BRIDGING THE GAP: A POLICY BRIEFING ON NEXT STEPS FOR TACKLING ANTIMICROBIAL RESISTANCE

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From basic healthcare to the latest advances in organ transplants and chemotherapy, antibiotics have become indispensable. The important momentum begun with the World Health Assembly's adoption of a Global Action Plan on Antimicrobial Resistance continued this past year with the UN General Assembly's adoption of the Political Declaration on Antimicrobial Resistance. The commitments that Member States have made to respond to the challenge of antimicrobial resistance must be followed by global and national action. Effective antibiotics are fundamental to the realisation of the Agenda 2030, and growing antimicrobial resistance has a negative impact on many of the global Sustainable Development Goals.

Across multiple provisional agenda items of the 140th session of the WHO Executive Board, antimicrobial resistance plays an important role:

- 7.2 Antimicrobial resistance
- 8.3 Addressing the global shortages of medicines and vaccines
- 8.5 Follow-up on the report of the CEWG
- 9.1 Global Vaccines Action Plan
- 11.1 Progress in the implementation of Agenda 2030 for Sustainable development

This briefing lays out key evidence, offers guiding principles, and suggests opportunities for policy action to tackle antimicrobial resistance, both directly and through the lens of related issues.

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Provisional Agenda Item 7.2: Antimicrobial resistance

In updating the Member States on the United Nations General Assembly High-level Meeting on Antimicrobial Resistance (New York, 21 September 2016), the Report by the Secretariat highlights three major requests to WHO and its partners: 1) Finalizing the global development and stewardship framework on antimicrobial medicines and resistance; 2) Support national action plans and other activities to counter antimicrobial resistance at the national, regional and global levels; and 3) Provide consultation to the Secretary-General on an ad hoc interagency coordination group to provide practical advice on approaches to ensure effective action to address antimicrobial resistance.

1. Finalizing the global development and stewardship framework on antimicrobial medicines and resistance

In May 2016, the framework report to the World Health Assembly noted that "Resolution WHA68.7 also specifies that the framework promote affordable access to existing and new antimicrobial medicines and diagnostic tools." The UNGA resolution extended this charge by calling upon WHO, together with FAO and OIE, "to finalize a global development and stewardship framework, as requested by WHA68.7, to support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions, while preserving existing antimicrobial medicines, and promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries, and in line with the Global Action Plan on AMR."

1.1 Conserving antibiotics must be balanced by the need to ensure appropriate access to these life-saving drugs—access, but not excess.

Lack of access to antibiotics remains a serious concern. Treatable infectious diseases claim the lives of 5.7 million people a year.[1] If antibiotics were universally available to children under five years old, three quarters of the deaths in this age group from community-acquired bacterial pneumonia might be averted.[2] This lack of access, however, is not just from stockouts or shortages of these drugs, but also from drug resistance rendering these antibiotics ineffective. A WHO surveillance survey of 114 countries found that at least half of the *E. coli* and *K. pneumoniae* samples were resistant to 3rd generation cephalosporins across nearly all or all WHO regions, leaving only carbapenems as last-line option for such infections.[3] Resistance to first-line antibiotics has been estimated to result in over 56,000 neonatal deaths in India and over 25,000 neonatal deaths in Pakistan.[4]

According to UNICEF, pneumonia and diarrhea account for more than one out of every four children dying under age 5 globally. If we could lift the level of care for these two diseases across the 75 countries with the highest mortality such that the bottom 80%

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[1] Daulaire N, Bang A, Tomson G, Kalyango JN, Cars O. Universal Access to Effective Antibiotics is Essential for Tackling Antibiotic Resistance. *The Journal of Law, Medicine & Ethics*, 2015; 43(S3): 17-21.

[2] Laxminarayan R, Matsoso P, Pant S, Brower C, Rottingen JA, Klugman K, Davies S. Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016; 387: 168-75.

[3] World Health Organization. *Antimicrobial Resistance: Global Report on Surveillance*. Geneva, Switzerland: World Health Organization, 2014.

[4] Laxminarayan R, Bhutta ZA. Antimicrobial resistance—a threat to neonate survival. *The Lancet Global Health*. 2016; 4(10), e676-e677.

were treated as well as the top 20% of households in each country, by 2015, two million children could have been saved from dying of pneumonia and diarrhea.[5]

Yet fewer than a third of children with suspected pneumonia received antibiotics globally.[6] And the situation is worse for the poorest children in low-income countries. While stock-outs and shortages of inventories of antibiotics are a problem in some places, do second-line antibiotics for drug-resistant infections ever make it to local hospitals? By contrast, less than four in ten children receive appropriate treatment with oral rehydration therapy for diarrhea. Ironically many of these children will receive inappropriate treatment with antibiotics. Importantly, WHO is supporting a multi-country clinical trial to assess whether antibiotics should play a role in treating diarrhea in children under two years of age with dehydration or malnutrition.[7] The key is to ensure access, but not excess.

These twin goals of access and conservation should not be at odds with one another, but are both integrally part of an effective response to ensuring access to effective antibiotics.

WHO's Monitoring and Evaluation framework for countries should measure access to first- and second-line antibiotics as surely as it captures compliance with infection control measures that help healthcare systems conserve the use of these drugs.

1.2 "Development" involves supporting a sustainable ecosystem of antibiotic innovation, including public-private partnerships that ensure fair returns on the public's investment and open, collaborative models of R&D.

The key scientific bottleneck to bringing novel antibiotics to market is in the drug discovery phase. R&D for novel antibiotics has a much lower yield of promising compounds in the discovery stage than other therapeutic areas.[8] Compared to all drug classes, antibacterial drugs have a ten-fold lower yield in this initial stage of identifying promising new compounds. Incentives to target this scientific bottleneck in antimicrobial drug development are critical. Importantly, upfront investments early in the R&D pipeline can stretch the public investment funding further. Discounting over time erodes the value of later investments. So when compared by present value, a push incentive that pays for inputs of R&D early on can be significantly smaller—in one model, 95% smaller--than the equivalent pull incentive (such as extended exclusivity).[9]

To build a more sustainable ecosystem of antibiotic innovation, R&D financing should work to transform strategically the innovation ecosystem rather than solely make bets on one company or one drug at a time. Resources directed to early stage R&D could enable

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[5] UNICEF. *Pneumonia and diarrhoea: Tackling the deadliest diseases for the world's poorest children.* New York, New York: UNICEF, 2012.
[6] UNICEF and WHO. *Ending Preventable Child Deaths from Pneumonia and Diarrhea by 2025: The integrated Global Action Plan for Pneumonia and Diarrhea (GAPPD)*. Geneva, Switzerland: World Health Organization, 2013.
[7] University of Washington. "Department Part of Major Study to Test Antibiotics as a Treatment for Diarrheal Disease in High-Risk Children in Low Resource Settings," August 10, 2016. Available at: http://globalhealth.washington.edu/news/2016/08/10/department-global-health-part-major-study-test-antibiotics-treatment-diarrheal
[8] Payne DJ, Gwynn MN, Holmes DJ, Pompliano L. Drugs for bad bugs: confronting the challenges of antibacterial discovery. *Nature Reviews Drug Discovery* 2007; *6*(1): 29-40.
[9] Spellberg B, Sharma P, Rex JH. The critical impact of time discounting on economic incentives to overcome the antibiotic market failure. Correspondence. *Nature Reviews Drug Discovery* 2012; 11(2): 168.

this by targeting investment and incentives towards more collaborative approaches, including by:

- building innovation platforms that engage others to embark on finding new classes of antibiotics yet undiscovered by conventional means, including through natural products and traditional knowledge across low- and middle-income countries;[10]
- sharing clinical trial data and creating clinical trial networks to enroll patients with drug-resistance infections; and
- developing an open source, diagnostic platform for point-of-care tests that might help multiple drug companies more rapidly enroll patients with drug-resistant, Gram-negative infections into clinical trials.[11]

Growing out of the Global Action Plan on Antimicrobial Resistance, WHO and the Drugs for Neglected Diseases Initiative (DNDi) proposed the creation of the Global Antibiotic Research and Development Partnership (GARDP), a product development partnership focused on developing new antibiotic treatments and on ensuring their responsible use and equitable access to those in need.[12]

WHO and Member States should work to transform the innovation ecosystem for antimicrobial drug R&D and support the development of open source innovation platforms for drugs and diagnostics to tackle antimicrobial resistance, such as those advanced by WHO/DNDi GARDP.

1.3 Greater resources must be mobilized and targeted to where there remain gaps in innovation to tackle antimicrobial resistance, both across healthcare delivery and agricultural systems.

Research need	Human Use	Animal Use
Innovation of Technology	Drugs, vaccines, diagnostics and other health technologies	Vaccines and diagnostics for animals
Innovation of Practice (Stewardship)	Practices that encourage access, but not excess in Healthcare Delivery	Practices that encourage Sustainable Agriculture, while curbing non-therapeutic use of antibiotics

Policymaker and funder attention has disproportionately focused on innovation of health technologies for human use, most notably antibiotic drugs. However, both diagnostics and vaccines could play key roles in extending the effective life of antibiotics, but substantially less new funding has come forward for these complementary technologies. Yet developing and delivering a rapid diagnostic test for bacterial pneumonia suited for

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[10] So AD, et al., Duke University Program on Global Health and Technology Access and ReAct. *Establishing a Drug Discovery Platform for Sourcing Novel Classes of Antibiotics as Public Goods* (Proposal for WHO Innovation Demonstration Project), available at: http://www.who.int/phi/implementation/16.pdf

[11] So AD, Shah TA. New business models for antibiotic innovation. *Upsala Journal of Medical Sciences* 2014; 119: 2: 176-180.

[12] WHO and DNDi. *Investing in the Development of New Antibiotics and Their Conservation: A Proposal for a Global Antibiotic Research and Development Facility to Promote Research, Responsible Use, and Access to New Antibiotics*, Updated Concept Note, December 18, 2015. Available at: http://www.dndi.org/wp-content/uploads/2016/03/Global_Antibiotic_RD_Facility_Concept_Note.pdf

use where there is minimal infrastructure could save more than 405,000 lives each year, much of it by reducing overtreatment with antibiotics.[13] With most of the antibiotics though used in food animal production and agriculture as opposed to humans, a One Health approach is critically important, and this would require investing in the development of new diagnostics and vaccines for animal health as well. As demonstrated years ago in Norwegian salmon aquaculture, the introduction of vaccines contributed significantly to lowering the use of antibiotics.[14]

Similarly, investment in antibiotic stewardship efforts in both the healthcare delivery system and in agricultural practices must proceed apace if society is to conserve these life-saving drugs. Investment in the innovation of practice, both in clinical medicine and in animal husbandry and aquaculture, would pay significant dividends. According to one calculation, delaying the need for the proposed $1 billion USD market entry reward for a new antibiotic by just one year would be worth $60 million (assuming a discount rate of 6 percent).[15]

The quadrant diagram above shows how investments in innovation must cut across both human and animal sectors as well as from technology to practice. The Global Antimicrobial Resistance Surveillance System (GLASS) proposes to advance AMR surveillance across countries, and the UK's Fleming Fund might provide modest support for some of these efforts. Other initiatives such the Global Antimicrobial Resistance Innovation Fund and the Joint Programming Initiative on Antimicrobial Resistance's Fifth call for proposals on "Prevention and Intervention Strategies to Control AMR Infections" also may support such efforts.[16] Similarly, increased funding of infection prevention programs, public awareness campaigns, and more human resources in low- and middle income countries—as called for in the proposed Global Antimicrobial Conservation Fund[17]--would be welcomed. However, these efforts still leave gaps among the four quadrants of needed investment in innovation, especially on the side of animal use of antibiotics.

The WHO should build upon these initiatives by bringing together key funders and stakeholders to set clear priorities and options for financing the other neglected areas of innovation in healthcare delivery and agriculture.

1.4 To ensure sustainable access to effective antibiotics, the "Development" component of the global development and stewardship framework must support approaches for financing R&D and product procurement consistent with delinkage.

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[13] RAND Research Highlights. *Estimating the Global Health Impact of Improved Diagnostic Tools for the Developing World.* Santa Monica, California: RAND Corporation, 2007.

[14] Tveteras S. Norwegian salmon aquaculture and sustainability: the relationship between environmental quality and industry growth. Discussion Paper No. 4/2002, Centre for Fisheries Economics, Institute for Research in Economics and Business Administration, February 2002.

[15] Laxminarayan R. Antibiotic Effectiveness: Balancing conservation against innovation. *Science* 2014; 345(6202): 1299-1301.

[16] The Global Antimicrobial Resistance Innovation Fund and the Joint Programming Initiative on Antimicrobial Resistance's Fifth call for proposals on "Prevention and Intervention Strategies to Control AMR Infections". Available at: http://www.jpiamr.eu/pre-call-announcementfifthcall/

[17] Mendelson M, Dar OA, Hoffman SJ, Laxminarayan R, Mpundu MM, Røttingen JA. A global antimicrobial conservation fund for low-and middle-income countries. *International Journal of Infectious Diseases* 2016; 51: 70-72.

If drug companies realize greater returns by selling more antibiotics, then the economics of drug R&D will run counter to the goal of conserving these life-saving drugs for those truly in need. There is broad agreement that an R&D system that delinks fully the return on investment from both end product prices and sales volumes of the drug would help resolve this tension. The concept of delinkage, as originally framed by the WHO's Consultative Expert Working Group on Research and Development: Financing and Coordination, sought to divorce the return on investment from the price of the product. Applied to antibiotics—where greater use generates greater drug resistance—the goal needs to control volume. The concept of delinkage for antibiotic R&D has been advanced by ReAct,[18] supported by the Davos Declaration by industry,[19] recognized as an important organizing principle for a new business model for antibiotic R&D in a Chatham House report,[20] and called for in both the Global Action Plan on Antimicrobial Resistance [21] and the UNGA Political Declaration.[22]

WHO and Member States should work to ensure the application of the Global Development and Stewardship Framework and the piloting of delinkage mechanisms in funding vehicles, from Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and the Global Antimicrobial Resistance Innovation Fund (GAMRIF) to initiatives under consideration at the G20 and other policy fora.

2. Support national action plans and other activities to counter antimicrobial resistance at the national, regional and global levels

As of early December, thirty-two countries had completed national action plans, and at least another fifty-nine countries reported making progress in drafting them. Political engagement and support is uneven across the Member States, and coordinating across sectors on AMR has been a challenge. Complementing WHO's efforts, within its modest resources, ReAct has provided technical assistance and feedback on draft national action plans and has organized resources to support these efforts through the ReAct Toolbox-– a free online tool that compiles existing guiding material, country experiences and intervention examples.

Various civil society groups have mounted workshops in support of the global action plan on AMR. In December 2015, the ReAct Strategic Policy Program coordinated an international workshop with technical experts, civil society organizations, and government stakeholders to discuss monitoring for accountability, from how to collect

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[18] So AD, Ruiz-Esparza Q, Gupta N, Cars O. 3Rs for innovating novel antibiotics: sharing resources, risks, and rewards. *British Medical Journal*, 2012; 344(3), e1782.

[19] *Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance*, January 2016. Available at: https://amr-review.org/sites/default/files/Declaration_of_Support_for_Combating_AMR_Jan_2016.pdf

[20] Outterson K, Gopinathan U, Clift C, So AD, Morel CM, Røttingen JA. Delinking Investment in Antibiotic Research and Development from Sales Revenues: The Challenges of Transforming a Promising Idea into Reality. *PLoS Med* 2016; 13(6), e1002043.

[21] World Health Organization. *Global Action Plan on Antimicrobial Resistance*. Geneva, Switzerland: World Health Organization, 2015. Available at: http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1

[22] UN General Assembly. *Political declaration of the high-level meeting at the UN General Assembly on antimicrobial resistance*. New York, NY: United Nations, 2016. Available at: http://www.un.org/pga/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf

actionable data in resource-limited settings to how to shape markets through consumer campaigns. The workshop participants approached this from a range of vantage points—some focused on antibiotic use in humans and others on its use in animals—but convergent on a One Health approach to hold key actors, from intergovernmental agencies, industry and country governments accountable. ReAct Latin America has worked closely with the government of El Salvador as well as their National Forum for Civil Society in co-organizing a series of workshops to provide technical assistance for national action plan development across sectors. During the 2016 World Antibiotic Awareness Week, ReAct Africa co-hosted a policy meeting on AMR with representatives from the Kenyan ministries of health and agriculture, university researchers, civil society, and other stakeholders to discuss the country's national action plan and identify entry points for stakeholders to take action on AMR. In November 2016, the Centre for Science and the Environment in India held an International Workshop on National Action Plan on Antimicrobial Resistance for Developing Countries with a focus on the environmental aspects of antimicrobial use. Still these efforts offer only a starting point. Not all of the national action plans make SMART goals (SMART=specific, measurable, agreed upon, realistic and time-based), and much work lies ahead in mobilizing the needed resources—both financial and technical--and setting clear priority among the goals.

2.1 To be meaningful, National Action Plans should demonstrate SMART goals, clear priority setting, and resource commitments commensurate to their proposed plans.

As the deadline for Member States to put forward national action plans draws near, it would be useful to take stock of the process and product at the country level. Did the process by which the national action plan was formulated engage key constituencies, or was it planned without such input? Are there measurable, time-bound goals specified in the national action plan? Were resources—financial and technical—identified, secured and appropriated to implement the national action plan? Does the national action plan reflect a whole-of-government, multisectoral commitment? Does the national action plan have clear priorities set, with recognition of what local investments would yield the greatest return? For these national action plans to be impactful, they must reflect the local context and go beyond "cut and paste" assemblages of what sound like good policy, but which have little anchoring in reality. Data gaps, particularly of AMR surveillance, hinder planning efforts. However, the act of putting on paper a national action plan is an important first step.

Not all governments will have sufficient resources to implement a national action plan. And Member States face vastly different baseline resources. For example, an OIE survey found very weak infrastructure for veterinary services in developing countries, even where food animal production featured prominently in the local economy.[23]

To assist countries in directing and assessing where resources are required and optimally deployed, WHO could offer critical assistance by supporting the development of a needs assessment tool and a priority setting decision framework.

2.2 Implementing national action plans on AMR will require adequate resources, both financial and technical.

[23] Bonnet P, Lancelot R, Seegers H, Martinez D. Contribution of veterinary activities to global food security for food derived from terrestrial and aquatic animals. Paris, France: 79th General Assembly of the World Organization for Animal Health, 2011, pp. 22-27.

Undertaking the implementation of a national action plan on AMR requires both financial and technical resources. Global commitments for AMR fall far short of what is required. Both the UK Review on AMR and the World Bank have projected massive, future economic losses from AMR—at least US$100 trillion by 2050--that would make a multiple of today's investment a bargain.

Working with available resources, WHO is well positioned to support, in concert with its partners, clearinghouse efforts, regional and local technical assistance webinars, access to pools of relevant experts, and a community of practice among those grappling with similar challenges to tackle AMR.

2.3 Mobilizing key constituencies to implement the national action plans requires more than just raising public awareness: it requires a strategy for engaging and enlisting these groups in a campaign.

Gauging public awareness of antimicrobial awareness, WHO commissioned a survey of over 9700 individuals in 12 countries and found mixed results on their knowledge of antibiotics and of antibiotic resistance.[24] Various groups have called for public awareness campaigns.[25] While greater awareness among healthcare providers, veterinarians, patients and consumers, farmers and others would be welcomed, such funding might be more strategically targeted towards mobilizing key constituencies through campaigns. Some of these campaigns on reducing consumer demand for antibiotics draw from examples in high-income settings, but with adaptation and piloting, might inform efforts in less well resourced settings.

Various groups, from governments to professional societies, have carried out campaign-style efforts to promote rational use of antibiotics. Thailand's Antibiotic Smart Use (ASU) project offers a useful exemplar from an LMIC setting.[26] Piloting this innovative model before scale up, ASU sought to avert the unnecessary use of antibiotics for treatment of non-bacterial infections. Focusing on three target conditions (upper respiratory infections, acute diarrhea and simple wounds), the project applied a range of modalities. These included providing materials for health professionals to educate their patients, incorporating ASU practice in the pay-for-performance criteria of the country's universal health care coverage scheme, and providing herbal alternative, non-antibiotic therapies to relieve symptoms of viral infection. The initiative emphasized ownership by its local partners, but also encouraged exchange of best practices across the ASU network and its champions.

Beginning as an informal partnership between experts and government authorities, Strama (The Swedish Strategic Programme Against Antibiotic Resistance) working with the National Board of Health and Welfare laid the groundwork for a national action plan on antibiotic resistance.[27] Its network of local groups of communicable disease control, at

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[24] World Health Organization. Antibiotic resistance: multi-country public awareness survey, 2015. Available at: http://apps.who.int/iris/bitstream/10665/194460/1/9789241509817_eng.pdf?ua=1

[25] UK Review on Antimicrobial Resistance, chaired by Jim O'Neill (May 2016). *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. Available at: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

[26] Sumpradit N, Chongtrakul P, Anuwong K, et al. Antibiotics Smart Use: a workable model for promoting the rational use of medicines in Thailand. *Bulletin of the World Health Organization* 2012; 90:905-913.

[27] Olstad S, Cars O, Struwe J. STRAMA-A Swedish working model for containment of antibiotic resistance. *Eurosurveillance* 2008; 13(46):1-4.

the level of county departments, brought physicians, pharmacists and healthcare professionals together in common cause. Sharing of local data, developing local treatment guidelines, and sharing their efforts at national meetings fed into the work of a national office. In turn, the national office supported local activities, provided analysis of these local data, and developed interventions as well as organized educational events. Strama undertook analysis of antibiotic consumption in Sweden, surveys of clinical prescribing practice, point prevalence studies, and targeted studies such as of antibiotic prescribing in nursing home settings. Strama's efforts successfully lowered national antibiotic use in Sweden and also provides a useful model of a campaign enlisting multidisciplinary teams of professionals.

Civil society organizations have also shown how campaigns can reshape policy on AMR while raising consumer and provider awareness of these issues. Over the past few years, members of the Antibiotic Resistance Coalition (ARC)[28] and its allies have called upon retail outlets to make time-bound commitments to source food animal products without the routine use of antibiotics. Waging these campaigns against prominent franchises, like Wendy's and Burger King, has heightened public attention to AMR issues. Using scorecards to track the progress of restaurant chains on their antibiotic policies has already registered a difference. Between the first and second year of the *Chain Reaction* report, twice the number of companies among the top 25 largest fast food and fast casual restaurant chains in the United States received a passing grade.[29] Consumers International and its members have sought to globalize such efforts, and their report, "Antibiotics off the Menu," targeted KFC, McDonald's and Subway to make global commitments to stop serving food animal products routinely given antibiotics important in human medicine.[30] Health Care without Harm, another ARC member, partners with hospitals to "source and serve foods that are produced, processed, and transported in ways that are protective of public and environmental health." Shaping procurement practices, their "Healthy Food in Health Care" campaign has targeted hospitals not to procure meat raised with the routine use of antibiotics. Together such interventions help shape procurement practices and market signals in the food supply chain.

As part of the Institute for Healthcare Improvement's 100,000 Lives, later the 5 Million Lives, campaign in the U.S., hospitals pledged to implement a select number of targeted interventions to reduce preventable errors in healthcare.[31] These included reducing methicillin-resistant *Staphylococcus aureus* (MRSA) infection through basic improvements in hospital infection control. Hospitals also made public commitments to achieve specific, numeric goals in improving patient safety through these measures. In the 5 Million Lives Campaign, over 4000 hospitals participated, of which over 2000

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[28] Formed in May 2014, the Antibiotic Resistance Coalition is comprised of twenty-five civil society and intergovernmental organizations committed to the shared principles outlined in the Antibiotic Resistance Declaration, available at: http://abrdeclaration.org/home/.

[29] Stashwick S, Brook L, Halloran J, Bohne M, Hamerschlag K, Harsh C, Roach S. *Chain Reaction II: How Top Restaurants Rate on Reducing Use of Antibiotics in Their Meat Supply*, September 2016. Available at: http://webiva-downton.s3.amazonaws.com/877/c1/e/9136/1/NRDC_ChainReaction2_ExecSumm.pdf

[30] Consumers International (February 2016). *Antibiotics Off the Menu: How Global Restaurant Chains Can Help to Tackle Antibiotic Resistance*, February 2016. Available at: http://www.consumersinternational.org/news-and-media/resource-zone/antibiotics-off-the-menu/

[31] Institute for Healthcare Improvement. "Protecting 5 Million Lives from Harm: Some is Not a Number. Soon is Not a Time." Available at: http://www.ihi.org/engage/Initiatives/completed/5MillionLivesCampaign/Pages/default.aspx

facilities pursued all 12 targeted interventions, and 200 hospitals served as mentors—sharing their experiences as peers--to others in the Campaign.

Complementing such campaigns was the Institute for Healthcare Improvement's Breakthrough Collaborative model—an approach for structuring learning and action that engaged healthcare organizations to make system improvements.[32] Experts served as Improvement Advisors, teaching and coaching healthcare teams on how to improve and apply these methods in their local settings. Participating healthcare organizations apply to become part of a Collaborative and agree to meet certain expectations, from engaging in the Learning Sessions and prework conference calls to carrying out "small-scale tests of change" that lay the groundwork for larger changes in standard practices. They describe the improvement process as having four key elements: "specific and measurable aims; measures of improvement that are tracked over time, key changes that will result in the desired improvement, and a series of testing 'cycles' during which teams learn how to apply key change ideas to their own organizations."

Through the 5 Million Lives Campaign and the Breakthrough Collaborative model, the Institute for Healthcare Improvement helped to create communities of practice across hospitals working to achieve these goals. These efforts recruited support from local institutions and funders.

As in tobacco control and efforts to encourage handwashing by healthcare workers, there is considerable promise in taking a campaign approach, with measurable targets, a community of practice and the opportunity for tangible, local investment.

Calling upon funding agencies to support the work of partners, WHO should transform public awareness raising into organized campaign efforts that mobilize and enlist key communities of practice and civil society to tackle AMR.

2.4 Monitoring for accountability will require improved surveillance and data collection, defining targets that are meaningful and sensitive to the local context, and ensuring that data made transparent is actionable.

Monitoring is key to ensuring accountability. Yet significant data gaps exist. In both the healthcare delivery system and in food animal production, systematic and reliable data on sales, pricing, and use of antibiotics are hard to come by. UN COMTRADE data do not distinguish between antibiotics destined in trade for human vs. veterinary uses. Resistance data from hospitals are spotty, and for farms, often not accessible apart from occasional research studies. A commissioned paper for the UK Review on AMR provides a preliminary assessment of these data gaps in costing the lowering of antimicrobial use in food animal production.[33]

With parallels to the Global Health Security Initiative's Joint External Evaluation approach, the WHO has embarked on a survey of Member States using a similar

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[32] Institute for Healthcare Improvement. *The Breakthrough Series: IHI's Collaborative Model for Achieving Breakthrough Improvement.* Cambridge, Massachusetts: Institute for Healthcare Improvement, 2003. Available at: http://www.ihi.org/resources/pages/ihiwhitepapers/thebreakthroughseriesihiscollaborativemodelforachievingbreakthroughimprovement.aspx

[33] So A.D., Ramachandran R., Love D.C., Korinek A., Fry J.P., Heaney C.D. (2016). *A Framework for Costing the Lowering of Antimicrobial Use in Food Animal Production.* Commissioned paper for the UK Review on Antimicrobial Resistance. Available at: https://amr-review.org/sites/default/files/ReAct_CLF_Hopkins_UKAMRReview_CommissionedPaper.pdf

methodology in their Monitoring and Evaluation instrument. Across a range of dimensions the instrument seeks a self-report of country performance on measures related to AMR. Self-appraisal is an important and valuable step in implementing the national action plans. The monitoring and evaluation framework calls for posting one response per country, "validated by all involved sectors," to the on-line survey. However, it is challenging to know whether countries may err in underreporting or overreporting their progress. If countries believe these self-reports will be used in regional comparisons or a global scorecard, there is the risk of overreporting progress. If these self-reports form part of a needs assessment for funding, say, from the Fleming Fund or other sources, one could imagine the risk of underreporting. To ensure more effective capture of these data, ReAct has also asked that the WHO allow civil society, academic institutions and others to share supplemental information on-line and alongside the one response per country.

Accountability also requires having a set of shared principles against which to benchmark one's efforts. After all, resolving the challenges of antibiotic overuse does put economic interests of different stakeholders in opposition. What is the pharmaceutical industry's responsibility as opposed to the provider's in ensuring rational use of these products? Do late-stage market entry rewards for antibiotic innovation favor larger pharmaceutical companies or smaller start-ups? Does delinkage—divorcing the return on investment from sales price and volume of antibiotics—allow for close-to-marginal cost pricing or topping off monopoly rents by drug companies? The Antibiotic Resistance Coalition, comprised of twenty-five or so civil society organizations, has committed to such a shared set of guiding principles in its Antibiotic Resistance Declaration. Already its members are involved in monitoring different parts of the supply chain of antibiotics, from antibiotic innovation to the sourcing of food animal products in retail outlets. And there will remain an important need for independent watch efforts, particularly as the implementation of the Global Action Plan goes forward.

There is also important work to be done to set targets—milestones by which progress might be measured. These selected measures will require ensuring relevant surveillance and data collection as well as holding stakeholders accountable to their commitments. One group has proposed setting global targets, whereby no country's consumption of antibiotics exceeds the current median global level of 8.5 defined daily doses (DDD) per capita per year.[34] The use of medians as targets—unadjusted for local context--warrants a deeper analysis that it would not exacerbate underuse as opposed to reduce overuse in low- and middle-income countries. Proposals for an antibiotic tax on the animal use of antibiotics might have applicability in some settings. However, the potential disparate impact on the livelihoods of small scale farmers and aquaculture operations as opposed to large-scale agribusiness need to be considered. If those with marginal livelihoods are forced to forego the therapeutic use of antibiotics in response to such taxes—or as has been suggested in India, resort to less expensive antibiotics meant for human medicine—will the policy aims be sustainable, let alone achievable? As illustrated by these examples, countries need workable options appropriate to the local context when responding to targets. Analysis of these policy options is urgently required.

The WHO should provide guidance on how to set measurable and impactful milestones—sensitive to the local context--for tracking progress on AMR, analyze workable policy

[34] Laxminarayan R, Sridhar D, Blaser M, Wang M, Woolhouse M. Achieving global targets for antimicrobial resistance. *Science* 2016; 353(6302): 874-875.

options suited for differently resourced settings, and call upon Member States, industry and other stakeholders to make data available and publicly transparent for independent watch efforts to monitor for accountability.

3. Provide consultation to the Secretary-General on an ad hoc interagency coordination group to provide practical advice on approaches to ensure effective action to address antimicrobial resistance.

The UNGA's Political Declaration on AMR created an Interagency Coordination Group, co-chaired by the Executive Office of the Secretary-General and WHO. The Interagency Coordination Group provides an important mechanism for (1) "drawing, where necessary, on expertise from relevant stakeholders, to provide practical guidance for approaches needed to ensure sustained effective global action to address antimicrobial resistance"; (2) "request the Secretary-General to submit a report for consideration by Member States by the seventy-third session of the General Assembly on the implementation of the present declaration" in September 2018; and (3) report on "further developments and recommendations emanating from the ad hoc inter-agency group, including on options to improve coordination, taking into account the global action plan on antimicrobial resistance."

3.1 Importantly, the Interagency Coordination Group should embrace the principles of transparency, openness and accountability in its operations and enlist the cooperation of other partners, especially civil society.

Understandably, changes at the helm of the United Nations and shortly the World Health Organization may slow the ramp up of the activities of the Interagency Coordination Group. However, there is currently little clarity about where the process stands, what mandate the coordination group will have, its governance structure, who decides what agencies and other non-UN actors it will include nor who will lead it.

WHO should work to improve the transparency of the process to establish the ad hoc Interagency Coordination Group (IACG) and ensure that other partners are consulted in this process, especially civil society.

3.2 To avoid the perception of financial conflict of interest in its governance and workings, an independent expert advisory committee should be established to support the work of the Interagency Coordination Group.

The independence of the Interagency Coordination Group is essential for its success. If its deliberations are captive to a few UN agencies or Member States or swayed by concerns over those with financial conflict of interest, the credibility and broader buy-in to its work will be undermined.

To help ensure that the work of the Interagency Coordination Group is grounded in evidence and not unduly influenced by potential financial conflict of interest, WHO should recommend that an expert advisory committee be established to support the work of the IACG with relevant scientific and policy input. Appropriate conflict of interest policies should be developed for such a committee.

Several other items on the WHO Executive Board agenda relate to antimicrobial resistance and also present opportunities to advance policies supportive of work on this issue.

PROVISIONAL AGENDA ITEM 8.3:
Addressing the Global Shortages of Medicines and Vaccines

One problem faced by many countries is shortages and stockouts of essential antibiotics. India—a country with a significant TB disease burden--has reported concerns over shortages of kanamycin, a drug for treating multi-drug resistant tuberculosis.[35] Even for industrialized countries, antibacterial drug shortages have commonly occurred. From 2001 to 2013, the United States experienced 148 shortages of antibacterial drugs, a median of 10 new shortages per year.[36] In a survey of infectious disease physicians in the United States, over three-quarters reported having to modify treatment regimens because of antibacterial drug shortages over a two-year period.[37] Such shortages have spurred price increases, such as the 8000% rise in the price of an old antibiotic, doxycycline, from $20 to $1849 between October 2013 and April 2014.[38] Shortages and stockouts are not limited to the United States.

Nor is the problem limited to commonly used antibiotics. With growing resistance, older antibiotics are being brought back for use. In a study of 38 countries including Europe, United States, Canada and Australia, two-thirds of the systemic antibacterials surveyed were available in only just half of the 38 countries.[39] Of the 33 antibiotics reviewed, 31 had activity against resistant bacteria or unique clinical value, confirmed by literature review. Many of these drugs are now generic, but discontinued largely because of the economics of maintaining their supply. Lack of availability may be due to shortages and/or stock-outs, but are also a result of lack of registration in countries, import restrictions or undesired market withdrawals of important antibiotics by companies for commercial reasons.[40]

By history, WHO has worked to improve the availability of essential drugs and vaccines through various means—prequalification of manufacturers; the negotiation of concessionary prices in exchange for country plans for their rational use and scale-up, as the Global Drug Facility has done for second-line TB drugs; and technology transfer hubs to enable the manufacture of such products more broadly as WHO has done for influenza

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[35] Chaudhuri M. Now multi-drug-resistant TB stock crisis looms. *The Hindu*, June 29, 2013. Available at: http://www.thehindu.com/sci-tech/health/now-multidrugresistant-tb-stock-crisis-looms/article4860970.ece

[36] Quadri F, Mazer-Amirshahi M, Fox ER, Hawley KL, Pines JM, Zocchi MS, May L. Antibacterial Drug Shortages from 2001 to 2013: Implications for Clinical Practice. *Clinical Infectious Diseases* 2015; 60(12): 1737-1742.

[37] Gundlapalli AV, Beekmann SE, Graham DR, Polgreen PM. Perspectives and concerns regarding antimicrobial agent shortages among infectious disease specialists. *Diagnostic Microbiology & Infectious Disease* 2013; 75(3): 256-259.

[38] "Ranking Member Cummings and Chairman Sanders Investigate Staggering Price Increases for Generic Drugs," available at http://www.sanders.senate.gov/download/face-sheet-on-generic-drug-price-increases?inline=file

[39] Pulcini C, Bush K, Craig WA, et al. Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia. *Clinical Infectious Diseases* 2012; 54: 268-274.

[40] Ibid.

vaccine, adjuvant vaccine technologies, and a biosimilar to palivizumab, a treatment for respiratory syncytial virus infections.

WHO and Member States should develop a strategy for ensuring the sustainable production and registration of old antibiotics that may help address growing problems of drug resistance and of other antibiotics that face serious shortage or stockouts. This may require designing approaches to facilitate their registration across countries, transferring technology to other manufacturers, or providing appropriate economic incentives to encourage their development and commercial availability.

PROVISIONAL AGENDA ITEM 8.5:
Follow-up on the report of the consultative expert working group on research and development: financing and coordination (CEWG)

Pursuant to Resolution WHA69.23, the World Health Assembly requested that the Director-General to "expedite the full implementation of the strategic workplan" including the:

- development of WHO's Global Observatory on Health Research and Development;
- full implementation of the strategic workplan;
- establishment of an Expert Committee on Health Research and Development to provide technical advice on the prioritization of health research and development;
- exploration of the feasibility of a voluntary pooled fund to support research and development for Type III and Type II diseases and specific research and development needs of developing countries in relation to Type I diseases.

The Global Observatory on Health R&D has conducted several important R&D landscapes, including ones for drugs and vaccines for neglected diseases and health technologies for HIV, tuberculosis and hepatitis C.

The Global Observatory is well positioned to monitor the antibiotic R&D pipeline. Continuous monitoring of the state of the antibiotics pipeline, overview of on-going clinical trials, investment streams, research gaps and the patent landscape would be hugely beneficial. Such analysis can also usefully support developing priorities for R&D.

PROVISIONAL AGENDA ITEM 9.1:
Global Vaccine Action Plan (GVAP)

In their summary report to the WHO Secretariat, the Strategy Advisory Group of Experts on immunization offer a number of concrete recommendations towards achieving the goals of the global vaccine action plan by 2020. These recommendations include measures for national governments and other partners to strengthen and sustain disease surveillance capacity, secure investments to sustain immunization efforts, resolve barriers to ensure timely access to affordable vaccines, and secure investment of R&D of priority vaccines, particularly for low- and middle-income countries.

Vaccines serve as a critical technology complementing the use of antimicrobials and importantly reducing the selection pressure on these drugs, thereby curbing drug resistance in both human and animal health. Studies suggest that full coverage of the pneumococcal conjugant vaccine (PCV), aside from alleviating unnecessary death and

suffering, could nearly halve antibiotic use to treat pneumonia in children under five years of age.[41] Similar benefits are also suggested to occur from broader coverage of the rotavirus vaccine. In India, a rotavirus vaccination program has been estimated to prevent over 40,000 deaths and 250,000 hospitalizations annually.[42]

WHO and other stakeholders such as UNICEF[43] and GAVI[44] have carried out important work in scaling the introduction of existing vaccines. Still more clearly needs to be done. Between 2001 and 2014, Médecins Sans Frontières notes that the full vaccine package now covers 12 diseases rather than six, but has climbed in price from US$0.67 to US$32.09-45.59, prompting concerns over the sustainability of financing these health interventions.[45] Moreover, the development of new bacterial vaccines deserves greater attention.

By convening an expert consultation, WHO could spur development of a strategy for identifying priority vaccines to reduce the use of antimicrobials. Such a consultation could also suggest approaches for vaccine development that ensure affordable uptake across countries and across sectors. Priority might be measured, in part, by the number of antibiotic treatment courses averted.

PROVISIONAL AGENDA ITEM 11.1:
Progress in the implementation of the 2030 agenda for sustainable development

The Political Declaration adopted at the 2016 UN High-Level meeting on AMR noted that progress towards achieving several of the Sustainable Development Goals (SDGs) is threatened by the emerging threat of antimicrobial resistance. This reaches beyond health care to global food and agricultural systems as well as the environment. Appropriate and affordable access to effective antimicrobials is necessary for attaining universal health coverage as well as reducing maternal and child mortality and communicable diseases (SDG3), while excess of antimicrobials further contributes to resistance. The inappropriate use of antimicrobials in the agriculture and aquaculture sectors will also further limit treatment options for sick animals, which could lead to increased mortality of food animals and threaten food security (SDG 2). The WHO Secretariat's report notes that "by encouraging joint action across different sectors of society, and by taking advantage of positive feedback loops, synergies, co-benefits and cost efficiencies, the Sustainable Development Goals offer new ways to confront today's major challenges to health, including in particular: ageing and disabilities, antimicrobial resistance, the consequences of climate change, environmental degradation and pollution, sustainable financing, health inequities within and between countries,

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[41] Laxminarayan, R., Matsoso, P., Pant, S., Brower, C., Røttingen, J. A., Klugman, K., & Davies, S. (2016). Access to effective antimicrobials: a worldwide challenge. *The Lancet*, *387*(10014), 168-175.
[42] Esposito, D. H., Tate, J. E., Kang, G., & Parashar, U. D. (2011). Projected impact and cost-effectiveness of a rotavirus vaccination program in India, 2008. *Clinical Infectious Diseases*, *52*(2), 171-177. Available at: http://cid.oxfordjournals.org/content/52/2/171.full
[43] WHO, UNICEF, World Bank. *State of the world's vaccines and immunization*, 3rd ed. Geneva, Switzerland: World Health Organization, 2009.
[44] GAVI. *Keeping Children Healthy: The Vaccine Alliance Progress Report 2015.* Geneva, Switzerland: GAVI, the Vaccine Alliance, 2015.
[45] Médecins Sans Frontières Access Campaign. *The Right Shot: Bringing Down Barriers to Affordable and Adapted Vaccines*, 2nd Edition. Geneva, Switzerland: MSF Access Campaign, January 2015.

migration, and urbanization and rural poverty." As the Twelfth General Programme of Work from 2014-2019 and Programme Budget 2016-2017 predate the adoption of the SDGs, the WHO Secretariat acknowledges that further alignment is needed in the area of antimicrobial resistance.

Monitoring of progress towards defined targets is key in measuring progress in addressing AMR while ensuring accountability of various stakeholders in different, parallel international processes. However, the current list of Sustainable Development Goal Indicators does not include indicators dedicated to measure milestones in tackling antimicrobial resistance.

The WHO along with other organizations across the UN system should provide technical assistance to countries in incorporating AMR-specific metrics in their Voluntary National Reviews to the UN General Assembly on progress achieved on the SDGs.

ReAct—Action on Antibiotic Resistance is a global network tackling the challenge of antimicrobial resistance, with regional nodes on five continents. This policy briefing for the WHO Executive Board was prepared with contributions from Anthony So, Reshma Ramachandran (Johns Hopkins Bloomberg School of Public Health, Department of International Health, IDEA (Innovation + Designing Enabling Access) Initiative, ReAct North America/Strategic Policy Program; Anna Zorzet, Helle Aagaard, Dusan Jasovsky, Otto Cars (Uppsala University, ReAct Europe); Sujith Chandy (CMC Vellore, ReAct Asia Pacific); Mirfin Mpundu, (Ecumentical Pharmaceutical Network, ReAct Africa).