Antibiotic development and usage, and antibiotic resistance in particular, are today considered global concerns, simultaneously mandating local and global perspectives and actions. Yet such global considerations have not always been part of antibiotic policy formation, and those who attempt to formulate a globally coordinated response to antibiotic resistance will need to confront a history of heterogeneous, often uncoordinated, and at times conflicting reform efforts, whose legacies remain apparent today. Historical analysis permits us to highlight such entrenched trends and processes, helping to frame contemporary efforts to improve access, conservation and innovation.

Heterogeneity of National Responses

Antibiotics were the best known and most widely prescribed of the post-WWII “wonder drugs,” allowing medicine to powerfully rebrand itself in such industrialized states as the United Kingdom (U.K.) and the United States (U.S.). From the beginning, however, clinicians and infectious disease experts expressed concerns regarding the unique ecological features of antibiotics and the hazards of overuse. As early as 1954, Britain’s Lindsey Batten, in the context of widely documented staphylococcal resistance, could wonder aloud at the Royal Society of Medicine: “Those deadly staphylococci...are not pirates or privateers accidentally encountered, they are detachments of an army. They are also portents...We should study the balance of Nature in field and hedgerow and throat and gut before we seriously disturb it. Again, we may come to the end of antibiotics. We may run clean out of effective ammunition and then how the bacteria and moulds will lord it.” Yet attempts to reform the antibiotic market and to ensure the rational use of antibiotics took very different forms in different states, both with respect to therapeutic prescribing, and with respect to the agricultural use of antibiotics.

In the U.S., the largest producer of antibiotics throughout the antibiotic era, would-be reformers have long expressed concerns about the dangers of indiscriminate usage. During the early 1950s, in particular, Ernest Jawetz drew repeated attention to the role of the laboratory — and hoped-for improvements in diagnostics — in offsetting “shotgun” therapy, guiding “rational” therapy in its place, and reducing the incidence of missed diagnoses, adverse effects, super-

History Teaches Us That Confronting Antibiotic Resistance Requires Stronger Global Collective Action

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Yet throughout ensuing decades, the most iconic antibiotic reforms in the U.S. focused on the market entry of individual new drugs, rather than on the overall supply of antibiotics or on prescribing itself. As of the 1950s, the Food and Drug Administration (FDA) only formally adjudicated drug safety, rather than efficacy. And in the setting of widespread staphylococcal resistance, not only to penicillin but to such “broad-spectrum” drugs (introduced in the late 1940s and early 1950s) as chloramphenicol and tetracycline, companies began introducing and widely marketing “fixed-dose combinations” of two or more antibiotics. Therapeutic reformers like Maxwell Finland and Harry Dowling tested such remedies and found them no more efficacious than their component parts. They used these results to rally around the need to test new drugs via rigorously controlled studies, rather than through “testimonials” masquerading as serious science. These efforts contributed to the passage of the 1962 Kefauver-Harris amendments that mandated that new drugs be proved efficacious via “well-controlled investigations.”

By 1966, the FDA, through the National Academy of Sciences-National Research Council, instituted the Drug Efficacy Study and Implementation (DESI) process, whereby pre-1962 drugs could be retrospectively reviewed; and by 1969, all of the fixed-dose combination antibiotics would be withdrawn from the market. One of the most financially successful withdrawn drugs was Panalba (a mixture of tetracycline and novobiocin), produced by the Upjohn Company. The company took the FDA to court. They stated not only that Upjohn had conducted a number of “substantial, very substantial studies” — including in vitro, animal, and uncontrolled human studies — to justify Panalba’s utility, but that the FDA’s actions impinged on the prescribing prerogative of the clinician. Yet the judiciary found in favor of the FDA, representing both the conceptual apotheosis of the controlled clinical trial in therapeutic evaluation in the U.S., as well as a key moment of FDA empowerment with respect to antibiotics. But no agency was authorized to govern antibiotic use more generally, and by the 1970s, when “irrational” antibiotic prescribing was becoming increasingly documented and stewardship programs were first being implemented and studied in the U.S., it appeared that the withdrawal of the fixed-dose combination antibiotics had only engendered resentment and agitation over the prospect of the further centralization of therapeutic autonomy.

Scandinavia represents an instructive alternative approach, grounded in an ongoing concern with the overall ecology of the market. Norway, in 1928, was among the first countries to mandate centralized approval prior to entry of drugs onto the market-place. Its regulations were from the beginning oriented against a “flood” of dubious drugs, requiring new drugs to be “medically justified,” and from 1938, “needed.” Scandinavian health authorities argued that drugs — and especially antibiotics — could not solely be treated as market commodities. This regulatory framework was able to accommodate early concerns over antimicrobial resistance; and as early as 1947, the possibility of antibiotic resistance led to the rejection of penicillin products thought to invite indiscriminate use. The so-called “clause of need” — facilitated by the presence of a relatively small pharmaceutical industry, but also politically motivated and largely supported by the medical community — was actively used to maintain a low number of drugs

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on the market. From the 1960s, antibiotics were singled out for a particularly strict registration practice, with new drugs rejected when these met no specific clinical need not already covered by well-known or cheaper drugs. For example, the cephalosporins for a long time remained in marginal use in large part due to this practice. The regulations do not by themselves explain low levels of antibiotic use in Scandinavia, but provided one powerful tool among many in the hands of concerned experts, and took part in shaping prescribing patterns and patient expectations that appear to persist to this time.

The point of such examples is that not only are a variety of national responses possible, but that such a variety of national responses has in fact been taken, permitting us to consider the contexts in which they were taken and the legacies they retain today. The same heterogeneity has applied to the use of antibiotics in agriculture, especially with respect to growth promotion. In Great Britain, by the 1960s, concerns (especially as voiced by Andy Andersen) over the spread of antibiotic resistance from animals to humans led to the 1969 Swann report, banning therapeutically relevant antibiotics such as penicil-
lin and tetracyclines for growth promotion.\textsuperscript{15} Yet the impact of the Swann report was limited. In Britain and other European states who adopted the Swann recommendations, while non-therapeutic antibiotic usage could be banned, veterinarians could simply switch to therapeutic overprescribing.\textsuperscript{12} And in the U.S., the FDA was preoccupied with the regulation of carcinogens in food and heavily influenced by a 1966 ad hoc committee report on agricultural antibiotics that reflected scientific uncertainty over the relationship between such antibiotics and the development of resistance in humans. As a result, the FDA failed to assert itself against industry opposition and did not convince Congress to enact Swann-inspired bans in 1972 and 1977.\textsuperscript{13}

As described elsewhere in the series,\textsuperscript{14} beginning in the 1980s several European states began to enact more aggressive measures. Nevertheless, such approaches still retain a regional, if not national, character. The U.S. only began addressing antibiotic usage in agriculture with voluntary, but permanent label restrictions on medically important antibiotic growth promoters in December of 2013, pointing to the enduring heterogeneity of responses to this seemingly global concern.

The Limits to Global Responses

Indeed, such global concerns would seem to call for a global response, but attempts at such a coordinated response to antibiotic usage and resistance have been slow in coming. The initial “global” efforts in the 1940s of organizations like the United Nations Relief and Rehabilitation Administration – focused on the transfer of antibiotic-producing capabilities to war-torn states – did not concern antibiotic overuse, but rather the potential lack of antibiotic availability in such countries.\textsuperscript{15} By the late 1950s, though, the World Health Organization became concerned with antibiotic misuse and resistance, convening a meeting in Geneva in May of 1959. “Counter-propaganda” regarding antibiotic “misuse consequent on unscrupulous advertising” was considered, along with proposed efforts to reduce “self-medication” in “countries in which antibiotics are freely available by the public,” and members considered the need to standardize and coordinate antibiotic resistance testing as a prelude to guiding antibiotic usage at both local and global levels.\textsuperscript{16} However, the debate over laboratory standardization would dominate WHO antibiotic involvement over the ensuing decade;\textsuperscript{17} and while the organization would make scattered efforts to address antibiotic resistance, its efforts remained inconsistent for many years. At the same time, faith in the capacity of the pharmaceutical industry to keep up with evolving bacteria helped to mute potential concerns.

By the late 1960s and 1970s, though, concerns over the horizontal transmission of antibiotic resistance via plasmids that knew neither species nor state boundaries, and parallel concerns regarding the emergence of so-called “superbugs,” served to reinvigorate efforts to confront antibiotic resistance as a potentially globally connected phenomenon.\textsuperscript{18} In January of 1981, Stuart Levy convened a meeting in Santo Domingo on the “Molecular Biology, Pathogenicity, and Ecology of Bacterial Plasmids,” at which 147 scientists from around the world signed a joint “Statement Regarding Worldwide Antibiotic Misuse.”\textsuperscript{19} Among other things, the gathered scientists called for focusing attention on the over-promotion of antibiotics, the worldwide usage of antibiotics without prescription, and their use in animal feeds; and Levy used the Statement as a springboard to the formation of the Alliance for the Prudent Use of Antibiotics, intending for the organization to serve as an explicitly international (the 31 members of its initial scientific advisory board came from 25 different countries) catalyst for efforts to confront antibiotic misuse and overuse. Levy’s efforts, while critical to the rise of an explicitly global focus on antibiotic usage and resistance (and helping to further stimulate the re-engagement of the WHO with antibiotic resistance and surveillance), were nevertheless limited by the lack of U.S. federal engagement with public health concerns throughout the 1980s.\textsuperscript{20}

By the late 1980s and early 1990s, however, Levy would find a key ally in Joshua Lederberg, who had won the Nobel Prize in 1958 for his discovery of bacterial genetic exchange, and who had coined the very term plasmid in 1952.\textsuperscript{21} Lederberg served as the head of the Rockefeller University in New York City at the height of the AIDS epidemic, becoming concerned that AIDS would not be the last of such coming plagues. He called on his country’s Institute of Medicine to convene a committee on emerging infections; and the ensuing 1992 report, which linked antibiotic resistance concerns to the larger emerging infections discourse, served as a truly catalytic factor in the ensuing global response to antibiotic resistance.\textsuperscript{22} At the same time, industry’s appreciation of antibiotics had changed. In the 1950s and 1960s, resistance had created markets and effectively fostered the development of antibiotics like the Beecham Group’s methicillin.\textsuperscript{23} By the 1980s, however, disenchantment with the commercial potential of such medicines had developed within the companies, further creating spaces for antibiotic reformers.

In this context, the WHO convened a series of working groups and meetings on antibiotic resistance throughout the 1990s, while European countries – amid the formation of the European Union — began
to take more aggressive measures with respect to antibiotic resistance, initially epitomized by the establishment of the European Antimicrobial Resistance Surveillance System (EARSS, now EARS-Net). Countries outside Europe could by 2001 draw on the WHO’s “Global Strategy for Containment of Antimicrobial Resistance” in designing their own efforts, at the same time that global efforts concerning HIV, tuberculosis, and malaria were scaling up.\textsuperscript{24}

Such momentum has persisted to this point, with multiple national efforts initiated to confront antibiotic resistance, and scattered bilateral or multilateral attempts rendered to harmonize efforts. The WHO, in 2014, provided its own first global report on antibiotic resistance surveillance\textsuperscript{25} and a Global Action Plan is being adopted in 2015. And yet, despite the WHO's reports, neither adequate funding nor the related implementation of suggested measures has followed. And despite successful political mobilization against antibiotic resistance, no formal global mechanism for harmonizing individual national efforts exists to this time. The globalization of antibiotic resistance discourse and efforts, slow to develop, still bears the imprints of its state-centered origins.

### This is, in many ways, a propitious time to consider a global framework addressing antibiotic resistance. Antibiotic resistance has been surfaced and politicized as a global concern mandating global coordination. Yet contemporary efforts will need to confront both the structural factors that impede the rational delivery of antibiotics worldwide, as well as legacies of heterogeneity, in order to confront this critical public health concern.

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### Historical Context to an Integrated Approach

What does historical reflection tell us about contemporary approaches to unite access, conservation, and innovation within a single global regulatory framework? Overuse and underuse represent two sides of the same coin, pointing to the structural and economic factors that impede the rational delivery of health care more broadly. The efforts of those working to rationally treat HIV, tuberculosis, and malaria — and their engagement with issues of access — have historically been separated from those working to confront antibiotic resistance more generally. Yet recent attention to antibiotic resistance in India has served to further focus attention on such structural factors; and those considering broader issues of antibiotic resistance, in both the developing world and the developed world, would do well to examine the biosocial approaches taken in addressing HIV, tuberculosis, and malaria.

With respect to conservation — and its grounding in surveillance and stewardship — the aspiration to a worldwide surveillance infrastructure guiding rational therapy is longstanding, dating back at least to the interest of the WHO in the 1950s. At the very least, history reminds us in this respect — as with calls for improved diagnostics — that merely surfacing the need for an intervention does not ensure the material investment in making that intervention a reality. Stewardship efforts, moreover, have had to confront differing notions of therapeutic autonomy in differing states and cultures, grounded in complex relationships between doctors and their patients, through which physicians in certain countries have long gained the trust of their patients through prescribing antibiotics, while resenting interference into this complex relationship from external regulators, managers, and insurance companies. Regarding antibiotics in agriculture, would-be reformers continue to confront powerful interests and lobbies, further pointing to the challenges facing those who would reform these policies.

Finally, with respect to innovation, there is a clear need for ongoing investment in new vaccines, diagnostics, and therapeutics. Yet we should be mindful of prior faith in technological fixes to antibiotic resistance, epitomized by early enthusiasm over methicillin in the 1960s. And there are historical ironies in contemporary discussions about lowering regulatory standards in order to speed new antibiotics to market. The present FDA clinical trial standards for pharmaceuticals, as described earlier, was constructed in the 1960s out of concern for poorly designed antibiotic studies; we should be wary of the downstream effects of weakening that regulatory machinery.

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