

ANTIBIOTIC RESISTANCE
COALITION RESPONSE TO THE
INTERAGENCY
COORDINATION GROUP ON
ANTIMICROBIAL RESISTANCE
PUBLIC CONSULTATION

INVEST IN
INNOVATION
AND RESEARCH,
AND BOOST
R&D AND
ACCESS

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Introduction:

The IACG commendably has taken up the critically important and linked issues of innovation and access and the need to invest in such efforts to tackle AMR in the healthcare delivery system, the food system and the environment. Interested members of the Antibiotic Resistance Coalition (ARC) convened to develop this joint response to the questions posed to stakeholders and to provide useful input to IACG's discussions of recommendations. We understand that this discussion paper represents the work of a subgroup of the IACG members and that its work is ongoing. This discussion paper's analysis is quite limited; the questions posed, wide ranging; and the public consultation period, too short to generate analyses across the breadth of issues raised. So we trust this will be just the beginning of a process of engaging stakeholder inputs as the IACG focuses on more specific, potential recommendations. We also hope this will complement the [earlier sent input](#), particularly on the work on *Innovation, R&D and Access*, by 28 ARC members and its civil society allies around the time of the Divonne meeting.

1. Policy coherence with the UN Political Declaration on AMR, which gave rise to the IACG, and with the Global Development and Stewardship Framework under development by the Tripartite agencies would be important. The UN Political Declaration on AMR¹ provides a guiding beacon to what the IACG should address in its recommendations in channeling R&D funding.

1.1 Certain key principles should underpin the IACG's proposals on research and development. This will require an end-to-end approach, whereby these principles are an integral part of the target product profiles, public financing of R&D and licensing of these products, not an afterthought upon market entry.

“...all research and development efforts should be needs-driven, evidence-based and guided by the **principles of affordability, effectiveness and efficiency and equity, and should be considered as a shared responsibility...**[emphasis added]”

1.2 The attention of the discussion paper to the important concept of delinkage—and the failure of some potential approaches like market exclusivity to reflect this core principle—could be clearer.

“...in this regard, we acknowledge the importance of **delinking the cost of investment in research and development on antimicrobial resistance from the price and volume of sales** so as to facilitate equitable and affordable access to new medicines, diagnostic tools, vaccines, and other results to be gained through research and development...[emphasis added]”

¹ Draft political declaration of the high-level meeting of the General Assembly on antimicrobial resistance. Available at: https://www.un.org/pga/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf

1.3 *The need to create an enabling environment, infrastructure and financing for piloting new innovation models, notably those that embrace delinkage, would also be key.*

“all relevant stakeholders, including Governments, industry, non-governmental organizations and academics, should continue to explore ways to support innovation models that address the unique set of challenges presented by antimicrobial resistance, including the importance of the appropriate and rational use of antimicrobial medicines, while promoting access to affordable medicines.

1.4 *The Global Framework for Development and Stewardship to Combat Antimicrobial Resistance will be a critical instrument to steer the design and coordination of an end-to-end approach to supporting R&D, including incentive mechanisms.*

As described in the Global Framework, its reach spans from bench to bedside:² “As mandated in WHA68.7, the framework will 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 Antimicrobial Resistance (GAP-AMR).”

2. Recognizing that the IACG’s work continues in this area, we would flag that priority setting and financing for R&D and access can be better coordinated.

2.1 *In establishing a “Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics,” WHO has provided the basis for measuring whether R&D funding is ‘needs-driven’ in the area of new antibiotic drugs.*

2.2 *Investments in R&D should not focus exclusively on bringing new antibiotic drugs to market, but also on other areas of innovation that are needed to more effectively combat AMR. As acknowledged in the discussion paper, a successful response to AMR will also need to address vaccines and diagnostics. In these areas, further work is needed to set global priorities in order that R&D funding can be aligned.*

2.3 *In funding R&D, supporting a portfolio of approaches remains important, but all parts of that portfolio should strive to adhere to principles of delinkage, transparency of R&D costs, fair return on public investment, and an end-to-end approach in safeguarding access and stewardship. Product development partnerships like DNDi have a track record of setting target product profiles with affordability as a key criterion, negotiating arrangements with drug manufacturers consistent with the aims of meeting the needs of resource-limited settings, and investing in local*

² WHO. *Global Framework for Development & Stewardship to Combat Antimicrobial Resistance: Draft Roadmap* (WHO/EMP/IAU/2017.08). Geneva, Switzerland: WHO, 12 May 2017. Available at: http://www.who.int/phi/implementation/research/WHA_BackgroundPaper-AGlobalFrameworkDevelopmentStewardship.pdf

infrastructure like clinical trial networks. This approach is being further developed and applied to AMR by The Global Antibiotic Research & Development Partnership (GARDP), a joint initiative of DNDi and the WHO, which aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists. However, we are unclear whether the significant public investment that CARB-X has managed through drug-by-drug, company-by-company investments follows these principles. The IACG should recommend that all public funding for antibiotic R&D be evaluated and held accountable to these core principles.

The product development partnership model, as reflected in DNDi's approach with treatments for neglected diseases and through GARDP, is one that might be emulated for innovation of diagnostics and vaccines in the animal health sector.

2.4 In financing access to health technologies to address AMR, extending the mandate of already existing funds, such as UNICEF, Global Fund, UNITAID, GAVI, would be most efficient and effective in the short term. In the long term, as the capacity and structures grow within the existing mechanisms, there might be an opportunity to split off these parts into a self-sustained and dedicated AMR fund. Over time, it could further grow to cover needs in animal, plant and environmental health.

- If several different funds extended their missions to include AMR, it would be important to have some strategy for how to coordinate and base the funding on some common principles and guidance on how to include considerations of stewardship.
- A review of previous and ongoing funding initiatives might have value in shaping how AMR-related funding might be directed. The Fleming Fund's experience in setting priority country targets might offer useful insights. The EU model of co-funding of animal health measures to monitor, control and eradicate zoonoses could be an approach to be explored and expanded further.³ National funds for animal health and welfare can also take a larger responsibility to address AMR.

2.5 The discussion paper takes as given the "limited expected return on investment (ROI) of antibiotics," but this claim deserves more careful and empirical analysis than presented. While the pharmaceutical industry has worked to keep actual R&D costs and drug-specific returns on investment non-transparent, peak revenue can be compared between first-in-class antibiotics and me-too antibiotics. First-in-class antibiotics such as linezolid and daptomycin both placed in the top 100 drugs by sales in the United States.⁴ Tygacil, an antibiotic with a poor benefit-risk ratio and mortality risk, nonetheless commanded global revenues of \$323 M, \$304 M and

³ Report from the Commission to the European Parliament and the Council on the outcome of the EU co-financed programmes for the eradication, control and monitoring of animal diseases and zoonosis over the period of 2005-2011. Available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52014DC0115>

⁴ Based on data from Evaluate Pharma

\$274 M in the years 2014-2016.⁵ The uncertainty of investment seems to describe largely non-novel classes of antibiotics, which the drug industry continues to bring to market. In a study of systemic antibiotics approved by the U.S. FDA over a two-decade period (1980-2009), over 40% were withdrawn from the market.⁶ Twenty out of 26 of these withdrawals were not for safety reasons. This raises the question whether the lower net present value for antibiotics is driven primarily by shorter treatment times to cure or just remarkably high failure rates because drug companies were given the wrong incentives to bring me-too drugs to market with little value added.

3. R&D funding could be significantly better channeled.

3.1 *R&D should follow an end-to-end approach, from bench to bedside, by which upstream incentives are coupled with access and stewardship measures downstream.* The value chain depicted in this discussion paper stops short of making this connection. The full value chain spans from bench to bedside, not just from fundamental research to approval. This requires engaging actors in healthcare delivery systems, not just drug companies, in designing such incentives. Delinkage is only part of this end-to-end approach, but to ensure access and stewardship of new antibiotics, providers, payers and patients have to be involved.

Shaping such a model requires a combination of push and pull incentives, rather than a focus on pull incentives such as late stage market entry rewards or extended market exclusivity which increase the cost of antibiotics, often fail to deliver affordability or availability of products to those in need, and do not ensure antibiotic stewardship. Transferable IP exclusivity proposals that transfer monopoly pricing from antibiotics to other medicines also may reduce access to patients in need when they cannot afford those medicines as a result of delayed generic entry or extended monopoly pricing.

3.2 *To be clear, every dollar paid for the purchase of antibiotics is a pull incentive. For the public sector, the key issue is targeting--where and how to invest those monies for R&D. The key bottleneck in the antibiotic R&D pipeline is upstream in the drug discovery phase, where public investments could help transform the innovation ecosystem.* Bringing a new drug to market can take upwards of a decade, so time discounting can seriously erode the value of public monies put in as pull incentives as opposed to push incentives upfront. In fact, a study authored by those closely tied to industry modeled this problem and concluded: “However, an analysis by Sharma

⁵ Copenhagen Economics. *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe. Final Report*, May 2018. Available at: <https://www.copenhageneconomics.com/dyn/resources/Publication/publicationPDF/5/445/1527517171/copenhagen-economics-2018-study-on-the-economic-impact-of-spcs-pharmaceutical-incentives-and-rewards-in-europe.pdf>

⁶ Outterson K, Powers JH, Seoane-Vazquez E, Rodriguez-Monguio R, and Kesselheim AS. Approval and Withdrawal of New Antibiotics and Other Antiinfectives in the U.S., 1980-2009. *Journal of Law, Medicine & Ethics* Fall 2013, pp. 688-696.

and Towse found that a key pull incentive—extended market exclusivity—had minimal impact on improving the net present value (NPV) of antibiotics. By contrast, push incentives may be of greater value. Because pull incentives should result in larger amounts of revenue than push incentives, the assertion that pull incentives are less economically valuable than push incentives may be counterintuitive. However, as we show below, **push incentives may be 95% smaller than pull incentives and still yield similar value.** [emphasis added]⁷

3.3 Expectations of industry returns on investment of new antibiotics should not be benchmarked against blockbuster drugs like cancer. Such returns are, in significant measure, a result of the industry’s own lobbying for extended exclusivity on these products that result in monopoly pricing. Fairer benchmarks might include what the public sector would pay if there were generic competition, an alternative pathway with a product development partnership bringing the drug to market, or a marginal cost plus model for establishing appropriate pricing.

3.4 Target product profiles set by the public sector can play an important role in better channeling R&D funding and coordinating R&D efforts globally. This receives little attention in the IACG discussion paper. First of all, target product profiles should enable more effective delivery in resource-limited settings. Heat stability, for example, can obviate the need for a cold chain for vaccines. Secondly, target product profiles should also include affordability as a criterion. After all, an innovation that is not accessible by those in need has no value at all.

Product development partnerships such as the Drugs for Neglected Diseases Initiative and Medicines for Malaria Venture include target price points for products they develop. The Boston Consulting Group failed to do so on the premise that “Most high-need drugs developed as a result of this initiative will be needed in both low-/middle-income countries and high-income countries, allowing for significant price differentiation in many cases. Because pricing is critical from an access perspective in low- and middle-income countries and, as many would argue, from a stewardship perspective in high-income health systems, we propose to define differentiated pricing and access requirements for new drugs in all funding contracts entered into with GUARD.”⁸ We believe the Boston Consulting Group analysis is seriously wrong on this key point:

- High prices are certainly a deterrent to access, but to suggest that high prices would ensure appropriate stewardship in high-income health systems is just erroneous. Effective diagnostics might improve stewardship, ending misaligned economic incentives might help, but high drug prices paid by public and private insurers and patients have no clear and consistent connection to enabling effective stewardship.

⁷ Spellberg B, Sharma P, Rex JH. The critical impact of time discounting on economic incentives to overcome the antibiotic market failure. *Nature Reviews Drug Discovery* 2012; 11(2): 168.

⁸ Boston Consulting Group. *Follow-up Report for the German GUARD Initiative. Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development.* Berlin, Germany: German Federal Ministry of Health, February 2017, page 20.

- The BCG report does not provide evidence, example or clarity that its proposed funding contracts could make good on differentiated pricing and access requirements. In fact, the report states: “Profit potential may be slightly reduced via price and availability obligations, but the recipient would maintain the right to market the antibiotic in the major markets (with some minor restrictions (see 7.1.6).”⁹
- Time and again, civil society has shown that voluntary, tiered pricing is insufficient to ensure affordability of life-saving drugs, neither for patients in low- and middle-income countries nor in industrialized countries. Patients have died for lack of affordable insulin prices in the United States.

Relying largely on “differentiated pricing and access requirements” to ensure affordable access is a useful example of how NOT to coordinate design of incentive mechanisms globally. An end-to-end approach signals the market, beginning with target product profiles, at the start of the R&D process.

3.5 Moving beyond bets—drug by drug, and company by company—the IACG should consider public investments that transform the R&D innovation ecosystem. In the short term, there should be an increased focus on push incentives. With an empty pipeline in AMR related research for now, the major challenge and opportunity lies within innovation and research rather than the development and production phase. The success rate of high-throughput screens to leads is very low, in the neighborhood of 7% in the experience of leading pharmaceutical companies.¹⁰ This is ten-fold lower than therapeutic classes overall. The fact that first-in-class antibiotics can command top sales figures on the U.S. market, yet this is not sufficient incentive to bring forward novel classes of antibiotics suggests a scientific bottleneck. Investments for breakthrough R&D should consider how to recruit a wider array and non-traditional entrants in the drug discovery process and how to build and scale innovation platforms that might enrich, for example, publicly available compound libraries with promising natural products as future classes of antibiotics and clinical trial platforms and specimen repositories that might speed the development of drugs and diagnostics.

Pooling the building blocks for enabling R&D into these health technologies is another key investment approach to transforming the innovation ecosystem. The Medicines Patent Pool has importantly shown its value in pooling the licenses of end-products that might be used in combination, notably for AIDS, TB and hepatitis C. Pooling of reagents, research tools, innovation platform technologies and compound libraries also could play an important role in lowering the barrier to new

⁹ Boston Consulting Group. *Follow-up Report for the German GUARD Initiative. Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development*. Berlin, Germany: German Federal Ministry of Health, February 2017, page 41.

¹⁰ So, AD, Gupta N, Brahmachari SK, Chopra I, Munos B, Nathan C, Outtersson K, Paccaud JP, Payne DJ, Peeling RW, Spigelman M, Weigelt J. Towards new business models for R&D for novel antibiotics. *Drug Resistance Updates* 2011;14(2), 88-94.

entrants to R&D or to allowing other companies to take the risks of breakthrough innovation.¹¹

3.6 *To ensure sustainable financing, there must be ongoing assessment of the technology landscape, an economic case made for continued strategic investments in R&D, and monitoring for accountability (including early signs) by both government and non-governmental watch efforts.*

Various ongoing efforts can help complete an assessment of the technology landscape. On the human health side, through the Global Observatory on Health R&D, WHO has begun to track the R&D pipeline for novel antibacterial drugs. Their snapshot released in September 2017 reveals a persistent dearth of novel antibiotics, particularly targeting Gram-negative pathogens.¹² Only one or two novel antibiotics are expected to enter the market over the next 5 years, far too few to address the growing challenge of drug-resistant bacterial infections. Most are only modifications of existing classes of antibiotics. Similarly, WHO also recently published an Essential Diagnostics List and has plans to update it annually.¹³ While the first list focuses on *in vitro* diagnostics, subsequent editions will expand to cover additional areas such as antimicrobial resistance. Complementing these efforts, WHO has worked to identify priority pathogens affecting human health.¹⁴ However, there remain gaps to be filled.

The economic case for continued strategic investments in R&D builds upon the needs assessment and anticipated return on investment from the resulting technologies developed and distributed. Intergovernmental agencies, funders and country governments all would benefit from a priority setting framework and a project that would effectively model the anticipated benefits and returns on investment in various AMR-related interventions. SimSmoke served a useful role in projecting country-wide prevention gains from different kinds of tobacco control programs, from advertising restrictions to tobacco taxes, that would take years to show returns in health or lowered healthcare expenditures.¹⁵ By supporting the development of

¹¹ So AD, Stewart E. “Sharing Knowledge for Global Health” in *The U.S. Commitment to Global Health: Recommendations for the Public and Private Sectors*. Washington, DC: Committee on the U.S. Commitment to Global Health, Institute of Medicine, 2009, Appendix F Commissioned Paper.

¹² Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.11). Licence: CC BY-NC-SA 3.0 IGO. Available at: http://www.who.int/medicines/news/2017/IAU_AntibacterialAgentsClinicalDevelopment_webfinal_2017_09_19.pdf?ua=1

¹³ World Health Organization Model List of Essential In Vitro Diagnostics, First Edition (2018). Geneva, World Health Organization; 2018. Available at: http://www.who.int/medical_devices/diagnostics/EDL_ExecutiveSummary_15may.pdf

¹⁴ Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery and Development of New Antibiotics, World Health Organization, 2017. Available at: http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1

¹⁵ Levy DT, Mabry PL, Graham AL, Orleans CT, Abrams DB. Exploring Scenarios to Dramatically Reduce Smoking Prevalence: A Simulation Model of the Three-Part Cessation Process. *American Journal of Public Health* 2010;100(7):1253-1259.

simulation modeling, governments and funders alike could gauge what mix of interventions would be worthwhile and lead to hoped-for gains in addressing AMR.

3.7 HIV/AIDS, tuberculosis and vaccines reveal the challenges and the successes in mobilizing and sustaining donor and private funding for R&D and for ensuring affordable access to these products. In these efforts, a key component to sustainable financing was affordable pricing (to be discussed below), and a key player in keeping the pressure up for continued funding was civil society. The IACG should consider how to create an enabling environment for both of these key factors.

The Stop TB Partnership provides support to civil society groups working at the country level through its Challenge Facility for Civil Society. Funding agencies like the Global Fund dedicate seats on their governance boards to civil society representation.

3.8 Better channeling of R&D funding also means targeting the players which might make the most difference in bringing forward innovation. For example, would small and medium-sized enterprises be more likely to take up truly novel classes of antibiotics, and could designing targeted incentives to these firms work better? Might they also have lower expectations of return on investment, and if so, would that also make public investment more cost-effective?

In LMICs, POC diagnostics compete for limited space in the laboratories of peripheral clinics and secondary hospitals. Local healthcare delivery systems cannot afford to purchase, let alone maintain, parallel laboratory equipment for a basic battery of diagnostic testing. Are some manufacturers more willing to invest in an interoperable diagnostic platform into which their diagnostic test would plug and play? Efforts to advance such a vision and targeting financing for diagnostic R&D accordingly might also make it possible to evolve the diagnostic testing technology more quickly, without having to replace the equipment with each advance. A WHO consultation on in June 2015 began discussions along these lines on diagnostic interoperability standards,¹⁶ but rekindling this process and focusing it on the urgent need for POC diagnostics to address AMR could be another area for IACG recommendation.

4. Both to safeguard and expand access, several types of mechanisms would be critical to creating the enabling policy environment to achieving these aims—those mechanisms assuring access to the product, those that safeguard affordability, and those that enable monitoring for access.

4.1 Access to product, in part, refers to the challenge of underuse, quality antibiotics, and drug shortages.

¹⁶ WHO. Global consultation on diagnostics interoperability standards. Geneva, Switzerland: WHO, 11-12 June 2015. Available at: http://apps.who.int/iris/bitstream/handle/10665/181059/9789241509305_eng.pdf?sequence=1

Underuse as well as overuse of antibiotics costs lives. The Monitoring and Evaluation Framework for benchmarking progress on antimicrobial resistance must include indicators that capture access, such as to second-line antibiotics, and affordability of these life-saving drugs. Otherwise this will communicate to key actors in the healthcare delivery system that governments or intergovernmental agencies care about complying with stewardship measures to preserve the effectiveness of antibiotics, but not whether those same settings have access to life-saving antibiotics. And that is no foundation upon which to build a shared commitment to tackling AMR.

Access to quality antibiotics is important as well. Strategies to empower drug regulatory agencies as well as consumer groups with tools to monitor for substandard and falsified drugs should be developed. A University of Edinburgh study commissioned by WHO models the human toll if we fail to address the use of substandard and falsified antibiotics to treat childhood pneumonia.¹⁷

Finally access to antibiotics can be compromised by drug shortages. The fragility of the supply chain, particularly for old antibiotics that may provide last-line defense against drug-resistant pathogens, must be addressed with 1) sentinel warning system when existing suppliers might exit, 2) demand forecasting and pooling procurement so that suppliers can reliably count on year-to-year sales, and 3) a financing mechanism that can boost reimbursement when margins are too thin, support entry of generic suppliers to meet GMP requirements, and provide wider margins on international procurement tenders. These steps might be taken through a pooled procurement mechanism. The experience of procurement agents, from UNICEF to the Global Drug Facility for TB drugs, could usefully be tapped to propose how the procurement of antibiotics might be better coordinated across key public sector buyers, from church-based healthcare systems to these global procurement agents.

In a recent *Lancet Infectious Diseases* commentary, several strategies to ensure availability of old, effective antibiotics were put forward, including the “formation of a multidisciplinary working group that would identify obstacles and solutions; disclosure and mapping of current production and supply chains; agreements on quality criteria, continued production, and stock management; collaboration between national regulatory agencies to secure the availability of effective antibiotics; predictable joint procurement that might result in an incentive for producers.”¹⁸

¹⁷ A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva, Switzerland: World Health Organization, 2017. Available at: http://www.who.int/medicines/regulation/ssffc/publications/SE_Study_EN.pdf?ua=1

¹⁸ Tängdén T, Pulcini C, Aagard H, Balasegaram M, Hara GL, Nathwani D, Sharland M, Theuretzbacher U, Cars O. Unavailability of old antibiotics threatens effective treatment for common bacterial infections. *Lancet Infectious Diseases* 2018; 18(3), 242-244. Available at: [https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099\(18\)30075-6.pdf](https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(18)30075-6.pdf)

4.2 Affordability of products, both in LMICs and in high-income countries, remains a concern. Safeguards against high pricing that goes well beyond marginal cost plus might include ensuring multiple generic suppliers in the procurement scheme and benchmarking against what a product development partnership might be able to do to bring the drug to market.

Fulfilling the goals of sustainable innovation and access requires transparency about R&D costs, clinical trial data, and prices, fair return on public investment, and R&D that takes an end-to-end approach, by which upstream incentives are coupled with access and stewardship measures downstream. Such transparency requirements could be made at the national level or by procurement agents as a requirement of those drug companies submitting bids for tenders. Claims of commercial sensitivity over such information seem to have little foundation, and the burden of proof should be on manufacturers to prove how such disclosure does not serve an overriding, public interest purpose.

Where other approaches like pooled procurement fail to result in affordable pricing, the use of TRIPS flexibilities and compulsory licensing should be an option. Even the threatened use of compulsory licensing has resulted in more reasonable pricing behavior by drug manufacturers, both in the country in question and sometimes more globally. Brazil, for example, threatened to use compulsory licensing for the AIDS medication, Efavirenz by Merck and Nelfinavir by Roche. After negotiations with the pharmaceutical industry between 1999 and 2001, Merck and Roche reduced their drug prices by 59% and 40%, respectively. In the end, Brazil did not use a compulsory license, but still saved tens of millions of US dollars.¹⁹ Thailand actually used a compulsory license to lower the price of Abbott's Kaletra HIV drug, and as a result, Abbott responded by cutting its price in over forty countries.²⁰

Pooling of building blocks for health technologies or of the health technologies themselves can also help facilitate market entry of firms that might either provide a more efficient market price or a more competitive price that ensures greater affordability. The Medicines Patent Pool has expanded its mandate to include patented medicines of WHO's Model List of Essential Medicines in its patent pooling and voluntary licensing initiative and could be a good vehicle to promote access, and ensure good stewardship through its licensing, of novel antibiotics.^{21,22}

¹⁹ Guennif, S. (2017). Evaluating the usefulness of compulsory licensing in developing countries: a comparative study of Thai and Brazilian experiences regarding access to AIDS treatments. *Developing world bioethics*, 17(2), 90-99. Available at: <https://onlinelibrary.wiley.com/doi/epdf/10.1111/dewb.12124>

²⁰ Public Citizen, Kaletra – Abbott's Abusive Practices. Available at: <https://www.citizen.org/our-work/access-medicines/kaletra-campaign/kaletra-abbotts-abusive-practices>

²¹ Medicines Patent Pool, Exploring the expansion of the Medicines Patent Pool's mandate to patented essential medicines. Available at: <https://medicinespatentpool.org/uploads/2018/05/Feasibility-Study-Expansion-of-the-MPP-Mandate-And-Appendix-2018.05.24.pdf>

²² Medicines Patent Pool Foundation – TB Stewardship Report (2016) Available at: https://medicinespatentpool.org/uploads/2017/07/STEWARDSHIP-REPORT_FINAL-1.pdf

4.3 *Monitoring for access by government and non-government actors can play an important part.* As noted, the need to monitor for access, not just stewardship, has already been noted. The twin goals of access and stewardship come together in the guiding principle of delinkage—separating drug company investment into R&D from the price and quantity of drug sold. Delinking on price assures affordability; delinking on quantity of drug sold, stewardship. Delinkage mechanisms cannot be struck with drug companies alone, but rather must involve those in the healthcare delivery system. In fact, the obligations of stewardship must be carried out at the level of the encounter between healthcare provider and patient, and neither drug companies nor healthcare professionals would likely support a delinkage approach whereby drug companies reached into that relationship to shape clinical decision making.

Drug companies should be prevented from mispromoting health technology products, in particular antibiotics. Drug company manufacture and marketing of unregistered combinations of antibiotics should be stopped.²³ Prohibitions against such mismarketing should be enforceable in local statute, and a system that makes such problems transparent might serve to speed local enforcement, both by governments and the drug companies involved.

Finally, we might note that monitoring for access gained an important tool in the WHO Essential Medicines List's Access, Watch and Reserve designations of antibiotics. But this tool is also one which we need further work and guidance to operationalize.

5. Guiding principles for investing in R&D and access should build upon those laid out in the UN Political Declaration on AMR and the Global Development and Stewardship Framework process.

5.1 *The principles of delinkage, transparency of R&D costs, fair return on public investment, and an end-to-end approach in safeguarding access and stewardship would be important to build into the design of public efforts to invest in R&D and access.* Global public benefit, equity, gaps in response, and value for money are certainly a useful starting point for evaluation criteria for return on investment from public investments in R&D and access.

5.2 *There needs to be an intersectoral, interagency, intergovernmental coordination body that can take in an overview of the whole AMR field.* There is a need for R&D to be seen as an integral component within the larger cycle of needs and priority setting, R&D and public health action, and monitoring, evaluation and review towards progress of commitments.

²³ McGettigan, P., Roderick, P., Kadam, A., & Pollock, A. (2018). Threats to global antimicrobial resistance control: Centrally approved and unapproved antibiotic formulations sold in India. *British journal of clinical pharmacology*. Available at: <https://bpspubs.onlinelibrary.wiley.com/doi/epdf/10.1111/bcp.13503>

5.3 *Monitoring and transparency for accountability will be necessary to ensure that R&D and access principles are operationalized.* External stakeholders such as governments, civil society and the public should have access to open data to be able to conduct the evaluation of progress of government and company benchmarking.

6. To have the greatest impact on One Health, one must better prioritize innovation of both technologies and of practice in the food production sector and the environment.

6.1 *It may be challenging to model the return on making AMR-related investments in healthcare delivery, food production and the environment together.* Admittedly, averting the use of a widely used, old antibiotic against avoiding the overuse of a last-line, novel antibiotic is not easily reducible to a common metric. However, the opportunities to avert unnecessary use of antibiotics are so much larger—from the near elimination of the use of antibiotics in salmon aquaculture as in Norway^{24,25} to halving the number of antibiotic treatment days in children under age 5 with universal pneumococcal vaccination.²⁶

6.2 *Making the calculus for specific interventions in differently resourced settings should not be a static exercise, but rather the IACG should consider what enabling, systemic factors might tip this calculus radically in favor of adoption.* For example, might product development partnerships which have begun to show success for bringing to market treatments for neglected diseases in humans be applied as a model for bringing public goods, like diagnostics and vaccines, in the food production system?

6.3 *For some areas of technology, the IACG may call for additional mapping of the landscape, from technologies for the removal of antibiotic pollution from the environment to the reengineering of medical instrument surfaces to make them resistant to bacterial colonization.* At a time when the pharmaceutical industry is calling for billions of dollars in additional incentives to bring new antibiotics forward, the benefits and costs of making breakthrough improvements in efforts to address AMR through these approaches should be weighed against the societal benefit and cost of bringing a new drug to market.

6.4 *Training the next generation of scientists in the One Health approach and finding sufficient resources to attract such researchers involves more than boosting near*

²⁴ WHO. “Vaccinating salmon: How Norway avoids antibiotics in fish farming.” October 2015. Available at: <http://www.who.int/features/2015/antibiotics-norway/en/>

²⁵ Use of Antibiotics in Norwegian Aquaculture. Oslo, Norway: Norwegian Veterinary Institute, 2016. Available at: https://www.vetinst.no/rapporter-og-publikasjoner/rapporter/2016/use-of-antibiotics-in-norwegian-aquaculture/_attachment/download/03528c2b-8849-4a07-bbe8-98358aceb176:f8e3f50d9442a35da57158ce9b5d0c43f165ce53/2016_22_Use%20of%20Antibiotics%20in%20Norwegian%20Aquaculture.pdf

²⁶ Laxminarayan, R, Matsoso, P, Pant, S, Brower, C, Røttingen, JA, Klugman, K, & Davies, S (2016). Access to effective antimicrobials: a worldwide challenge. *The Lancet*, 387(10014), 168-175.

term educational opportunities and research funding, and a systemic solution likely will not come from investing in one or more organizations to take lead. Taking a systems approach, the IACG might consider what points of intervention will drive sustained change and demand for this knowledge that such scientists might generate. Does credentialing of veterinarians and physicians in One Health competencies feed a system demand for designing interventions with such research insights? Would the advent of product development partnership focused on bringing much needed veterinary diagnostics and vaccines excite a new generation of scientists? The IACG needs to move beyond patching the innovation system with a fix and a fund here and there when more systemic change is needed.