



# Antimicrobial Resistance The Role of Regulation

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# FOREWORD



Antimicrobial resistance, or AMR, is one of the most complex and urgent issues facing the world today.

Drug-resistant infections already contribute significantly to mortality and morbidity worldwide. If we fail to act soon, by 2050 AMR could lead to more deaths each year than currently caused by cancer. But this is not only a human health issue. Unchecked, AMR will have devastating consequences on the global economy, food security and agricultural livelihoods, and will undoubtedly jeopardise the achievement of the Sustainable Development Goals.

A complex, multi-sectoral issue requires a multifaceted response. One component of this response is regulation. Concerted action from around the world has brought us some real triumphs in this area, the peak of which was 193 Member States signing up to the

UN political declaration on AMR in 2016. But clearly commitments need to be followed up with tangible action.

Regulation can promote policy implementation by enabling the right incentives and disincentives. Take industry, for example. Regulation can be used to push industry to take measures to control the amount of active pharmaceutical ingredient that companies release into waterways. On the other hand, harmonising regulatory pathways for new drugs could incentivise industry to bring new products to market.

There is no 'one size fits all' when it comes to regulation to address AMR – it must be tailored to different country settings, sectors and stakeholders. As we look to strengthen the governance of AMR globally, regulation is a key tool in our toolbox.

I was delighted when UCL decided to convene a workshop on these issues, and was pleased to discuss them, and more, with a broad range of stakeholders in December 2018. I very much look forward to continuing this conversation and exploring innovative ways of mitigating this escalating global threat.



**Prof. Dame Sally Davies FRS**

# INTRODUCTION

The impending danger of antimicrobial resistance (AMR) is such that Professor Dame Sally Davies, the Chief Medical Officer for England and Chief Medical Advisor to the UK government, has warned that ‘the world is facing an antibiotic apocalypse’.<sup>1</sup> Currently available antibiotics are losing effectiveness faster than they are being replaced by new, innovative drugs or alternative treatment options. AMR is now recognised as one of the most serious threats to global public health and it is estimated that by 2050, deaths worldwide from AMR could reach a staggering 10 million a year.<sup>2</sup> Unfettered AMR would also be economically crippling, with the cumulative costs of inaction potentially amounting to 100 trillion USD.<sup>3</sup> These costs will asymmetrically impact low- and middle-income countries (LMICs), worsening global poverty and economic inequality.<sup>4</sup>

The worldwide scope, critical scale and imminent nature of this ‘problem without a passport’ call for swift coordinated action. AMR is a multi-sectoral issue that requires diverse actors to collaborate across issue areas and national borders. This is reflected in the Global Action Plan (GAP) on AMR, which brings together the World Health Organization (WHO), the World Organization for Animal Health (OIE), the Food and Agriculture Organization (FAO) and the United Nations Environment Programme (UN Environment) – also known as the Tripartite Plus – in an unprecedented attempt to build an effective AMR global governance apparatus based on a holistic ‘One Health’ approach.<sup>5</sup>

Effective regulation will be essential to successfully tackling AMR while ensuring access to appropriate and affordable antimicrobial treatment when needed, in particular in LMICs. On 10 December 2018, the Global Governance Institute (GGI) at University College London (UCL) and the UK Department of Health and Social Care (DHSC), in collaboration with the UCL Institute for Global Health and supported by UCL Grand Challenges, brought together academics, policy-makers and practitioners for a workshop on ‘Antimicrobial Resistance: The Role of Regulation’. This Policy Brief serves a summary of the discussion. It does not necessarily reflect the views of all workshop participants.

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<sup>1</sup> Professor Dame Sally Davies, qtd in: McKie (2017).

<sup>2</sup> O’Neill et al (2016).

<sup>3</sup> Ibid.

<sup>4</sup> World Bank (2017).

<sup>5</sup> WHO (2015).

## EXPLAINING THE DECREASE IN ANTIBACTERIAL DRUG DISCOVERY

In the decades immediately following World War II, an influx of new antibiotic medicines flooded the markets, but since the 1980s this has dramatically subsided, with no new antibiotics being developed. This can partly be explained by scientific challenges: the ‘low-hanging-fruit’ of easily isolated antibiotic products have been plucked and early genomic screening techniques first used in the 1990s have failed to deliver.<sup>6</sup> This is aggravated by the fact that the development of novel antibiotics is considered financially risky. The result is severe under-investment by both industry and public funders in antibiotic research and development (R&D). Indeed, less than 5% of pharmaceutical venture capital investment was channelled into antimicrobial development between 2003 and 2013<sup>7</sup> and the world’s largest funder of health and biomedical R&D, the US National Institutes of Health (NIH), allocated just 1.2% of its grants to AMR research between 2009 and 2014.<sup>8</sup>

## SELF-REGULATION AND INVESTMENT DRIVEN CHANGE

The workshop’s opening session addressed the role of private sector self-regulation and the impact of investment in reducing the threat of AMR. Although this section focused on private industry commitments, with the discussion largely drawing on the AMR Industry Alliance and its 2016 Davos Declaration<sup>9</sup> and 2018 progress report<sup>10</sup>, it should be noted that underpinning these commitments is a pressure on governments to implement effective AMR regulation. Importantly, ‘regulation’ does not necessarily refer to formal, legally binding rules – it can also encompass soft law, incentive schemes or the reduction of legal barriers in certain areas.

### AMR INDUSTRY ALLIANCE

Following the recommendations of the Review on Antimicrobial Resistance, commissioned in 2014 by UK Prime Minister David Cameron and chaired by Jim O’Neill, over 100 biotech, diagnostic, generic and research-based pharmaceutical companies and associations came together to form the AMR Industry Alliance at Davos in 2016 with the shared goal of curbing AMR globally. This diverse array of firms aims to contribute to and measure their efforts across four key areas: (1) encourage greater investment in R&D, (2) support and promote appropriate use, (3) improve access to high quality products and manufacturing, and (4) reduce environmental pollution when manufacturing. A progress report is to be published biennially.

Since the 2016 Davos Declaration, there has been progress in all four of the fundamental assessment areas, most significantly in regard to pollution reduction, suggesting positive steps are being taken by the private sector towards self-regulation. As suggested by SustainAbility, the advisory firm and think tank that compiled the 2018 progress report, it is more helpful to measure success in terms of aggregate progress, rather than pitting Alliance members against one another through comparative benchmarking.

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<sup>6</sup> Payne et al (2007).

<sup>7</sup> O’Neill et al (2016), Renwick et al (2016).

<sup>8</sup> O’Neill et al (2015a).

<sup>9</sup> AMR Industry Alliance (2016).

<sup>10</sup> AMR Industry Alliance and SustainAbility (2018).

## Investment in antibiotic R&D

Since the Davos Declaration, the industry has increased investment in antibiotic R&D, in particular early-stage R&D efforts, with Alliance members collectively furnishing at least 2 billion USD in 2016.<sup>11</sup> We are starting to see a flow of money from philanthropic sources, too. However, as warned by the 2018 progress report, ‘current activities are threatened’ and ‘urgent action is needed to address economic challenges to AMR-relevant R&D’.<sup>12</sup> A major hurdle to successful antibiotic R&D is that it is simply not cost effective. The development process is costly and lengthy and it may take up to 23 years for pharmaceutical companies to see a profit on their investment in new antibiotics (by which time the product may be off-patent).<sup>13</sup> The fact that antibiotics are generally taken as short-course treatments also contributes to a comparatively low return on investment.<sup>14</sup> Thus, the market price of antibiotics does not reflect their true value as public goods, including their ‘insurance value’ in reducing collective risks. This means that, in this particular area, private sector self-regulation can only work to a certain extent. Possible solutions include government interventions such as milestone payments that incentivise innovation by ‘de-linking’ sales and returns on investments.<sup>15</sup> The UK government is currently exploring such a delinked purchase model, with payments to be based on the ‘health’ value of the medicines rather than the quantity of antibiotics sold.<sup>16</sup>

## Supporting and promoting appropriate use

There appears to have been progress in this area. According to the 2018 progress report survey, over 80% of responding companies are engaged in supporting and promoting appropriate antibiotic usage, including through the collection of surveillance data and through educational and stewardship activities, and many have put in place concrete strategies, policies and plans to this end. More than half of all responding companies and 70% of those with an AMR-relevant product on the market are currently engaged in activities to stimulate learning about appropriate use, either directly or collaboratively.<sup>17</sup> That said, there is still a need for more private sector support for public awareness campaigns on AMR, the appropriate use of antibiotics, and infection prevention (including through the wider use of vaccines). In line with the O’Neill Report’s recommendations, significant progress must also be made to improve veterinarians’ and farmers’ awareness of AMR and appropriate use.<sup>18</sup> Unfortunately, only one Alliance member develops and produces antibiotics for animals. Encouraging more companies of this ilk to join the Alliance would likely create new possibilities for education on antibiotic usage and animal health.

## Improving access

Ensuring equitable access to high-quality antibiotics remains a key challenge, in particular in LMICs, where significant supply chain disruptions and a weak regulatory infrastructure mean that antibiotics cannot be adequately stored and often do not reach patients in need. While self-regulation has obvious limits in the area of improving access, Alliance members have taken positive steps to make improvements in their own purview. Nearly 50% have established specific strategies to reduce the prevalence of substandard or falsified products, and 75% have policies and plans in place to improve access to AMR-relevant products. However, more must be done to improve access in LMICs, for example through collaboration with global organisations such as Gavi, a global public-private health partnership which works to increase access to immunisation in poor countries.<sup>19</sup>

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<sup>11</sup> Ibid.

<sup>12</sup> Ibid, p. 6.

<sup>13</sup> O’Neill et al (2015b).

<sup>14</sup> Ibid.

<sup>15</sup> Rex and Outterson (2016), Hoffman et al (2015), Simpkin et al (2017), World Economic Forum (2018), CIDRAP (2018).

<sup>16</sup> Payments will be based on assessments led by the National Institute for Health and Care Excellence (NICE). See: HM Government (2019).

<sup>17</sup> AMR Industry Alliance and SustainAbility (2018).

<sup>18</sup> O’Neill et al (2016).

<sup>19</sup> AMR Industry Alliance and SustainAbility (2018).

Companies involved in the development of new antibiotics should put in place concrete plans to ensure access and promote stewardship *before* a new antibiotic product enters the market.<sup>20</sup> Another, often neglected, priority is the provision of old, out-of-patent antibiotics. Although many old antibiotics are still effective in the treatment of infections, their small market size does not provide financial incentives for pharmaceutical companies to manufacture and distribute them, highlighting again the need for new procurement models that address these skewed incentives.<sup>21</sup>

## Reduction of manufacturing pollution

Although a proportionally small amount of antibiotic waste is expelled to the environment through the manufacturing process in comparison to that excreted by humans and animals (10-20% of waste vs 50+%), manufacturing pollution is far more localised (roughly 200 companies in India and China)<sup>22</sup>, increasing the likelihood of these areas becoming breeding grounds for resistance.<sup>23</sup> As such, Alliance members have shared their expertise to produce a common framework for managing environmental pollution which instigates the O'Neill Report's recommendation of antibiotics producers using onsite water treatment facilities, as the aquatic environment is believed to be most vulnerable.<sup>24</sup> This framework is to be rolled out further, with additional companies signalling that they will adopt it. As a growing number of firms take on responsibility, control and accountability of negative externalities in antibiotic production, this is a promising area for industry self-regulation. However, while voluntary frameworks and privately defined standards are important tools for defining good practice, they do not automatically equate to action, highlighting the need for mechanisms to monitor implementation and assess impact.

## Next steps

The private sector clearly has a key role to play in global efforts to prevent an 'antibiotic apocalypse'. Corporate self-regulation and voluntary commitments such as the Davos Declaration are increasingly promoted governance tools across policy domains. Yet, their effectiveness is likely to be limited in areas where market failures necessitate government interventions. In the absence of robust enforcement and monitoring mechanisms for self-regulation and voluntary frameworks, collective progress assessments are of particular importance. The section above has reflected on progress made by the AMR Industry Alliance and highlighted areas for improvement. However, a caveat should be noted: just 36% of Alliance members responded to the survey that formed the basis of the 2018 progress report. Thus, responses merely represent a subset of the Alliance, and this is even less representative when scaled up to the entire industry.<sup>25</sup> To address biases and self-selection concerns, industry self-reporting should therefore be considered in conjunction with independent evaluations, such as the AMR Benchmark.<sup>26</sup> Going forward, we also need to look at private sector activities beyond the healthcare and life sciences industries. Led by actors such as Aviva and FAIRR (the Farm Animal Investment Risk & Return Initiative), global investors have started to appreciate the risks associated with AMR.<sup>27</sup> Pressure from investors and consumers has led a number of global restaurant chains to commit to phasing out the routine use of antibiotics in their meat supply. Food producers are still lagging behind, however, they too are facing mounting public and investor pressures, including through sustainability assessments such as FAIRR's Protein Producer Index.<sup>28</sup>

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<sup>20</sup> Access to Medicine Foundation (2018).

<sup>21</sup> Pulcini et al (2017).

<sup>22</sup> Thomson Reuters Newport database.

<sup>23</sup> O'Neill et al (2016), Larsson et al (2007).

<sup>24</sup> AMR Industry Alliance (n.d.).

<sup>25</sup> Encouragingly, all of the large research-based biopharmaceutical companies were willing to respond, but only half of the generics and diagnostics companies and a third of biotechnology companies replied.

<sup>26</sup> Access to Medicine Foundation (2018).

<sup>27</sup> Wardle, Rose and Herron (2016).

<sup>28</sup> The Protein Producer Index assesses 60 leading global suppliers of meat and fish based on nine sustainability risk factors, of which antibiotic mismanagement has been shown to be the 'most poorly addressed'. See: FAIRR (n.d.).

## NATIONAL REGULATION

The second workshop session focused on the development and implementation of AMR regulatory policies and legislation across sectors at the national level. In 2015, the World Health Assembly endorsed the Global Action Plan (GAP) on AMR which mandates Member States to devise their own complimentary national action plans (NAPs). Tailoring NAPs to the specificities of their country and region, whilst bearing in mind the GAP's central framework, State Parties were urged to innovate and reflect upon the following: (1) *Whole-of-society engagement including a one-health approach*, (2) *Prevention first*, (3) *Access*; (4) *Sustainability*, and (5) *Incremental targets for implementation*.<sup>29</sup> The intergovernmental organisations collaborating on One Health approaches to AMR – WHO, FAO, OIE and, more recently, UN Environment – are assisting Member States in developing, refining and implementing their NAPs. It is crucial that NAPs take into account context-specific issues such as resources, institutional capacities, social realities and other potential barriers to expediting regulation on AMR.

### Bridging the gap between globally determined aims and national realities

Due to the transnational nature and multi-sector scope of AMR, there is an urgent need for specific, clear and coherent guidance from the global level to enable countries to devise impactful NAPs in line with the GAP. The Tripartite Plus can take a number of steps to better assist countries in this process. Firstly, it is imperative that conscious efforts are made to ensure that guidance documents are translated into a greater number of languages, with special attention given to AMR-relevant terminologies. Secondly, there must be greater specificity when making recommendations for AMR regulation, whether legislation (primary or secondary), guidelines, or government policy decisions. And finally, due to the great complexity of AMR and significant variability in national capacities and resources, it is essential that globally defined guidelines and frameworks are responsive to different national contexts. The AWaRe categorisation of antibiotics<sup>30</sup>, for example, promotes worldwide recognition of when and when not to use certain antibiotics, however, this may not be equally implementable across different countries. With lack of access posing a greater imminent risk to some countries than AMR, blanket bans on certain antibiotics would be counter-productive. LMICs will thus need support and a certain degree of flexibility when implementing AWaRe.

Going forward, greater clarity and continued support from the Tripartite Plus is needed to assist countries in devising meaningful NAPs and to help bridge the implementation gap, in particular in LMICs. Expediting NAPs to implement effective national regulation on AMR will require ongoing dialogue through intergovernmental fora, complemented by global schemes such as AWaRe and monitoring and surveillance platforms such as the Global AMR Surveillance System (GLASS).<sup>31</sup>

### Legislation and regulatory tools

Legislation and regulatory tools play a key role in driving policy change and expediting NAPs. In 2015, an FAO-led Interdepartmental Working Group began work on a methodology devised to analyse national legislation and regulation relevant to AMR in all areas under the FAO mandate. In 2018, the FAO and OIE jointly revised the methodology to incorporate analysis of legislation pertaining to the food, agricultural and animal health sectors. There are plans to expand the methodology further with input from all Tripartite Plus organisations to include the human health and environment sector.<sup>32</sup> One of the Working Group's key findings was that a single AMR law or regulatory instrument should be avoided, as attempts to combine all relevant areas and laws would

<sup>29</sup> WHO (2015), pp. 5-6.

<sup>30</sup> Antibiotics are listed within three AWaRe categories in the 2017 revised WHO Model List of Essential Medicines: *Access*, *Watch* and *Reserve*, indicating which antibiotics should be widely available in health care settings, which have greater risk of developing resistance, and which should be reserved for specific circumstances. WHO (2018), p. 21.

<sup>31</sup> *Ibid*, p. 10.

<sup>32</sup> In the environmental sector, in particular, AMR-relevant legislation and regulation is still underdeveloped.

lead to legal fragmentation. Instead, the group developed a regulatory framework for AMR which can be used to identify gaps and weaknesses in existing legislation at the national level. It was found that legislation is especially relevant in the following areas:

- Authorisation/registration of veterinary medicine products (VMPs), with clear labelling, packaging and advertising rules;
- Licensing schemes/rules on production, distribution, sale, and disposal of waste from VMPs;
- Restriction/prohibition of antimicrobials for non-therapeutic reasons; and rules on correct usage for therapeutic reasons;
- Rules on the disposal of waste and water from the production and remains of antimicrobials;
- Regulatory systems to inspect, monitor, and enforce the above.

The Working Group has also encountered a range of challenges, including identifying concrete regulatory options and compliance mechanisms that countries could introduce without risking legal fragmentation. In addition, a number of research gaps remain that inhibit sound and comprehensive regulation, in particular in the environmental sphere. Finally, levels of AMR awareness diverge significantly across countries and regions. It is therefore key that legislation is accompanied by educational and awareness-raising efforts to ensure compliance and induce real behavioural changes. When incorporating legislation and regulatory tools into NAPs, it is also important to consider all relevant stakeholders and their role throughout the implementation process. To this end, countries may want to set up ministerial, multi-sector working groups and inter-coordination mechanisms to help identify gaps, define key areas for legal reform, coordinate activities, improve clarity of responsibilities and define long-term national goals.

The OIE's Veterinary Legislation Support Programme (VLSP) also offers important insights into challenges and opportunities for regulatory reform on the national level. The VLSP was set up in 2008 to help member states identify gaps and weaknesses in their existing veterinary legislation and provide recommendations for reform.<sup>33</sup> AMR-relevant issues form an increasingly important part of VLSP assessments. The OIE found that legal frameworks around VMPs are often weak and/or incomplete. However, the biggest challenge may not be the legal frameworks themselves but their implementation and enforcement. This is complicated by the fact that competent authorities, such as Ministries of Health, frequently lack veterinary expertise and are unable to properly fulfil their mandate on VMPs. The OIE experience points to the need for further collaboration at the human-animal interface as well as an enhanced focus on implementation while maintaining realistic expectations in LMICs, where enforcement is often inhibited by resource restraints.

## GHANA'S EXPERIENCE

The Ghanaian experience demonstrates how legislation can be used to drive AMR-related policy making and assist the implementation of NAPs. Ghana developed an institutional regulatory framework under FAO guidelines to identify legislative gaps and areas of overlap between relevant ministries and departments of state. It was found that although several departments, pertaining to the environment, fisheries, health, food and agriculture, trade and industry, bore legislation relevant to AMR, only two addressed the problem specifically. Significant gaps and challenges were identified with regards to veterinary and human pharmaceutical production, food safety, crop and animal production, environment and waste management, water quality, and human health. Analysis of legislation also found conflicts, gaps and overlaps in regulatory agency mandates – demonstrating the risk of legal fragmentation at the national level.

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<sup>33</sup> OIE (n.d.).

To address gaps and overlaps, it was decided that existing regulatory bodies would continue to perform their functions. Subsidiary legislation would be passed to address gaps in areas where laws already existed and new legislation developed where there was none. To strengthen Ghana's NAP, a framework to coordinate activities of regulatory bodies was devised, as well as a coordinating Committee for the Regulation of AMR. This committee was set up as a multi-stakeholder body, made up of major state ministry departments, agencies of state, the private sector and civil society. To ensure effectiveness of this institutional arrangement going forward, it is crucial that the committee is not just backed by law but also receives sufficient funding to maintain a permanent secretariat, headed by an executive secretary.

The Ghanaian experience also demonstrates how context-specific details can be navigated and incorporated into NAPs. For example, 'quacks' and unauthorised doctors that sell antibiotics are often tolerated by Ghanaian District Assemblies as they provide unofficial sources of revenue. In addition, Ghana's porous borders enable the smuggling of substandard and falsified medical products, including antibiotics. Facing the realities of such context-specific situations is key to expediting NAPs endorsed by numerous bodies with competing interests.

## Differences in national context

Mapping and analysing NAPs reveals important differences in national context and the additional challenges many LMICs face when devising and implementing regulation on AMR. Gaps, overlaps and conflicts in legislation and departmental mandates, for example, pervasively hinder AMR regulation in LMICs. This is driven by several factors, including a lack of capacity to draft legislation, incomplete legal frameworks and inadequate enforcement capabilities. It is therefore the continued task of the Tripartite Plus to provide tools and expertise to willing participant countries, to chart appropriate pathways, and to set realistic expectations.

While global coordination is essential to ensure impactful NAPs and effective AMR regulation, realities of resource scarcity and consumer demands at the local level must also be taken into account. With regards to animal health, for example, farmers in certain LMICs are receptive to the idea of changing practices when they are able to implement them, however, in other circumstances, alternative farming practices are simply not practical. Similarly, from a human health perspective, regulation for rational use may be constrained by local realities such as weak healthcare infrastructure, lack of access, and insufficient knowledge of the threat of resistance. With regard to the latter, multi-sector workshops can provide one way forward to enhance knowledge of AMR and promote dialogue and understanding between stakeholders.

These factors tie in with the issue of political will in different national contexts. Regulation and legislation will only go so far if countries do not prioritise AMR as a political issue. Countries may demonstrate the political will to develop NAPs but be unwilling to change legislation and/or invest resources to enforce them. For this reason, innovative incentive mechanisms and public awareness schemes could be key to expediting NAPs.

## THAILAND'S EXPERIENCE

Thailand's experience demonstrates the development of innovative mechanisms as way of responding to internal and external challenges. Incorporating local needs and reacting to international developments, Thailand's NAP is an example of incremental improvements towards better AMR regulation.

- **Encouraging rational use:** Like in many other LMICs, one of major challenges in Thailand has been the ready availability of over-the-counter antibiotics for self-treatment and excess use in hospitals. Thailand has responded by developing policies to help incentivise appropriate antimicrobial use, most notably through introducing its Antibiotics Smart Use (ASU) programme in 2007.<sup>34</sup> To encourage better antibiotic practice in hospitals, for example, rational use and lower prescribing rates of primary care networks have been monetarily rewarded through a Pay-for-Performance (P4P) mechanism. The project specifically targeted three conditions that do not require antibiotic treatment: upper respiratory infections, acute diarrhoea and simple wounds. A couple of years ago, a second incentive scheme was announced that monitors executive's performance. However, a lack of appropriate surveillance has hindered the efficacy of this scheme.
- **Reducing use of antibiotics as growth promoters in food animals:** Thailand's experience also demonstrates the potential influence of international trade and policy decisions on national AMR regulation. In 1998, crisis occurred when antimicrobial resistant bacteria were detected in frozen poultry exports from Thailand, resulting in significant business losses. In the following years, increased regulation of non-therapeutic drug use in food and agriculture, by the likes of the EU and US Food and Drug Administration (FDA), encouraged Thailand to ban certain antimicrobials from animal feed. Commitment to reducing non-therapeutic use of antimicrobials in Thailand has since continued through participation in the global 'Raised Without Antibiotics' certification programme.
- **Antibiotics reclassification:** Reclassification of antibiotics remains a priority issue in the Thai context. The ASU programme for human health has sought to reclassify certain antibiotics so they are available by prescription-only in authorised pharmacies. With a technical sub-committee looking to review new possible classifications of antibiotics, this has been deemed a crucial step towards more rational usage. There have been challenges, however, including significant public backlash in response to reduced access, highlighting the need to factor in potential social resistance in any re-classification efforts. There are also gaps in monitoring antibiotic use in clinics and pharmacies due to a lack of infrastructure, a persistent challenge for Thailand and other LMICs.

## Next steps

Regulation on the national level is key to combat AMR but it is not a 'magic bullet'. It is likely to be most impactful if it goes in tandem with global collaborative action. To bridge the gap between globally determined aims and national realities, NAPs need to be globally assisted and locally focused, with realistic, context-specific expectations. The Tripartite Plus can play an important role in providing clear and coherent guidance, thematic expertise and practical support, as well as mechanisms for evaluation and surveillance. One of the key reasons context-specific local and national focus is required is to galvanise the political will necessary to carry through effective and targeted NAPs. Using legislation to solidify commitments and incentives where possible to increase the likelihood of compliance, national AMR strategies must link the local with the global.

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<sup>34</sup> Sumpradit et al (2012).

## INTERNATIONAL AND REGIONAL REGULATION

The final workshop session examined the need for regulation above the nation state, be that through regional or international frameworks and organisations. Though global coordination schemes such as the GAP have certainly highlighted the need for urgent action on AMR, the issue remains peripheral on many national policy agendas – particularly in resource-constrained states where access to antibiotics remains the primary concern and there is insufficient funding or political will to set up monitoring and surveillance frameworks. Therefore, international and regional regulation has a vital role to play in stemming the emergence and spread of resistant pathogens. Framing AMR containment as a global public good can help legitimise and drive forward future collaborative action on a worldwide scale.

### Global governance of AMR

Posing an undeniably global threat to human health, animal health, food security and the global economy, the spread of AMR requires a coordinated international response if it is to be effectively contained. The WHO has emerged as the leading forum for global action on AMR, orchestrating a comprehensive ‘One Health’ approach in collaboration with OIE, FAO and UN Environment. Its AMR-relevant activities range from awareness-raising to standard-setting and the coordination of surveillance mechanisms such as GLASS. However, there are multiple areas in which the WHO and its partners can further initiate or bolster globally coordinated AMR regulation:

- **Regulatory framework on rational use:** Although the GAP calls for states to ‘optimise the use of antimicrobial medicines’, global regulatory guidelines on appropriate prescription, distribution and use of antimicrobials are still under development.<sup>35</sup> A global framework would help to harmonise stewardship policies, particularly in areas where antibiotic prescription rates remain high. From a human health perspectives, a key ethical concern is how to weigh individual patient needs against AMR concerns, balancing access to medicine with efficacy of usage.
- **Enforcing surveillance:** Building on the objective of the GAP to ‘strengthen the knowledge and evidence base through surveillance’, the WHO and its partners must seek to address the international disparity in AMR surveillance capability.<sup>36</sup> While GLASS has raised awareness of the need to establish more national surveillance sites and laboratories, LMICs frequently lack the resources, political will and/or public support to do so, leaving significant surveillance gaps in regions at the highest risk of AMR.<sup>37</sup> Through harder regulation for a mandatory basic surveillance system, the WHO could raise the profile of AMR and help to overcome domestic support issues and legitimise budgetary support for vital laboratories. This would need to come with appropriate training as well as guidelines for harmonised data collection in different settings and across different sectors. Where LMICs lack the financial and technical capacity to develop AMR surveillance systems, initiatives such as the Fleming Fund can play a crucial role.<sup>38</sup>
- **Framework convention on AMR:** The Framework Convention on Tobacco Control (FCTC) marked the first international treaty to be negotiated under the auspices of the WHO, enforcing international regulation on the contents of tobacco products, while also demanding that nations introduce tax and price measures to limit demand.<sup>39</sup> Securing commitment from 40 states, many of which took swift action in anticipation of the Convention objectives, the FCTC could be used as a blueprint for a global regulatory framework to

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<sup>35</sup> WHO (2017).

<sup>36</sup> Ibid, p. 8.

<sup>37</sup> Wernli et al (2011), p. 194.

<sup>38</sup> Among other priority areas, the Fleming Fund provides country grants to support the development of laboratory and analytical capacity in LMICs. See: Fleming Fund (n.d.).

<sup>39</sup> WHO (2003).

combat AMR, setting the precedent for harder measures against unnecessary usage of antimicrobial medicines, and for harmonising international standards on the quality of active product ingredients (APIs) to limit the development of AMR through substandard medicines. However, while the FCTC provides a useful model for a potential framework convention on AMR, such a treaty should ideally be negotiated and adopted at the UN level to ensure it goes beyond the human health focus of the WHO.

### **International regulation for Good Manufacturing Practice**

Good Manufacturing Practice (GMP) regulations are a vital component of AMR containment strategies, certifying the quality of pharmaceutical products, and thus preventing the sale of substandard medicines which can accelerate the emergence of resistant pathogens. Yet these quality control measures currently remain decentralised and their efficiency varies greatly between countries and regions. For example, although India is one of the world's largest medicine producers and has one of the highest AMR rates globally, its domestic GMP standards are poorly enforced.<sup>40</sup> While pharmaceutical exports are subjected to more regular and rigorous inspection upon arrival in markets such as the EU, India's own market remains 'flooded with suboptimal medications'.<sup>41</sup>

Shifting GMP regulation from the national/regional to the global level could help standardise quality across borders and crack down on the sale of substandard medicines. Such regulation, however, would need to strike a balance between product quality and economic viability, guaranteeing that antimicrobial medicines remain as affordable as possible, in particular in LMICs. Centralising and strengthening GMP regulation could ensure that quality control inspections in countries such as India are not limited to exports but also target products for domestic consumptions. Yet, if quality control is to be extended into poorer communities where AMR is increasing most rapidly, then international regulatory bodies must be granted a mandate to exert pressure in those national markets.

### **Expanding the International Health Regulations**

The International Health Regulations (IHR) 2005 offer another global regulatory tool to address AMR. The IHR provide a legally-binding framework for 196 State Parties on how to report and contain public health threats that have the potential to cross borders. In March 2018, for instance, IHR criteria were used to determine the international threat of 'super gonorrhoea', after a case emerged in the UK of a strain that was resistant to frontline antibiotics. Providing universal criteria for recognising a transnational health concern, IHR regulation ensured that the international community was swiftly notified of the threat, and that information was shared between the UK and the country in which the patient contracted the illness.

While the IHR provide a useful notification mechanism for international health concerns, they could go further in regulating against international AMR transmission, setting out an international framework for diagnosing and responding to new resistant diseases. A vital area for further regulation could be travel and migration, in particular the repatriation of at-risk patients from countries with high rates of AMR and improved health screenings before cross-border movement. The data in this area is currently sparse and not shared well, raising the question of whether a basic surveillance system could be mandated to prevent the international transmission of new resistant pathogens. However, there are also potential barriers to using the IHR to address AMR. Some countries lack the financial, technical and human resources to fully implement the core public health capacities mandated by IHR. In addition, there is a perception among at least some LMICs that the IHR are applied selectively by high-income countries (HICs) in a way that does not benefit all State Parties equally.<sup>42</sup>

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<sup>40</sup> India exported over 6 billion USD of pharmaceutical products in 2010 (UN Commodity Trade Statistics Database). A WHO report found that raids or inspections of Indian pharmaceutical factories almost 'never take place' (WHO Regional Office for South-East Asia, 2011, p. 9). Some of the most dangerous AMR-pathogens such as the Carbapenem-resistant Enterobacteriaceae (CRE) are believed to have originated from India before spreading globally (Wernli et al, 2011, p. 1).

<sup>41</sup> WHO Regional Office for South-East Asia (2011), p. 9.

<sup>42</sup> Lillywhite, L. (2016).

## Regional regulation

Regional-level regulation offers another potential strategy to combat AMR, offering a fruitful middle ground between global regulatory frameworks (which might not provide enough flexibility) and national responses (which are only loosely coordinated). Efforts such as the African Union's AMRSNET, for example, have served to complement the surveillance objectives of the WHO's GAP, while adjusting its aims to the specific challenges of the region's political realities and healthcare systems.<sup>43</sup> Regional-based coordination is often more pragmatic since it draws upon pre-existing political networks between neighbouring states – a factor that may serve to boost state compliance in a political climate that proves increasingly averse to the authority of international organisations. Moreover, since pharmaceutical supply chains are often unique to particular regions, cooperation at such a level may prove to be a more feasible option for regulating the production and demand of antimicrobial medicines, allowing for a flexible and customised approach to secure compliance from both state and business actors.

Nevertheless, caution must be exercised when formulating regional approaches, particularly in the realm of market regulation and price controls. Where there is regional regulation for pharmaceutical products, yet national regulation of prices, this can create arbitrage opportunities for pharmaceutical companies and discourage antibiotic sales in lower-priced markets, creating shortages. For example, while Romania's entry into the EU subjected its market to new European GMP regulation, increasing the production costs of antimicrobial medicines by 30%, nationally-enforced price caps and 'claw back' taxes meant that said medicines continued to be sold at EU-minimum prices, reducing the profitability of their production.<sup>44</sup> Not only did this lead to manufacturers withdrawing 2,000 out of 6,200 generic products from Romanian markets, but the medicines were increasingly bought by businesses and 'sold to more expensive European markets such as Germany', worsening national shortages.<sup>45</sup>

The ramifications of national price caps within regionally-regulated markets can furthermore increase the risk of AMR. National shortages can boost demand for substandard or falsified medications that lead to ineffective therapies, providing a window of opportunity for resistant bacterial strains to develop.<sup>46</sup> In addition, limiting the profitability of medicines can lead pharmaceutical producers to seek cheaper, poor-quality active product ingredients (APIs), with Chinese manufacturers reporting that price decreases of 20% are associated with a 0.4% fall in purity – again increasing the likelihood of sub-therapeutic dosage, and increasing the risk of AMR.<sup>47</sup> Strict risk surveillance is therefore needed to guarantee that national policies do not clash with regional objectives. Regional approaches to regulation must remain conscious of national variations in drug prices, limiting the opportunities for arbitrage and ensuring consistent medicinal quality across the board.

### FLEXIBILITY AND NATIONAL CONTEXT

A point repeatedly echoed throughout the workshop was the necessity that new regulations on the international or regional level be implemented through a phased approach, providing country-specific guidelines and trainings that recognise the varied national realities in which regulations will play out. In fact, imposing standardised approaches might not be feasible or desirable in all areas, such as the regulation of healthcare professionals. For example, whereas South Africa has benefited from a strong pharmacy inspection council, with the power to remove licenses and de-register non-complying pharmacies, this approach would clearly

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<sup>43</sup> AMRSNET (2018).

<sup>44</sup> Pisani et al (2018), p. 10.

<sup>45</sup> Ibid.

<sup>46</sup> WHO Regional Office for South-East Asia (2011), p. 9.

<sup>47</sup> Pisani et al (2018), p. 11.

be less useful in the national context of Nigeria, where the majority of medicine is ‘purchased from un-licensed stores without prescription from a physician’.<sup>48</sup> Instead, Nigeria has adopted a different yet similarly effective regulatory approach by enforcing compulsory training programmes for unlicensed drug vendors. The vendors are temporarily taken off the streets, trained in the correct distribution and administration of generic antimicrobial medicines, and then rewarded with the certification to legally dispense said drugs. Though punitive measures proved effective in the more professionalised pharmaceutical industry of South Africa, complementary measures were more practical in the Nigerian context to regulate illegal and untrained vendors, reduce the widespread use of antimicrobial medicines, and crack down on the administration of sub-therapeutic doses.<sup>49</sup> Different regulatory logics must therefore be applied to the heterogeneous reality of national healthcare systems, ensuring that international measures do not impose restrictions on access to pharmaceuticals in countries where unlicensed drug stores are prevalent.

## Next steps

AMR requires urgent action beyond the national level. Regional regulation and collaboration is already an important tool in addressing AMR, led by actors such as the EU. On the international level, a comprehensive governance regime on AMR is not (yet) in place. However, there is growing recognition that a shared global vision and strategy is essential to tackle AMR and mobilise all relevant stakeholders. A recently published document by the Ad hoc Interagency Coordination Group (IACG) on AMR offers a number of concrete recommendations in this regard.<sup>50</sup> New regulatory strategies on the global level could range from a comprehensive treaty to more specific interventions aimed at preventing the cross-border spread of new resistant strains, supporting the development of a global AMR surveillance system and limiting the widespread sale of substandard medicines, in particular in LMICs. However, as the above illustrates, any attempts to regulate AMR on the global or regional level must carefully balance national needs and capabilities with internationally defined priorities. Detailed risk assessments must accompany any regulatory effort, ensuring that access to antimicrobial medicines is not limited through shortages, arbitrage or significant price increases. In addition, financial and capacity-building support must be made available for LMICs that are not otherwise able to build and maintain sustainable surveillance systems.

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<sup>48</sup> Ajibola et al (2018) p. 1.

<sup>49</sup> A rational drug use survey found that, out of 12 developing countries, Nigeria has the third highest percentage of antibiotic prescriptions (48%) (Hogerzeil et al, 1993, p. 1408).

<sup>50</sup> See: IACG (2019). The IACG was established following the 2016 UN High-level Meeting on AMR. Its mandate is to provide practical guidance for sustained and effective global action on AMR.

## FUTURE POLICY AND RESEARCH AGENDAS

AMR increasingly poses a major global threat to human and animal health as well as to the global economy, with the World Bank forecasting a loss of 1.1-3.8% of global GDP by 2050 due to AMR-related consequences.<sup>51</sup> LMICs in particular remain disproportionately vulnerable to resistant infectious diseases, threatening to derail development efforts and compound the oncoming impact of climate change. If AMR and its devastating consequences are to be effectively contained, more global coordination and a bolder international political response are urgently needed. Framing high-quality and effective antibiotics as a vital global public good can help raise AMR up the policy agenda.

This workshop and accompanying policy brief has served to identify the potential role of regulation in combatting AMR and harmonising the global response – be it through private, national, regional or international frameworks and tools. Perhaps one of the key take-away points is the multi-sectoral challenge posed by AMR and its overlapping relevance to separate regulatory agencies. Whilst the majority of the debate centred on pharmaceutical regulation and human health, a lengthier discussion is needed to broach the equally daunting challenge of addressing AMR in veterinarian/agricultural and environmental sectors. Nevertheless, the workshop highlighted some fundamental areas for future regulation, with participants advancing a number of specific recommendations (see below).

### CONCLUSIONS AND RECOMMENDATIONS

- Industry self-regulation can play a vital role in addressing AMR but it has limits when it comes to incentivising investment in antibiotic R&D. Governments, particularly in high income countries, must seek to collaborate with private actors such as the AMR Industry Alliance to accelerate the development of a new generation of antimicrobial medicines.
- A privately developed standardised framework to promote corporate responsibility in the manufacturing process offers a promising strategy to ensure that antibiotic producers are accountable for the negative externalities of their waste and do not contribute to AMR through reckless pollution.
- Clear guidance and support from the Tripartite Plus is needed to assist countries in devising NAPs and implementing them, in particular in resource-poor settings. A comprehensive methodology to analyse gaps, overlaps and conflicts in existing national legislation for all AMR-relevant sectors promises to be an effective tool in expediting NAPs.
- Because AMR is a complex multi-sector issue, all relevant stakeholders should be considered when drafting and implementing NAPs, in particular with regard to legal and regulatory reform. Multi-sector working groups or implementation committees as well as mechanisms for inter-ministerial coordination can promote awareness and mutual learning.
- Without appropriate surveillance systems and data sharing processes, the emergence of a new resistant strain might go unnoticed until it becomes endemic. Building on momentum under the GAP, the WHO and others must frame AMR surveillance as a vital public good and strengthen international regulation to address persistent gaps in this area – perhaps through a treaty that mandates a basic surveillance system in all states. Importantly, such obligations must come with additional financial and capacity-building support for LMICs that are not currently able to build and maintain sustainable surveillance systems.

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<sup>51</sup> World Bank (2017), p. 17.

- From agricultural policies to pharmaceutical GMPs, greater global coordination is vital to harmonising long-term strategies and priorities in the containment of AMR. However, any regional or global regulatory framework must be flexible and responsive to context-specific national realities and risks, in particular the danger of restricting access to vital medicines in resource-poor settings.
- Nonetheless, pressure must still be exerted in national markets to challenge the widespread production of substandard medicines, limiting the spread of resistance by ensuring that drugs are administered in appropriate doses and remain of the necessary purity.

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