does not serve this purpose effectively (see useful terms below). Matching problems are common: they arise with organ transplants, school choice and even online dating; matching theory to fix problems in these areas is well-developed, and though no solutions are perfect, they improve on the price mechanism (Niederle et al., 2008; Roth, 1982).[15] For antibiotic use, however, the informational requirements for matching are extremely high. Instead, regulation and medical best practice aim to perform its function, with mixed results. But without better information, direct regulatory solutions may be insufficient.

While considerable progress has been made in developing new technologies for the detection of infectious diseases, clinicians face sharp trade-offs between speed, cost, and accuracy. For example, new diagnostics can be faster, but they tend to be less accurate and more expensive than bacteria culturing in laboratories,[16] which often remains the preferred option for most clinicians in hospitals. In most primary care settings in much of the world, the lower accuracy or greater cost of new tests means they are not used, though evidence shows that, though less accurate, they can nevertheless reduce unnecessary use of antibiotics (Carlton et al., 2021; Gentile et al., 2023). In practice, therefore,

15 In economic theory, matching theory typically describes a narrower class of problems than the one we describe here, and the mechanisms developed in matching theory are not sufficient here. However, the economics underlying the problems are similar.

16 Developed by Louis Pasteur in 1860, this technique involves the time-consuming step of growing bacteria on a petri-dish for 24–72hours before the bacteria can be analysed (Bonnet et al., 2020; Pliakos et al., 2018; Rentschler et al., 2021).

there has been little improvement in the methods used by primary care physicians to determine the specific infection a patient has, and the appropriate antibiotic for its treatment. This information failure is at the heart of the mismatch problem outlined above. Without accurate information, clinicians must use their own judgment, and they are understandably more likely to put the patient in front of them ahead of wider societal need of the patients yet to come. They may therefore use Watch or Reserve antibiotics unnecessarily, even when Access drugs would work—and use of both Watch and Reserve antibiotics is more likely to generate resistance (see below note on the AWaRe classification) (Fazaludeen Koya et al., 2022; Review on Antimicrobial Resistance, 2015b).

These problems mean that though uneven access to antibiotics is inequitable, making ability to pay and access more equitable would not fully solve the problem. Without better information there would still be a difficulty of matching antibiotic use to its highest value uses and reducing use where consumers have high willingness to pay even when the antibiotic provides little benefit to the patient.

Negative externalities: environmental pollution

Active pharmaceutical ingredients (APIs) and other manufacturing by-products can be released into the environment during any stage of the manufacturing process. Once released, these ingredients can place selective pressure on bacteria in the environment, and/or be consumed by people (particularly through drinking water) and then place selective pressure on the person's gut bacteria. Research has found that antibiotic rates in 20 percent of Chinese waterways were high enough to pose a medium risk of resistance (Hu et al., 2018), and a study in India found rates of antibiotics in waterways exceeding bloodstream levels of someone taking the drug (Fick et al., 2009). This is a classic negative externality in production; appropriate taxation or regulation, effectively administered, would internalise these costs to private producers and reduce API release to socially acceptable levels.

The costs of deactivating APIs to make them safe for disposal varies greatly by the type of antibiotics, but are very low for most drugs. Pruden et al., 2013 show that waste can "in many cases be reduced at little or no cost". That such practices have not been taxed or regulated to socially efficient (low) levels suggests a policy failure, but one that is in principle possible to resolve.

Negative externalities: inappropriate use in agriculture

Over 70 percent of medically important antibiotics are used in agriculture, causing resistance in humans in three ways: through transmission of resistant pathogens to humans, excretion of active pharmaceutical ingredients by animals, and (much lower) risk from consumption of undercooked meat that contains resistant bacteria (Review on Antimicrobial Resistance, 2015a). Although it is difficult to determine the exact extent of the impact of agricultural use on human health, the issue remains a clear global health threat.

Antibiotics are used in agriculture to treat and prevent illness (prophylactic use), as well as for growth promotion. A small course of antibiotics can prevent an otherwise healthy animal being put down; this is generally considered a worthwhile trade-off (Review on Antimicrobial Resistance, 2015a).

Growth promotion is however less likely to be worth the harm it causes. The social costs (in terms of increased resistance) are generally believed to outweigh the social benefits (in terms of higher yields from farm animals). The impact of antibiotics on the price of meat is small: estimates suggest that meat from farms that did not use antibiotics in the US costs between one and two percent more to produce (Kaniyamattam et al., 2021; Sneeringer et al., 2015). This takes into account the cost of the upfront investments that are needed in infection control systems to make this transition, though this investment might discourage change. On the other hand, while there is consensus on the fact that antibiotic use in agriculture causes some resistance in humans, there is a lack of consensus on how much of a problem this is (Durso & Cook, 2014; Review on Antimicrobial Resistance, 2015a). Nonetheless, it seems likely that a one percent increase in meat production costs would represent an acceptable cost for slowing the rise in resistance.

This is another uninternalised negative externality. Antibiotic use in agriculture is too high because the benefits accrue privately to producers (in the form of lower production costs) and consumers (in the form of lower prices), whilst the health costs are incurred by everyone, whether a consumer of meat and dairy or not. While countries can ban this practice, such regulation is very difficult to enforce effectively: information asymmetries make it very hard for the state to distinguish growth promotion from prophylactic use. Many states have banned growth promotion only to see consumption patterns remain similar, with use instead being justified as prophylactic (Hall et al., 2018).

Prophylactic use is sometimes very important, such as when some animals in a herd are ill and a short, low-dose course for other animals would prevent infection and so minimise overall antibiotic consumption (Callens et al., 2012). However, much of it is used to overcome poor infection control on farms (Review on Antimicrobial Resistance, 2015a). It can be very difficult for regulators to separate these types of use.[17]

Solutions

As we have seen, the common pool problem which gives rise to ABR is a global problem arising from extensive market and regulatory failures whose solution requires action at individual, commercial and governmental levels. If markets and/or regulation were perfect, behaviours would be different

17 This does suggest that a tax on antibiotics used on farm animals would be more effective. Set correctly, it would increase the cost of antibiotic use above the benefit of use for growth promotion purposes, but not so high that it rules out prophylactic use.

at each level. Individuals would seek antibiotics only for significant bacterial infections, and practice good infection control such as handwashing, internalising the external costs of antibiotic use; doctors would be more sparing in their prescription practices, with incentives and information more closely aligned with maximising social welfare; and information would be sufficient to match use of antibiotics with their highest value applications. Firms and farms would use antibiotics more sparingly, for specific purposes, again, internalising all of the costs to antibiotic use. Private and public entities would invest in antibiotic research, and regulation of clinical trials would be appropriate for public health focussed antibiotic trials. Governments would fund infrastructure and health systems with improved infection control and effectively enforce regulations.

Clearly, this is not the world we live in. Instead, active public policy will be required to approximate these outcomes. In designing such public policy, we can draw on a great deal of economic literature on how to resolve the market failures we identified above. This section considers each of the market and regulatory failures we have identified and briefly considers the solutions appropriate.

Creating a market that reliably supplies effective antibiotics

Developing effective funding structures for innovation

Since innovation in antibiotic development is under-rewarded relative to its social value, a mechanism to bring the social and private value of innovative effort is required. Typically, this has been achieved through patent protection but as we have shown, this solution is inappropriate for antibiotics since it raises prices and restricts supply (and hence worsens the mismatching problem, to which we return below). Instead, to generate these innovations, whose benefits accrue globally and not just to the citizens of any individual state, requires a global funding mechanism since each state and country has an incentive to underprovide the good itself. Public and philanthropic funding—which accounts for more than half US health R&D—plays an important role in generating novel ideas, leading to future products (Chakravarthy et al., 2016; Moses et al., 2015).

The mechanism by which innovation is funded matters, too. Sustained support for early-stage antibiotic research, through initiatives like CARB-X, GARDP, the AMR Action Fund and increased government funding, is necessary in the medium-term (McDonnell et al., 2022). This is best achieved through 'push financing', in which researchers are funded directly for their effort and time. Later stage innovation may best be structured as an Advance Market Commitment, in which payment is made for delivery (at appropriate scale) of functioning, effective antibiotics. This helps direct efforts towards the specific solutions needed, though by-passing risk back on to innovators it may increase the per unit cost of antibiotics. (Note, though, that by paying only in the event of success it is also likely to reduce the overall outlay on research and development.)

There are ways to keep down the costs of funding new antibiotics. Optimising existing knowledge is essential. This could be achieved by creating combination drugs to minimise resistance

and repurposing old drugs for new uses (Brown & Wright, 2016). Many antibacterial molecules discovered between 1940 and 1970 may now hold greater value as the antibiotic pool diminishes. Funding mechanisms should be established to test old libraries for potentially useful antibiotics. These funding mechanisms should be truly global, given the global positive externality nature of these activities. A collective action problem exists between countries when it comes to funding resistance since it is in each of their interests to free ride on the spending of other countries. This can be overcome through global agreements or commitments to funding, potentially building off the G7 leaders' 2023 commitment "to exploring and implementing push and pull incentives to accelerate R&D of antimicrobials" (Leaders of the G7, 2023).

Finally, funding is needed for large pragmatic clinical trials that can provide much needed information, specifically evidence-based guidelines and country-level assessment of the public health importance of new antibiotics.

Paying for the insurance value of reserve antibiotics

Because much of the value of new antibiotics will be their insurance value rather than their use per pill, patent-and-payment models of incentivising investment in innovation are particularly inappropriate. Public funding can go some of the way to solving this, but without some payment mechanism may become prohibitively expensive. The development of new payment models can help mitigate this problem. New purchasing models can shift away from a price-per-pill approach that fails to recognise this value. The United Kingdom (UK) and Canada have launched subscription models, where an annual sum is paid for each new antibiotic, rather than per tablet used (Barlow et al., 2022). These models promote innovation without incentivising use. Subscription models are also being explored in the US, and other high-income markets.

This approach can help governments solve the public good problem around new drugs. While the UK and Canada's markets, alone, are too small to drive global innovation, involvement of either the US or EU paying an equivalent share of their GDP toward a high-quality drug would result in a significant incentive. For example, the UK is willing to pay up to £200 million per drug over a decade; equivalent GDP shares for the US and EU would amount to funding of $2.2 billion or $1.4 billion, respectively.[18] The return on investment for funding new pull incentives (incentives that reward successful innovation) has been estimated at 28:1 in the US (Silverman Bonnifield & Towse, 2022).

These incentives need to be carefully designed so that removing the cost per prescription does not lead to greater use. For example, under the NHS's system hospitals still must pay for the drug, but that money goes back to the NHS rather than to the pharmaceutical company. Such designs need to be tailored for a country's health system. A challenge with this in low- and middle-income countries

18 Authors calculation based on World Bank 2022 GDP data and exchange rates from the 1st of February 2024. GDP for England was assumed to be 84.3 percent of the UK's, in line with its share of population.

(LMICs) is that the current literature is heavily skewed towards high-income countries. Currently, there are between four and nine studies of solutions to ABR in high income countries for every study of solutions in LMICs (McDonnell et al., 2022).

Resolving regulatory failure

Better aligning the private and social value of innovation will help increase innovative effort; but it does little to resolve the problem of regulatory failure that makes the effort required to show efficacy of a new antibiotic unreasonably high. This, though, is fully within the control of public policy, and has far more modest resourcing implications. Governments can implement policies to ease clinical trial burdens and expedite registration, thus reducing the cost of approving new antibiotics. This requires more flexible regulatory approaches, and reconsideration of the balance of tolerance between Type 1 and Type 2 error for some kinds of clinical trial, given the difficulty of achieving sample sizes large enough for a clinical trial to have a high statistical power.

One approach is using non-inferiority trials, which compare new drugs to existing ones based on a predefined margin. However, these trials can be more expensive due to larger sample sizes (Schumi & Wittes, 2011). Additionally, small follow-up studies may be required to show superiority for patients with resistant infections, which are challenging to recruit. Animal models can aid the evaluation, particularly for efficacy against resistance, but regulatory and commercial barriers persist. However, using non-inferiority trials risks exacerbating a situation where we do not know enough about the clinical benefits of new antibiotics.

It would thus be better for governments to establish a system that encourages pharmaceutical companies to generate more evidence on the efficacy of a new drugs post approval and widening the range of acceptable evidence. This could be done by linking renumeration from new pull incentives to trial outcomes that clinicians would find most useful such as large global clinical trials on patients with carbapenem resistant infections, using novel study designs, to compare new agents with existing best-in-class treatment.

Governments could also harmonise registration requirements between different jurisdictions for a more accessible global rollout, and establish clinical trial networks to reduce costs by an estimated 23 percent (McDonnell et al., 2016).

Resolving supply chain fragility

Supply chain resilience can be increased by investing in redundant capacity in either volume of production or in diversity of production lines. Redundant production capacity involves having a production process that can be scaled up easily, with inputs on hand to increase production in response to demand surges. There will be logistical challenges to this (including the maintenance or alternative use of idle capital stock and storage and use of inputs to avoid wastage). This will

increase costs. Similarly, diversifying the upstream portion of the supply chain to increase the number of sources of APIs will involve early investment costs, as well as the additional cost of sourcing APIs from a wider range of geographical locations. These higher costs can be borne publicly by the state or be forced onto the producer through regulation. In either case, the cost of antibiotics would increase;[19] this is the trade-off for greater supply chain resilience. If the cost increase can be kept relatively small, the public health benefits may outweigh them, but further research into this is necessary.

Reforming public procurement systems to consider a wider range of criteria than cost can also make supply chains more robust. Denmark, Iceland, and Norway have recently come together to form a joint pooled procurement system for antibiotics. The goal is to incentivise manufacturers to build supply chains that manufacture antibiotics in an environmentally sustainable way (Årdal et al., 2021). Tenders are assessed on a range of criteria, and the top two bids are selected to ensure a diversity of supply. Of the total possible score, thirty percent is awarded based on good environmental practices, 20 percent for reliable delivery, 30 percent for user preferences and just 20 percent for price. Similar procurement systems could be used to build robust supply chains elsewhere, but governments must recognise that reducing supply chains fragility will cost money and make an assessment as to the net benefit of doing so. Whilst this will increase the cost of these specific tenders, if the system creates a much more reliable supply chain for antibiotics this may offer good value for money overall. In the longer term, it may reduce overall costs, as stockouts of antibiotics often mean treating patients for longer, or giving them more expensive drugs, both of which are very costly (Khumra et al., 2018). However, implementing such a system can be challenging because it can be difficult to quantify any increase in supply, it introduces greater subjectivity into procurement decisions which increases the risk of corruption, and where there are costs savings these often occur in the future or to different parts of the health system that have different budgets.

A recent CGD working group proposed overcoming supply chain fragility in LMICs by establishing a sustainable access hub (or hubs) (McDonnell et al., 2023). The hub would serve primarily as a backstop to facilitate access to essential antibiotics and diagnostics in settings where the market is currently failing. It could be a global entity or a series of regional initiatives; its functions could be handled by one organization or divided among and led by several. The key functions put forward include: supporting procurement of an essential portfolio of key access antibiotics and diagnostics; facilitating registration and distribution of these products; shaping the antibiotic market as a large procurer; improving the tracking of global antibiotic consumption; ensuring that purchasers meet the WHO's stewardship and access standards; and managing or supporting financial and technical assistance for resource-constrained countries to implement stewardship and surveillance systems.

19 Direct costs to the consumer, especially in LMIC settings, would need to stay low enough to achieve optimal levels of consumption, which, as we discuss elsewhere, requires higher consumption in some settings and lower consumption in others.

Finally, a strategically managed stockpile of selected antibiotics offers several benefits (Yadav, Forthcoming). Stockpiling can buffer against supply disruptions from manufacturing glitches, logistics issues, or manufacturer exits. It also helps meet sudden demand spikes, ensuring continuous supply during high-demand periods. Stockpiles can encourage market growth in low-demand areas, stabilize markets by managing supply-demand fluctuations, and reduce volatility. They aid in combating routine stockouts caused by poor forecasting or late orders. Examining stockpiles like the US Strategic National Stockpile and others reveals their multifaceted roles, dependent on their primary function. Decisions about stockpile levels and responsible entities (manufacturers, government agencies, or distributors) must be carefully evaluated based on the product market's characteristics. While creating antibiotic stockpiles can be beneficial, their cost-effectiveness must be assessed to justify additional expenses and detailed operational planning is necessary (McDonnell et al., 2023).

Reducing demand and the selective pressure that causes resistance

The supply and demand sides of the antibiotic market are inherently linked. If systems were put in place to generate the supply the world needs, but without demand side reform, then much of the hard work would be wasted, as we need to continuously replace those drugs lost to resistance.

Furthermore, a market that reliably supplies effective antibiotics will reduce the occurrence of several scenarios which promote antibiotic resistance. For example, new antibiotics that can treat highly resistant infections will result in patients carrying these infections for less time, reducing the selective advantage of bacteria with this resistance. Readily available Watch and Reserve antibiotics appropriately used will prevent patients receiving sub-optimal treatments that would give resistant pathogens greater opportunities. Similarly, availability of effective first-line treatments would avoid having to treat patients with second- or third-line treatments, which are more likely to drive broader resistance. Thus, protecting antibiotics from unnecessary use includes ensuring sustainable access to them (Hellamand et al., 2022).

Solving the mismatch problem

At the moment, patients often do not know whether or not they need an antibiotic, and without better information, are often unwilling to adhere to advice on reducing use. Rapid diagnostics have the potential to greatly improve the market for antibiotics, by highlighting when more expensive drugs are needed and when they are not. An ideal diagnostic test would identify not only whether the cause of illness is bacterial (rather than viral), but also identify the specific bacteria responsible and indicate which treatments would be most effective, allowing us to optimise the use of our existing pool of antibiotics. That said, the scientific challenges are not trivial. One area holding back diagnostics is that where tests exist, they often cost more than the antibiotic itself. For example, a course of treatment for amoxicillin can be as cheap as $0.20 USD. In these instances, it can make financial sense for individuals to ignore the positive externalities and to simply take the drug without a diagnostic.

Therefore, the state should either look to mandate the use of diagnostics where they exist or, as the AMR Review proposed, drive down the cost of diagnostics using an adapted version of an advanced market commitment, to increase production capacity and incentivise cost reductions (Review on Antimicrobial Resistance, 2015b). This idea has recently been taken up by the University of Chicago.[20]

Investing to reduce overuse of antibiotics

Diagnostic tests would help avoid the unnecessary use of antibiotics, but better diagnostics alone may not be sufficient to decrease consumption to an appropriate level, so should be part of a wider package of stewardship measures. Where available, vaccines can also help both to avoid infections and reduce onward transmission. This is particularly relevant in agriculture, where the close proximity of animals means a single infected animal can infect many other animals and cause an outbreak (Review on Antimicrobial Resistance, 2016b). As with improved infection control, vaccines would solve the matching problem by elimination. However, as with new antibiotics, people undervalue vaccines because many of the benefits accrue to society at large. Many of the push funding programmes for new antibiotics are also open to vaccines; there is a strong case for ensuring they are included in pull funding systems, too.

Investing in infection control

The failure to invest in infection control is partly private and partly public. One way of aligning the privately and socially optimal levels of infection control is to make it easy and lower the cost of it: handwashing stations in strategic locations and sanitation facilities can reduce the private cost of infection control. Similarly, to the extent that small costs or frictions reduce the prevalence of basic infection control some behavioural interventions (such as the use of reminders or signs) may help, while using social pressure can increase the cost of non-compliance with basic hygiene.[21]

But much of the problem is public, usually in the form of infrastructure, often public goods: the state must step in to build the clean water and sanitation systems needed to prevent infection. An estimated 673 million people practise open defecation worldwide, 2.2 billion people lack access to safely managed drinking water, and 4.2 billion people, or 55 percent of the global population, lack access to safely managed sanitation facilities. What's more, around 60 percent of the global population, and 3 billion people, do not have access to handwashing facilities with soap and water at home (United Nations Children's Fund, & World Health Organization, 2019). This needs to change if we're going to slow the development of resistance, and donor countries must play an important role in funding the required infrastructure (McDonnell & Klemperer, 2022b). Handwashing facilities could be provided to all households in the world's 46 least developed countries for less than

20 https://marketshaping.uchicago.edu/news/a-closer-look-at-innovation-challenge-phase-ii-ideas-antimicrobial-resistance-amr-diagnostics/

21 Or, equivalently, bring the private and social benefit of infection control closer into alignment.

$1 per person per year, saving hundreds of thousands of lives (United Nations Children's Fund and World Health Organization, 2021). This investment is estimated to pay for itself up to fifteen times over (Adhanom Ghebreyesus, 2020). If such public goods are underprovided because of a mismatch between political time horizons and the accrual of the benefits of infrastructure provision, organised public campaigns that increase public pressure for the provision of basic infrastructure may help; alternatively, this may be an area where donors can be effective in direct provision or funding.

Resolving negative externalities in production and agriculture

Both the production of pharmaceutical products and agricultural practices are associated with negative externalities that increase rates of resistance. The state has multiple tools for dealing with negative externalities, through a mix of regulation that limits or bans behaviour that is deemed damaging to the rest of society and taxation to discourage use and 'internalise' the externality borne by others.[22]

For pharmaceutical production, this is largely a regulatory and enforcement problem. Properly enforced bans should be used to stop active pharmaceutical ingredients polluting rivers. If there are molecules that prove too costly to remove all harm, then these harms should be mitigated as much as possible, in clear and transparent ways. Though the political economy problems of solving them may not be trivial, the solution is well understood and has worked in other countries.

In agriculture, one approach is to ban the use of antibiotics as growth promoters, although this can be difficult to enforce as antibiotics are often used both as growth promoters and as prophylaxis. Most prophylactic use could be banned, since this is often used to make up for poor farm hygiene and to aid growth promotion (Review on Antimicrobial Resistance, 2015a). In high-income countries, an upfront investment in infection control reduces both antibiotic demand and farm costs in the medium-term (Hall et al., 2018)—though more research on this is needed in LMICs. However, since some prophylactic use can be justified, a better approach might be internalising externalities through a Pigouvian tax on antibiotics or setting targets for absolute use. For example, the AMR Review recommended 50mg of antibiotics per kg of animal per year (Review on Antimicrobial Resistance, 2015a). Both these solutions work, in part, because antibiotics are most valuable for farmers when used to treat sick animals, and there is a strong ethical case for maintaining this type of use. A tax or a per-animal limit would work by incentivising the farmer to allocate antibiotics to their most high-value uses, usually treating sick animals, and reducing overall use.

22 An alternative solution is to assign property rights and allow bargaining over externality-generating behaviour. This is not appropriate in this case, both because it is unclear who should hold the property right for 'viable antibiotic treatment' and because it is only an efficient solution when transactions costs between parties are sufficiently low (Coase, 1960), clearly not the case given the scale of global use of antibiotics. It is therefore not pursued further here.

Conclusion

Antibiotic resistance is a major challenge that already contributes to almost five million deaths per year. Without action, this number will likely rise substantially. At its most basic level, this is a scientific problem: we are not generating enough new antibiotics to keep up with the speed of bacterial evolution. This challenge is underpinned by a series of market failures which this paper outlined.

Much can be done to improve the supply of new antibiotics: improving funding for early-stage research, removing regulatory barriers, and fixing the market for new drugs. The current price by volume purchasing model does not consider the insurance value that new drugs provide, nor their positive externalities. It also means that when public health officials protect drugs from unnecessary use, there are reduced incentives for innovators. In wealthy countries, significant work has taken place to find policy solutions to this problem which now require enacting; in low-and middle-income countries, more research is needed to determine the best approach.

There also needs to be greater protection of the drugs we have—and here, too, economic challenges cause difficulties. People taking antibiotics do not sufficiently value the societal impact of resistance. That leads to large amounts of pollution being generated in agriculture and antibiotic manufacturing: in many cases, this would not be difficult to reduce. Stronger regulation and/or diagnostics are needed to stop unnecessary use. Individuals and countries also undervalue the importance of infection control. Finally, we need supply chains that ensure that antibiotics are available to people who need them.

Many of these problems have been confronted for decades by economists in other disciplines. Often, there are clear answers on how to fix them for ABR too. It is time that we start implementing these solutions.

Useful terms

Economic terms

Advanced Market Commitment (AMC): An Advanced Market Commitment is a financing mechanism designed to incentivise the development and production of new products, such as vaccines or medicines, by guaranteeing a market and pre-determined price for these products once they are successfully developed. AMCs typically involve commitments from governments, international organizations, or other funding entities to purchase a specified quantity of the product at an agreed-upon price. By providing a guaranteed market, AMCs reduce the financial risk for developers and manufacturers, encouraging investment in research and development for products that address pressing global health needs, particularly for diseases affecting low- and middle-income countries.

Collective action problem: A collective action problem arises when multiple individuals or groups would benefit from working together to achieve a common goal, but each participant has an incentive to free-ride or rely on the efforts of others, resulting in the goal not being achieved or being achieved less efficiently. Examples include managing shared resources, like fisheries, or addressing climate change. Governments and international organizations often play a role in coordinating collective action to overcome these challenges.

Common pool goods: Goods that are non-excludable (that is, members cannot be stopped from using the resource), rivalrous (that is, one members' use of the good reduces the amount available for others to use), and finite. Common pool goods that are not regulated by an effective price mechanism typically suffer from overconsumption and diminishment.

Diminishing marginal returns: Diminishing marginal returns occur when the addition of a variable input to a production process, while keeping other inputs constant, results in smaller and smaller increases in output. For example, if a farmer keeps adding more workers to a fixed area of land, the additional output produced by each worker will eventually decline. This concept is important because it helps explain how resources are allocated within an economy. The general principle of diminishing returns applies widely (but not universally) in the economy, and not just relating inputs to outputs but consumption to utility, for example.

Discount rate: The discount rate is the interest rate used to determine the present value of future cash flows. It reflects the time value of money, meaning that a dollar received in the future is worth less than a dollar received today. Discount rates used in public cost-benefit analyses have two components: the social opportunity cost of spending (reflecting that resources can be invested in different things) and the social rate of time preference (which is a pure preference for gains today and costs in the future; the social rate of time preference can be 0). The discount rate is used in private economic analyses and investment decisions to account for the opportunity cost of not using resources in alternative investments or the risk associated with future cash flows.

The UK government can usually borrow very cheaply, so it places a low discount rate on future earnings, of 3.5%. For pharma companies borrowing is expensive as there's a much greater chance of default, to cover they thus have a much higher discount rate, usually over 10% for even the largest and safest companies. At 3.5% discount a dollar earnt in 20 years' time is worth, $0.49 today, with a 10% discount rate it is worth only $0.12 today. This means that to increase the net present value of an investment case by a dollar, a return in 20 years' time would need to provide $8.22. This increases to $25.80 for a 15% discount rate. It would cost the UK government $4.03 and $12.65 respectively in present day costs to make these payments. Far more expensive than a near term payment. Whilst there are reasons to delay future payments extending patents tends to offer quite poor value for money to governments and other payers.

Externalities: An externality when a decision taken by one party, leads to a cost or benefit on wider society. Example of a negative externality come from burning hydrocarbons—the passengers on a flight gain most from the benefit from flying, whilst the costs in terms of $C0_2$ emissions are shared by the whole world. Vaccines, in contrast, have positive externalities, protecting not just the individual but wider society. People underuse products that have positive externalities and overuse those with negative externalities because they are incentivised to maximise their own returns.

Information asymmetry: Information asymmetry occurs when one party in a transaction has more or better information than the other party, which can lead to an imbalance of power and suboptimal outcomes. In healthcare, for example, doctors typically have more information about treatments and their effectiveness than patients, which can lead to overtreatment or patients making uninformed decisions. Information asymmetry can contribute to market failures and may justify government intervention or regulation to protect consumers or improve overall welfare.

Market failure: A market failure occurs when the allocation of goods and services by a market is not efficient, often leading to a net loss in social welfare. This can be caused by various factors, such as externalities, information asymmetry, and public goods. Market failures often provide a rationale for government intervention to correct the inefficiencies and improve overall welfare.

Matching theory: A term in economics for the challenge of optimally pairing entities from two distinct groups, considering individual preferences and specific constraints. This often involves allocation of resources, such as jobs to workers, students to schools, or organ donors to recipients, aiming to maximise overall efficiency and satisfaction. These problems are often underpinned by problems such as information asymmetries, externalities, high transaction costs, or of imperfect competition.

Pigouvian tax: A tax on a good which generates negative externalities. It seeks to make the price of the good equal to the social cost.

Pooled procurement: Pooled procurement refers to the joint purchasing of goods or services by multiple organizations or countries, leveraging their collective buying power to achieve economies of scale, reduce costs, and improve access to products. In the context of healthcare, pooled procurement is often used to purchase essential medicines, vaccines, or medical equipment, particularly for low- and middle-income countries. By aggregating demand and negotiating with suppliers, pooled procurement can help secure more favourable prices and enhance the availability of critical health products.

Principal-agent problems: Principal-agent problems arise when one party (the agent) is hired to act on behalf of another party (the principal), but their interests do not align perfectly. P-A problems have three components: misaligned incentives, asymmetric or unverifiable information and incomplete contracting. This can lead to the agent taking actions that benefit themselves at the expense of the principal. Examples include managers making decisions that benefit their careers rather than maximising shareholder value or doctors recommending unnecessary treatments to increase their income.

Product development partnership (PDP): A product development partnership is a collaborative effort between various stakeholders, such as governments, non-governmental organizations, academic institutions, and private companies, to develop and deliver new products, such as medicines or vaccines. PDPs often focus on addressing public health needs that are not met by traditional market mechanisms, particularly for diseases that disproportionately affect low-income populations. By pooling resources, expertise, and risk, PDPs can help accelerate the development of innovative products and increase their accessibility.

Public goods: Public goods are goods or services that are non-excludable and non-rivalrous, meaning that individuals cannot be effectively excluded from using them, and one person's use does not reduce availability to others. Examples include clean air, national defence, and public parks. Because public goods are difficult for private markets to provide efficiently, they often require government intervention to maintain and allocate resources.

Pull funding: Pull funding is a financial incentive mechanism that rewards innovation and development of new products, such as medicines or vaccines, upon the achievement of specified goals. It is called "pull" funding because it attracts researchers and companies to invest in the development of new products by promising financial rewards upon successful completion.

Push funding: Push funding refers to financial support provided upfront to researchers or companies to develop new products, such as medicines or vaccines. This type of funding helps reduce the financial risks associated with research and development, making it more attractive for researchers and companies to invest in innovative projects.

Statistical power: Is the probability that a test correctly rejects a false null hypothesis, meaning it accurately detects an effect when there is one. High power reduces the risk of Type II errors (false negatives), increasing confidence in the results when finding significant differences or relationships. It's influenced by sample size, effect size, significance level, and variability.

Type 1 error: A Type 1 error, also known as a false positive, occurs when a test incorrectly indicates the presence of a condition, such as a disease, when it is not actually present. In medical research, a Type 1 error could occur when a study falsely concludes that a new treatment is effective when it is not.

Type 2 error: A Type 2 error, also known as a false negative, occurs when a test incorrectly indicates the absence of a condition, such as a disease, when it is actually present. In medical research, a Type 2 error could occur when a study falsely concludes that a new treatment is not effective when it actually is.

Medical terms

AWaRe classification: The Access, Watch, and Reserve (AWaRe) classification is a system developed by the World Health Organization (WHO) to categorise antibiotics based on their recommended use to preserve their effectiveness and combat antibiotic resistance. Access antibiotics are those that should be widely available, Watch antibiotics should be prescribed more cautiously, and Reserve antibiotics should be used as a last resort.

Active pharmaceutical ingredients (API): Active pharmaceutical ingredients are the biologically active components of a drug product that produce the intended therapeutic effects. APIs are responsible for the benefits of the drug and are combined with other substances, called excipients, to create the final drug product.

Non-inferiority trial: A non-inferiority trial is a type of clinical trial designed to demonstrate that a new treatment is not worse than a standard treatment by a pre-defined margin. This type of trial is often used when the new treatment has advantages, such as fewer side effects or lower cost, but may not necessarily be more effective than the existing treatment.

Orphan drug: An orphan drug is a pharmaceutical product developed to treat rare diseases or conditions, which often affect a relatively small number of people. Because the potential market for these drugs is limited, financial incentives and regulatory support are often provided by governments to encourage their development.

Prophylactic use: Prophylactic use refers to the administration of a medication or treatment to prevent the onset of a disease or condition, rather than treating it after it has occurred. Examples of prophylactic use include taking antibiotics before surgery to prevent infection or using vaccines to prevent the spread of infectious diseases.

Reproduction number (R0): The reproduction number, or R0, is an epidemiological metric that represents the average number of new infections caused by a single infectious individual in a completely susceptible population. If R0 is greater than 1, the infection will likely spread, whereas if R0 is less than 1, the infection will likely die out. R0 is an important factor in understanding the potential spread of infectious diseases and informing public health interventions.

Superiority trials: Superiority trials are a type of clinical trial designed to demonstrate that a new treatment is more effective than a standard treatment or placebo. The objective of these trials is to show a statistically significant improvement in a predefined outcome, such as symptom relief or disease prevention, in order to support the approval and adoption of the new treatment.

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