

# 9 *The role of civil society in tackling antimicrobial resistance\**

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## **The role of civil society: From public health to AMR**

For decades, civil society has served as a critical catalyst in the public health arena. Civil society groups have played a role in moving policy-makers and other stakeholders towards a new future, ensuring the right to access to essential medicines, and embracing the precautionary principle for environmental health risks. During the 1980s, organizations such as Health Action International (HAI) emerged onto the global policy scene, under the umbrella of Consumers International, to counter the pharmaceutical industry's promotion and pricing practices. The research and campaigns led by HAI and its allies resulted in increased public scrutiny of the marketing tactics used by the pharmaceutical industry for problem drugs, such as anabolic steroids used as appetite stimulants and vitamin tonics containing alcohol. Later, attention was drawn towards the impact of mark-ups on prices of medicines on their availability to populations worldwide (World Health Organization/Health Action International, 2008). This work contributed to international adoption of policies that ban direct-to-consumer advertising on prescription medicines. At the World Health Organization (WHO), these civil society organizations helped to shape the concept of the Essential Medicines List. At the country level, they also carried forward the WHO's Model Essential Medicines List by advocating and providing technical assistance towards the development and implementation of National Essential Medicines Lists, helping governments to secure affordable pharmaceutical prices. These initial efforts laid the groundwork for the access to medicines movement.

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The efforts made by civil society groups have increased public and policy-maker recognition of other health issues such as HIV/AIDS, non-communicable diseases, Ebola, tuberculosis, and tobacco use. Among these issues, civil society has played an active role in raising awareness on the necessity for rational use of antibiotics in reducing antimicrobial resistance (AMR) across the global north and south. During the 1980s, consumer organizations, such as HAI, the International Organization of Consumer Unions, the Medical Lobby for Appropriate Prescribing, and Oxfam, were already working on ending the promotion and marketing practices by multinational pharmaceutical companies, which targeted antibiotics among other pharmaceutical products in developing countries. These industry actions had contributed to the inappropriate use of these drugs and rising resistance (Kunin, 1993). Professional societies within the USA and Europe, such as the Infectious Diseases Society of America, the American Academy of Pediatrics, and Strama, developed updated antimicrobial treatment guidelines as well as stewardship programmes for physicians and other health care professionals to better conserve these life-saving drugs. In animal husbandry, Consumers International worked across countries to implement regulations around the nontherapeutic use of antimicrobials in food animal production and the rising levels of resistance in these products. In June 2000, Consumers International also provided a perspective at a WHO global consultation that focused on “general, overarching principles to reduce misuse and overuse of antimicrobials in animals intended for food” (World Health Organization, 2005).

In 1998, the WHO Member States already recognized AMR as a key global health issue and adopted a resolution at the 51<sup>st</sup> World Health Assembly that requested countries and the WHO to take action on research and development (R&D), access, and stewardship of antimicrobials across sectors (World Health Organization, 1998). In response to this mandate, the WHO put forward a Global Strategy for Containment of Antimicrobial Resistance in 2001 (World Health Organization, 2001). The Alliance for Prudent Use of Antibiotics had prepared an accompanying report compiling recommendations from groups around the world flagging the challenge of antibiotic resistance (Levy, 2010). However, the scheduling of the press conference to launch the release of this report could not have been more ill-fated as it coincided with the events of September 11, 2001, and thus never took place (Mack et al., 2011). Rekindling the WHO’s return to this issue would become

a priority for ReAct – Action on Antibiotic Resistance. Organized as a global policy network, the ReAct group formulated a Strategic Policy Program and met with WHO officials in support of the WHO’s Patient Safety Programme, which examines AMR and patient safety. Their efforts were well received and supported by internal champions within the WHO, like Dr David Heymann, then a WHO Assistant Director-General. These key leaders then developed an international consultation process leading to the WHO monograph, *The evolving threat of antimicrobial resistance: options for action* (World Health Organization, 2012a). Margaret Chan, the WHO Director-General, announcing the release of the report, memorably described the threat of AMR: “A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child’s scratched knee could once again kill” (Chan, 2012).

The WHO’s rekindled interest in AMR spurred others to follow, and global momentum quickly picked up pace with a number of key actions. The World Economic Forum highlighted antibiotic resistance in its *Global risks 2013* report (World Economic Forum, 2013). The World Health Assembly adopted a resolution in 2014, instructing the Secretariat to draft a Global Action Plan to combat antimicrobial resistance. Later the same year, the US President’s Council of Advisors on Science and Technology released a report on antibiotic resistance, timed with an announcement from the White House of a National Strategy for Combating Antibiotic-Resistant Bacteria. Harnessing this global momentum, civil society groups continued their efforts to reset the policy-making process across sectors. Organizations such as Médecins sans Frontières (MSF) and HAI focused on ensuring equitable access to antimicrobials and preventive vaccines while others, such as the Alliance to Save Our Antibiotics and Food Animal Concerns Trust, advocated for regulations curbing the nontherapeutic use of antimicrobials in food animal production. However, this mobilization was disjointed, with organizations working within their own sectors of human and animal health.

### Formation of the Antibiotic Resistance Coalition

Despite this, increased recognition of the One Health concept in AMR brought further awareness of the connections between using antimicrobials across human and animal health, as well as their impact on the

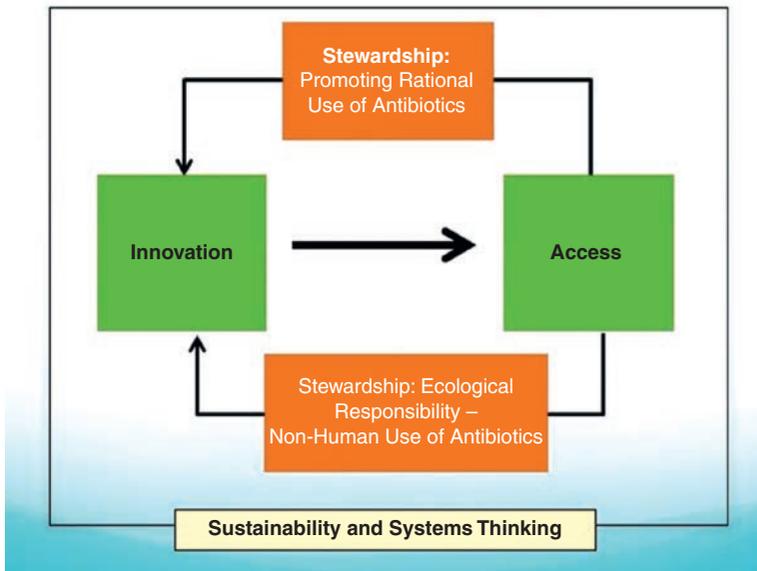
environment. In March 2013, the Strategic Policy Program of ReAct – Action on Antibiotic Resistance proposed the creation of an intersectoral coalition of civil society groups that would tackle antibiotic resistance in collaboration with key organizations. This led to meetings between ReAct and several civil society organizations on how best to unify work on the human and animal use of antimicrobials. In so doing, these organizations considered how AMR policy concerns intersected with their priorities.

While recent policy declarations had signalled growing recognition of the challenge of antibiotic resistance, most avoided the political challenges of tackling the tougher issues: standing up to pharmaceutical industry calls for premium pricing, extending market exclusivity and efforts to lower drug regulatory and safety standards. Civil society groups also sought fair returns for public investment; conservation of existing antibiotics; and halting nontherapeutic use of antibiotics for not only growth promotion, but also routine preventive use in food animal production. These issues were shared concerns across civil society groups.

In the process, the ReAct Strategic Policy Program developed a systems framework (Figure 8.1) to provide a unifying framework to these discussions:

- access to life-saving antibiotics is a global concern, not just one of neglected diseases endemic in low- and middle-income countries (Access);
- the way antibiotic drugs are developed and brought to market influences how accessible these drugs will be (Innovation);
- the practices that govern antibiotic use in health care delivery affect how long these drugs can remain effective for use (Stewardship–Health Care Delivery);
- the use of antibiotics in the food production system, particularly for nontherapeutic purposes, poses risks of cross-species resistance (Stewardship–Food Production System); and
- antibiotics entering the environment, from wastewater discharge in manufacturing to point source pollution from hospitals and farms, indicates the need for an ecosystem approach to tackling antimicrobial resistance (Reimagining Resistance: Sustainability and Systems Thinking).

This systems framework became the foundational architecture of building buy-in, consensus towards the launch of a new coalition on antibiotic resistance, and the development of shared principles that comprised the Declaration of Shared Principles across these civil society groups (Figure 9.1).



**Figure 9.1** Systems diagram of the challenge of antimicrobial resistance

*Source:* So, 2014.

Building on a planning meeting around the World Health Summit in 2013, ReAct and a Steering Group of civil society organizations undertook a six-month process to lay the groundwork for a new coalition. The results of this process culminated in a conference hosted by the South Centre, an intergovernmental think tank for developing countries based in Geneva, and organized by the civil society Steering Group. The Steering Group worked to identify key civil society partners, common ground for collective concern and action, and a strategy for the launch of an intersectoral coalition and a Declaration of Shared Principles. In addition to the series of Steering Group teleconference calls, the ReAct Strategic Policy Program fielded an online consultative questionnaire of civil society groups to elicit early feedback. The founding meeting was held before the 2014 World Health Assembly where Member States would consider the adoption of a WHO resolution to develop a Global Action Plan on AMR.

The Geneva conference laid out the policy landscape, the challenges ahead, and importantly, cross-sectoral linkages. The conference agenda was designed to allow for group discussions over the five pillar areas highlighted in Figure 9.1. Each pillar corresponds to potential common ground – Innovation; Access but Not Excess; Human Use

of Antibiotics; Non-Human Use of Antibiotics; and Sustainability and Systems Thinking. A drafting group emerging out of the Geneva conference undertook the writing of the Declaration on Antibiotic Resistance. The Declaration naturally coalesced around the pillars taken up at the conference. The drafting group hammered out the consensus over several weeks in the lead up to the World Health Assembly in mid-May. HAI announced the finalized Declaration and the launch of the Antibiotic Resistance Coalition during the debate over a World Health Assembly resolution calling for a Global Action Plan against AMR. Twenty civil society organizations from north and south, on both sides of the Atlantic, and across human and veterinary sectors, signed in support of the Declaration. These included key consumer organizations, such as Public Citizen, the Center for Science in the Public Interest in the United States, and the Centre for Science and the Environment in India, and global networks including HAI, the People's Health Movement, Third World Network, and the Universities Allied for Essential Medicines.

Notably, the Declaration affirmed a shared set of key principles and a commitment to safeguard the policy process from efforts that might masquerade as solutions to tackling antibiotic resistance. Its principles cut across sectors and call for:

- Realigning incentives in the health-care delivery system to support antibiotic stewardship;
- Curbing improper promotion and advertisement of antibiotics that might exacerbate inappropriate use of these drugs;
- Rethinking the metaphor of being at war with bacteria and instead to learn how to better live in harmony with the microbiome;
- Strengthening surveillance and transparency of antibiotic sales, use and resistance patterns;
- Eliminating the nontherapeutic use of antibiotics in producing food and encouraging the procurement of food products produced without nontherapeutic antibiotics by hospitals;
- Supporting incentives for pharmaceutical R&D for novel antibiotics and complementary technologies that delink a company's return on investment from volume-based sales;
- Opposing measures that undermine consumer safety by lowering clinical trial standards or place life-saving antibiotics out of affordable reach of those in need by extending monopoly pricing of drugs.

The Antibiotic Resistance Coalition (ARC) continues to be comprised of the original signatory organizations behind the Declaration. As part of the induction process into ARC, members are required to sign onto the Declaration on AMR principles and provide documentation of any potential financial conflicts of interest. A Nominating Committee of existing ARC members invites other aligned civil society organizations to join, and the ranks of the ARC have grown to include the Natural Resources Defense Council, the American Medical Student Association, MedAct, the Ecumenical Pharmaceutical Network, and the US Public Interest Research Group (PIRG). ARC serves as a platform for the member organizations to discuss key policy issues related to AMR, share organizational expertise across sectors and countries, and mount collective responses across policy forums, notably intergovernmental organizations such as the WHO and the UN.

Since its founding, the ARC has organized an annual WHO–NGO dialogue, a global teleconsultation that offers an opportunity for leading civil society groups to meet with key AMR leadership at the WHO to outline key concerns around ongoing policy processes. The dialogues are held strategically in advance of the World Health Assembly. These discussions allow civil society organizations, including those in developing countries, to engage directly with policy-makers on key upcoming decisions. In April 2015, ARC held its first WHO–NGO dialogue with the WHO Assistant Director-General Keiji Fukuda and AMR Coordinator Charles Penn. This dialogue focused on the draft Global Action Plan on AMR in advance of its discussion and anticipated adoption at the World Health Assembly in May 2015. Here, civil society put forward interventions on technical and financial support for implementing the Global Action Plan, the challenges of innovation, access, and rational use of antimicrobials, the intersectoral concerns over the use of antimicrobials in agriculture, and how trade treaties influence the use of these drugs in food products, and the need for accountability, monitoring, and evaluation. Subsequent WHO–NGO dialogues, held again in advance of the World Health Assembly, have touched on the implementation of the Global Action Plan including the global development and stewardship framework, the WHO’s role in supporting the creation and implementation of national action plans, and the UN High-Level Meeting on Antimicrobial Resistance held in September 2016. Each year, full summaries of the teleconsultation are

published, providing a record and roadmap of the interventions made by ARC members and allies (Antibiotic Resistance Coalition, 2017).

As AMR discussions unfolded at the United Nations, the ARC has played a key role in advocating for the coalition principles to be reflected within the Political Declaration from the UN High-Level Meeting on Antimicrobial Resistance. Leading up to the negotiations around the Political Declaration, ReAct co-hosted a UN briefing on AMR along with the Dag Hammarskjöld Foundation and the UN Secretary-General's "Every Woman Every Child" initiative. Here, ARC members and civil society allies including ReAct, Food Animal Concerns Trust, and MSF delivered interventions outlining specific points around innovation, access, and stewardship across sectors to Member States and UN agencies in order to influence upcoming negotiations around the Political Declaration on AMR. The findings of this discussion called for the final UN Political Declaration on AMR to ensure broader interagency accountability beyond the tripartite collaboration of the WHO, the Food and Agricultural Organization (FAO), and the World Organisation for Animal Health (OIE) to the UN level. Additionally, in advance of the UN High-Level Meeting on AMR, ARC members and allies met with country missions in New York and Geneva to call for parity between human and animal health. These points were reflected in the final document adopted during the High-Level Meeting on AMR at the UN General Assembly in September 2016.

## Innovation

The need to bring new antibiotics to market gave momentum to growing policy-maker concerns over drug resistance. Civil society has played a key role in triggering this policy concern by documenting the dearth of novel antibiotics in the R&D pipeline, rekindling this discussion at the WHO and in other key forums, and connecting this to larger concerns over innovation and access to essential medicines. The lens of antibiotic resistance presented an opportunity to revisit policy issues from a different vantage point. *Access*, but not *excess* meant striking the right balance in stewardship of these resources. This would also require aligning the economics with the biology of drug resistance. The traditional business model of drug companies earning returns on investment from volume-based sales fails to do this. Moreover, the need for life-saving antibiotics is not limited to low- and middle-income countries, which places these

issues beyond the exceptionalism or special regard argued for neglected diseases that primarily affect the world's poorest populations.

Almost all novel classes of antibiotics that were brought to market in recent decades were discovered before the 1990s. This faltering R&D pipeline became the focus of civil society attention. An early study focused on the shortfall of antibiotic drug candidates in the pipeline of multinational drug firms (Spellberg et al., 2004). Going further, ReAct partnered with the European Medicines Agency and the European Centre for Disease Prevention and Control to produce an analysis that examined all known antibacterial drug candidates in the R&D pipeline. Among these candidates, the study found not a single drug with a novel mechanism of action targeting Gram-negative pathogens (Freire-Moran et al., 2011).

This evidence supported the Swedish European Union (EU) conference, "Innovative Incentives for Effective Antibacterials" in 2009 and the establishment of the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) with the United States. With Swedish government support, ReAct convened in 2010 an international conference "The Global Need for Effective Antibiotics: Moving Towards Concerted Action" to follow up. The conference notably brought existing public-private partnerships together to discuss "Reengineering the Value Chain for Research and Development of Antibiotics: Applying Lessons from Neglected Diseases". To facilitate this discussion, the conference featured a panel that included the TB Alliance, India's Open Source Drug Discovery Initiative, and the Drugs for Neglected Diseases Initiative (DNDi). Prior to the conference, ReAct's policy team held discussions with the Director-General of the Swedish pharmaceutical industry trade association, Richard Bergström (later the Director-General of the European Federation of Pharmaceutical Industries and Associations). At the conference, Bergström acknowledged in a report (Braine, 2011) that:

[i]ncentives that separate the financial return from the use of a product are the only way to change this behavior. Intelligent pull incentives, such as advance commitments and prizes, provide financial rewards to the developer that are not based on the volume of use of the novel antibiotic.

Following the conference, proceedings focused on new business models for R&D of novel antibiotics and echoed this conclusion to delink a

company's return on R&D invested in a drug from its volume-based sales (So et al., 2011).

The concept of delinkage has its roots in debates about ensuring access to medicines. Delinkage represented an approach, advanced by civil society, that promised fairer drug pricing and returns on public investments in R&D. This is typically accomplished by divorcing the drug company's return on investment from R&D from the price of the drug. Back in 2004, Jamie Love of Knowledge Ecology International and Tim Hubbard (Hubbard & Love, 2004) envisaged that countries might commit a small percentage of their gross domestic product to global health R&D in exchange for lifting Trade-Related Aspects of Intellectual Property Rights requirements on World Trade Organization (WTO) members to comply with patent protections that blocked the market entry of generic medicines.

This concept of delinkage became a key principle in the WHO's Consultative Expert Working Group on Research and Development report in 2012 (World Health Organization, 2012b). With respect to antibiotic innovation, delinkage also has to separate the return on R&D investment from volume-based sales, or in other words, the price and quantity of antibiotics sold (So & Shah, 2014). Increasingly, delinkage has entered policy discussions on both sides of the Atlantic, from Chatham House to the US President's Council of Advisors on Science and Technology (Clift et al., 2015; US President's Council of Advisors on Science and Technology, 2014). Civil society also actively supported its inclusion in the WHO's Global Development and Stewardship Framework on AMR and the UN Political Declaration on AMR.

The call for greater support of drug development came not only from the pharmaceutical industry, but also from the public sector. The UK Review on AMR proposed that \$16 billion would be required to reinvigorate the R&D pipeline, assuming that 15 new antibiotics – including four breakthrough drugs – would come to market over the next decade (O'Neill, 2016). The Boston Consulting Group's report for the German Ministry of Health recommended that the investment for each commercialized product would amount to \$1 billion, plus \$200 million per year for a Global Research Fund to develop the infrastructure for developing promising projects, and \$200 million annually for a Global Development Fund to support all stages of clinical development (Stern et al., 2017).

By January 2016, the Davos Declaration by Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance signalled the industry's commitment for "appropriate incentives (coupled with safeguards to support antibiotic conservation) for companies to invest in R&D", "pricing of antibiotics [that] more adequately reflects the benefits they bring", and "novel payment models that reduce the link between the profitability of an antibiotic and the volume sold" (International Federation of Pharmaceutical Manufacturers & Associations, 2016a). Later that year, a subgroup of these companies developed an "Industry Roadmap for Progress on Combating Antimicrobial Resistance". In this roadmap, the industry noted that the "receipt of an adequate Market Entry Reward will greatly facilitate global access and stewardship for that product" and "progress incentives, such as lump-sum payments, insurance models and novel IP [intellectual property] mechanisms, that reflect the societal value of new antibiotics and vaccines and will attract further investment in R&D" (International Federation of Pharmaceutical Manufacturers & Associations, 2016b). However, the Roadmap fails to mention delinkage as such.

By contrast, MSF has called for full delinkage between a company's return on R&D investment from price and volume of the drug sold (Sanjuan, 2017). ReAct has not only advanced the concept of delinkage, but also has questioned whether the emphasis on market entry rewards fails to address adequately the key scientific bottleneck in the R&D pipeline (So et al., 2017). ReAct's Strategic Policy Program put forward proposals for collaborative R&D approaches, two of which Regional WHO Offices advanced to the top 22 proposals for global consideration as part of the WHO's Health R&D Demonstration projects. One proposal focused on building a diagnostic innovation platform to address antibiotic resistance, while the other concerned establishing a drug discovery platform for sourcing novel classes of antibiotics as public goods. These civil society positions on AMR derive from their previous advocacy on access to medicines for treatment of HIV/AIDS, tuberculosis, malaria and other neglected diseases.

However, AMR also moved policy discussions beyond the exceptionalism of neglected diseases. Product development partnerships (PDPs) had focused on neglected diseases, the treatment of which posed little competition to industrialized country markets. These PDPs had successfully recruited in-kind contributions from industry; however, such approaches were considered part of the exceptionalism of non-paying

markets. By contrast, AMR affects patients everywhere in the world, and new approaches to innovation in this area could not be viewed as exceptionalism. Civil society's efforts brought to the fore what the industry was slow in acknowledging – 30 years of a faltering antibiotic R&D pipeline demanded public sector intervention.

The WHO laid important groundwork for a public–private partnership to support antibiotic innovation. A series of policy discussions with stakeholders would lead to the launch of the Global Antibiotic Research and Development Partnership (GARDP) as a project within the DNDi. Civil society played an important role, from advancing a range of potential proposals to supporting the WHO's own concept of a publicly-financed global consortium to tackle antibiotic resistance (World Health Organization, n.d.). Notably among PDPs, DNDi, which had received start-up funding from MSF, has worked to build access and capacity in countries where these most neglected diseases are endemic, and has included key research institutions and government ministries from low- and middle-income countries on its governance board. GARDP, in the spirit of DNDi's previous work, has also held consultations with civil society groups as it has begun to chart its course in developing new antibiotics.

Tackling AMR means more than simply bringing new drugs to market or making existing ones more available to those in need. It involves decreasing the selective pressure on existing antibiotics through improved diagnostics and vaccines. Civil society has actively worked on both. MSF and ReAct worked with the Foundation for Innovative New Diagnostics, a product development partnership focused on diagnostics, and the WHO to bring experts together to discuss biomarkers that might distinguish bacterial from other infectious causes of acute fever (World Health Organization et al., 2015). The MSF Access campaign waged a global effort to lower the price of the pneumococcal conjugate vaccine, manufactured by Pfizer and GlaxoSmithKline (GSK). MSF's "A Fair Shot" campaign argued that with one million children dying each year from pneumonia, Pfizer's and GSK's pricing of the vaccine limited the possible reach of this potentially life-saving intervention (Médecins sans Frontières, n.d.) (Figure 9.2). In fact, if universal coverage with pneumococcal conjugate vaccine had been achieved in the 75 countries where vaccination rates fell short of 80%, nearly half the days of antimicrobial therapy to treat children less than 5 years old for pneumonia could have been averted (Laxminarayan et al., 2016) (Figure 9.2).

## HERE'S WHY YOU SHOULD CARE



Figure 9.2 “A Fair Shot” pictograph by the Médecins sans Frontières Access Campaign

Source: Médecins sans Frontières, n.d.

### Access not excess

As proposals to invigorate the antibiotic pipeline began to emerge, questions loomed large on how access as well as stewardship of these drugs might be achieved. Civil society had been advancing the idea of full delinkage. However, other proposals were put forth and ran counter to these full delinkage models. These partial delinkage models would still apply close-to-marginal cost pricing and controls over quantity in low- and middle-income countries, but would not apply the same to industrialized country markets. Civil society had opposed such proposals in forums, ranging from DRIVE-AB to the UK Review on AMR (ReAct, 2017). In their analysis of the final recommendations from the UK Review on AMR, MSF expressed concern that market entry rewards were only seen as a way to delink volume, but not price of the product. MSF opposed this reframing of delinkage as a tool that ensures stewardship, but did not address affordable access (Médecins sans Frontières, 2016).

In the USA, consumer groups, including ARC members, and allies, including Public Citizen and MSF, have squared off with industry, the Infectious Diseases Society of America, and the Pew Charitable Trusts over

a number of incentive proposals introduced as legislation in Congress. In response to the Generating Antibiotic Incentives Now (GAIN) Act, which awards extended data exclusivity to newly approved antibiotics, consumer groups noted how such monopoly protections give companies an incentive to sell more of the new drug. Instead of providing upfront investments in R&D, such incentives just risk imposing higher drug prices on consumers (So & Weissman, 2012). Rationing antibiotics by monopoly pricing will not ensure appropriate use by doctors or patients.

These groups and others, including professional societies, also expressed concern over proposals, such as the 21<sup>st</sup> Century Cures Act, to lower regulatory standards for approval of new antimicrobials. The 21<sup>st</sup> Century Cures Act weakened the Food and Drug Administration's (FDA) drug regulatory protections by replacing gold standard reliance on clinical trials with "adaptive" pathways and surrogate end-points. In a post in the *Health Affairs Blog*, members of the National Physicians Alliance FDA Task Force noted that lowering regulatory standards would incentivize the development of more expensive, me-too drugs of "marginal or ultimately insignificant effectiveness" (Molchan et al., 2015). Civil society has also expressed concern over proposals for transferrable exclusivity extensions allowing manufacturers facing patent expiry to acquire additional monopoly price protections (Alas, 2017; Seabury & Sood, 2017).

Besides countering proposals that would hinder affordable access to novel antimicrobials or other complementary technologies, civil society has advocated for a set of core principles established in the access to medicines movement and the Antibiotic Resistance Declaration. These core principles include delinkage, affordability, availability, effectiveness and quality. Civil society has carried forward these principles – initially adopted as part of the recommendations of the WHO's Consultative Expert Working Group (CEWG) on R&D – to other intergovernmental policy forums in an effort to create coherence around these processes. In November 2015, the UN Secretary-General announced the creation of the High-Level Panel on Access to Medicines with the mandate of examining proposals and recommending solutions that would address the policy incoherence between inventors and trade rules, on the one hand, and international human rights law and public health, on the other. Seeing this as an opportunity to shape the language of global governance and demonstrate an alternative vision for the future, civil society quickly became activated.

Civil society put forward over half of the almost 200 contributions towards the High-Level Panel's recommendations, while representatives from organizations such as MSF, Oxfam, the Health Global Access Project and Lawyers Collective served as part of the Expert Advisory Group to the High-Level Panel. In the panel's final report, AMR was highlighted as a case-study with the recommendation that innovation models applying delinkage be pursued as a way to ensure sustainable access to novel antimicrobials. This inclusion of AMR as a specific case study and the accompanying call for delinkage, rather than market-based models, again demonstrates how the issue has become an item on the global health policy agenda because of support from civil society groups.

As part of implementing the Global Action Plan on AMR, the WHO Director-General was mandated at the 68th World Health Assembly (2015) to develop options for a global development and stewardship framework on AMR. As the WHO and its partners within the tripartite collaboration began to develop this framework, civil society called for the CEWG principles, including full delinkage from both price and quantity, to be reflected in the policy documents. ARC members and allies including the South Centre, Third World Network, MSF, and ReAct urged Member States and the WHO to safeguard access to antimicrobials and other complementary technologies such as vaccines and diagnostics. As the consultative process has continued, these principles have been incorporated into key policy documents reflecting civil society's success in shaping the policy language on these points. Through continued efforts by civil society, these principles were also incorporated into the Political Declaration adopted at the UN High-Level Meeting on AMR.

As reports of rising resistance to last-line antimicrobials continued to emerge around the world, so did the urgency to ensure stewardship to preserve the effectiveness of these life-saving drugs for those in need. The conservation of these drugs must also be balanced by the need for appropriate access – access, but not excess. The lack of access to antibiotics remained a serious concern, particularly in developing countries. Treatable infectious diseases are estimated to claim the lives of 5.7 million people a year (Daulaire et al., 2015). Additionally, as civil society has pointed out, three quarters of deaths from community-acquired bacterial pneumonia could be averted if antibiotics were universally available to children under 5 years old (Laxminarayan et al., 2016). This lack of access, however, is not just from shortages or stockouts of these medicines, but also from drug resistance rendering

these antimicrobials ineffective. Resistance to first-line antibiotics has been estimated to result in over 56 000 neonatal deaths in India and over 25 000 neonatal deaths in Pakistan (Laxminarayan & Bhutta, 2016). According to UNICEF, pneumonia and diarrhoea account for more than one out of every four children dying under the age of five. Yet, fewer than a third of children with suspected pneumonia received antibiotics. Additionally, while fewer than four in 10 children receive treatment with oral rehydration for diarrhoea, they instead receive inappropriate treatment with antibiotics (UNICEF, 2016). The key is to ensure access, but not excess.

“Access but not excess” became an important refrain advanced by civil society, from its contribution to the Lancet Infectious Diseases Commission to the WHO–NGO dialogue discussions. Concerns over underuse, not just overuse, parallel the public statements made by low- and middle-income delegations such as India and Brazil. At the 70<sup>th</sup> World Health Assembly in May 2017, Dr Lav Agarwal of the Permanent Mission of India noted that India objects to any “unbalanced emphasis” on a Stewardship Framework focused on limiting access to antibiotics as opposed to R&D and affordable access to new and existing antibiotics and diagnostics (Agarwal, 2017). In October 2016 at the WHO/WIPO/WTO Joint Technical Symposium on AMR, Dr Lucas Vinícius Sversut of the Permanent Mission of Brazil stressed that “avoiding unnecessarily restrictive policies is particularly important for developing countries, where the lack of access to antimicrobial medicines kills more than the resistance itself” (Sversut, 2016).

Enlisting health care professionals in antimicrobial stewardship is critical. In the United States, Health Care Without Harm and the PIRG have also engaged health professionals around both human and animal use of antimicrobials. Working across hospitals, Health Care Without Harm has developed a number of procurement guidelines for purchasing meat and seafood products raised without the nontherapeutic use of antibiotics (Health Care Without Harm, 2015). Going further, regional Healthy Food in Health Care programmes were established to allow for collaborative efforts across hospitals and institutions locally to boost the market demand for meat raised without routine antibiotics. The organization also formed the Clinician Champions in Comprehensive Antibiotic Stewardship (CCCAS) Collaborative as an initiative to raise awareness among health-care professionals on the link between antibiotic use in agriculture and AMR. Along with increased awareness, this

should contribute towards the promotion of policies for the judicious use of these therapies across sectors (Health Care Without Harm, 2015). In collaboration with the Pediatric Infectious Disease Society and Sharing Antimicrobial Reports for Pediatric Stewardship group, Health Care Without Harm provides tools for clinicians to take local action at their home institutions to change their purchasing practices. CCCAS members are also trained to relay their professional experiences on the impact AMR has had on their patients and public health as a way to promote policy action for stewardship. PIRG has also mobilized over 40 000 health care and public health professionals through its Health Professionals Action Network to call on major restaurant chains to source meat products raised without the routine use of antibiotics and to adopt public policies with this commitment (US Public Interest Research Group, n.d.). Through this network, clinicians are also given the opportunity and support to voice their experiences with AMR to policy-makers.

### **Non-human use of antibiotics**

Unlike most other areas of access to medicines, antimicrobial resistance has a One Health dimension. Although challenging to quantify, a significant proportion of all antibiotics, by volume, are sold for use in agriculture and aquaculture. In the US, this figure approaches 70% (US Food and Drug Administration, 2015). This situation has created an unusual convergence of interests across civil society movements. Traditionally, groups working on nutrition, the environment, animal welfare and worker justice have focused on the food system. Their work involves a quite different set of stakeholders – agribusiness concerns and those more focused on the FAO and OIE.

The use of antibiotics to enhance productivity in food animal production goes back decades. In the interval, livestock production has undergone growing intensification, reliant on practices requiring greater antibiotic use. Between 2010 and 2030, antimicrobial consumption in food animal production is predicted to rise by 67%. Two thirds of this increase can be traced to the increase of animals in food production, and a third, to the shift towards more intensive farming operations (Van Boeckel et al., 2015). Antimicrobials have an appropriate role in treating diseased animals, but a significant part of what is used for food animal production is nontherapeutic. Civil society groups working to curb the unnecessary use of antibiotics in food animal production consider

therapeutic use as treatment when there is a diagnosis of disease. The use of antibiotics for growth promotion – to reduce losses in production or increase weight gain – would thus be considered nontherapeutic. In Europe, bans on the use of antimicrobials for growth promotion in food animal production in 2006 did not curb the sales of antimicrobials critically important for human medicine. Only when further measures were taken to restrict the routine preventive use of these antibiotics, as in Denmark, did antibiotic use decrease.

For these groups, nontherapeutic use extends to routine preventive use of antibiotics. In a report by the Alliance to Save Our Antibiotics (2016), Cólín Nunan observed that:

The shocking overuse of farm antibiotics shown by these data is a result of the continued failure by most countries to ban routine preventative mass medication in intensive farming. Spain now uses 100 times more antibiotics per unit of livestock than Norway, 80 times more than Iceland and 35 times more than Sweden. The main reason for the difference is that Spain, like most of Europe, allows routine mass medication, whereas the Nordic countries do not.

He further notes that to meet the UK Review on AMR's target of 50 mg of antibiotic per kilogram of livestock, Europe would need 65 years to achieve this goal starting at 152 mg/kg and reducing use at the current rate of 2% per year.

In the United States, the Food and Drug Administration (FDA) brought therapeutic uses of antibiotics in food animal production under the supervision of veterinarians. It also successfully obtained agreement from the veterinary drug manufacturers producing medically important antibiotics to remove voluntarily indications on their products for growth promotion or improving feed efficiency. This approach could readily be implemented in a country where there are only 26 manufacturers (Food and Drug Administration, 2013). However, Keep Antibiotics Working, a coalition of US-based groups, argued that such measures fell short because it did not ban the use of antibiotics for routine disease prevention (Keep Antibiotics Working, 2014). The FDA acknowledged civil society's "concern that drug manufacturers may promote extra-label production uses for products approved only for therapeutic use, thereby undermining the spirit and intent of [agency guidance]" (Hopkinson, 2014). In the lead up to the implementation of this agreement between

veterinary drug manufacturers and the FDA, Keep Antibiotics Working pointed to examples of advertising from Novartis and Elanco who were still touting the use of their drugs for growth promotion (Zuraw, 2014).

Despite the fact that over 10% of the world's antibiotics in food animal production are used in the US, policy-makers in that country have moved much more slowly than policy-makers elsewhere to curb nontherapeutic use of antibiotics. Failing to make significant headway in changing US government policy, key civil society groups took up a different strategy. These groups included the Consumers Union, PIRG, the Center for Food Safety, Friends of the Earth, the Natural Resources Defense Council (NRDC) and the Food Animals Concerns Trust. Together, they called upon the country's largest restaurant chains to source their food from animal products produced without the routine use of antibiotics. Their demands were threefold (NRDC, 2015):

- 1) Immediate action to end the routine use of antibiotics important for human medicine.
- 2) A time-bound action plan to phase out any routine use of antibiotics across the supply chain.
- 3) The adoption of third-party auditing and verification of compliance with the antibiotics use policy, implementing and bench-marking results to show progress in meeting the goals described above.

The campaign has reached a larger scale in recent years. Targeting *Yum! Brands*, the conglomerate owner of KFC, Pizza Hut and Taco Bell, PIRG canvassers went door-to-door, gathering over 475 000 petition signatures. This generated thousands of calls to KFC customer service lines. PIRG's "KFC Save ABX" campaign resulted in hundreds of social media actions directed at the company, particularly by young people whom KFC had been targeting to rebrand its appeal.

Targeting Subway's employees, NRDC also commissioned a billboard outside the company headquarters that read "Is Subway Buying Meat Produced with Antibiotics?" A few days later, the company added to its website:

Our commitment to serve high quality, affordable food to our customers has always been a cornerstone of the SUBWAY brand. We support the elimination of sub-therapeutic use of antibiotics. Elimination will take time and we continue to work with our suppliers to reach that goal (Brook, 2015).

As with public-facing brands, these restaurant chains have proved sensitive to consumer pressure and have begun to respond. The consumer groups created a public scorecard grading the top 25 companies on the US market. In each of the first three years, the *Chain Reaction* report has registered significant gains. Fourteen of these companies have begun to address limiting antibiotics in their supply chain. These initial steps have largely occurred in the poultry supply chain. Commitments to remove routine use of antibiotics in pork and beef supplies have lagged behind. Despite this, Chipotle and Panera have led with exemplary policies while Subway plans to address pork and beef, but on a much longer timeline (Friends of the Earth, 2017). Most of these commitments though are limited to US restaurants and franchises. However, in August 2017, McDonald's announced that it would meet its goal of serving broiler chicken not treated with antibiotics a year ahead of schedule in the USA. Updating its "Vision for Antimicrobial Stewardship for Food Animals", McDonald's plans to extend this commitment to eliminate the use of highest priority critically important antibiotics from its poultry supply chain globally. It will carry this out stepwise between 2017 and 2027 (McDonald's, 2017).

Other groups have targeted procurement efforts at different points in the supply chain. For example, Health Care without Harm's "Healthy Food in Health Care" programme draws upon the purchasing power of health-care institutions to advance sustainable food system practices. Partnering with over 1 000 hospitals across North America, Healthcare without Harm has worked to shape procurement policies in the health care sector to support goals, such as sourcing food animal products raised without the routine use of antibiotics. School Food FOCUS and the Pew Charitable Trusts developed the Certified Responsible Antibiotic Use standard for chicken sold to institutional purchasers, which disallows the use of "antibiotics with analogues in human medicine routinely or without clear medical justification" and requires third-party certification to audit the supply chain for compliance (USDA, n.d.; Antibiotic Resistance Action Center, 2016). NRDC supported the Urban School Food Alliance, which includes six of the largest city school districts in the USA (New York City, Dallas, Orlando, Chicago, Los Angeles, and Miami-Dade), in its efforts to adopt the Certified Responsible Antibiotic Use Chicken policy. New York City's school system ranks as one of the country's largest institutional providers of meals, second only after the Department of Defense, and serves 860 000 meals per day.

Similar efforts can also be seen in non-western countries. In the Republic of Korea, the Ministry of Agriculture, Food, Forestry & Fisheries began to phase out the routine use of antibiotics in commercial compound feed in 2003 (USDA Foreign Agricultural Service, 2011). After initially reducing the number of antibiotics permitted in commercial compound feed from 53 to 25 in 2005, the process continued until all remaining antibiotics were removed by 2011. At a UN briefing on AMR, co-organized by the UN Secretary-General's "Every Woman Every Child" Initiative, the ReAct Network and the Dag Hammarskjold Foundation, Yong-Sang Kim (Director of Animal Health Management Division for the Ministry) acknowledged the important role of consumer groups in supporting these policy changes (Figure 9.3).

As the global dialogue has unfolded on AMR, the WHO's work with its sister intergovernmental agencies, notably the FAO and OIE, has grown. Codex Alimentarius, whose work is supported as part of the Joint FAO/WHO Food Standards Programme, has also received attention from



Figure 9.3 Dutch Minister of Health, Welfare and Sport, Edith Schippers, poses for photo with US Public Interest Research Group at the 2016 UN General Assembly

Source: Austin Donohue, US Public Interest Research Group (PIRG), September 2016.

the civil society as it examines the standards, guidelines and codes of practice affecting the use of antimicrobials in food production. Codex's role as the key organization in setting trade rules for food safety as an organization is recognized by the World Trade Organization's Sanitary and Phytosanitary Agreement. Several of those engaged in civil society actions on AMR in the USA have represented consumer interests on these issues before WHO expert committees, such as the Advisory Group on Integrated Surveillance of Antimicrobial Resistance, or as part of Consumers International's delegation before the Codex Alimentarius Commission. The Antibiotic Resistance Coalition has also channelled civil society concerns into the public consultation process held by the UN Interagency Coordination Group on AMR and by the Tripartite Monitoring and Evaluation framework on indicators to benchmark progress on AMR. Of particular importance, ARC has sought to be inclusive of civil society groups from low- and middle-income countries.

### **Sustainability and systems thinking**

From its outset, the Antibiotic Resistance Coalition recognized the importance of sustainability and systems thinking in civil society's work on AMR. It was one of the pillars of the Antibiotic Resistance Declaration, and all corners of the coalition approach sustainability from differing vantage points – economic, environmental and cultural.

Civil society has focused on how to ensure the long-term sustainable access to antibiotics. This requires ensuring fair returns on R&D investment, affordable pricing of antibiotics, and effective stewardship such that these products can have lasting value in human medicine. From an economic vantage point, the concept of delinkage seeks to unify these three goals. The emergence of a product development partnership committed to such goals could be a game changer in how new models of innovation become piloted.

In addition to human and animal health, the third part of the One Health triangle addresses the role and impact of AMR on the environment. A growing number of publications document wastewater contamination with antibiotics, beginning with the manufacturing plants producing active pharmaceutical ingredients of these life-saving drugs. The antibiotic effluent from these plants has reached levels toxic to local life forms, but has also resulted in inducing drug-resistant pathogens in the environment. A series of reports from the Changing Markets

Foundation exposed these polluting practices among Indian and Chinese drug manufacturing plants, where much of the world's drug production occurs. Amplifying a recommendation from the UK Review on AMR, these reports also called for those buying generic antibiotics to consider the environmental track record of the manufacturers from which the drugs are sourced in making procurement decisions (Changing Markets et al., 2016).

Under the umbrella of the Antibiotic Resistance Coalition, other civil society groups have discussed how to address the point sources of antibiotic pollution into the environment. The motivations of industry efforts to reduce pollution from generic manufacturing plants in India and China were also considered. The question has also been raised as to why the same industry groups are not equally concerned about the likely far greater point source pollution posed by antibiotic use in agricultural run-off and hospital waste discharge. Are some multinational firms looking for an advantage in a competitive market, or are they truly concerned about the environmental contamination posed by the production and use of antibiotic drugs?

The 2016 Davos “Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance”, signed by over 100 companies, makes a brief mention of support for measures to curb antibiotic effluents into the environment (IFPMA, 2016a). Later that year, a far smaller number of companies signed the “Industry Roadmap for Progress on Combating Antimicrobial Resistance” (IFPMA, 2016b). The industry roadmap calls for several measures to mitigate the environmental impact from the production of antibiotics, but remained silent on the environmental impact from use of antibiotics. Most antibiotic residues are clearly not discharged from manufacturing plants, but rather from hospitals and farms.

Tackling this environmental discharge, Healthcare without Harm has begun to examine the waste management practices of hospitals. In lieu of medical waste incineration, the organization has identified no-burn technologies as part of an inventory of safer solutions (Emmanuel & Stringer, 2007). The Centre for Science and Environment (CSE) in Delhi has looked more broadly at how to integrate animal and environmental aspects into the development of National Action Plans on AMR in developing countries. With participants from 18 countries, the CSE organized a workshop that shared challenges and best practices in addressing surveillance and responsible use of antibiotics in food

animal production and in the environment (Centre for Science and Environment, 2017).

Going further, the environment can also shape the response to the challenge of AMR. From its founding in 2005, ReAct has sought to go beyond the “war metaphor” in addressing AMR. Not long after, an Institute of Medicine report, *Ending the War Metaphor: The Changing Agenda for Unraveling the Host–Microbe Relationship*, described the rising tide of new pathogens and the need for a new paradigm, one that:

incorporates a more realistic and detailed picture of the dynamic interactions among and between host organisms and their diverse populations of microbes, only a fraction of which act as pathogens ... The time has come to abandon notions that put host against microbe in favor of an ecological view that recognizes the interdependence of hosts with their microbial flora and fauna and the importance of each for the other’s survival. Such a paradigm shift would advance efforts to domesticate and subvert potential pathogens and to explore and exploit the vast potential of nonpathogenic microbial communities to improve health (Forum on Microbial Threats, Board on Global Health, and Institute of Medicine, 2006).

Taking a cultural approach, ReAct Latin America has rooted their call for holistic solutions that address the interconnected relationship of bacteria and humans in the indigenous peoples’ concept of *sumak kawsay*. An ancient Quechua phrase, *sumak kawsay* refers to “good living” or the “good life”, living in harmony with ourselves, our community, and nature. Closely aligned to these efforts, ReAct also supported the *Microbes and Metaphors* project, in which a dialogue among scientists, artists and activists took place. Those involved in the project have raised important questions about the shortcomings of the biomedical paradigm. The editors of a volume of their collected works argue:

One of the main reasons for this lack of progress in dealing with the phenomenon of “resistance” seems to be the flawed “war metaphor” which shapes the way antibiotics are used against pathogenic bacteria ... even more fundamentally we need to ask whether it is productive at all to constantly frame questions about the microbial world in an anthropocentric manner without considering the breathtaking diversity and even aesthetic beauty of the microbial world? (Sivaraman & Murray, 2015).



**Figure 9.4** Book on microbes by children for children from ReAct Latin America

Source: ReAct, n.d.

From this corner of civil society, they draw inspiration from artists and ask “Can artists, sensitive to the ecological processes that govern all life forms, help us frame our questions in a better manner or gather new insights where our stale words fail us?” (Figure 9.4).

## Conclusion

Just as civil society catalysed global attention over monopoly pricing of patented HIV/AIDS drugs, new civil society actors have redirected attention from rational use to the dearth of novel antibiotics in the R&D pipeline. Rekindling attention to AMR at the WHO contributed to the policy momentum that brought the issue to the world stage. This was supported by a Global Action Plan and a UN Political Declaration. AMR, by its nature, demands an intersectoral response. This gave impetus to efforts to create an intersectoral alliance, the Antibiotic Resistance Coalition, which brought together a number of civil society

groups unified by shared principles. Civil society organizations have successfully introduced the concept of delinkage into the policy vernacular and mobilized consumer pressure on major restaurant chains to source food animal products raised without routine use of antibiotics. This work is remarkable because of the complexity of the AMR issue, its intersectoral nature, and the fact that its victims do not readily identify themselves with this shared global health challenge. While ReAct's vision of ensuring a future free from the fear of untreatable infections is years away, the remarkable richness of the contributions that civil society has made to the policy discussions and debates over AMR offers a useful compass for future policy-making.

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