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The Not-So-Invisible Hand of "Stewardship," Within and Beyond Antibiotics: Implications of Non-Monetary Pharmaceutical Controls for Access to Medicines

RACHEL SILVERMAN BONNIFIELD AND KATHERINE KLEMPERER

Abstract

One of the main drivers of antimicrobial resistance is the misuse and overuse of antimicrobials. However, lack of access to antimicrobials causes a large mortality burden and can also contribute to the spread of resistant infections. Policies to control use therefore need to tread a careful balance between preventing inappropriate use and enabling necessary use. Such stewardship policies are often considered unique to the field of antimicrobials but are in fact ubiquitous across drug classes. This paper considers how learnings from the use of control policies in other areas of medicine can be translated into lessons for antimicrobial stewardship policy design. We describe the rationale(s) behind imposing controls on medicines and catalogue a list of control policy options, considering the potential impact of each policy on access and stewardship goals. We then offer two deep dives on specific policy levers—prescription policy and mandatory reporting/databases—to demonstrate how stewardship policies work in practice. We conclude with learnings and recommendations for policymakers when formulating and reviewing policy, both for antibiotics specifically and for all drug classes more broadly.

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Introduction

Since the AIDS crisis of the late 1990s, the imperative for "access to medicines"—the ability of individuals to receive "affordable access to safe, effective and quality medicines and health products" (WHO, 2023a)—has emerged as a central concern within global health. Historically, global health discourse on access to medicines has fallen into four broad and interrelated buckets:[1]

1. **Pricing and Affordability, including through Insurance Mechanisms:** Are medicine prices affordable to individual patients, and/or to pooled purchasers buying on behalf of a given population? Do insurance schemes require pre-authorisation or use tiered formularies and laddered access? Included within this bucket are concerns about the role of national and international intellectual property (IP) protections in preventing generic competition, and therefore sustaining monopoly pricing, as well as healthy competition and manufacturing efficiency for off-patent medicines.

2. **Availability of Medicines within Countries:** Are safe and effective medicines approved and registered in low- and middle-income countries (LMICs), and available in sufficient quantities to meet population needs? Included within this bucket are concerns about supply security and overall global medicine shortages, including those caused by supply chain disruptions or natural disasters; budget allocation and procurement practices by governments and other health payers; hoarding or unequal distribution of medicines (e.g., COVID-19 vaccines); delays in registration/market entry for novel health technologies, especially vis-à-vis smaller or less lucrative national markets; and international controls that limit access to some medicines, e.g., narcotics.

3. **Availability and Delivery of Medicines at the Point of Use:** Are supply chains effectively delivering medicines from central warehouses/importers to front-line facilities, and are human resources for health (HRH) sufficient to distribute/administer the medicines to those in need? Included within this bucket are concerns about stockouts, logistics, diversion/corruption, and HRH capabilities.

1 Note that several authors have proposed frameworks to formalise discussions on access, for example Frost and Reich (2008). This framework consists of the general categories of availability (including manufacturing, forecasting, procurement, distribution, and delivery), affordability (at the government, nongovernmental agency, and end-user level), and adoption (at global, national, provider, and end-user level). Comparing our categorization to this framework, bucket 1 would fall under affordability; bucket 2 relates to manufacturing, forecasting, and procurement; bucket 3 relates to distribution and delivery; and bucket 4 is not covered by the framework.

4. **Medicine Quality and Authenticity:** Are the medicines purchased and administered to patients high-quality, safe, and authentic? Included within this bucket are concerns about counterfeit medicines and medicine quality assurance (including WHO pre-qualification and the capabilities of national regulatory authorities[2] for pharmacovigilance).

While all of the above are critically important, we propose that there is a fifth bucket of access considerations that has been largely neglected within the global health discourse: the role of domestic pharmaceutical policies for ***control of medicines***. In this bucket, we include all national or subnational policies that in some way restrict or seek to guide the free sale, use, exchange, import, or production of pharmaceutical and other health products. These are policies are that imposed *by* national and subnational governments themselves—not *on* them by external donors, corporations, or trade agreements. These controls on medicine are ubiquitous, widely accepted, and only rarely called into fundamental question. While control policies could be categorized in the distribution and delivery section of Frost and Reich's (2008) framework, these sections often instead focus on active processes to deliver medicines, rather than considering how removal of controls can improve access.

Perhaps the simplest way to explain the enormous scope covered by such policies is to describe a world without them. In such a scenario, any party could produce, sell, import, distribute, administer, and consume any pharmaceutical/medicinal substances in any quantity, with no interference by the government. Pharmaceutical companies would not need to have their products approved by regulatory agencies, nor registered by national authorities. Pharmacies, convenience stores, and even individuals could sell any pharmaceutical substance to anyone, in any quantity. There would be no controlled or illegal substances, nor a requirement for a physician's prescription before dispensing.

Every measure laid on top of this "state of nature" is, in some way, a control on medicines. Collectively, these measures can be termed "stewardship"—a concept which has heretofore been closely associated with antibiotics. While its precise definitions and conceptualizations vary in the literature and across policy bodies, the word is generally used to refer to policies and other measures intended to promote responsible use, prevent overuse, and conserve the efficacy of antibiotic drugs (Dyar et al., 2017). Though the rationale for conserving efficacy is specific to antibiotics, there is no theoretical or practical reason why the concept of "stewardship," more broadly, should apply to antibiotics alone. "Stewardship," we propose, can be equally applied to *all* medical substances, and refers to the set of legal, regulatory, professional, and normative controls imposed on medicines intended to promote the "effective, safe, and sustainable use."[3]

2 For the purpose of this paper, we consider an archetypical national regulator with full control. However, we recognize that there may be a complex and/or fragmented regulatory system, with different bodies responsible for different elements of regulatory control.

3 Alberta Health Systems is one of the few systems we identified with a focus on "drug stewardship" that extends beyond antibiotics across all classes of drugs. See https://www.albertahealthservices.ca/phm/Page17557.aspx

Such controls on medicine exist for very good reasons. They are intended to protect patients from unproven or potentially harmful drugs and to promote the safe, effective, and appropriate use of medicines, therefore helping to optimize individual medical outcomes and public health objectives. Nevertheless—for antibiotics and other medicines alike—even the most well-justified policies have a mechanical effect of reducing access to medicines below the level that would exist in an unregulated state of nature. The benefit of any such measure (e.g., the averted harms of unsafe or inappropriate use) must be weighed against its costs (e.g., people who will forego or lose access to needed/useful treatments as a result).

Drawing from the concept of "stewardship" as used with respect to appropriate use of antibiotics, this paper aims to catalogue and contextualize non-price pharmaceutical controls and their implications for access to medicines. Its goals are twofold. First, it aims to expand the potential policy space for *antibiotic stewardship* specifically by considering controls/models used across classes of medicines in different contexts, and to identify promising models which might be useful in the national or subnational contexts. Second, it aims to shed light on the access trade-offs posed by such measures *across all drug classes*, considering the design of policy approaches from first principles, and recognizing that their suitability and effects will vary substantially across health systems and local contexts.

The paper is limited in scope, with important caveats. First, it does not attempt to identify the "right" or optimal approach for control of medicines. Instead, it seeks to better understand the range of tools available, and their theoretical and practical implications for patient access and outcomes, as well as related social outcomes and externalities. Second, it limits its focus to non-monetary policy levers, since the importance of monetary and price-related barriers for patient access are broadly understood, and related policy levers have been well studied in previous literature. For example, this paper does not consider the impact of price/insurance coverage on access, nor measures like direct tax, subsidy, restrictive formularies, nor insurance prior approval that might be used to control costs or raise government revenue. Third, its narrow focus on legal, regulator-imposed controls also excludes any number of voluntary and/or programmatic interventions that might impact either stewardship or access, e.g., physician training or voluntary accreditation processes for pharmacies. Finally, this paper focuses specifically on the policy levers that are directly controlled by autonomous, sovereign countries and subnational units. This is not intended as a statement of relative importance; countries are rightly concerned about access restrictions that are beyond their direct control, e.g., unaffordable prices for on-patent medicines or restrictive international quota systems for use of narcotics (Nickerson and Attaran, 2012). Nevertheless, there is a very large policy space *within the control* of national and subnational governments, and it is worth considering how this can be better used to advance health outcomes and equity.

This paper offers a brief narrative review about reasons for the control of medicines, strategies to do so, and the implications for access and equity. It begins with a discussion of how "stewardship" is conceptualized within the antibiotic space, building a broader understanding of stewardship

that can apply across all classes of medicines. It then describes the rationale(s) for the imposition of controls on medicines, including concerns about safety, toxicity, psychoactive properties, and addiction, among others. Next, it offers a typology of policy controls on medicines, including brief discussion of their potential intended and unintended effects on access to medicines. It offers two narrative deep dives on specific levers of pharmaceutical policy (prescribing policy; and reporting/database mechanisms for specific controlled or otherwise protected substances). It concludes with a discussion of implications for policy.

Why control medicines? The "stewardship" imperative and its trade-offs

For antibiotics specifically, the primary goal of stewardship is to provide access to patients with true medical need, while managing the externality of individual, veterinary, and public health use of antibiotics (i.e., the reduction in collective antimicrobial efficacy), thereby slowing the emergence of antimicrobial resistance (AMR). While the overall goal of conserving antibiotic efficacy is broadly shared across all countries, the priority placed on stewardship relative to access varies markedly by setting.

This tension is particularly acute in LMICs, where problems of overuse/inappropriate use of antibiotics co-exist with persistent access barriers; one paper estimates that universal access to antibiotics could save 444,500 children under-5 each year from bacterial pneumonia alone (Laxminarayan et al., 2016). Specific stewardship interventions or regulations—for example, requiring physician or other health system prescriptions for antibiotic dispensing, or requiring laboratory-confirmed diagnosis prior to prescription—can thus be contentious in lower-resource settings due to their potential adverse impact on prompt patient access to lifesaving treatment. These general dynamics drive important policy debates in this space about the appropriateness of placing limits on where and how antibiotics can be accessed, and the potential perverse effects of such restrictions on access to treatment in settings with limited diagnostic capabilities, health system resources, and human resources for health.

The primary rationale for antibiotic stewardship (e.g., conservation of efficacy) is unique to antimicrobials; global efficacy for most other drugs does not decline with increased use. Nevertheless, there are many other reasons why governments or health providers may seek to restrict "free" access to drugs and other health technologies, most of which are specific to the individual characteristics of any given drug. These include:

- **Unknown Efficacy or Safety:** Some drugs do not yet have established safety and efficacy profiles; the risks and benefits of their use therefore remain unknown. Example: experimental drugs.

- **Promote Diagnosis, Use of Health Services, and Long-Term Adherence:** Free access to drugs may encourage self-diagnosis, leading to delayed or inappropriate treatment, and thereby increasing the risk of complications and long-term or serious harm from the underlying condition. Some controls on medicine are thus intended to channel patients to diagnostic evaluation and professional health services to promote more effective medical intervention. Relatedly, more frequent touchpoints with health services may be considered desirable to support adherence to long-term regimens.[4]

- **Cost Control and Promoting Value for Money:** Governments may want to ensure that scarce public and private health expenditure is used as efficiently as possible to generate better health, in this case by deterring or otherwise limiting unnecessary or inappropriate care or treatments.

- **Safety Risks:** Some drugs offer important clinical benefit in some patients, but nevertheless carry substantial safety risks– for example, potential side effects, interactions with other drugs, toxicity, susceptibility to infection, or overdose risk. Example: lithium; chemotherapy; immunosuppressants.

- **Addiction/Abuse/Diversion Risks:** Some drugs can be addictive if used improperly/for long durations, and/or may have recreational uses beyond the intended clinical application. Governments and health providers may seek to prevent the patient from developing addiction or dependence; they may also worry about diversion of drugs if sold/repurposed on the black market. Examples: opiate painkillers; clonazepam; Adderall; pseudoephedrine.

- **Potential or Unavoidable Externalities to Others:** Use of some drugs has the potential to harm others, either by driving drug resistance (as in the case of antimicrobials) or by producing psychotic effects or impairment (e.g., driving) in the patient to whom they are administrated. Examples: sleep aids; antibiotics; antiepileptic drugs; steroids.

- **Potential Use in Suicides:** Many common medicines can cause death if consumed in very high quantities, and therefore may be used as part of a death by suicide (or a suicide attempt). Examples: ibuprofen; antidepressants.

- **Psychoactive Effects:** Some drugs (with or without clinical benefit) may also cause psychoactive effects. Examples: marijuana; psychedelics; stimulants.

- **Harms from Long-Term Use:** Some drugs are safe for short-term use but may cause harm if used over a longer time horizon. Example: naproxen (anti-inflammatory painkiller).

4 However, controls on medicine can at times have the opposite, undesired effect of *decreasing* long-term adherence by imposing additional barriers; these tensions are discussed later in this paper.

- **Social Norms or Disapproval:** Some governments may wish to restrict access to certain medicines based on social or religious norms; moral judgments; or if the medicines are perceived to enable or reduce harms from behaviors perceived as "undesirable." Examples: contraception; methadone; naloxone; mifepristone.

Most drugs fall into at least one of the aforementioned categories, and many (e.g., opioids) would fall into several. It is therefore unsurprising that most medicines are controlled in most settings, albeit with different levels of stringency across drug types and jurisdictions. It is also likely, therefore, that at least *some* controls (i.e., stewardship) on *most* medicines would be preferable to the "state of nature" from a cost-benefit perspective. However, it does not necessarily follow that *all* controls on medicines are well justified by the rationales described above; it is plausible that some controls on medicine are substantively unnecessary, and instead attributable to overcaution or inertia.

More broadly, as with antimicrobials, degree of control is quite relevant and should be thoughtfully considered relative to the risks and benefits of any given drug, situated within a specific local context. All controls will reduce access; policymakers must therefore carefully weigh a control's effect in *averting harm* from inappropriate use against the *opportunity cost foregone* from the marginal patients who would have accessed or continued treatment in its absence. The cost-benefit calculation will depend on the characteristics of the drug itself; the capabilities, accessibility, and nature of the local health system; and the characteristics of the local population, including degree of trust in medical professionals, patient awareness/education, and norms/patterns of medication use.

Toolkit of policy levers for national and subnational governments

In seeking to mitigate the concerns listed in the previous section, policymakers have a wide arsenal of potential levers available at their disposal. Together, these policy levers comprise an "extended stewardship universe," which is governed by a country's legal regime and regulatory code, and typically enforced through some combination of applicable civil and criminal penalties. Here, we present a non-comprehensive list of the non-price/subsidy measures available to national policymakers, without prejudice to their effectiveness or desirability for any particular drug in any specific context:

Drug approval/registration

Most countries only allow a drug to be sold after it has received regulatory approval and registration with the local regulatory authority. This represents a *de facto* ban on the sale or use of any drugs that have not yet received marketing authorization, except in extraordinary circumstances, including clinical trials. Such processes are intended to ensure the safety and efficacy of drugs before they

reach market. However, some patients may wish to access drugs that are not yet approved/still under investigation, and in turn are willing to accept the personal risk of ineffective or dangerous treatment—often because they have life-threatening conditions or very poor quality of life, without other available treatment options.[5] To help meet this need, some countries allow "compassionate use" or "expanded access pathways" for investigational drugs under specific conditions. Slow or overly onerous drug approval and registration processes can also delay access to drugs that have already demonstrated safety and efficacy.

Prescription requirements

Some drugs may only be dispensed/administered if a patient has received a prescription from a physician or other authorized health worker (e.g., a nurse or pharmacist). Such requirements are intended to ensure that drugs are used appropriate, safely, and following correct diagnosis; however, they increase patient time and financial costs to access medicines, and therefore may pose a barrier to prompt treatment or adherence to long-term therapies, which would require frequent/indefinite prescription refills. Prescription policy can vary substantially in its stringency across multiple dimensions and is discussed in further detail in the following section (Deep Dive 1).

Limited drug pack sizes

Some countries regulate the number of pills that can be sold in a single pack/sale, and/or require that the pills be separated and individually wrapped. Such measures are generally intended to encourage appropriate dosing, thus preventing toxicity, accidental overdose, or use in suicide.[6] However, these requirements can reduce access in two ways. First, they may raise the per-pill price, since labelling, packaging, shipping, and display costs may be higher and amortized across fewer pills. Second, smaller packs/limits on individual sales increase the time-cost of acquiring larger quantities of a medicine by requiring a patient to make more frequent trips to the pharmacy/drug seller. The latter increases the risk that a patient will run out of medication and/or interrupt their regimen.

Labelling

Regulatory authorities may have stringent and specific requirements about labelling of medicines, including dosage/administration/storage instructions, as well as mandatory disclosures on side effects and safety risks. In most cases, such measures should have limited to no effect on patient access.[7]

5 As one example, US AIDS activists in the late 1980s successfully advocated that the US Food and Drug Administration authorize access to experimental AIDS drugs; at that time, no other treatments were available (Aizenman, 2019).

6 For example, paracetamol pack sizes are restricted in the UK, given the potential for liver damage or death from overuse (Hawton et al., 2013).

7 Indeed, labelling can be beneficial for medication adherence (Conn et al., 2015).

Databases/mandatory reporting

Governments may require doctors to electronically log and report their prescriptions for specific substances, or alternatively require pharmacists to log their dispensations. Reporting requirements provide a disincentive and psychological "check" on prescribing, which may deter inappropriate use. However, the deterrent effect may be overly strong; physicians may not want to incur the time/effort cost of data entry, or the reporting requirements may create a "chilling effect" that deters legitimate and needed prescribing. Such measures are discussed in further detail in the following section (Deep Dive 2).

Patient education and consent requirements

Doctors may only be authorized to administer a drug after the patient has read and signed disclosure and consent documents. This is more common for drugs that are administered within a health facility or inpatient setting. In most cases, such measures should have limited to no effect on patient access.

Quotas

Policymakers can choose to place a hard upper limit (quota) on the total quantity of a drug that can be distributed. To the extent that they restrict supply below the level of population demand, quotas will mechanically result in rationing.

Limits or bans on advertising

Governments can ban advertising of medicines, or they can limit advertising to certain medicines and/or media formats. Such limits are intended to reduce inappropriate or unnecessary use of medicines, as patients may ask/pressure doctors to prescribe medicines even if they are not indicated. However, there may be some positive functions of drug advertisement (Parekh and Shrank, 2018). For example, advertisements can increase awareness of new treatment options among the population with specific conditions, who otherwise might not seek care because they do not know there are treatment options available (Sinkinson and Starc, 2019). Advertisements can also increase drug adherence (Alpert, Lakdawalla and Sood, 2023). In theory, the positive benefits could be captured through government- or nonprofit-sponsored advertisements, while avoiding the problems associated with for-profit promotion.

Limits or bans on pharmaceutical industry interactions with physicians

In the absence of regulation to the contrary, it is common for representatives of pharmaceutical companies to interact closely with health providers in an effort to introduce and increase prescribing of their products. Such interactions range from free samples and educational materials/outreach, on

one side, to gifts of branded merchandise, meals, entertainment, and travel on the other (Schwartz and Woloshin, 2019). In extreme cases, pharmaceutical industries may explicitly incentivize health workers to prescribe their products with kickbacks or other monetary incentives. Many countries have introduced policies to limit or ban such practices, or at least to make the process transparent,[8] with the justification that such practices promote over- and inappropriate prescribing; increase costs; and, more generally, compromise and corrupt health worker judgment and ethics. While such restrictions are generally harmless from a patient access perspective, there is a risk that overly zealous bans might compromise legitimate educational activities, resulting in delayed patient access or lower physician awareness of new treatment options.

Legal liability for prescribers

In some jurisdictions, health workers can be sued for malpractice if a patient experiences adverse medical outcomes from neglect or inappropriate treatment. In general, fear of litigation tends to incentivize *over*-diagnosis and -prescribing,[9] driving a "better safe than sorry" approach. Rarely, however, fear of litigation may limit health workers' willingness to prescribe medications, including those with addictive properties or safety risks, even if they are medically indicated and the patient were to offer informed consent.

Criminalization

Countries may take punitive measures to limit or prevent use of specific drugs/pharmaceutical compounds, ranging from minor penalties like confiscation/fines, all the way to imprisonment and even capital punishment. Criminalization is most common when drugs are perceived to be highly dangerous and addictive to the user; to create serious social externalities; or to enable behavior that is not socially sanctioned within a given local context. Criminal penalties can be applied uniformly to entire drugs or drug classes (e.g., cocaine or heroin); to recreational use of drugs outside of prescribed medical indications (e.g., opiate pain relievers or stimulants); or to specific uses of drugs that are illegal within a given jurisdiction (e.g., medical abortion). Criminalization of drug use is fiercely contested, and there are ongoing policy debates about emerging medical indications of "street drugs" (e.g., cannabis and psychedelics).

8 For example, the Physician Payments Sunshine Act in the US mandates that all drug and device makers must disclose payments of $10 or more to physicians and hospitals (Silverman, 2013).

9 For example, doctors tend to prescribe higher levels of antibiotics when at risk of malpractice suits (Panthöfer, 2022).

Deep dive 1: Prescription policy

Perhaps the most recognised method of medicine control is the use of prescriptions. By forcing people to see a medical professional before accessing medication, this policy aims to ensure accurate diagnoses and thereby limit inappropriate and unnecessary use. Additionally, medical professionals should be able to prevent harmful drug interactions, advise about side effects, and ensure appropriate dosage.

Prescription policy can be considered on a sliding scale of stringency. At the lowest level is the "state of nature," where anyone can obtain the medication from any shop. Moving up from this, medicines may be available only in pharmacies under the dispensation supervision of pharmacists (*Pharmacist-Only Medicines*, 2013). An intermediate level of control is where pharmacists or nurses are authorised to write prescriptions. The most common level of prescription is where a doctor's approval is required. At the strictest level, prescriptions of medicines may be limited to certain in-patient locations such as tertiary hospitals and specialist treatment centers.[10]

Prescription policy can be further tweaked by enforcing handwriting requirements or mandating words and figures be used to describe the dosage to ensure prescribers focus sufficiently.[11] Policies can also dictate maximum prescription lengths and/or opt to allow or disallow prescription refills. Shorter prescription lengths require more touchpoints with a doctor or pharmacist; this increases chances for assessment and potential prescription alternations, but also increases risk of improper discontinuation.

The evidence on best prescription length is mixed, depending on the patient groups and medicines dispensed. Some studies find that longer prescriptions are associated with better prescription adherence, but with more medication waste (King et al., 2018). For stable HIV/AIDS patients, the evidence supports longer prescription lengths: one study found 6-month antiretroviral treatment refills were beneficial compared to 2-month refills, and increased health system efficiency (Keene et al., 2020), while another found that extending up to 4 month dispensing increased adherence (Parrish et al., 2021). Some countries, such as the US, allow prescriptions to be refilled, so while the patient will have to see a pharmacist each time they acquire more medicine, they will not have to see the doctor again. (Refills are not available for all types of medication, such as drugs used to treat acute infections or controlled substances (Express Scripts, 2022)). The doctor can dictate how many refills are allowed, thus allowing them to control how frequently they will see the patient. Longer dispensing can help to reduce the burden on physicians and reduce congestion in health systems, which is particularly important in resource-limited settings (Daniel P. and Christopher, 2022).

10 For example, the UK's NHS has a set of "Specialist Only" medicines which should only be dispensed in secondary or tertiary care and under the supervision of a specialist (NHS, 2023).

11 For example, there are additional requirements for prescriptions of controlled drugs in the UK (Community Pharmacy England, 2022).

While prescriptions may be an effective option in areas with good health coverage and infrastructure, there is concern that issues with accessing healthcare professionals could limit access to medicines. Most obviously, this will be an issue in regions with low density of healthcare providers, and thus where patients are physically unable to access providers. Additional concerns arise from potential access barriers posed by the financial cost of healthcare appointments and the time cost of seeking healthcare (Taber, Leyva and Persoskie, 2015). For example, when women could obtain birth control pills from a pharmacy without a prescription, more continued with their medication regimen (Potter et al., 2011) – and over three-quarters of surveyed women reported they would benefit from receiving birth control from a pharmacist rather than a physician (McIntosh et al., 2011). Additionally, traditionally stigmatised groups may be fearful of seeking healthcare or mistrustful of healthcare providers (Dawkins et al., 2021). People may also be anxious about seeing doctors for intimate issues and thus prefer to purchase medicine discreetly.[12] Finally, prescriptions can have a hidden cost on other aspects of healthcare, as the use of physician time for prescription appointments will detract from physician availability for other health concerns, potentially driving longer wait times and deferred care. Cumulatively, these adverse effects from prescription policies risk exacerbating health inequalities.

The access impact of prescription requirements will also differ according to the intrinsic properties of a medicine. For example, patients requiring infusion drugs will need to see a healthcare worker irrespective of prescription requirements, so will be less impacted by the additional onus of prescription policies than patients taking oral medicines which could be self-administered at home.

Prescription requirements often vary dramatically across national settings and may be contested by advocates and national authorities. For example, a 2013 study found that oral contraceptives were legally available without prescription in 32 percent of countries; informally available without prescription in 38 percent of countries; and required prescriptions in 31 percent of countries (Grindlay, Burns and Grossman, 2013). Today, they are available over the counter (OTC) in over 100 countries – mainly LMICs – but most high-income countries still require prescriptions. However, there is recent movement to make at least some oral contraceptive accessible OTC. In May 2023, advisors to the Food and Drug Administration in the US voted unanimously to switch a progestin-only oral contraceptive pill from prescription to OTC use (Hassan, 2023). (Already, over half of states had allowed pharmacists to prescribe contraceptives (Power to Decide, 2023)). This illustrates the constant rethinking of prescription requirements globally.

A further interesting example is that of statins, where the UK's approach differs from everywhere else. Statins require a prescription in almost all countries – but in 2004, the UK controversially revised its policy to allow low-dose statins to be sold OTC ('OTC statins: a bad decision for public health', 2004). In 2019, there was even consideration of making high-dose statins available OTC in

12 For example, confidentiality was a major concern for female students seeking contraception in the US (Hickey and White, 2015).

the UK (*NHS England*, 2019). By contrast, in the US, several applications for statins to be reclassified as OTC have been rejected (Stomberg et al., 2013). While proponents of the switch say that improved access can improve population health and result in cost savings of billions of dollars (Stomberg et al., 2016), others argue that this is outweighed by the risk of very rare but serious adverse side effects, the risk of people who require statins switching to OTC versions which are lower dose and so have less risk reduction, and inappropriate use in people with contraindications. This example demonstrates the complexity of prescription decisions, and the need for context-specific policies.

In the context of antibiotics, where unnecessary use is one of the main drivers of resistance, prescriptions can be an effective tool to reduce the burden of AMR. However, given the concern around access, it should not be used as a blunt instrument, but tailored to the context and to the class of antibiotics. In the WHO's AWaRe categorization (WHO, 2021), different classes have a different balance of access and stewardship concerns. Access drugs are most important to ensure access to and have a lower resistance potential. Reserve drugs are vital to steward effectively and less frequently required. Watch drugs fall in the middle. Therefore, differential prescription requirements can be used to help resolve tensions of access and stewardship. For example, it may be appropriate to limit Reserve prescribing to specific in-patient locations; to require a doctor's prescription for Watch antibiotics; and to allow Access prescribing by authorized nurses (Ness et al., 2021) or other lower-level providers.

Enforcement challenges may also limit the efficacy of prescription policy, and some studies have found limited impact of tightening prescription rules (Cadogan, Bradley and Bennett, 2021). Often, people bypass prescription rules and get medicines from friends or relatives (Preuss, Kalava and King, 2023); one systematic review of non-recreational prescription sharing found a prevalence rate of between 5 and 51.9 percent for borrowing someone else's prescription medication (Beyene, Sheridan and Aspden, 2014). People may also obtain medicines abroad, where specific substances are less tightly controlled than in their home regions. Pharmacies in border towns or tourist destinations often advertise the availability of medicines without prescription to appeal to travelers from countries with stricter requirements (see Picture 1). Similarly, online marketplaces can allow people to access medicines without needing prescriptions (Mainous et al., 2009; Boyd et al., 2017).[13] While this can at times be concerning with regards to stewardship, it can also help people access medicines when there are privacy concerns (for example, people seeking contraceptive care). In remote regions, online pharmacies can be crucial sources of access – for example, the organization Kasha, which delivers pharmaceutical and health products discreetly to low-income consumers in East Africa. In general, the difficulty in enforcing prescription drug requirements, and the profitable market for online websites and pharmacies in border towns, itself illustrates the access cost to prescription

13 Similarly, the US has developed a cottage industry of dedicated telehealth, and web-based services now offer quick, easy, and discreet prescriptions for a number of high-demand drugs, including those for erectile disfunction, hair loss, contraception, acne, HIV pre-exposure prophylaxis, and so forth.

Picture 1. Drugs&Deli retail pharmacy storefront. Found across the Caribbean, this chain often serves tourists and visitors with medicines that are more tightly controlled in their home regions. *(Brian Snelson/Flickr. CC BY 2.0)*

rules: the fact that people are forced to seek alternative methods to acquire medicines (and are willing to pay out of pocket for the convenience/privacy of websites) implies that prescription requirements are creating a barrier to necessary use.

Given the access issues, the appropriate level of prescription policy is not fixed based on the intrinsic properties of a drug, but also a function of availability, accessibility, affordability, and competence of doctors and diagnostic equipment; trust in healthcare providers; and enforcement capability. In particular, antibiotic prescriptions may not be appropriate in LMIC contexts (Khan, Rego and Spencer, 2018) – although tweaks to the severity of the policy may help mitigate downsides. Applicability of prescription policies can also be regularly reviewed, and policies updated accordingly. There are several examples of medications being reclassified in both directions. For instance, in 2018 oral lidocaine-containing teething products in the UK were reclassified from the General Sales List to Pharmacy-Only to ensure that parents were provided advice on correct use (Hannbeck, 2018). In the other direction, Flonase was reclassified in the US from prescription-only to OTC; this was deemed appropriate because the drug treats very common conditions which are easy

to self-diagnose, and consumers can competently use the product with safety guidelines (Chang et al., 2016). Emergency contraceptives are a well-studied example of downgrading from prescription-only to OTC access: many studies find that this change leads to increased access, and more consistent and timely use, without significantly different reproductive health outcomes (Gainer et al., 2003; Atkins et al., 2022). Evidence from other drugs also indicates that downgrading to OTC increases access: an analysis of nine drug classes found that introduction of the first OTC drug increased utilization at the class level by an average of over 30 percent (Stomberg et al., 2013).

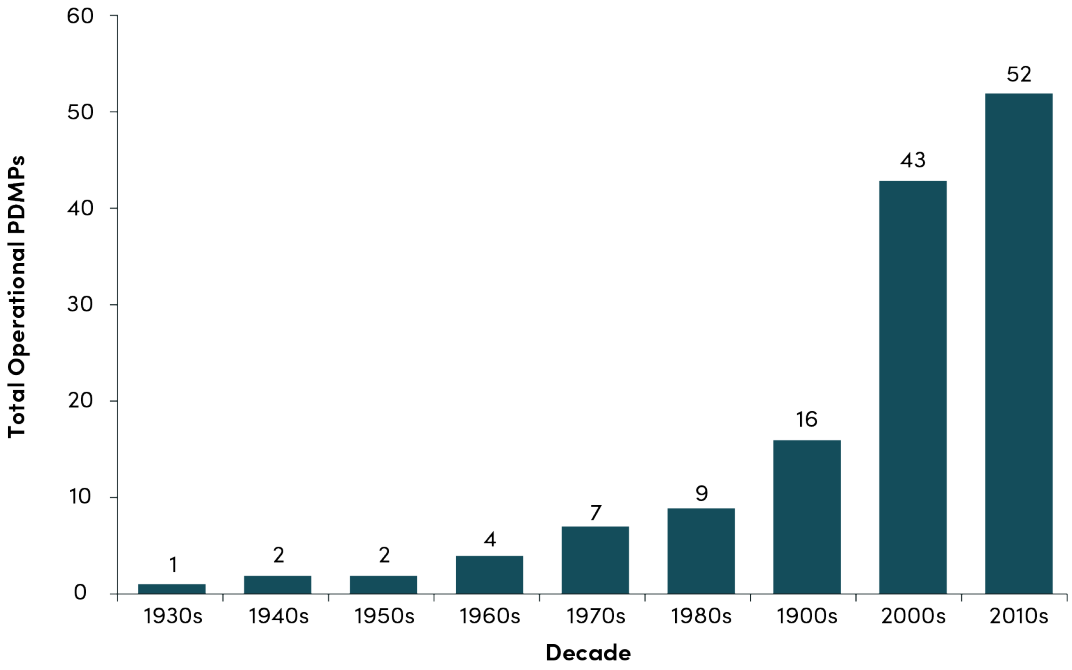
Deep dive 2: Reporting and databases

Another method for controlling access to medicines is use of prescription drug monitoring programs (PDMPs) (D'Souza, Lang and Eldrige, 2023). Under such schemes, healthcare providers are required to access databases with patients' prescription history before dispensing medications, and/or prescribers are required to report all prescriptions (CDC, 2021).[14] This has several benefits: firstly, the psychological impact of being tracked can motivate prescribers to take extra care to ensure all prescriptions are appropriate. Educational trainings could also be targeted at prescribers found to be dispensing at unreasonably high levels. Use of databases can also help prescribers avoid inappropriate prescriptions by allowing them to detect "doctor shopping" – when patients visit different doctors until they find one who will prescribe them the drugs they want (Sansone and Sansone, 2012). Finally, the database records allow for better tracking of use levels across regions (both necessary and unnecessary) which can reveal policy-relevant trends (Islam and McRae, 2014). The popularity of PDMPs has dramatically grown in recent years: from the establishment of the first PDMP in 1914 in New York (Holmgren, Botelho and Brandt, 2020), they are now used across the United States and in Canada, Australia, and parts of Europe (Tay et al., 2023). Figure 1 shows the dramatic increase within the US, with the number of operational PDMPs increasing by over 150 percent from 2000 to 2009.

However, there is concern that the additional requirement of using databases could be costly and inconvenient for already over-stretched healthcare workers, and an inefficient use of their time (Bachhuber et al., 2018; Robinson et al., 2021). This may be especially true for physicians – but task-shifting to lower-level providers may be possible in some instances. For example, the reporting requirements could be imposed at the level of the pharmacist, rather than the level of the prescriber. Additionally, drug monitoring programs could potentially act as too strong a deterrent for providers to prescribe, and so may impact necessary dispensing. For example, doctors serving regions with high disease burden may rightly need to prescribe at higher rates than doctors in other regions, but may be concerned about seeming to be overly lax with dispensing (Islam and McRae, 2014). This can lead to the "chilling effect" (Oldenhof et al., 2019) – when doctors do not prescribe to patients with

14 A related approach can be used for non-prescription, pharmacist-dispensed medicines, whereby pharmacists must keep a log of purchasers. For example, purchasers of pseudoephedrine in the US must show photo identification and sign a log before purchase (American Addiction Centers Editorial Staff, 2022).

Figure 1. Total operational PDMPs in the US over time



Source: Holmgren et al., 2020

genuine need – and has been seen when PDMPs are used for patients on combinations of medications needing greater supervision and thus greater effort from the prescriber. Alternatively, doctors may react by prescribing different (less effective or appropriate) medicines – known as the "substitution effect" (Wastila and Bishop, 1996). On the other hand, the impact of PDMPs may not be sufficient to deter unnecessary prescribing: evidence about the efficacy of drug-monitoring programs for opioids is mixed (Finley et al., 2017), with some studies finding no impact on prescribing decisions (Pomerleau et al., 2017).

In the context of AMR, one key benefit of PDMPs would be to improve our understanding of antibiotic consumption in different regions. Antimicrobials, unlike many other drugs, have negative externalities of use (since usage in one patient can impact efficacy of use in another). Therefore, surveillance of consumption is essential to inform policies and to understand how resistance patterns may change. To this end, the WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015 (World Health Organization, 2021) – but currently only 77 countries are enrolled in the antimicrobial consumption reporting stream of GLASS (WHO, 2023b). Moreover, while country National Action Plans (NAPs) should "strengthen the knowledge and evidence base through surveillance"(World Health Organization, 2015), an analysis of NAPs revealed strategic gaps in mechanisms for achieving sustained surveillance (Charani et al., 2023). Therefore, PDMPs could provide an important source of information for collecting consumption data without imposing additional data collection burdens on country governments.

As with prescriptions, monitoring requirements for antibiotics would need to be tailored according to drug classes. PDMPs would be especially beneficial for Reserve class antimicrobials for which resistance is a particular concern. Since Reserve drugs are the most important to protect, and should be used the least, adding this additional requirement to their dispensation should not be too great a burden and is unlikely to deter necessary use. By contrast, the PDMP system might be less appropriate for Access class antibiotics: since these drugs need to be frequently dispensed (the WHO has set a target that at least 60 percent of total antibiotic consumption should be of Access antibiotics (WHO, 2023c)), the additional time requirement of using a PDMP for these might be too onerous a burden.

Discussion and recommendations

In this paper, we examine the suite of tools available to governments to promote "stewardship" of medicines. We highlight the ubiquitous nature and wide acceptance of such tools by comparing the status quo to a hypothetical "state of nature" in which drugs are entirely unregulated and uncontrolled. We also consider the rationale for the controls on medicines, as well as the intended and unintended effects that such measures have on patient access.

This rapid review was not methodologically powered to offer a comprehensive view of all possible tools, nor to evaluate the suitability of any given tool for a specific drug within a specific local context. However, our analysis points to some general findings.

First, there is an extensive list of reasons why governments might seek to limit access to medicines. In most cases, the rationale is for the patient's "own good"—that is, to promote effective diagnosis; ensure medicines are safe, effective, and appropriately indicated for the patient's medical needs; and to prevent adverse effects including addiction, side effects, drug interactions, or toxicity. However, exceptions exist. Some controls are at least in part motivated by concern for drugs' broader effects on society, for example to preserve efficacy (in the case of antimicrobials), or to limit collateral damage from impairment or psychoactive effects. And in some cases, controls are in service of moral or socio-normative judgments about appropriate behavior, for example in the cases of contraception or medical abortion.

Second, governments can leverage a large suite of non-price policy levers to promote safe and rational use of medicines; however, most (though not all) such measures have potential downsides for patient access (among other possible negative effects). Given that most drugs have potential adverse effects on patient and social outcomes, it is very likely that some controls on medicine are appropriate in most cases. Nevertheless, policymakers should explicitly acknowledge and consider the access implications of control measures, both to tweak/optimize their stringency by weighing benefits against harms, and to mitigate potential negative impacts with supplementary access-promoting efforts.

Third, the appropriate level of controls on medicines is necessarily contextual. A drug's intrinsic properties—clinical benefit, safety, addiction risk, side effects, and so forth—are clearly relevant in this determination. But so too are characteristics of the local health system, disease burden, and population. It is far easier to require physician prescription for a given drug, for example, in settings with universal health coverage; high density of physicians; short waiting times for a physician appointment; high population trust in the health sector; and relatively low prevalence of acute, life-threatening disease. The access costs of doing so, in contrast, would be far elevated if many patients needed to incur substantial financial/time costs, travel long distances, and/or endure long waiting periods before obtaining urgent, potentially life-saving treatment.

Fourth, many potential controls on medicines—for example, prescription policy—exist on a sliding scale of stringency. This allows for extensive policy space to tweak and optimize policy design, in contrast to blunt "on/off switches" that can only be applied or removed. The potential for incremental adjustment of controls can also facilitate iteration and learning-while-doing, where slightly stricter/looser controls are trialed and evaluated before taking more radical steps.

Finally, we can identify a subset of policy levers from our long list of potential controls that are particularly relevant or applicable to antibiotic access and stewardship. These include prescription policies and mandatory reporting and databases, which are considered at length in Deep Dives 1 and 2, respectively. Other potentially applicable (though not necessarily wise or appropriate) policy levers are quotas; limits or bans on advertisements; and limits or bans on interactions between pharmaceutical representatives/companies and physicians/pharmacists/other prescribers.

The complexity and contextual nature of these policy decisions limit our ability to be prescriptive about the appropriate level of controls. Moreover, given that each policy will impact a diverse range of actors, each in different ways, it can be hard to predict the precise impact of different policies, and thus hard to make generalized statements. However, based on our review, we suggest that policymakers consider the following high-level recommendations for rational control of antibiotics:

1. **Calibrate controls across the WHO's AWaRe categories of antibiotics.** As with all medicines, stringency of control should be based on a cost-benefit analysis of ease of access versus costs of excess access. In the case of antibiotics, access is important to reduce the still unacceptably high level of morbidity and mortality from treatable infectious diseases, which are largely (though not exclusively) concentrated in LMICs. The major concern is conservation of efficacy. The WHO's AWaRe categories (Access, Watch, and Reserve) offer a useful paradigm to distinguish and differentiate levels of appropriate controls across antibiotic drugs/classes, thereby helping strategically expand access while conserving long-term efficacy of the full antimicrobial "portfolio."

2. **Consider relatively liberal controls on AWaRe Access antibiotics, particularly in settings with low density of health workers and facilities.** This paper has documented the potentially serious implications of pharmaceutical controls on access to medicines. Given these costs and barriers, relatively easy access to AWaRe Access antibiotics—which are narrow-spectrum drugs intended to treat the most common infections, and which run relatively low risk of resistance—should be prioritized, especially in LMICs with continued high mortality and morbidity burden from infectious disease. This implies a strong rationale for relatively liberal controls on AWaRe Access antibiotics, particularly in countries or regions with low density of health workers and diagnostic capabilities, potentially including over-the-counter dispensing, or alternatively pharmacist, community health worker, or nurse practitioner prescribing authority.

3. **Impose relatively strict prescription and reporting controls on AWaRe Reserve antibiotics.** In contrast to AWaRe Access drugs, the cost-benefit calculus for AWaRe Reserve antibiotics suggests that a more restrictive control regime is likely warranted, as these are drugs of last resort which should only be used when other, first- and second-line options have failed. Regulators should thus consider tight controls on AWaRe Reserve antibiotics, which should only be used under close supervision of a physician or specialist. For example, it may be appropriate to limit dispensing to specialized inpatient settings; likewise, the costs of mandatory reporting/databases are more likely to be warranted, given the relative rarity of their appropriate use and the paramount importance of rationalizing all administration.

4. **Consider other potential policy levers through contextual, cost-benefit analyses, with due consideration of access implications.** We did not conduct deep dives on the additional, applicable policy options for antibiotic control—quotas, controls on advertisements, and controls on industry outreach to physicians or prescribers—and we are unable to offer strong recommendations on the appropriateness of their use. Our shallow review suggests the following "priors" for policymakers to consider as a starting point, while recognizing that deeper and contextual analyses are needed before coming to any firm conclusions:

    - **Quotas** are unlikely to be a desirable policy choice, given their strong and crude access implications; more agile policy options are available that are unlikely to have such dramatic negative impacts on access.

    - **Bans or limits on antibiotic advertisements** are likely to be appropriate in some settings to reduce inappropriate demand. However, some advertisements may play a useful role in educating the public about treatment options for specific conditions/symptom profiles. Regulators should consider the extent to which advertisements play a useful educational role and potentially consider calibrated regulations/limits/guidelines versus outright bans.

- **Bans or limits on pharmaceutical interactions with medical professionals** should be undertaken with caution. While interactions of pharmaceutical representatives with healthcare providers can lead to perverse prescribing incentives, there is an important role for the pharmaceutical company in educating providers and driving market entry of novel antibiotics, particularly in settings with few other fora for continuing medical education.

More broadly, we suggest that policymakers consider the following general recommendations vis-à-vis controls on medicines during the policy formulation and review process:

1. **Conduct cost-benefit analysis to determine the appropriate level of controls on new medicines.** At drug approval, regulators should conduct a cost-benefit analysis to determine the appropriate type and level of controls that are applied to the drug, with consideration of the drug's intrinsic characteristics, plus local needs, disease burden, and system constraints.

2. **Evaluate whether controls on medicines are fulfilling their intended purpose.** Given the potential for controls on medicines to compromise access, it is important to rigorously evaluate whether controls are achieving their intended *positive* effects, e.g., promoting diagnosis, improving safety, and so forth. Policymakers should build in regular evaluation into control measures and programs, particularly for novel efforts like PDMPs.

3. **Regularly review and potentially modify the stringency of controls on medicines.** Controls on medicines are not set in stone; they can and should be regularly reviewed to assess and compare the necessity/benefit/effectiveness of controls against the potential adverse effects on access. In doing so, priority should be given to drugs with (1) high unmet need, particularly if the need is concentrated in poorer/more marginalized segments of society; (2) requirements for long-term use, where ensuring/promoting long-term adherence is a challenge; and (3) potential to cause unexpected harms, including higher than anticipated levels of addiction, overdose, or diversion to recreational use.

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