Personal view

Sustainable AMR Surveillance: time for a global funding mechanism?

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Summary

Antimicrobial resistance (AMR) is predicted to outstrip malaria, HIV and tuberculosis combined as a leading infectious cause of death by 2050. Strengthening the knowledge and evidence base for AMR through surveillance and research is one of the five main objectives of the WHO Global Action Plan on AMR. While recent efforts to strengthen diagnosis and surveillance have been encouraging, these are unlikely to be sustainable without continued funding support in most low-resource settings.

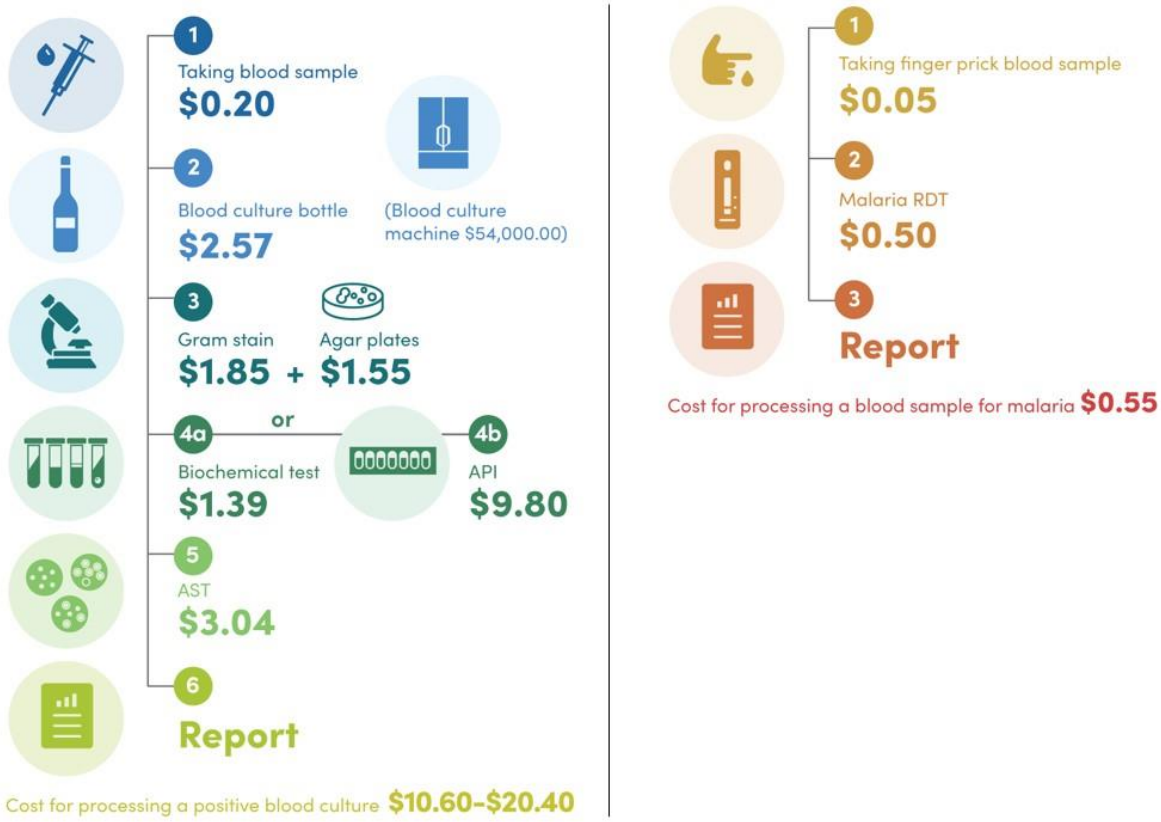
We estimated the continued costs of a standard national AMR surveillance system in low- and middle-income countries (LMICs). For 46 LMICs the costs would account for more than 2% of their total domestic general government health expenditure (GGHE-D), and for 28 of these countries they are more than 5% of their total GGHE-D. This is not sustainable without a long-term global financing mechanism.

Keywords: AMR, surveillance, low resource settings, economics, financing

Microbiological diagnosis has improved steadily in high-income and higher-middle-income countries over decades and is the cornerstone of antimicrobial resistance (AMR) surveillance in humans. The time from specimen collection to results has been getting progressively shorter, and more patients get appropriate antimicrobial treatment. Introduction of new technologies and automation in the laboratory have contributed to this progress, e.g. matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF MS) reduces the time to pathogen identification by 24-36 hours. Automation of data analysis at the facility level has been adopted and implemented in Thailand, an upper-middle-income country, leading to improved actions against AMR at both facility and national levels.[1-3] In low-resource settings, use of similar technology is the exception, due to high cost (initial outlay for MALDI-TOF is approximately 350,000 USD followed by more than 30,000 USD annually for maintenance) and other barriers such as stockouts and unstable power supply.[4,5] Laboratories in low-resource settings are more likely to be understaffed and underused, with technicians working across all pathology disciplines. Achieving turnaround times to results shorter than the average length of stay of the patients is challenging. Data from microbiology laboratories in low-resource settings are rarely used for actions at the facility level due to lack of data expertise and potential bias caused by underutilization of microbiology diagnostic tests. [1,6-9] Expanding AMR surveillance to animals and the environment presents even greater challenges since capacity is currently even lower than in the human health sector.[10,11]

The standard approach to AMR surveillance in bacteria causing human infections proposed by the World Health Organization Global Antimicrobial Resistance and Use Surveillance System (GLASS)[12] is surveillance based on routine microbiological investigations from representative sites (hospitals) in a country. The AMR Diagnostic Initiative launched by WHO in 2023 highlights the importance of access to high quality diagnostics for bacterial and fungal pathogens and AMR.[13] WHO GLASS (2023) recommends countries gradually increase the number of surveillance sites over time without pre-specifying the optimum number.[12,14] A previous economic analysis has shown that routine diagnostic microbiology in a low-resource setting using established methods which permit bacterial identification to species level, plus antimicrobial susceptibility testing, can cost anywhere between USD 11 to 31 per specimen (Figure 1) or USD 105–304 per bacterial isolate.[15] This is considerably higher than the cost of common antibiotic treatments, which are often available over-the-counter without involvement of healthcare professionals or prescription. This cost is also higher than the cost of diagnosis of other high burden infectious diseases (e.g. a rapid diagnostic test for malaria costs around 0.5-1.5 USD). This cost difference is just for reagents and does not take into account the infrastructure, training and quality management needed to deliver microbiology testing.

Figure 1. Steps and cost of processing a blood culture versus a malaria rapid diagnostic test. Example of processing a blood culture positive for an ESBL-producing *E. coli* which includes 1st and 2nd line antimicrobial susceptibility testing (AST) and ESBL confirmation testing



Note: costs are based on actual costs in Lao PDR (see breakdown in Supplementary Material)

Using routine diagnostic microbiology as the platform on which AMR surveillance is based has clear benefits for case-management, infection prevention and control, and antimicrobial stewardship,[16] but it will take time to achieve high coverage in most countries. Alternative lower cost models of surveillance are being evaluated by the WHO such as interval national AMR prevalence surveys.[17] These are not viewed as a long term solution but rather to fill a gap while sustainable surveillance systems are built up. The survey methodology proposes alternative approaches to sampling ranging from all hospitals in small countries to more complex multi-stage cluster sampling of larger populations. Using the latter approach it is envisaged that "*the number of hospitals in the final sample will range from ≥ 30 (to improve the precision of the estimators) to ≤ 60 (for logistic and resource considerations).*"[17]

Recommended add-on activities to routine surveillance include surveillance of drug susceptibility of *Neisseria gonorrhoeae*, surveillance for extended-spectrum beta lactamase (ESBL)-producing *E.coli* in human, animal and environmental sectors ("Tricycle"), and implementation of the WHO attributable mortality protocol.[18]

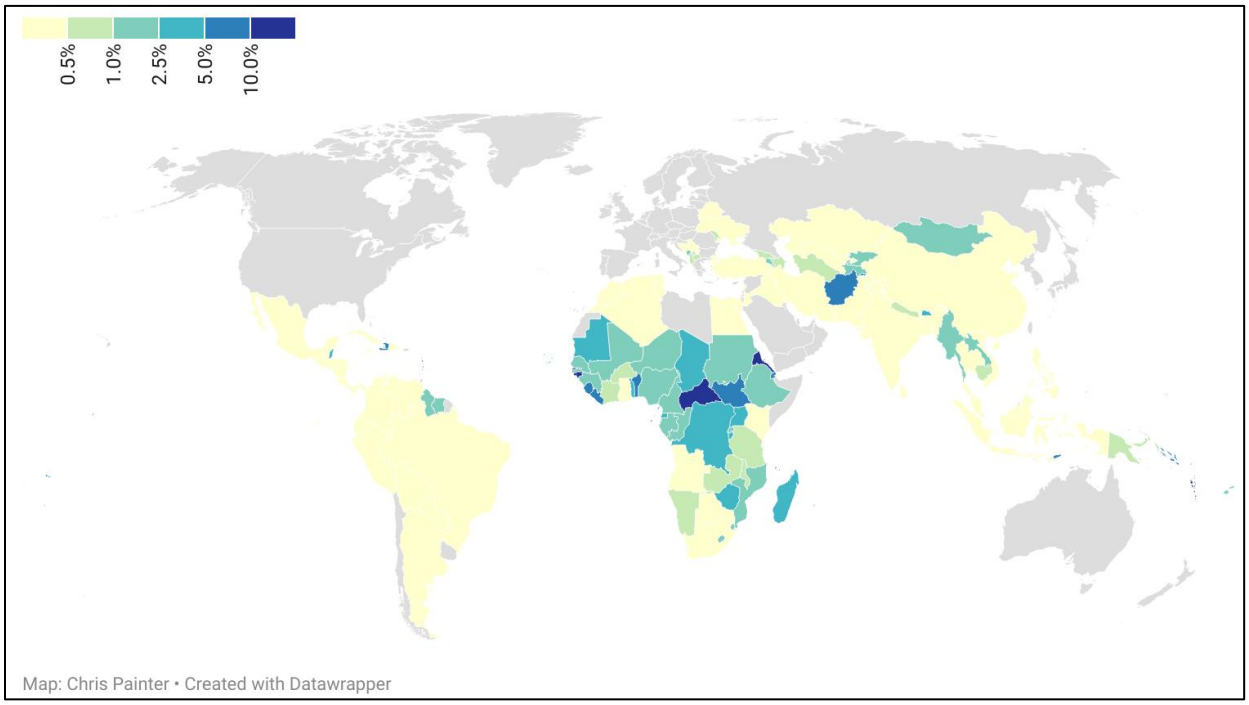
Over the last five years, with support from external donors such as the UK Fleming Fund (active in 24 LMICs in Africa and Asia), several countries have begun to kick-start or, in some cases, revive their microbiology laboratory capacity in order to generate AMR surveillance data. This is a very positive development but, given the high costs of microbiological testing and maintenance of diagnostic instruments procured during these initiatives, there are serious concerns about sustainability once this support ends. There is inevitably a lag between establishment of diagnostic laboratories and optimal utilization by clinicians. Such delays may result in the perception of a poor return on investment, in the sense of production of reliable and representative AMR surveillance data.

To investigate whether AMR surveillance is a sustainable routine activity for low-resource settings we estimated the sustained cost burden required to conduct target AMR surveillance in humans, animals and the environment in all LMICs (as categorised by the Organisation for Economic Co-operation and Development (https://www.oecd.org/en/about.html) Assistance Committee's list of official development assistance recipients). We searched PubMed (for terms "AMR" and "Surveillance" and "cost" in Title/Abstract) and Google for estimates of costs of AMR surveillance. The annual costs per surveillance site were obtained from Seale et al. 2016,[19] using an average obtained from three LMIC countries (Ethiopia, Kenya and Vietnam), and inflated to 2019 cost values. First-year costs were omitted as these included set-up costs and this analysis was focused on the longer-term financial sustainability of AMR surveillance. The cost estimates were combined with the number of surveillance sites required to achieve target levels of human AMR surveillance. In the base case, the number of surveillance sites required was conservatively estimated as the minimum of two options: a) one site per first-level administrative division[20] in the country, which we anticipated would be a standard approach for most countries; or b) one site per five million population, with a minimum of five sites per country (an assumption also used by Seale et al. 2017).[19] The median number of estimated sites per country was five. The maximum number of sites estimated using this approach was Indonesia with 38, whilst 84 countries had the minimum of five sites.

The Fleming Fund states that their country grants typically support 4-10 human health surveillance sites and 1-3 animal health laboratories, so we assumed that conducting appropriate target levels of animal and environmental AMR surveillance would incur an additional 25% of costs. The total cost estimates were combined with domestic general government health expenditure (GGHE-D) per capita (PPP) data and population estimates from 2019,[21] to produce estimated costs of AMR surveillance as a percentage of total GGHE-D. Data from 2019 was used instead of 2020, which was the most recent year with comprehensive data coverage across the countries, as government health spending was irregular in this year due to the COVID-19 pandemic. Estimates were generated for 129 of 136 LMICs, as the required data were unavailable for seven countries. The results are displayed in Figure , and show that for many LMICs the estimated cost required to conduct AMR diagnosis and surveillance is substantial. We estimate that for 46 LMICs the costs would account for more than 2% of the total GGHE-D, and for 28 of these countries it is more than 5% of the total GGHE-D, and a burden of over 10% of total GGHE-D for 17 of this same group. The mean and median burden as a percentage of total GGHE-D was 4.02% and 0.98%, respectively. The results and interactive data map are available at: https://datawrapper.dwcdn.net/GoCj3/1/ and all of the data and calculations performed, including the total cost estimates for each country, can be found in the Supplementary Material. The Supplementary Material also includes a set of results where the maximum of the number of sites calculated under

option a) or b) was used (with a maximum number of five sites for countries with populations under 1.5 million), rather than the minimum as was used in the base case.

Figure 2. Estimated costs of target AMR surveillance as a percentage of total domestic general government health expenditure in 2019



Note: Colour scale displays percentage values.

Discussion

AMR is predicted to outstrip malaria, HIV and tuberculosis combined as a leading infectious cause of death by 2050.[22] Since 2002, the Global Fund for AIDS, TB and Malaria has transformed the ability of more than 100 countries to respond to these diseases and saved millions of lives.[23] Eligibility for funding/investment depends on country income status and disease burden with high income countries and OECD-DAC members ineligible for funding. As proposed in an editorial in 2022,[24] a similar system will be needed to enable all countries to respond to AMR, including conducting AMR surveillance – one of five main objectives of the WHO Global Action Plan on AMR.

The recent Lancet series emphasized the need for sustainable access to effective antimicrobials to treat drug-resistant infections and proposed different models of funding or incentivization to achieve this, e.g. PEPFAR (U.S. President's Emergency Plan for AIDS Relief)-type approaches.[25] However, facilitating appropriate use of newer antimicrobials will only be possible if diagnostic microbiology is widely available to guide therapy. Without this, a new antibiotic is more likely to be overused in LMICs and at risk of becoming ineffective globally within a few years. AMR is a global problem and does not respect borders.[26] Efforts to monitor and reduce AMR should be considered as a global public good. There is an economic and humanitarian incentive for high-income countries to contribute to AMR surveillance and control in countries that are less able to foot the bill. We estimated the mean and median cost of conducting AMR diagnosis and surveillance as a percentage of total GGHE-D at 4.02% and 0.98%,

respectively. To help to put this into perspective, Gavi low-income and middle-income countries spent 3.3% and 2.4% of total government health expenditure on immunization in 2021.[27]

Global financing initiatives with a narrow focus can have unwanted effects on health systems, shifting national priorities and forgoing opportunities for cross-sectoral integration.[28] Focusing on obtaining AMR surveillance data and sustained access to antimicrobials in a vertical programme may be disadvantageous, especially since drivers other than antimicrobial use may be particularly significant;[29] however the increasing number of deaths that are associated with AMR makes both urgent priorities to address. An added benefit of a new global funding mechanism would be to accelerate progress to make testing more affordable and improve supply chains.[30] Currently, the diagnostic market is dominated by a small number of biotech companies with few incentives to lower the costs of their products. The Global Fund uses pooled procurement and price negotiation to strengthen supply chains and reduce the costs of drugs and diagnostics for HIV, TB and malaria, something that is sorely needed for AMR. A comprehensive international funding mechanism for AMR surveillance could also result in other efficiencies, by avoiding duplication of efforts and supporting consistent reporting which will facilitate better understanding of spatial/temporal trends. Comprehensive AMR surveillance data could also improve allocative efficiency and enable funders or governments to designate resources more appropriately.

Although the estimates of the number of sites required was performed quite simplistically, by using two estimates of the number of sites that would be required we have attempted to find a pragmatic balance between strictly population-derived estimates and other contextual factors such as population density and geographical barriers that may result in the administrative decentralisation of health services. Contextual factors which could mean the cost estimates used are an under- or over-estimate may exist in some of the considered countries, particularly due to differences in the number of sites required in reality or because the costs per site used do not accurately reflect the situation in certain countries (for example, due to staff wage disparities between or within regions of countries). To avoid overstating the costs, the lowest estimates of the number of sites were conservatively assumed in the base case results. What we believe to be the best cost estimates for conducting effective AMR surveillance available were used, using an average obtained from three LMIC countries (Ethiopia, Kenya and Vietnam).

More complex and contextualised estimates would be beneficial, including accounting for existing reimbursement of diagnostic tests through health insurance schemes. In addition, our estimate of the number of sites per country does not take into account technical feasibility of scale-up to reach these numbers. For most countries the number of sites was lower than the maximum number set by the WHO survey methodology and similar or lower than the number of laboratories supported by the Fleming Fund country grants.[31] CHINET has 74 surveillance sites currently which is substantially more than our base case estimate of 31, but much lower than our alternative higher estimate of 282 (see Supplementary material). It could also be argued that the high costs of surveillance as percentages of GGHE-D produced in the analyses reflect low levels of GGHE-D in countries that should be increased, though that is a nuanced macroeconomic policy debate beyond the scope of this article.

While governments in low-resource settings should continue to commit a proportion of their health spending to AMR diagnosis, surveillance and control, it is unrealistic to imagine they can fully cover all costs. Past experience with other infectious diseases shows us that delaying addressing this will only lead to more deaths. The 2024 World AMR awareness week campaign ‘AMR is invisible, I am not’ of the

WHO brings the human cost of AMR to the forefront. Accurate microbiological diagnosis can be life-saving for individuals and underpins global AMR decision-making. Availability of a global evidence base of AMR in time and space is crucial to identify trends and hotspots and to inform treatment guidelines locally. A global funding mechanism is needed to make it happen.

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Declaration of interests

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References

1. Lim C, Miliya T, Chansamouth V, et al. Automating the Generation of Antimicrobial Resistance Surveillance Reports: Proof-of-Concept Study Involving Seven Hospitals in Seven Countries. *J Med Internet Res* 2020; **22**(10): e19762.
2. Srisuphan V, Klaytong P, Rangsiwutisak C, Tuamsuwan K, Boonyarit P, Limmathurotsakul D. Local and timely antimicrobial resistance data for local and national actions: the early implementation of an automated tool for data analysis at local hospital level in Thailand. *JAC Antimicrob Resist* 2023; **5**(4): dlad088.
3. Tuamsuwan K, Chamawan P, Boonyarit P, et al. Frequency of antimicrobial-resistant bloodstream infections in Thailand, 2022. medRxiv; 2024.
4. Okeke IN, Feasey N, Parkhill J, et al. Leapfrogging laboratories: the promise and pitfalls of high-tech solutions for antimicrobial resistance surveillance in low-income settings. *BMJ Glob Health* 2020; **5**(12).
5. Ombelet S, Ronat JB, Walsh T, et al. Clinical bacteriology in low-resource settings: today's solutions. *Lancet Infect Dis* 2018; **18**(8): e248-e58.
6. Lim C, Ashley EA, Hamers RL, et al. Surveillance strategies using routine microbiology for antimicrobial resistance in low- and middle-income countries. *Clin Microbiol Infect* 2021; **27**(10): 1391-9.
7. Lim C, Hantrakun V, Teerawattanasook N, et al. Impact of low blood culture usage on rates of antimicrobial resistance. *J Infect* 2021; **82**(3): 355-62.
8. Musa K, Okoliegbe I, Abdalaziz T, Aboushady AT, Stelling J, Gould IM. Laboratory Surveillance, Quality Management, and Its Role in Addressing Antimicrobial Resistance in Africa: A Narrative Review. *Antibiotics (Basel)* 2023; **12**(8).

9. K.C. Iregbu, C.S. Osuagwu, C.D. Umeokonkwo, et al. Underutilization of the Clinical Microbiology Laboratory by Physicians in Nigeria. *African Journal of Clinical and Experimental Microbiology* 2020; **21**(1): 53-9.
10. Mitchell MEV, Alders R, Unger F, Nguyen-Viet H, Le TTH, Toribio JA. The challenges of investigating antimicrobial resistance in Vietnam - what benefits does a One Health approach offer the animal and human health sectors? *BMC Public Health* 2020; **20**(1): 213.
11. Sabbatucci M, Ashiru-Oredope D, Barbier L, et al. Tracking progress on antimicrobial resistance by the quadripartite country self-assessment survey (TrACSS) in G7 countries, 2017-2023: opportunities and gaps. *Pharmacol Res* 2024; **204**: 107188.
12. World Health Organization. GLASS manual for antimicrobial resistance surveillance in common bacteria causing human infection. Geneva: World Health Organization, 2023.
13. World Health Organization. Antimicrobial Resistance Diagnostic Initiative: strengthening bacteriology and mycology diagnostic capacity, laboratory systems and service delivery, 2023.
14. World Health Organization. National antimicrobial resistance surveillance systems and participation in the Global Antimicrobial Resistance Surveillance System (GLASS) A guide to planning, implementation, and monitoring and evaluation. Geneva, 2016.
15. Roberts T, Luangasanatip N, Ling CL, et al. Antimicrobial resistance detection in Southeast Asian hospitals is critically important from both patient and societal perspectives, but what is its cost? *PLOS Glob Public Health* 2021; **1**(10): e0000018.
16. Jacobs J, Hardy L, Semret M, et al. Diagnostic Bacteriology in District Hospitals in Sub-Saharan Africa: At the Forefront of the Containment of Antimicrobial Resistance. *Front Med (Lausanne)* 2019; **6**: 205.
17. World Health Organization. Methodological principles of nationally representative surveys as a platform for global surveillance of antimicrobial resistance in human bloodstream infections. Geneva: World Health Organization, 2023.
18. World Health Organization. GLASS method for estimating attributable mortality of antimicrobial resistant bloodstream infections. Geneva, 2020.
19. Seale AC, Hutchison C, Fernandes S, et al. Supporting surveillance capacity for antimicrobial resistance: Laboratory capacity strengthening for drug resistant infections in low and middle income countries. *Wellcome Open Res* 2017; **2**: 91.
20. Central Intelligence Agency. Field Listing-Administrative Divisions. 2024. https://www.cia.gov/the-world-factbook/field/administrative-divisions/.
21. World Bank Group. World Development Indicators. 2024. https://databank.worldbank.org/source/world-development-indicators#.
22. United Nations Environmental Programme. Antimicrobial resistance: a global threat. 2024. https://www.unep.org/topics/chemicals-and-pollution-action/pollution-and-health/antimicrobial-resistance-global-threat#:~:text=By%202050%2C%20up%20to%2010,poverty%20in%20the%20next%20decade.
23. The Global Fund. The Global Fund to Fight AIDS, Tuberculosis and Malaria. 2024. https://www.theglobalfund.org/en/about-the-global-fund/.
24. The Lancet. Antimicrobial resistance: time to repurpose the Global Fund. *Lancet* 2022; **399**(10322): 335.
25. Laxminarayan R, Impalli I, Rangarajan R, et al. Expanding antibiotic, vaccine, and diagnostics development and access to tackle antimicrobial resistance. *The Lancet*.
26. Khan MS, Durrance-Bagale A, Legido-Quigley H, et al. 'LMICs as reservoirs of AMR': a comparative analysis of policy discourse on antimicrobial resistance with reference to Pakistan. *Health Policy Plan* 2019; **34**(3): 178-87.

27. World Health Organization. Situation Analysis of Immunization Expenditure. Key Facts, 2021, 2022.
28. Biesma RG, Brugha R, Harmer A, Walsh A, Spicer N, Walt G. The effects of global health initiatives on country health systems: a review of the evidence from HIV/AIDS control. *Health Policy Plan* 2009; **24**(4): 239-52.
29. Mendelson M, Laxminarayan R, Limmathurotsakul D, et al. Antimicrobial resistance and the great divide: inequity in priorities and agendas between the Global North and the Global South threatens global mitigation of antimicrobial resistance. *Lancet Glob Health* 2024; **12**(3): e516-e21.
30. Allen Mukhwana, Oluwaseyi Shorinola, Deborah-Fay Ndlovu, Osaso J. Slow, difficult and expensive: How the lab supplies market is crippling African science. Nature index; 2024. p. https://t.co/CXuJnn7BIZ.
31. Yang W, Ding L, Han R, et al. Current status and trends of antimicrobial resistance among clinical isolates in China: a retrospective study of CHINET from 2018 to 2022. *One Health Advances* 2023; **1**(1): 8.