

## Consultation on a draft Global action plan to address antimicrobial resistance

The questionnaire is divided into four sections. The questions are broadly framed and intended to give you the opportunity to enter into some depth and explain your organization's viewpoint. While only questions marked with \* are mandatory, we would appreciate answers to as many as possible. Where a choice of answer needs to be selected please highlight your answer.

Before answering the questions, please refer to our list of supporting documents.

<http://www.who.int/drugresistance/amr-consultation/en/index.html>

### About you

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- 2. Email address\* (preference for official email addresses):** [anthony.so@duke.edu](mailto:anthony.so@duke.edu)
- 3. Are you authorised to represent your organization or interest group?** Yes
- 4. Organization Name\*:** ReAct – Action on Antibiotic Resistance with the support and input from Otto Cars, Anna Zorzet, Mirfin Mpundu and Satya Sivaraman.
- 5. Address of the organization\*:** ReAct, Uppsala University, Box 256, 751 05 Uppsala, Sweden
- 6. Organization website (if available):** <http://www.reactgroup.org/>
- 7. Country\*:** Multiple country sites in the global network, including nodes based in Sweden, Kenya, Ecuador, Malaysia, and the United States.
- 8. Type of Organization\*:** Other (please specify) - An independent, global network for concerted action on antibiotic resistance
- 9. Main sectors of interest:** Human health, Animal health, Finance/economics, Agriculture and food, Environment, Communication, education and advocacy. Other—Innovation and access to health technologies, global health, ecosystem approach to ABR, social and economic development
- 10. Would you like to be added to our mailing list to receive updates on the development of the global action plan?\*** Yes

### General questions

- 1. From the perspective of your organization, what are the most important areas of concern in AMR?**

Across these building block areas, we have laid out some of the most important areas of concern in AMR in the following responses to this on-line, consultative questionnaire. More broadly, however, the main actions to consider are thoughtfully captured in the Declaration that serves as the organizing principles for the Antibiotic Resistance Coalition (see <http://sites.duke.edu/ghtaprogram/files/2014/05/ARC-declaration-May-22-2014.pdf>). In responding to the following questions, we only can highlight a subset of these issues for WHO's attention, but refer WHO to the larger set of issues described in the Declaration, supported by a broad array of civil society organizations. Taking many forms, antibiotic

resistance lacks a single disease face. As a consequence, greater coordination and funding, both within WHO and most governments, on this issue is needed.

**2. Is your organization currently involved in work related to AMR? If Yes, How? YES**

Over the past decade, ReAct as a global network has actively worked to raise policymaker awareness over antibiotic resistance and has contributed to WHO's expert processes on AMR, from its monograph on "The evolving threat of antimicrobial resistance: Options for action" to its efforts on mapping a roadmap for antibiotic innovation. Members of ReAct have served on the WHO's Strategic and Technical Advisory Group and contributed to the WHO Technical Consultation on Innovative Models for New Antibiotics Development & Preservation. ReAct has led the authoring of two AMR-related proposals advanced by WHO regional offices for consideration as potential innovation demonstration projects and has contributed to the stakeholder analysis of actors within ABR, done in collaboration with WHO. The regional node coordinators of ReAct, and others in the ReAct network, are or have been in collaboration with WHO regional and country offices on multiple occasions.

**Questions about the draft global action plan outline document**

**Before the WHA resolution was adopted, two WHO AMR Strategic Technical Advisory Group (STAG) meetings were held in anticipation, which included members plus a large number of representatives from other organizations. These meetings identified key issues, concerns and led to the development of a draft outline.**

**As this consultation progresses and stakeholder meetings are held, the secretariat will harvest and incorporate the input into the draft global action plan.**

**1. How would you rate your understanding of WHO's intention in the development of a global action plan to address AMR?**

Very Good

**2. From the perspective of your organization, are the major issues relating to AMR outlined in the draft global action plan? No**

**If No, what additional issues need to be addressed?**

The Global Action Plan needs to be dynamic and responsive over time to the growing recognition and changing nature of the ABR challenge, especially in different regional and local contexts. For example, one might consider a strategy that anticipates a range of policy scenarios:

- If, for example, a drug-resistant infection is treatable but with an antibiotic priced beyond the reach of many of those in need, what policy framework might effectively respond to this challenge? How can the experience of public-private partnerships for neglected diseases be implemented for tackling AMR?
- If a novel antibiotic reaches market but its production falls either short of the need or its marketing promotes overuse and unnecessary drug resistance, how is the Global Action Plan positioned to respond? Are there lessons from the experience of the Global Drug

Facility and Green Light Committee's handling of first- and second-line TB drugs that might inform this undertaking?

Each of these scenarios, as well as others, point to the need for an effective and rapidly responsive structure of global governance, coordination, and accountability for addressing AMR. This broader framework will necessarily require engaging other United Nations and intergovernmental agencies. A stepwise and extended process for building such shared commitment will involve putting in place a platform for ongoing consultation beyond this initial round of feedback.

To tackle the challenges of AMR, the Global Action Plan must also consider how to mobilize the considerable resources and financing that will be required to ensure that action follows intention. This financing will be needed to ensure that health technologies, from drugs to diagnostics, will be brought to market as public goods for those in need, that the infrastructure for surveillance and monitoring appropriate use is piloted and supported to ensure effective antibiotic stewardship, and that alternatives to non-therapeutic use of antibiotics in animal husbandry are found and implemented.

### **Questions on the 'Building blocks' described in the draft outline.**

**You will notice, the global action plan has been constructed around "building blocks" in recognition that different countries will have different starting points. In this situation, countries can choose building blocks to concentrate upon. Each building block specified has been identified as a key area where specific attention, planning and work are needed to achieve progress in addressing AMR. Through questions in this section, we would like to hear your opinions on these building blocks in more detail.**

#### **I. Building block-1: Increasing awareness and understanding about AMR and of the actions and changes needed**

##### **a) What do you consider to be the main issues under this priority?**

Laying the foundation for this priority area, it would be useful to analyze the reasons for the weak response by governments, despite decades of calls to action and expert policy pronouncements. The main issues under this priority should include increasing awareness and understanding about AMR at strategic intervention points, for example:

- Policymakers, healthcare providers and the public should have access to reliable data on the prices, sales, and drug resistance patterns to antibiotics, both in the human and non-human use sectors, to ensure improved accountability and transparency in the availability, affordability and use of these drugs.
- Providers and consumers alike need information and feedback on the rational use of antibiotics, both as part of surveillance and stewardship efforts. These data should be designed to be actionable, both at the individual provider-patient level and collectively at the community and health system levels. A global surveillance system should provide early warning in detecting novel resistance mechanisms.
- The health care and societal costs associated with growing drug resistance also need to feed back into this accountability loop.

- Policymakers should consider the potential synergy among measures that curb AMR and those currently being implemented to tackle HIV, TB and Malaria. Inappropriate or irrational use of treatments contributes to resistance for all of these diseases in the healthcare delivery system. Where these problems share common root--by building up the infrastructure for improved diagnostics, training healthcare workers for improved prescribing of medicines, and removing misaligned economic incentives that exacerbate the misuse of medicines can be tackled together--they should be.

Taking a systems approach, the Global Action Plan also will require research to develop a deeper understanding of how to respond to the challenge of AMR, for example:

- The complementarity of health technologies, such as diagnostics, vaccines and medical devices with surfaces resistant to bacterial colonization, that might reduce the use and selective pressure of antibiotic use;
- Novel financing approaches that delink the return on investment from volume-based revenues (price x quantity) for health technology R&D and that realign incentives to encourage rational use of antibiotics in the healthcare delivery system; and
- The ecology of the microbiome in designing novel approaches, such as probiotics, to mitigate the unintended consequences on gut flora from systemic use of antibiotics and redesign of hospital architecture to make them safer and greener.

This will require a coordinated, but pluralistic approach to supporting research and evaluation of potential policies, interventions, and treatment approaches. Such research will need to be global—potentially cross-applicable across different settings across the globe, but relevant to the local cultural and socioeconomic context where such approaches are undertaken. For example, offering a written prescription of an antibiotic but suggesting that it be only filled if symptoms persist for a period of time may not be a viable treatment approach in many LMICs, where patients must travel considerable distances for such medical attention or cannot access such treatment readily. However, approaches such as making available substitute treatments, like herbal treatments for symptomatic relief of viral and self-limiting illnesses, can help offset inappropriate use of antibiotics, and learning from the experiences of projects like Thailand’s Antibiotic Smart Use program can help empower others to emulate such efforts.

Importantly, the Global Plan of Action needs to remain vigilant against efforts that purport, but in actuality, that may threaten progress to tackle AMR. For example, some stakeholders may use the dearth of novel antibiotics as a pretext for seeking greater reimbursement and economic rewards for bringing antibiotics to market that have neither novel mechanisms of action nor greater effectiveness in treating patients with drug-resistant disease. Others will insist on lowering clinical trial standards for approving antibiotics, even if the drug candidates are not truly novel or value-added to existing therapies and even if the bottleneck to R&D is not regulatory, but scientific.

**b) What are the main actions that needs to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?**

Under each building block, the main actions that need to be done can be characterized at the global, regional and local levels, within and across sectors, across human and animal use

of antibiotics, and both in the public and private sectors. Under Building Block 1, the Global Plan of Action might focus on the afferent limb of collecting necessary data for policy action and the efferent limb of translating that information into actionable follow-up.

A broad range of actors and stakeholders will need to be recruited to take action on these objectives. Rather than stating the obvious, we would emphasize here the need to ensure representation and participation of those who are too often neglected in these policy dialogues, specifically the voices of consumers, civil society, and perspectives from LMICs. For example, in considering novel business models for pharmaceutical R&D, too seldom are perspectives from research institutions and/or pharmaceutical firms based in LMICs, as well as consumer groups and public interest civil society groups, recruited alongside those of multinational or biotechnology companies based in high-income countries. Health care payors, including private and public insurers, also need to be present at such meetings. Given the importance of the work on AMR, we would also caution that the policy processes of the Global Action Plan should be transparent and free of financial conflict of interest.

**c) What steps have already been taken to address this priority? (please provide references where possible)**

Various activities that communicate greater awareness and understanding of AMR have been undertaken. Rather than offer an inventory here, we note several examples that help fill out a framework of approaches undertaken to address this priority.

Some activities have focused on healthcare providers as partners in tackling ABR. The Swedish Strategic Programme Against Antibiotic Resistance (STRAMA) is a nation-wide network which organizes providers, both from primary care and hospitals, hosts annual gatherings and conducts national projects studying the problem and the causes for the wide variations in local antibiotic prescribing. Their efforts led to notable declines in inappropriate antibiotic use in the country and contributed to increased patient awareness of the risks of unnecessary antibiotic use.<sup>1</sup>

Other activities focus on mobilizing communities. Under ReAct's Civil Society Organization program supported by Sida, the Reimagining Resistance project has sought to tackle antibiotic resistance through an ecological and arts for social change approach. For example, in 2011, ReAct (Latin America) developed a tool based on documentary photography, to build a holistic perspective of bacterial resistance, emphasizing its social, economic and cultural determinants. Health professionals received training and mentoring during the FotoResistencia project and work is on-going to disseminate the images with their stories and to discuss bacterial resistance with communities using the photo-documentary as the central input.

Activities in Africa have included working with partners such as the Ecumenical Pharmaceutical Network (EPN) on highlighting issues surrounding antimicrobial resistance. In 2009, ReAct and EPN launched a campaign focused on highlighting the issue of AMR, promoting rational drug use, and educating both health providers and communities. Other

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<sup>1</sup> Mölsted S, Cars O, Struwe J. Strama-Swedish working model for containment of antibiotic resistance. *Eurosurveillance* 2008; 13(46): 1-4.

activities have included hosting of workshops, dissemination of IEC materials and posters, and the use of drama.

With the view of approaching ABR holistically and involving more stakeholders, ReAct organized a workshop in April this year that brought together 27 participants from 10 countries to discuss a common approach and strategies for AMR on the continent. These participants were from different professional sectors and practice, but demonstrated a shared concern and commitment to address AMR. Currently ReAct Africa is working on testing IEC materials using an ecological approach for various African audiences.

Still other activities might provide WHO and intergovernmental agencies with important data, such as on the availability and pricing of key antibiotics. Health Action International and the World Health Organization have fielded a standardized survey of medicine prices that captures price components of key drugs, gauges their affordability benchmarked against the lowest paid government worker's wages, flags stockouts at retail pharmacies, and compares these findings across a sampling of public and private outlets. Antibiotics have featured on the core list of essential medicines monitored in the medicine prices survey, and in 2009, the project also conducted a one-day global snapshot of the price of the antibiotic, ciprofloxacin. Such findings can help catalyze policymaker awareness and understanding of the various dimensions of antibiotic access and availability.

**d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)**

Concrete and measurable indicators of progress for this priority could be constructed from measures of knowledge, attitude and practices (KAP and the KAP-gap) related to improved antibiotic prescribing and use by providers on the supply side and on consumer satisfaction in doctor-patient encounters where antibiotics are withheld in the setting of likely viral infection on the demand side. Providing a useful starting point, the European Commission has conducted an EU-wide survey capturing the use, levels of public knowledge, and impact of antibiotic awareness campaigns as perceived by the public.<sup>2</sup> Other indicators could allow for continuous quality improvement tracking of compliance with infection control measures (process measures) or of lower incidence of multi-drug-resistant infections (outcome measures). The power of comparison, through audit and feedback, at the provider, institutional and community-wide levels also could offer actionable data and motivate change. The key is to be parsimonious and strategic in the selection of indicators, for wading in a sea of indicators allows those who otherwise might be held accountable to highlight the spurious bright spots while evading responsibility for where such measures fall short.

**II. Building block-2: Identifying the most important approaches for preventing development of infections and the steps needed to move beyond guidance to more effective implementation of such approaches**

**a) What do you consider to be the main issues under this priority?**

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<sup>2</sup> TNS Opinion & Social. Antimicrobial Resistance Report: Special Eurobarometer 407. Brussels, Belgium: European Commission, November 2013.

A mix of priorities relating to infection prevention in both humans and animals fall under this Building Block. Two types of measures--infection prevention through practices like hand hygiene and through technologies like preventative vaccines--receive attention.

Insofar as infection prevention relies on modifying human behavior, much more can be done to consider how to realign incentives, take advantage of default choice architecture favoring rational use of antibiotics, and provide audit and feedback. However, a broader perspective of the main issues under this priority might involve:

- examining how the healthcare environment might be reengineered to improve infection control, from building design, to medical instrument surfaces (a different kind of technology for prevention than vaccines).
- extending infection control for human populations outside of the healthcare setting, from cultural practices of boiling water for beverages to improved food handling and storage; and
- detecting and addressing sources of foodborne outbreaks of disease.

By analogy, steps can be taken to reduce the non-therapeutic and inappropriate use of antibiotics in animal husbandry. The guiding principle should be that healthy animals have no need for antibiotics. Providing guidance on levying a tax on non-human use of antibiotics, developing and piloting alternatives to antibiotics, and removing financial incentives for veterinarians prescribing antibiotics could help realign incentives. Restricting the use of medicated feeds and ensuring veterinary oversight also might change the default choice architecture in animal husbandry. Making data available on the sales and use of antibiotics as well as the presence of drug-resistant pathogens, by livestock product, would also be useful.

**b) What are the main actions that needs to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?**

Implementing existing knowledge can should involve simple and affordable interventions, but to do so, we need to engage a broader range of stakeholders, including civil society organizations. For example, going beyond the status quo, the circle of main actors and stakeholders might include:

- 1) religious leaders as the World Alliance for Patient Safety's hand hygiene campaign discovered when local production and use of alcohol-based handwash benefited from their approval;
- 2) engineers in the redesign of medical instrument surfaces as some have begun to do so to emulate shark skin in a biomimetic fashion to resist bacterial adhesion and colonization; and
- 3) those working on potable water systems in resource-limited settings.
- 4) those working on improving access to nutrition among the rural and urban poor in LMICs, such as through urban kitchen gardens, aquaculture and poultry farming.

Taking a page from the Institute for Healthcare Improvement's breakthrough collaboratives, it takes more than just identifying the main actors and stakeholders, but rather it requires building a community of practice where challenges and lessons, as well as best practices, can be shared.

**c) What significant work has already been done to address this? (please provide references where possible)**

The Global Plan of Action might benefit from the lessons learned in mounting other efforts to tackle bacterial infections. For example, the SAFE strategy packaged a well-defined set of interventions (**S**urgery for inturned eyelids, **A**ntibiotics to treat and prevent active infection, **F**acial cleanliness to prevent disease transmission, **E**nvironmental change to increase access to water and sanitation) that collectively would make a difference to treat and prevent trachoma. The World Alliance for Patient Safety undertook a Hand Hygiene campaign that has engaged hundreds of hospitals across the globe, but an ongoing challenge will be finding ways of stemming the attenuation of the commitment of healthcare providers to disinfect hands when seeing patients. Maintaining infection control efforts, ensuring continuous quality improvement, and providing booster campaigns when efforts flag will also require attention under the Global Plan of Action. And the U.S.-based Institute for Healthcare Improvement (IHI) has effectively used a process of continuous quality improvement among like-minded institutions that share best practices as part of a breakthrough collaborative. To reduce incidents of medical harm in the nation's hospitals, IHI targeted MRSA infections through changes in hospital infection control processes and surgical complications through its Five Million Lives campaign. This approach of setting numerical targets lent strategic backing to the campaign's motto, "Some is not a number, soon is not a time."

**d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)**

Process and outcome measures could be developed as indicators of the uptake of infection control efforts, from hand hygiene practices and infection rates in healthcare institutions to the use of preventative vaccines. However, the Global Plan of Action should not only make such indicator tools available to target groups, but also hold intergovernmental agencies responsible for ensuring its implementation accountable. A scorecard that provides feedback on the performance of such global campaigns could be designed to motivate key actors at global, regional and country levels. Importantly though, as with the development of any concrete and measurable indicators of progress, this will entail a process beyond an on-line consultative questionnaire, engaging key actors (for input, not decision making on how they should be held accountable) and ensuring that the implementation costs do not outweigh the benefits of the actionable results that may follow.

**III. Building block-3: Optimizing the use of existing antimicrobials for human and animal health and in agriculture**

**a) What do you consider to be the main issues under this priority?**

A range of proposals for ensuring effective antibiotic stewardship have come forward. These proposals deploy approaches such as conducting regional and local educational campaigns to reduce demand for antibiotics, limiting prescription to trained providers or contingent on prior approval, limiting dispensing to certified institutions or administration in specific healthcare settings, or requiring use of clinical algorithm and/or diagnostic test findings. These proposals differ in whom they hold accountable.

Some have proposed that these stewardship approaches be in the hands of drug companies. The FDA, for example, can require for cancer drugs that drug companies monitor and be



accountable for use of a drug whose use needs to be restricted under a Risk Evaluation and Mitigation Strategy (or REMS). Both the Health Impact Fund and the Strategic Antibiotic Reserve are proposals that similarly place the burden and responsibility on drug companies to ensure that health care providers using the drug conserve it appropriately, but some appropriately take issue over vesting more responsibility or influence of the drug industry over the practice of medicine.

On the other hand, providers and consumers could be held directly accountable for these stewardship approaches. Cochrane expert reviews have reviewed the literature on restrictive and persuasive interventions to accomplish these ends, but clearly further research and more inspired approaches drawing on techniques from default choice architecture to behavioral economics are required. Importantly, not all of these approaches translate well into resource-limited settings where there may be limited numbers of providers in the first place, no opportunity for specialist referral, consultation or approval, or lack of second-line antibiotics available. So ensuring controlled distribution for rational use will require local adaptation.

While each of these points in the pharmaceutical value chain from bench to bedside is important, the responsibility for stewardship is a shared one, both on the part of drug companies and of providers and consumers. A priority would be to develop strategies for enlisting this cooperation.

The experience and lessons of the Green Light Committee and Global Drug Facility in ensuring an adequate supply to meet patient demand, affordable pricing, and scale-up for rational use might inform a procurement-based strategy. To provide access to quality-assured, second-line TB drugs, the Green Light Committee reviewed country applications for delivering these medicines, made available at negotiated lower prices, and offered technical assistance to those seeking to implement such treatment programs. In partnership with IDA, the Global Drug Facility coordinated procurement of first- and second-line TB drugs. Such pooled procurement mechanisms can not only send useful market signals to manufacturers, but also give leverage to antibiotic stewardship efforts. Figuring out how to speed scale-up though is key. Otherwise the insistence on such requirements to access concessionary prices--slowed where local infrastructure is weak--may result in structural access problems to novel antibiotics.

**b) What are the main actions that needs to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?**

From bench to bedside, there are multiple strategic points for intervention to ensure access, but not excess in antibiotic use.<sup>3</sup> To undertake this work, the Global Plan of Action first needs a system to capture ongoing snapshots of antibiotic access. How do local

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<sup>3</sup> So AD, Bigdeli M, Tomson G, Woodhouse W, Ombaka E, Peralta AQ. Part 5: The access and excess dilemma. "Antibiotic resistance—the need for global solutions," *Lancet Infectious Diseases Commission* 2013 Dec; 13(12): 1057-98. Epub 2013 Nov 17. Available at: <http://www.reactgroup.org/uploads/news/The-Lancet-Infectious-Diseases-Commission-on-Antibiotic-Resistance-Nov2013.pdf>

antibiograms and available second-line antibiotics match up, particularly in low- and middle-income countries? Secondly, a toolkit and technical assistance program capable of working with healthcare delivery settings facing different resource constraints must be prepared to implement antibiotic stewardship efforts. This needs to be a community of practice able to learn from one another and share best practices. Thirdly, a sentinel surveillance network must be able to flag hotspots not only of emerging drug-resistant pathogens, but of failure to follow the practices of effective antibiotic stewardship. Fourthly, the strategic work of these programs will require public transparency of data on antibiotic sales, trade, use, and resistance patterns, both for human and non-human applications. Fifth, model regulatory packages, including the removal of financial incentives from physician or veterinarian prescribing of antibiotics, need to be developed.

In parallel, efforts to curb the non-therapeutic use of antibiotics in animal husbandry and aquaculture will be critical. This needs to go beyond voluntary guidance to bans on certain uses in medicated feeds, restricted therapeutic use under veterinary prescription, a tax on non-human use of antibiotics, and the development of safe alternatives to antibiotics critically important for human treatment.

We could enumerate a lengthy list of main actors/stakeholders for carrying forward this action, but in executing the Global Plan of Action, strategic convenings could map out a “coalition of the willing” and a clear theory of change that would identify some actors as more critical to taking next steps. For example, how might a process engage national professional societies in guideline development and implementation, church-based health care delivery systems, or networks of accredited drug dispensing outlets as starting points? Hospitals engaged in medical tourism boast of delivering the latest medical advances and have every reason to be at the vanguard of tackling antibiotic resistance and being institutional pacesetters in their home countries. Could a network of these leading hospitals take on the challenge of antibiotic stewardship? Certainly few institutions would have as much to lose if such efforts fail.

**c) What steps have already been taken to address this priority? (please provide references where possible)**

ReAct has recognized the importance of adapting guidance and tools for different settings. ReAct’s online resource center has assembled fact sheets, policy and reports, and references as well as ReAct-produced materials.<sup>4</sup> Much more work needs to be done to pilot, focus group test, repurpose, and evaluate the effectiveness of IEC approaches, but making available the building blocks of such knowledge available is a critical starting point.

To create a more dynamic and interactive resource, ReAct is currently working on a “Toolbox for ABR” – a part of ReAct’s strategy to gather and disseminate evidence on how interested stakeholders can take action on antibiotic resistance. Technical assistance efforts must be coupled to and follow on such efforts. The Toolbox will contain database of resources as well as a collection of best practice examples and practical guidance from within and outside of the ReAct network.

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<sup>4</sup> ReAct—Action on Antibiotic Resistance, “Welcome to the ReAct Resource Center,” available at: <http://www.reactgroup.org/resource-center.html>

Various groups have sought to build a community of practice for achieving these ends, for example, through the Institute for Healthcare Improvement's breakthrough collaboratives, California's state-wide Antibiotic Stewardship Program Initiative that brings together hospitals sharing common challenges, and the regional convenings and study visits facilitated by ReAct's CSO project in Southeast Asia, but each of these initiatives cover only a subset of the ABR problem.

The work of Health Care without Harm's Healthier Hospitals Initiative in organizing hospitals to leverage their procurement systems to support healthier food choices is noteworthy. In partnership with Health Care without Harm, a task force at the University of California, San Francisco called upon the University to switch to antibiotic-free meats. By organizing six other hospitals in California to join its efforts, UCSF persuaded its supplier, US Foods, to source a line of beef products that does not routinely use antibiotics in raising its cattle.<sup>5</sup>

**d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)**

The use of indicators for continuous quality improvement and monitoring efforts, such as in the Healthcare Effectiveness Data and Information Set (HEDIS measures), might offer a starting point, but convening relevant stakeholders and researchers would be important to establish measures that could apply across a range of differently resourced healthcare settings.

In consultation with experts and civil society groups working to ensure healthy food systems and to curb non-therapeutic use of antibiotics in animal husbandry and aquaculture, WHO could develop comparable indicators that provide direct or indirect measure of progress towards this priority. This would entail mandating, perhaps with the assistance of businesses procuring such products if not governments, disclosure of antibiotic sales, use, and resistance patterns, by livestock and geography, in a way that would ensure greater monitoring and accountability.

**IV. Building block-4: Identifying and closing critical gaps in knowledge needed to address AMR**

**a) What do you consider to be the main issues under this priority?**

The identification and closing of critical gaps in knowledge needed to address AMR warrants a process of continual review. As strategic direction under the Global Plan of Action takes shape, the critical gaps to fill may shift or become manifest.

However, from bench to bedside, fundamental knowledge is key to developing an effective response to AMR. These areas of fundamental knowledge include, but are not limited to:

- Discovery of new mechanisms of drug resistance and new families of antibiotics with novel mechanisms of action;

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<sup>5</sup> Chen I. "Rehabilitating hospital food: aiming for healthy, sustainable and savory." *The Guardian*, 23 June 2014. Available at: <http://www.theguardian.com/sustainable-business/2014/jun/23/bay-area-hospital-food-healthy-grass-fed-organic>

- Surveillance of antibiotic resistance, with sentinel identification of novel, multi-resistant plasmids and hotspots where such resistance is emerging;
- Data transparency along the pharmaceutical value chain, including of patents and licensing, sales, use, clinical trial data of antibiotics and of antibiotic resistance patterns;
- Understanding of provider and patient behavior, with insights from behavioral economics to sociology, that would enable better design of interventions to ensure rational use of antibiotics;
- Impact of the use of antibiotics on microbial ecology and the human microbiome.

**b) What are the main actions that needs to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?**

With each identified critical gap, one could imagine a corresponding main action and actors/stakeholders who might be well positioned to make a catalytic difference. However, here we will just note some starting points that might lend an overarching framework for response:

1. *Global research coordination center.* While important research efforts have begun on antibiotic resistance in the North, there is need for a global research coordination center, focused on and based in the South. An important role for such a center would be generating strategically germane questions for research on these issues and ensuring that this research is conducted in the relevant context.
2. *Drug discovery platform.* As ReAct proposed in the WHO's innovation demonstration project process, there would be value in "Establishing a Drug Discovery Platform for Sourcing Novel Classes of Antibiotics as Public Goods."
3. *Antibiotic data transparency initiative.* Accountability to tackle AMR begins with transparency of the needed data along the pharmaceutical value chain, from bench to bedside, and in both human medicine and veterinary sectors.

**c) What steps have already been taken to address this priority? (please provide references where possible)**

An inventory of ongoing research efforts addressing critical gaps in knowledge is beyond the scope of what we can describe at this juncture. However, WHO should consider supporting such a landscape. Important work is ongoing on antibiotic R&D, both in the public and private sectors. Publicly funded initiatives are taking place in product development partnerships focused on tuberculosis (TB Alliance) and diagnostics for TB (FIND); in government-funded research efforts (NIH's NIAID and Antibiotic Resistance Leadership Group, BARDA, EU Innovative Medicines Initiative). Though upstream R&D on novel antibiotics deserves greater support, the research for reshaping provider and patient behavior with improved interventions is both less visible and less well coordinated.

**d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)**

Measurable indicators of progress for this priority would be the establishment of the various proposed main actions. For example, a drug discovery platform could have both qualitative and quantitative measures of progress. Qualitatively, it might achieve consensus on a benefit-sharing arrangement for sourcing natural products from local biodiversity

repositories. Quantitatively, one might count the number of drug candidates its efforts spawn.

## **V. Building block-5: Developing an innovative and sustainable approach to develop and distribute critical products and technologies needed to address AMR**

### **a) What do you consider to be the main issues under this priority?**

To develop an innovative and sustainable approach for bringing to market critical products and technologies needed to address ABR will require an array of public sector interventions. Importantly, these will have to deal with the near-term dearth of novel antibiotics, but also look beyond to complementary health technologies that might reduce the selective pressure of antibiotic use. The main issues under this priority include:

- *R&D prioritization process*: An observatory needs to be put in place to continuously monitor the pipeline of novel antibiotics and other technologies. Establishing target product profiles, applying systems thinking in weighing R&D funding priorities for complementary technology approaches (diagnostics and vaccines, not just drugs), and looking for synergy in coordinating research efforts would be useful in defining an R&D prioritization process.
- *Scientific bottlenecks*: The low-yield from high-throughput screening efforts and the mismatch between promising novel antibiotics and proprietary compound libraries suggest the need for different approaches to finding breakthrough drug candidates. Sourcing novel natural products from the biodiverse repositories in LMICs, supporting basic research (approaches that find new ways of penetrating the Gram-negative cell wall that might minimize resistance and serve as alternatives to antibiotics, or that enhance our understanding of the human microbiome), and ensuring collaborative approaches to R&D can help overcome scientific bottlenecks to antibiotic R&D.
- *Innovative financing*: Given limited public sector resources, the Global Plan of Action should focus on targeting incentives for antibiotics with truly novel mechanisms of action or significant clinical added value, piloting innovative financing approaches from prizes to delinkage mechanisms, and ensuring fair returns for the public investment. To develop new business models that are sustainable but that yield affordable end-products may require engaging non-traditional actors, as well as approaches, in pharmaceutical R&D. Building on the experience of product development partnerships in neglected diseases and patient disease foundations focused on rare diseases may offer ingredients for new business models to pilot.

The Global Plan of Action can serve an important role not only in guiding policymakers to promising strategies, but also in steering them away from ideas without merit. For example, the extension of data exclusivity for antibiotics—not necessarily novel or even clinically value added—under the Generating Antibiotic Incentives Now (GAIN) Act will cost U.S. taxpayers the costs of longer monopoly pricing, without the surety of sufficient economic incentive to bring truly novel antibiotics to market nor even of any fair returns to the public in the form of affordable pricing or antibiotic stewardship of these drugs. The idea of a transferrable voucher to extend market exclusivity of another drug is similarly ill conceived. The transferrable voucher would impose costs greater than the R&D reward to the

developer of the antibiotic in the form of 1) extended monopoly pricing on a blockbuster drug paid for by insurers and other patients by delaying introduction of generic alternatives and 2) uncertainty and revenue losses imposed upon generic companies (or R&D-intensive companies with generic arms) whose anticipated market introduction of follow-on products would be upended by a transferrable voucher.

**b) What are the main actions that need to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?**

The main actions that need to be done follow the contours of the three main issues mentioned. ReAct has also put forward two innovation demonstration proposals, both selected among the twenty-two advanced by WHO regional offices for global review: 1) “Establishing a Drug Discovery Platform for Sourcing Novel Classes of Antibiotics as Public Goods” and 2) “Building a Diagnostic Innovation Platform to Address Antibiotic Resistance.” Both proposals would have a useful place within the Global Plan of Action, but at the very least, would provide additional useful details on main actions and actors to take these next steps.

An innovative and sustainable approach, however, will require recruiting non-traditional actors, from product development partnerships now involved in neglected diseases to government research institutions and pharmaceutical firms in LMICs. National biorepositories positioned to share finds from the local biodiversity of natural products, clinical trial networks, specimen banks, and regional research networks like the African Network for Drug and Diagnostic Innovation are among the partners that might support the priorities under this area of work.

**c) What steps have already been taken to address this priority? (please provide references where possible)**

To develop an innovative and sustainable approach to bringing critical technologies and products for AMR forward will require marrying new business models with traditional ones. Many of these steps are still fledgling, might be borrowed from R&D efforts for other neglected diseases, or only suggest part of the solution path. Still these examples may have elements worth emulating, if not lessons worth weighing.

Describing the range of collaborative R&D approaches, we put forward the 3Rs framework: sharing resources, sharing risks, and sharing rewards.<sup>6</sup> Efforts like the Indian Council on Scientific and Industrial Research’s Open Source Drug Discovery Initiative on TB drugs deserve closer examination.<sup>7</sup> The recently announced Longitude Prize will focus on developing a “cost-effective, accurate, rapid and easy-to-use test for bacterial infections that will allow health professionals worldwide to administer the right antibiotics at the right time.” Whether this £10 million prize will make a difference (or not) depends on how the incentive is structured and whether cost-effective translates into affordable in resource-limited settings.

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<sup>6</sup> So AD, Ruiz-Esparza Q, Gupta N, Cars O. 3Rs for innovating novel antibiotics: sharing resources, risks, and rewards. *BMJ* 2012;334:e1782. doi: 10.1136/bmj.e1782 Available at: <http://www.bmj.com/content/344/bmj.e1782>

<sup>7</sup> So AD, Shah TA. New business models for antibiotic innovation. *Upsala Journal of Medical Sciences* 2014; 119: 176-180. Available at: <http://informahealthcare.com/doi/abs/10.3109/03009734.2014.898717>

**d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)**

The concrete and measurable indicators of progress for this priority include both surrogate and outcome measures, from novel antibiotic drug candidates under development to number of novel antibiotics brought to market. In the short term the repurposing of existing drugs, for example, by optimized dosing regimens or possibly combination therapies, might be achievable. In the longer term, there will be no substitute for bringing novel classes of antibiotics or breakthrough alternatives to antibiotics to market. Case studies of novel approaches to encouraging collaborative R&D for antibiotic innovation, the use of diagnostics to reduce inappropriate use of these drugs, and new efforts to tackle ABR through an understanding of the human microbiome may be as important as indicators that we can count numerically.

**VI. Building block-6: Assessing the long term economic, developmental and social costs and implications of AMR as a basis for sustainable investment and action**

**a) What do you consider to be the main issues under this priority?**

In assessing the long term economic, developmental and social costs and implications of AMR, several issues come to the fore as critical:

- Recognizing the value of effective antibiotics in enabling the practice of modern day medicine, from chemotherapy to surgical procedures;
- Assessing the role of tackling antibiotic resistance in meeting the health-related MDGs and bringing ABR into the post-2015 discussions of the Sustainable Development Goals;
- Developing ways of financing and delivering antibiotics as a public good rather than a normal good;
- Ensuring that social valuation considers the marginal cost-effectiveness and affordability of the technology in LMICs, not just industrialized countries;
- Providing a framework for benchmarking the opportunity costs of public investment for AMR compared to other societal priorities;
- Studying yet unforeseen consequences of overuse of antibiotics, e.g., whether childhood exposure to antibiotics might contribute to increased risks of obesity and asthma among other conditions; and
- Examining the trade-offs in prioritizing R&D for different technologies tackling AMR and also for different interventions responding to AMR in the healthcare delivery system.

This list could certainly be expanded upon in policy dialogues with key stakeholders, particularly from LMICs. However, apart from the economic and epidemiologic tally of AMR burden of disease, this kind of framework would be important in weighing the long term costs and implications of AMR.

**b) What are the main actions that needs to be done -- and who are the main actors/stakeholders who need to take action -- to go beyond the status quo?**

Important work needs to be undertaken to develop the policy framework suggested by the issues enumerated in VI.a. Civil society groups such as the People’s Health Movement, Third World Network, Health Action International, and South Centre can provide useful perspective and critical reflection on these issues. However, to ensure that the Global Plan of Action on AMR takes these perspectives into account, we would propose that:

- A global citizen’s panel for discussing the ethical and social implications of tackling AMR (touching on issues such as access and excess, affordability, benefit sharing from natural products derived from LMIC sources of biodiversity) be constituted; and
- Spotlight studies be commissioned to understand the local context, particularly in resource-limited environments, of tackling AMR.

Steps such as these would help inform the assessment of long-term costs and implications of AMR.

**c) What steps have already been taken to address this priority? (please provide references where possible)**

Early on, ReAct embarked on work with the EMA and ECDC to understand both the R&D pipeline for novel antibiotics<sup>8</sup> and the costs of AMR in the European context.<sup>9</sup> Such studies have provided useful impetus for raising policymaker awareness, such that we are at a different stage in tackling AMR. Studies like the recently released analysis by the Eastern Research Group, commissioned by the U.S. Department of Health and Human Services, also make a useful contribution in that such studies offer a starting point in looking at the cost worthiness of investing public monies into different economic incentives for pharmaceutical R&D for antibiotic innovation.

However, ReAct as a global network has long recognized and emphasized in its regional work a more holistic approach, one more deeply rooted in the local context. This has led the organization to caution against the use of the war metaphor in tackling AMR. Approaches grounded in an understanding of the human microbiome and the larger ecosystem may prove pivotal in what the long-term economic, developmental and social costs and implications in tackling AMR are.

**d) What are concrete and measurable indicators of progress for this priority? (Including, for example, global and national goals to be achieved within 2, 5 and 10 years)**

Concrete and measurable indicators for this priority may be more challenging to put forward. In part, the difficulty will be how to measure and bound the trade-offs between different courses of action—both narrowly construed as focused on AMR (e.g., investing in novel drug R&D vs. investing in approaches to conserve antibiotics) and more broadly

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<sup>8</sup> Freire-Moran L, Aronsson B, Manz C, et al. Critical shortage of new antibiotics in development against multidrug-resistant bacteria—Time to react is now. *Drug Resistance Updates* 2011; 14: 118-124. Available at: <http://www.reactgroup.org/uploads/publications/other-publications/critical-shortage-of-new-antibiotics.PDF>

<sup>9</sup> ECDC and EMEA. “The bacterial challenge: time to react.” Stockholm, Sweden: European Centre for Disease Prevention and Control, 2009. Available at: [http://www.ecdc.europa.eu/en/publications/Publications/0909\\_TER\\_The\\_Bacterial\\_Challenge\\_Time\\_to\\_React.pdf](http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf)



between AMR approaches and approaches not strictly focused on AMR (e.g., investing in second-line treatment of bacterial infections vs. investing in infection control and potable water). However, benchmarks for the opportunity costs of public investment in AMR (that is, what are we not doing because of claims on resources for tackling AMR) may help keep our societal efforts more focused. There will be temptation to throw public monies at the problem, much as the efforts to extend data exclusivity on antibiotics in the United States have proven to be inadequate but nonetheless costly as economic incentives for greater antibiotic innovation.

## **Concluding questions**

### **1. What contribution would your organization be able to make in implementing the global action plan?**

ReAct—Action on Antibiotic Resistance is a network of nodal institutions based in Europe, Latin America, Africa, Asia and the United States. We have a shared vision of “a world free from the fear of untreatable infections,” and along these lines, ReAct and its partner organizations are working to generate and translate the evidence, develop strategic policy options, and educate, empower and extend the networks engaged in efforts to tackle AMR. We stand prepared to work with WHO and other partners in both formulating and implementing the global action plan.

Recognizing that our resources and reach are limited, we have worked this past year to help nurture and incubate the creation of an inter-sectoral coalition of civil society organizations—the Antibiotic Resistance Coalition (ARC). The work of ARC recognizes the need for solutions and expertise across human medicine and veterinary sectors, in a broader development context, and grounded in consumer concerns reflected by civil society. We believe that the Coalition will, for the first time, provide a nexus for finding common ground and useful exchange among these perspectives. We hope that the WHO and its partners will reach out to ARC as well on the road to developing a global action plan.

### **2. Additional input that you feel would facilitate development of the GAP.**

We would refer WHO to the principles embraced in the Declaration, put forward by the Antibiotic Resistance Coalition, available at:

<http://sites.duke.edu/ghtaprogram/files/2014/05/ARC-declaration-May-22-2014.pdf>