

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

SURVEILLANCE AND MONITORING FOR ANTIMICROBIAL USE AND RESISTANCE

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Introduction:

The IACG commendably has taken up the important concerns over surveillance and monitoring for antimicrobial use and resistance 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. Some of more technical questions posed would require either further study, dedicated expert consultations, and/or a longer timetable for response. We urge the IACG not to leave such technical questions to be answered by web-based technical consultation, but to stage the needed expert consultations to find the best answers (e.g., How can existing systems for collection of data on humans, animals and food be adapted to include data from plant production and environmental surveillance?). We also 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 *Surveillance and Monitoring for Antimicrobial Use and Resistance*, by 28 ARC members and its civil society allies around the time of the Divonne meeting.

1. Surveillance information needs to be channeled in strategic ways that inform other areas, from R&D needs to measuring the effects of stewardship. The discussion paper provides a useful framework for considering how to address challenges in mounting effective surveillance and monitoring over antimicrobial use, but could focus more purposefully on the key goal—to inform and help drive public health action.

1.1 *In the healthcare delivery system, surveillance might address clinical demands, public health demands and infection control demands.*¹ Clinical demands refer to using surveillance data to improve patient treatment by optimizing the empirical antibiotic treatment choices based on local epidemiology. Public health demands refer to using surveillance data to generate reliable estimates to determine the size of ABR as a national and international public health problem. Infection control demands refer to using surveillance data to track transmission and outbreaks and to uncover origins of high-risk strains.

1.2 *On the food system side, the importance of surveillance to guide policy action also holds. There are clear examples from the US and Europe.* Development of resistance in *Campylobacter* to fluoroquinolones led to a ban on the use of this class of antibiotics in poultry.² Detection of cephalosporin resistance in the US led

¹ Grundmann H. Towards a global antibiotic resistance surveillance system: a primer for a roadmap. *Ups J Med Sci* 2014 May; 119(2): 87-95. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4034565/>

² Price, Lance B., et al. "The persistence of fluoroquinolone-resistant *Campylobacter* in poultry production." *Environmental Health Perspectives* 115.7 (2007): 1035. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1913601/#b11-ehp0115-001035>

to an extra-label restriction³; detection of MRSA in pigs led to action in EU⁴; and in Canada, the detection of cephalosporin resistance in chickens and people in *Salmonella Heidelberg* led to a voluntary ban on the use of the drugs in hatcheries.⁵

- 1.3 *These connections between surveillance and policy action do not come across clearly in this discussion paper, but we hope they will be the foundation of the IACG's recommendations in this area.* Moreover, the promotion of surveillance systems should be tied to parallel efforts to promote regulation that allows for action when problems are detected. All of the Tripartite agencies (WHO, FAO and OIE), as well as bodies like the Codex Alimentarius Commission, have important roles in defining legal frameworks that could support such regulatory systems at the country level and the normative basis for what are not non-technical barriers to trade at the global level.
- 1.4 *Importantly, the impact of antibiotic use and discharge into the environment, from point source pollution from manufacturing plants to agricultural run-off and hospital wastewater, warrants attention in an integrated surveillance system.* Environmental surveillance should not just be limited to AMR in pharma manufacturing waste, but also include food production settings (farms, slaughterhouses, processing units), healthcare settings (human health and animal health), waste treatment facilities.

2. Effective surveillance and monitoring begins with availability of surveillance and monitoring data, laboratory infrastructure, and standardized instruments.

- 2.1 *On the healthcare delivery side, surveillance and monitoring can capture a) antimicrobial consumption and use, resistance levels and appropriateness of use; b) antimicrobial prices and affordability, availability and stockouts, by area (urban vs. rural); or c) pharmacovigilance, quality (substandard and falsified) and marketing of illegal drug combinations.*

We welcome that the IACG has noted point prevalence surveys as an alternative to continuous surveillance, and hope to see this lifted as a key message in the final recommendations. Sentinel point prevalence studies are key to overcome some of

³ Food and Drug Administration, Department of Health and Human Services, New Animal Drugs; Cephalosporin Drugs; Extralabel Animal Drug Use; Order of Prohibition Cephalosporin Order of Prohibition, January 2012. Available at: <https://www.gpo.gov/fdsys/pkg/FR-2012-01-06/pdf/2012-35.pdf>

⁴ European Food Safety Authority. "Analysis of the baseline survey on the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in holdings with breeding pigs, in the EU, 2008-Part A: MRSA prevalence estimates." *EFSA Journal* 7.11 (2009): 1376. Available at: http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1376.pdf

⁵ Government of Canada, Reductions in Antimicrobial Use and Resistance: Preliminary Evidence of the Effect of the Canadian Chicken Industry's Elimination of Use of Antimicrobials of Very High Importance to Human Medicine, Available at: <https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-integrated-program-antimicrobial-resistances-surveillance-bulletin.html>

the barriers for surveillance in low resource settings, and importantly, should not occur in isolation from already ongoing global surveillance efforts.

A standardized protocol to carry out sentinel point prevalence studies, particularly in low- and middle-income countries, is needed. Such studies can help establish case definitions for disease and serve as a baseline for subsequent full-scale surveillance efforts. While such sentinel point prevalence studies should be encouraged and supported, the trade-offs such as between scaling these efforts and building local infrastructure and capacity must be considered. Important lessons might be garnered from the experience and assessment of national TB prevalence surveys.⁶

Part of making surveillance more feasible low- and middle-income countries (LMICs) is increased support for: more robust and affordable tests better adapted to the needs of low-resource settings, including with longer shelf-life and stability at ambient temperatures; quality assurance and sustainable implementation of such tests both at point-of-care and centralized laboratories; training for the interpretation of results and/or simplification of reporting; and support for the analysis and publication of the results. In addition, when new technologies are available (e.g. mass spectrometry, rapid tests, WGS), they are often too complex, expensive or not sufficiently validated in low-resource settings to be used in local microbiology labs, thus further impeding equitable access to the best technologies.

2.2 *On the food system side, surveillance and monitoring can capture: a) drug resistance and resistance gene levels, antibiotic residues in food and the environment, and antimicrobial consumption or use by livestock species, and b) products on the market, including unregistered or irrational drug combinations.* The availability and use of combination antibiotics varies by country. In the United States, these concerns can arise from animal drug compounding, but are the subject of FDA regulation.⁷ In India, antibiotic combinations—some containing drugs critically important for treating human infections--have been approved for veterinary use in poultry.⁸

Similarly, a standardized survey approach would be useful in surveillance of food systems. Some countries have already collected national data on antimicrobial use by livestock species. This shows that it can feasibly be done. It should be done

⁶ Stanecki K, Binkin N, Hoa NB, et al. Independent Assessment of National TB Prevalence Surveys Conducted Between 2009-2015. Washington, DC: US Agency for International Development, February 2016. Available at: <https://www.usaid.gov/sites/default/files/documents/1864/TB-prevalence-surveys-assessment-2016-508-final.pdf>

⁷ Janice Steinschneider, US FDA. Compounding Regulatory Perspective. USP Veterinary Drugs Stakeholder Forum, November 9, 2012. Available at: <https://www.usp.org/sites/default/files/usp/document/get-involved/stakeholder-forums/6a-animal-drug-compounding-fda-perspective-2012-11-09.pdf>

⁸ Pearson NO, Limaye S. Antibiotic Apocalypse Fear Stoked by India's Drugged Chickens: Feeding chickens antibiotics may speed diseases costing \$100 trillion. Bloomberg News, March 29, 2016. Available at: <https://www.bloomberg.com/news/features/2016-03-29/antibiotic-apocalypse-fear-stoked-by-india-s-drugged-chickens>

because antimicrobial use varies widely by species, and the distribution of livestock by country also varies widely.

Publishing such data by farming system and by small-scale and large-scale producers would provide much needed insight into planning. How much to invest in looking at specific farms in point prevalence surveys and how much to invest in a sustainable and continuous national data collection system will depend on available resources and the local context.

2.3 *Harmonizing testing to enable comparison across countries is very important to create the enabling policies for curbing antimicrobial use.* On the animal side, for example, the EU introduced harmonized testing for antibiotic resistance in *E. coli*, *Campylobacter* and *Salmonella* in poultry and pigs for EU Member States and a few additional non-EU countries like Iceland, Norway and Switzerland. All the data are then published in reports by the European Centre for Disease Prevention and Control and European Food Safety Authority (EFSA), compared to results of resistance testing in humans.⁹ The testing reveals huge differences in antibiotic resistance between different European countries, as there are huge differences in antibiotic use. For example, in the 2016 report, approximately 80% of the *E. coli* from Iceland, Finland and Norway were sensitive to all 14 antibiotics tested, whereas in 15 countries this percentage was 10% or less. Denmark and the Netherlands have also started to collect data tracking antibiotic-usage by species.^{10,11} In the UK, the poultry council and the pig industry have established voluntary industry schemes for collecting usage data, which have already contributed to major cuts in antibiotic use.^{12,13} These voluntary industry schemes, however, should only be a steppingstone towards statutory data collection.

2.4 *Availability of laboratory infrastructure is also essential to carry out these surveys, and such facilities might be regional.* In some areas, regional labs capable of whole genome sequencing might provide such services. Such a strategy could help

⁹ EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control), 2018. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2016. EFSA Journal 2018;16(2):5182, 270 pp. <https://doi.org/10.2903/j.efsa.2018.5182>

¹⁰ DANMAP 2016 Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. ISSN 1600-2032. Available at: https://www.danmap.org/~media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202016/DANMAP_2016_web.ashx

¹¹ SDa, Netherlands Veterinary Medicines Authority. "Usage of antibiotics in agricultural livestock in the Netherlands in 2016." (2017). Available at: <http://www.autoriteitdieregenesmiddelen.nl/Userfiles/Eng%20rapport%20AB%202016/engels-def-rapportage-2016-deel-1-en-2-22-09-2017.pdf>

¹² British Poultry Council, Antibiotic Stewardship Report 2018. Available at: <https://www.britishpoultry.org.uk/bpc-antibiotic-stewardship-report-2018/>

¹³ Agriculture and Horticulture Development Board, UK Pig Industry Halves Antibiotic Usage in Two Years, May 2018. Available at: <https://pork.ahdb.org.uk/news/news-releases/2018/may/uk-pig-industry-halves-antibiotic-usage-in-two-years/>

leapfrog surveillance systems forward. Carrying out an assessment of where such regional capacity might be best positioned could be done at the global level.

2.5 *AMR surveillance programs should begin by building upon the existing infrastructure.* For example, there would be strategic value in integrating the AMR surveillance component into ongoing, national level infectious disease control programs such as TB/HIV control programs. AMR surveillance data generated as part of these programs should also feed into the overall AMR surveillance database. Lessons and best practices adapted from other successful AMR surveillance programs should be shared.

3. Integrated AMR surveillance should be a key goal of such systems.

3.1 *Across sectors, the WHO AGISAR, WHO GLASS's ESBL E. coli Tricycle AMR Surveillance project, and the ECDC/EFSA/EMA integrated surveillance efforts might provide useful lessons for scaling such efforts.* The work of the WHO Advisory Group for Integrated Surveillance of Antimicrobial Resistance (AGISAR) provides Member States with technical assistance on conducting integrated AMR surveillance programs.¹⁴ The WHO Global Antimicrobial Resistance Surveillance System (GLASS) has embarked on a demonstration project to develop a global protocol for a simplified, integrated surveillance approach focused on extended-spectrum beta-lactamase *E. coli* across three settings—the healthcare delivery system, the food system and the environment.¹⁵ The project is training personnel from pilot countries across the WHO regions. The European Centre for Disease Prevention and Control, European Food Safety Agency, and European Medicines Agency also has engaged in integrated surveillance of AMR in humans and food animals.^{16,17}

3.2 *Within the healthcare delivery system, an integrated surveillance system should capture not only measures of antimicrobial stewardship, but also of antibiotic access.* Striking the right balance in ensuring that curbing overuse does not exacerbate underuse would be important. Failing to do so sends the wrong message to those in resource-limited settings where both underuse and overuse remain challenges.

¹⁴ *Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria: Application of a One Health Approach: Guidance from the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR).* Geneva, Switzerland: World Health Organization, 2017. Available at:

<http://apps.who.int/iris/bitstream/handle/10665/255747/9789241512411-eng.pdf?sequence=1>

¹⁵ Matheu J, Aidara-Kane A, Andremont A. The ESBL Tricycle AMR Surveillance Project: A Simple, One Health Approach to Global Surveillance. *AMR Control*, July 31, 2017. Available at: <http://resistancecontrol.info/2017/the-esbl-tricycle-amr-surveillance-project-a-simple-one-health-approach-to-global-surveillance/>

¹⁶ ECDC. EU integrated surveillance of antimicrobial resistance. Available at: <https://ecdc.europa.eu/en/infectious-diseases-public-health/microbiology/eu-integrated-surveillance-antimicrobial-resistance>

¹⁷ ECDC/EFSA/EMA. Second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. *EFSA Journal*, 2017; 15(7): 4872 (135 pages).

4. Transparency of surveillance and monitoring data must follow from availability. Making the data publicly available would allow for analysis, comparison, and accountability from these findings.

4.1 *At the country level, non-transparency sometimes results not from lack of capacity to collect such data, but concerns of commercial confidentiality. Public health concerns should override concerns over commercial confidentiality.* While the IACG paper focuses on low- and middle-income countries, there is also notable lack of public transparency of data—even when such data are collected—in high-income countries where such infrastructure for surveillance exists.

In the United States, the Food and Drug Administration collects data on antibiotic sales, by livestock species, from drug companies, the US Department of Agriculture conducts voluntary farm surveys through the National Animal Health Monitoring System, and the Agricultural Resource Management Survey captures limited data on whether a farm used antibiotics for a particular purpose. Collectively, however, such data are inadequate for tracking trends and changes in AMR from the food system.¹⁸ Without transparency of collected data, efforts to ensure accountability for AMR benchmarks will be slowed.

The failure to disclose data on grounds of commercial confidentiality should be justified in terms of a public benefit test. The default should be public disclosure unless a compelling and overriding reason not to disclose is made. In setting such data access policies, the burden should be on those seeking to withhold such information to justify why the public's interest is not better served in knowing such information and holding such actors accountable.

4.2 *At the global level, non-transparency of surveillance and monitoring data also exists.* OIE, for example, reported that 10 countries mention colistin as an antimicrobial agent authorized for use of growth promotion, but OIE does not disclose which countries permit this use, perhaps concerned that doing so would jeopardize country participation in this global reporting system.¹⁹ The IACG should consider a recommendation that protects the integrity of such reporting system, but does not compromise the public disclosure of such information. One approach would be to release the data unless a country specifically requests that it not be done.

¹⁸ Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis. *Combating Antibiotic Resistance: A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock*. Washington, DC: Antibiotic Resistance Action Center, George Washington University Milken Institute School of Public Health and Natural Resources Defense Council, 2017, p. 24.

¹⁹ World Organization for Animal Health. *OIE Annual report on the use of antimicrobial agents in animals: Better understanding of the global situation*. Paris, France: OIE, 2016. Available at: http://www.oie.int/fileadmin/Home/fr/Our_scientific_expertise/docs/pdf/AMR/Survey_on_monitoring_antimicrobial_agents_Dec2016.pdf

- 4.3 *Civil society and academic institutions should be supported to conduct independent investigations using alternative data collection approaches to provide transparency of such findings. Such snapshots might prompt greater transparency at a systemic level.*

For example, Consumers Union analyzed pork samples from six U.S. cities as part of their Consumer Reports, and found harmful *Yersinia enterocolitica* in 69 percent of samples. A majority of these pathogens were resistant to medically important antibiotics. Based on these findings, Consumers Union put forth tips for consumers and launched its Meat Without Drugs campaign urging supermarkets to stop selling meat raised with routine antibiotics.²⁰ The Center for Science in the Public Interest also conducted analyses of antibiotic-resistant *Salmonella* outbreaks in the U.S. linked with meat and poultry to pressure the government to label antibiotic resistant *Salmonella* a food adulterant.²¹ The Center for Science and Environment also conducted independent analyses on the antibiotic policies of major fast food chains, revealing the double standards held by fast food companies which are making commitments to reduce the routine use of antibiotics used for their food animal products in the United States, but not in India.²²

- 4.4 *Public procurement agencies might also play an important role in encouraging greater transparency of such data. They could insist on disclosure of whether drug companies have manufactured and/or licensed drugs for dual markets, that is, for both human and veterinary use as well as where and what antibiotic sales were made.*

5. Prioritization is key in channeling global resources to where the return on investment would be greatest. The baseline consumption of antimicrobials in healthcare delivery and in the food system, the trajectory of growth, and the concentrated flows of export and import of food animal products could factor into a prioritization framework for policy interventions.

- 5.1 *By developing standardized data collection and reporting approaches, countries would be better supported in developing sustainable national or regional AMR*

²⁰ Consumers Union, New Study: Consumer Reports finds antibiotic-resistant bacteria in pork products, 2013. Available at: <https://consumersunion.org/news/new-study-consumer-reports-finds-antibiotic-resistant-bacteria-in-pork-products/>

²¹ Center for Science in the Public Interest, Petition for an Interpretive Rule Declaring Antibiotic-Resistant *Salmonella* Heidelberg, *Salmonella* Hadar, *Salmonella* Newport and *Salmonella* Typhimurium in Meat and Poultry to be Adulterants, October 2014. Available at: <https://cspinet.org/sites/default/files/attachment/oct-14-abr-petition.pdf>

²² Chandra Bhushan, Amit Khurana and Ananya Tewari 2017. Double Standards, Antibiotic Misuse by Fast Food Companies, Centre for Science and Environment, New Delhi. Available at: http://cdn.cseindia.org/attachments/0.68707600_1520933761_double-standards-antibiotic-misuse-by-fast-food-companies-20171113.pdf

surveillance strategies. Much of this work is ongoing. The Tripartite agencies' work on the Monitoring and Evaluation Framework provides a useful starting point as do efforts like WHO's Global Antimicrobial Resistance Surveillance System, WHO's Advisory Group on Integrated Surveillance of Antimicrobial Resistance, the Global Action Plan's Country Self-Assessment, FAO's ATLASS assessments, and OIE's country survey of antimicrobial use in animals. More work to integrate AMR-sensitive indicators from other UN and international agencies, from UNICEF to GAVI, requires a system-wide approach to coordinating such data collection beyond the Tripartite agencies. While some of these data points can be collected by country contact points, others will require fielding an instrument adaptable to the national and local context.

There may be useful lessons to be drawn from the work of the WHO-Health Action International (HAI) project on Medicines Prices and Availability²³. It developed a simple, gold standard methodology to collect evidence on the price, availability, affordability and price components of medicines. The instrument focuses on up to 50 essential medicines. It allows for benchmarking retail prices against the MSH reference index, enables comparisons between urban-rural and public, private and mission sector medicine outlets, and captures measures of availability and affordability of a treatment course.²⁴ The methodology has been fielded in over 120 countries and has been adapted to measure the price, availability and affordability of other commodities. The instrument has been widely emulated for its effectiveness in reliably measuring medicine prices and availability in a standardized way, thereby facilitating national and international comparisons.

In a staged approach, resources should go to where there continues to be demonstrable need, so a country's commitment to AMR surveillance and monitoring could be tied to sustaining these efforts.

5.2 *Baseline data on antimicrobial consumption and related patterns can provide initial direction of resources to where surveillance and monitoring efforts would have the greatest potential impact.* The IACG could, with the assistance of Tripartite agencies, develop a prioritization framework, where higher antimicrobial consumption (both measured in terms of aggregate and per capita/by biomass), the country's role as key exporter or importer of food animal products or as provider of medical tourism services, and infrastructure (e.g., laboratory testing, supply of prescribers in both healthcare and food production sectors), and of course, baseline efforts already dedicated to AMR monitoring and surveillance factor into where resources might be prioritized.

²³ World Health Organization, Health Action International. Measuring medicine prices, availability, affordability and price components. 2nd ed. Geneva: World Health Organization; 2008.

²⁴ Niëns LM, Cameron A, Van de Poel E, Ewen M, Brouwer WB, Laing R. Quantifying the impoverishing effects of purchasing medicines: a cross-country comparison of the affordability of medicines in the developing world. *PLoS Med* 2010; 7(8). Available at: <http://journals.plos.org/plosmedicine/article/file?id=10.1371/journal.pmed.1000333&type=printable>

5.3 *Surveillance systems can also help identify substandard and falsified medicines in the supply chain, and developing mobile kits and systems for reliable reporting of such findings could help equip both government authorities and civil society in monitoring for these problems.* Track-and-trace systems provide ways to ensure the integrity of drug product packages from the point of manufacture to the point of dispensing. However, substandard and falsified antimicrobials likely fall outside of these voluntary, track-and trace systems, and sampling pharmacy dispensing outlets and farming operations could be a considerable undertaking. Even where such sampling for surveillance and monitoring already exists, piggybacking the testing for substandard and falsified medicines requires both technical and financial resources. A useful steppingstone would be the development of a low-cost, easily implemented, mobile test kit for identifying key substandard and falsified antimicrobials and guidance on how to report reliably and credibly such findings. Such a test kit could then be integrated into surveillance and monitoring efforts carried out by governments, civil society or healthcare delivery systems. Safeguards and conflict of interest requirements would have to be put into place, so that such approaches were not used for branded, commercial marketing efforts to discredit quality generic suppliers. We would also note that “counterfeit” is no longer a recognized definition as it can lead to confusion between substandard and falsified products and the protection of intellectual property rights. The WHO definition of substandard and falsified products should be used.²⁵

Concerns have arisen that some published research has sought to raise doubts over the quality of generic medicines as being truly bioequivalent (as measured by drug regulatory agency established criteria of pharmaceutical equivalent, pharmacokinetic equivalence, or in vitro susceptibility testing). We also caution that the testing to identify substandard or falsified medicines carefully adhere to validated methods of establishing drug quality.

5.4 *A systems perspective should be taken in designing surveillance and monitoring efforts. Steps should be taken to mitigate problems that might come with prioritization, such as the neglect of tracking drug resistance to older antibiotics when focused on newer antibiotics for priority pathogens. Surveillance should also consider tracking not just the most worrisome, drug-resistant pathogens, but also trends of inappropriate use (e.g., using antibiotics for viral disease or uncomplicated diarrhea).*

In both healthcare delivery and especially in food production, older antibiotics may still be widely used. So integrated surveillance and monitoring efforts need to ensure that these drivers of drug resistance that tilt usage towards newer antibiotic alternatives are not neglected.

²⁵ WHO, Definitions of Substandard and Falsified (SF) Medical Products. Available at: <http://www.who.int/medicines/regulation/ssffc/definitions/en/>

We would also caution against adopting the Drug Resistance Index,²⁶ a composite measure “that combines the ability of antibiotics to treat infections with the extent of their use in clinical practice” until it is more robustly tested. The benefits of a composite index over tracking separately resistance to the top drug-bug combinations are not obvious, but the risks of a composite index in masking important underlying trends are.

5.5 Prioritizing efforts to integrate the environmental aspect of AMR into ongoing surveillance and monitoring systems is critical to ensuring greater policymaker buy-in to addressing these concerns in National Action Plans on AMR.

We would emphasize that environmental surveillance for AMR should not just be limited to antibiotic pollution from pharmaceutical manufacturing plants, but also should include both food production settings (farms, slaughterhouses, processing units) as well as healthcare settings (hospitals) and waste treatment facilities.

Surveillance of antibiotic use in the agricultural sector, surrounding environment and food products should also be integrated into the overall surveillance efforts. Countries need to be supported to better understand and address emergence and spread of AMR from agricultural systems, judicious antibiotic use practices and risk reduction approaches along with enforcement of standards for antibiotic residues in agricultural food products.

There is a need for greater global guidance for environmental surveillance for AMR. Defining the optimal methods, tools, breakpoints, sampling design and locations, and priority bacterial pathogens and antibiotics all require considerable work. A roadmap for scaling up such efforts is also much needed.

6. Comparability enables cross-country and cross-setting comparisons important for both prioritizing resources and policymaker attention. The development of standardized instruments, of course, need to accommodate implementation in differently resourced settings, but also should spur stepwise adoption of surveillance and monitoring approaches that only be possible with greater technical and financial inputs over time.

6.1 To advance efforts to ensure comparability in surveillance and monitoring systems across countries and similar settings, there will need to be a globally coordinated training and capacity building effort. The design and scale-up of such an effort should draw upon the lessons and many years of experience of similar efforts in public health and agricultural extension services. Best practice networks, learning collaboratives, and twinning programs are just some of the various tested approaches that might be emulated.

²⁶ Laxminarayan R, Klugman KP. Communicating trends in resistance using a drug resistance index. *BMJ Open* 2011; 1:e000135. Available at: <https://bmjopen.bmj.com/content/bmjopen/1/2/e000135.full.pdf>

6.2 *Conflict of interest in setting standards for comparability must be avoided.* For example, breakpoints for establishing antimicrobial susceptibility of bacterial pathogens are critical to determining what the levels of local drug resistance are. These breakpoints are set by committees, such as those of EUCAST or the Clinical Laboratory Standards Institute (CLSI). A study from Johns Hopkins flags concern how these antimicrobial susceptibility criteria are set. Investigators found that if the breakpoint for ceftriaxone were lowered as CLSI had recommended, they would have been a 300% increase in the number of cases classified as drug resistant, a finding that would prompt many healthcare providers to switch to more expensive, broader spectrum antibiotics. However, the investigators note that such a switch would have not made any difference in saving the lives of children treated for these infections. Worryingly, around that time and still today, a majority of members of the CLSI Committee setting these antibiotic breakpoints reported potential financial conflict of interest or ties to the pharmaceutical industry.²⁷ So it would be important that conflict of interest safeguards are in place wherever the process of setting standards for comparability is underway.

6.3 *Systematic reviews of published studies on magnitude and trends of antimicrobial resistance reveal a need for minimum reporting guidelines.* Academic institutions and other research groups could contribute more meaningfully not only to the literature, but also to surveillance and monitoring systems if the quality of reporting their findings met minimum standards. Reviewing 40 years of AMR research on enteric pathogens in East Africa, the authors of this systematic review concluded:²⁸

The majority (98%) of human studies were based on hospital- (rather than community-wide) sampling and although they report high levels of antimicrobial resistance in the region, study design and methodological differences preclude conclusions about the magnitude and trends of antimicrobial resistance. To remedy this, we discuss and propose minimum reporting guidelines for the level of detail that should be explicitly provided for antimicrobial resistance study designs, testing of samples and reporting of results that would permit comparative inferences and enable meta-analyses. Further, we advocate for increased focus on community- rather than hospital-based sampling to provide a better indication of population-wide trends in antimicrobial resistance. This approach, together with the establishment of a robust regional surveillance network, should over time build a pool of evidence-based data useful for policy decisions and interventions aimed at controlling antimicrobial resistance.

The Tripartite agencies engaged in joint monitoring and evaluation efforts would be well positioned to convene expert groups to define these minimum reporting guidelines for

²⁷ Clinical and Laboratory Standards Institute, Subcommittee on Antimicrobial Susceptibility Testing—Disclosure Summary, 5/17/2016. Available at: <https://clsi.org/media/1794/disclosure-of-interest.pdf>

²⁸ Omulo S, Thumbi SM, Njenga MK, Call DR. A review of 40 years of enteric antimicrobial resistance research in Eastern Africa: what can be done better? *Antimicrobial Resistance and Infection Control* 2015; 4:1. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4339253/pdf/13756_2014_Article_41.pdf

such studies, and groups like the International Council of Medical Journal Editors could support their adoption.

7. Sustaining investment in surveillance and monitoring systems requires a multi-pronged strategy of making the economic case for such funding and ensuring the value-added use of these data by governmental policymakers and non-governmental actors.

7.1 *At the country level, a framework for making the economic case for prioritization of AMR surveillance and monitoring, alongside antimicrobial stewardship and other interventions, could be important to ensuring the sustainability of these efforts.* Such a framework might include a model that allows country-level estimation of the World Bank's projected toll on economies, if AMR goes unchecked, in terms of increased drug resistance, losses in livestock productivity, and numbers pushed into poverty.²⁹ Complementing this picture, the framework might also consider the likely impact of restrictive antibiotic policies on food exports from the country and food imports into the country.³⁰ Emulating the impact model conducted the University of Edinburgh for WHO, another module in this framework might document the potential, anticipated country-level impact of substandard and falsified antibiotics in treating an index infection like pneumonia in children.³¹

7.2 *At the global level, the World Bank's analysis of drug-resistant infections suggests a significant economic toll globally, disproportionately falling on low- and middle-income countries.* The World Bank report argues that:³²

...our analysis shows that action on AMR constitutes one of the highest-yield development investments available to countries today... Different countries stand to benefit from AMR control in different ways. Low-income countries will see substantial economic payoffs, relative to the size of their economies. The largest absolute and per capita gains, however, will actually flow to upper middle-income and high-income countries. Assuming, very conservatively, that only 10 percent of the modeled costs were averted through AMR containment measures, high-income countries would still obtain benefits of \$0.9 trillion and \$2.7 trillion, in the

²⁹ World Bank. *Drug-Resistant Infections: A Threat to Our Economic Future*. Washington, DC: World Bank, 2017. Available at: <http://documents.worldbank.org/curated/en/323311493396993758/pdf/114679-REVISED-v2-Drug-Resistant-Infections-Final-Report.pdf>

³⁰ Johnson R. "Potential Trade Implications of Restrictions on Antimicrobial Use in Animal Production." Washington, DC: Congressional Research Service, July 11, 2011. Available at: <http://nationalaglawcenter.org/wp-content/uploads/assets/crs/R41047.pdf>

³¹ A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva: World Health Organization, 2017. Available at: http://www.who.int/medicines/regulation/ssffc/publications/SE_Study_EN.pdf?ua=1

³² World Bank. *Drug-Resistant Infections: A Threat to Our Economic Future*. Washington, DC: World Bank, 2017, page xx. Available at: <http://documents.worldbank.org/curated/en/323311493396993758/pdf/114679-REVISED-v2-Drug-Resistant-Infections-Final-Report.pdf>

low AMR-impact and high AMR-impact cases, respectively. This is four times and thirteen times more than the global investment cost of \$0.2 trillion.

The IACG could make the clear case as to how high-income countries would benefit disproportionately from investing in AMR and why they should make such an investment now rather than at some date in the future. In addition, positioning AMR as a development aid issue could mainstream this work into these funding streams.

7.3 *Ensuring that surveillance and monitoring data are transparent, actionable, and serve as policy triggers will also engage policymakers and enlist civil society in supporting sustainable investment in such systems.* Making sure that these data serve a continued, useful purpose is key to maintaining investment in their collection. This means that governmental agencies AND non-governmental groups should be encouraged to use these data as tools for accountability—creating scorecards, profiling institutions and providers, making comparison across farming operations. The more key actors are invested in the use of these data, the more likely investment will continue. The Yellow Card system in Denmark and the Chain Reaction report each represent examples of how such collected data can be made actionable.

The Yellow Card Initiative led by the Danish Veterinary and Food Administration (DVFA) incentivizes pig farmers to adhere to antibiotic consumption reduction targets in order to reach Denmark's goal of reducing antibiotic consumption in pig farms by 15% from 2015 to 2018. Each year, the DVFA establishes antibiotic consumption thresholds. Compliance occurs in a three-step process, starting with a yellow card for failure to comply. The measures escalate, and in the final stage, farms that do not reach the target threshold for antibiotic consumption receive a "Red Card," are fined a third time, and must make additional changes to their practice such as reducing their stocking density. Consequently, this strategy successfully led to decreased antibiotic consumption in the pig production sector.³³ The Yellow Card initiative is a valuable example of how enhanced surveillance of antibiotic use and resistance can facilitate the implementation of targets by targeting top users.³⁴

Another example is the *Chain Reaction* report, which is a scorecard developed by a coalition of consumer groups to benchmark progress towards a demand for socially

³³ Danish Veterinary and Food Administration (2017). Special provisions for the reduction of the consumption of antibiotics in pig holdings (the yellow card initiative). Available at: <https://www.foedevarestyrelsen.dk/english/SiteCollectionDocuments/Dyrevelfaerd%20og%20veterinaermedicin/Veterin%C3%A6rmedicin/Yellow%20Card,%20English%20version,%20180517.pdf>

³⁴ Expert Commission on Addressing the Contribution of Livestock to the Antibiotic Resistance Crisis. COMBATING ANTIBIOTIC RESISTANCE A Policy Roadmap to Reduce Use of Medically Important Antibiotics in Livestock. 2017. Washington, D.C. Available at: <http://battlesuperbugs.com/sites/battlesuperbugs.com/files/Final%20Report%208.25.17.pdf>

responsible antibiotic policies in the U.S. fast food industry.³⁵ The coalition recruited data and ranked the United States' top 25 restaurant chains on their antibiotic use policies. Based on networks of consumers, students, healthcare professionals and the public, this information was then leveraged through consumer demand to compel restaurants to make changes to their antibiotic policies and impose such requirements on suppliers of food animal products. Transparency allows these actions to be reflected back in the data put forth to civil society and consumers, who can subsequently hold companies accountable for the promised change.

³⁵ Friends of the Earth, Consumers Union, NRDC, Center for Food Safety, FACT, & U.S. PIRG (2017). Chain Reaction III: How Top Restaurants Rate on Reducing Use of Antibiotics in Their Meat Supply. Available at: https://uspirgedfund.org/sites/pirg/files/reports/ChainReaction3_Report_final.pdf