STUDY PROTOCOL

REVISED Systems Policy Analysis for Antimicrobial Resistance Targeted Action (SPAARTA): A Research Protocol

[version 2; peer review: 2 approved]

Raheelah Ahmad[1-4], Nina Zhu[1], Rishabh Jain[1], Jyoti Joshi[5], Mirfin Mpundu[6], Paola Amigo Gutierrez[7], Alison Holmes[1,4,8,9], Tillman Weyde[7], Rifat Atun[1,4,10]

[1]Department of Infectious Diseases, Imperial College London Faculty of Medicine, London, England, W21NY, UK
[2]Department of Health Services Research Management, City St Georges University of London School of Health & Psychological Sciences, London, England, EC1V0HB, UK
[3]Dow University of Health Sciences, Karachi, Sindh, 74200, Pakistan
[4]SEDRIC, London, NW12BE, UK
[5]International Centre for Antimicrobial Resistance Solutions, Copenhagen, Denmark
[6]REACT Africa, Lusaka, Zambia
[7]School of Science & Technology, City University of London Department of Computer Science, London, England, EC1V0HB, UK
[8]David Price Evans Chair in Global Health and Infectious Diseases, Pharmacology & Therapeutics, University of Liverpool Institute of Systems Molecular and Integrative Biology, Liverpool, England, L78TX, UK
[9]Imperial College Healthcare NHS Trust, London, England, W21NY, UK
[10]Department of Health Policy & Management, Harvard University T H Chan School of Public Health, Boston, Massachusetts, MA 02115, USA

v2 **First published:** 02 Dec 2024, **9**:700
https://doi.org/10.12688/wellcomeopenres.22923.1
Latest published: 30 Jul 2025, **9**:700
https://doi.org/10.12688/wellcomeopenres.22923.2

Abstract

Background

The majority of countries (88%) have an Antimicrobial Resistance (AMR) National Action Plan (NAP V.1.0), but many remain unimplemented, and lack funding for interventions. Intervention selection requires a systematic approach to explain and predict progress. Looking beyond AMR is important to ensure the capture of systemic factors at the country level, which can impede or accelerate success.

Aim

To provide innovative policy analysis to allow country comparison and refine targeted action, while developing and implementing NAPs (V.2.0).

Methods

Open Peer Review

Approval Status ✓ ✓

	1	2
version 2 (revision) 30 Jul 2025		✓ view
version 1 02 Dec 2024	✓ view	? view

1. **Olga Perovic**, University of Witwatersrand, Johannesburg, South Africa

2. **Anand Balachandran**, World Health Organisation, Geneva, Switzerland
Zlatina Dobreva, World Health Organization, Geneva, Switzerland

Any reports and responses or comments on the article can be found at the end of the article.

Mixed-method multi-country case study of policies and implementation strategies to address AMR across One Health. Starting with 17 countries, the sample includes each WHO region and emerging economies.

This investigation of structures, processes, and outcomes has three components:

a. Textual analysis of peer-reviewed literature, policy documents, global, national and state level progress reports, validated by global and in-country experts. An all-language article search conducted for 2000-2024, using broad search terms: 'Antimicrobial resistance policies', 'national action plan', 'surveillance', 'AMR systems' supplemented by hand searches. Deductive analysis using multi-disciplinary frameworks including the Expert Consensus for Implementation Research (ERIC).

b. Longitudinal quantitative analysis assessing country contextual determinants and Antimicrobial Use (AMU) and AMR outcomes. Data from global health indicator repositories and international and national AMU and AMR surveillance networks are analysed using econometrics and machine learning approaches.

c. Interactive Tableau dashboard development to display insights from a & b to allow visualisation and comparison of case-country AMR intervention context and components.

Discussion

This protocol provides a systematic, transparent approach for countries to benchmark their own AMR strategies. The interactive dashboard will allow comparisons between country clusters by geography or economy, and enable rapid knowledge mobilisation among strategic and operational stakeholders including policy makers and planners. This protocol facilitates others to perform this structured assessment and nominate their country for the next wave of analysis.

Plain Language Summary

Antimicrobial Resistance (AMR) is when microbes become resistant to the drugs (antimicrobials) used to treat them. As this poses a growing problem to society, many countries have developed a National Action Plan (NAP) to outline their strategies to address this problem of AMR. There is limited funding to carry forward the plans, and limited knowledge of which strategies are the most effective. We therefore, need a better understanding of why some countries are more successful than others in using antimicrobials only when needed and reducing infections that are non-treatable by antimicrobials. Our study aims to create a standardised approach for evaluating AMR NAPs through policy analysis as well as developing a tool to enable

countries to compare performance and promote knowledge sharing. The investigation has three components: a. Text analysis of the existing literature and policies from multiple countries, b. Data analysis of the factors within countries that affect the use of antimicrobials and the development of AMR, c. Developing a tool to visualise and compare country data on AMR interventions.

This will enable the creation of a method for countries to better understand their AMR situation, compare strategies and use resources most effectively.

Keywords
'Antimicrobial resistance policies', 'national action plan', 'surveillance', 'Health systems'

Corresponding author: Raheelah Ahmad (raheelah.ahmad@city.ac.uk)

Author roles: Ahmad R: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Methodology, Project Administration, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Zhu N**: Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Jain R**: Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Joshi J**: Conceptualization, Funding Acquisition, Writing – Review & Editing; **Mpundu M**: Conceptualization, Funding Acquisition, Writing – Review & Editing; **Gutierrez PA**: Data Curation, Visualization, Writing – Review & Editing; **Holmes A**: Writing – Review & Editing; **Weyde T**: Writing – Review & Editing; **Atun R**: Conceptualization, Funding Acquisition, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was supported by Wellcome [228072]. AH is funded by the Wellcome Trust CAMO-Net programme (Grant Ref: 226691/Z/22/Z). For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. RAh & NZ are affiliated with the Wellcome Trust-funded programme CAMO-Net (Grant Ref: 226691/Z/22/Z). RAh is affiliated with the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at Imperial College London in partnership with the UK Health Security Agency (previously PHE) in collaboration with, Imperial Healthcare Partners, University of Cambridge and University of Warwick (Grant Ref: NIHR200876). NZ is partially funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Healthcare Associated Infections and Antimicrobial Resistance at Imperial College London in partnership with the UK Health Security Agency (previously PHE) in collaboration with, Imperial Healthcare Partners, University of Cambridge and University of Warwick (Grant Ref: NIHR200876). The views expressed in this publication are those of the author and not necessarily those of the NHS, the National Institute for Health Research, the Department of Health and Social Care or the UK Health Security Agency (Grant Ref: NIHR200876).
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Ahmad R, Zhu N, Jain R *et al.* **Systems Policy Analysis for Antimicrobial Resistance Targeted Action (SPAARTA): A Research Protocol [version 2; peer review: 2 approved]** Wellcome Open Research 2025, **9**:700 https://doi.org/10.12688/wellcomeopenres.22923.2

First published: 02 Dec 2024, **9**:700 https://doi.org/10.12688/wellcomeopenres.22923.1

REVISED **Amendments from Version 1**

In response to the feedback from the reviewers, we have made the following revisions to the manuscript. The most recent data for countries with a National Action Plan for AMR has been used. More explicit framing of the research within a One Health context and how this will be conducted in phases. Additionally, we have expanded the range of search terms to more comprehensively capture the scope of One Health and AMR-related interventions.

The longitudinal analysis section has also been enhanced to provide greater methodological detail, the key additional details are: 1. the use of HIV/AIDS prevalence as an outcome variable for model training and development, conducted in parallel with AMU and AMR data collection; 2. Methodological approaches used to quantify the potential association between the contextual and intervention determinants and AMU / AMR levels, including beta regression, Extreme Bound Analysis (EBA), Bayesian Model Averaging (BMA), and Bayesian networks, to improve the overall confidence in the modelling outputs. EBA quantifies the extent to which the estimated impact of a determinant on the model outcome remains valid. BMA addresses model uncertainty by averaging over a set of plausible models rather than selecting a single best model to provide holistic estimates compared to a single model. For instance, if a selected linear regression model suggests that increasing current health expenditure (CHE) by 1% would decrease the level of AMR by 15% (the estimated coefficient of the variable CHE predicted by this model is -0.15), the EBA predicts whether this -0.15 coefficient can still hold if the variable CHE has more extreme values, and the BMA will estimate the averaged coefficient of CHE of all plausible models.

Any further responses from the reviewers can be found at the end of the article

Introduction

The majority of countries (88%) have developed a National Action Plan (NAP version 1.0) in response to the launch of the World Health Organization's Global Action Plan (WHO, 2015) (TrACSS, 2024) and many are developing the next NAP versions, while the burden of Antimicrobial Resistance (AMR) (Murray *et al.*, 2022) remains unabated. While policy formation is important and legitimises a cause, many NAPs remain to be implemented, and fewer (11%) have associated funding for agreed activities (TrACSS, 2024). Assessing country-level implementation strategies against the compendium of available options can help explain, and potentially predict progress (Murray *et al.*, 2022; WHO, 2019b). Mechanisms for ensuring that the evolving evidence base is used to refine policies at the national and local levels are not well established and policy planning processes are usually not agile enough to respond to such evidence (Charani *et al.*, 2021; Charani *et al.*, 2023; WHO, 2021). For most effective policy planning and implementation, we additionally need to learn from previous and concurrent global health challenges including successes, reasons for stagnation, and failures. Looking beyond AMR is important so that we do not re-invent solutions and ensure that we capture systemic factors at the country level, which can impede or accelerate success. This approach is also important due to the co-dependence between AMR and the Sustainable Development Goals (SDGs) (Jasovský *et al.*, 2016). Examples for learning include but are not limited to: other infectious diseases (such as TB, HIV/AIDS), mental health, and climate change (Pitchforth *et al.*, 2022). Epidemics and pandemics (Ebola, COVID) are another obvious source of learning (Ahmad *et al.*, 2021; Pitchforth *et al.*, 2022; Zhu *et al.*, 2021).

Evidence needs to be timely and needs to make sense to technical experts as well as wider decision-makers, and to ensure that the 'value proposition' is clear from scientific, economic, political, and sociological perspectives (Birgand *et al.*, 2022; Greenhalgh *et al.*, 2017). There are a wide range of perspectives which can be used to frame global AMR but at the national level this may need to be reframed in order to mobilise actions (Khurana *et al.*, 2023).

There is a need to explore innovative approaches to policy development and implementation to address AMR which could be useful and generalisable across countries. Resources and other contextual factors are important to consider, and there may be other ways to cluster countries to enhance comparative learning, aside from high, middle, and low-income groups (Cocker *et al.*, 2024; Mounier-Jack *et al.*, 2017). There needs to be theoretically sound, multidisciplinary analysis, which looks at process, determinants, and outcomes at country level and where results are validated by global and in-country experts to ensure relevance to context.

The current research addresses priority questions highlighted by the high level United National General Assembly (UNGA, 2024). Specifically, *What strategies can countries employ to leverage domestic resources effectively and sufficiently to address AMR across sectors, especially where there are competing development priorities? How can we ensure that AMR NAPs are costed, budgeted, and monitored? What strategies can be employed to enhance collaboration and coordination across sectors in countries for AMR response? How do we ensure the private sector is engaged and committed? Which countries are likely to work together in tackling AMR burden? Which countries have similar approaches in tackling AMR? What lessons have been learned from the implementation of the Global Action Plan on AMR over the past nine years? And how can the Global Action Plan be further strengthened?* (United Nations General Assembly (UNGA), 2024).

A recent *Lancet* series on AMR provides key evidence on interventions and investments to inform decision making to achieve sustainable access to effective antibiotics and accelerate progress in addressing AMR, as well as proposing achievable global targets in humans and animals for 2030. There is consensus (The Lancet, 2024) that the high overall burden of bacterial infection and AMR is a symptom of global health inequities that are not addressable unless the agenda is refocused on low and middle as well as high-income countries. Robust evidence of impact of preventative approaches including access to safe drinking water, effective sanitation, vaccination, and infection and prevention control in healthcare facilities shows that these interventions could prevent more than 750,000 deaths associated with bacterial AMR each year in lower middle income countries (LMICs), with additional health and societal benefits (Patel *et al.*, 2023; The Lancet, 2024).

From a health systems perspective, AMR-specific and AMR-sensitive activities need to be assessed to ensure that resources are effectively deployed and that monitoring of unintended consequences is in place. Many existing wider public health interventions have huge potential to reduce the spread of AMR if they are more broadly implemented. The rising resistance to first-line treatments poses a major risk to the success of HIV, TB and malaria programmes, so preventing AMR is already key to wider health outcomes (Jasovský *et al.*, 2016; Majumder *et al.*, 2020). There are lessons to be learned, and scope to build on the practical experiences of these programmes. Integrating approaches with existing programmes may result in efficiencies and more sustainable systems (WHO, 2019a).

The **aim** of this research is to provide innovative, systematic and comprehensive policy analysis to allow countries to compare, refine, and operationalise targeted action to address AMR, while developing and implementing AMR NAPs (version 2.0). Looking beyond AMR is important to ensure capture of systemic factors at the country level, which can impede or accelerate success.

This protocol follows the quality criteria for methods set by the Integrated Quality Criteria for Review of Multiple Study Designs (ICROMS), see Data Availability section (Zingg *et al.*, 2016).

Methods

This mixed-method multi-country case study will provide a systematic, comprehensive, and comparable situation analysis of policies and implementation strategies employed to address AMR at country level across One Health (OH).

This investigation of relevant structures, processes, and outcomes at country level, has three components (Figure 1) including a. Textual qualitative analysis to identify and code interventions for addressing AMR b. Longitudinal quantitative analysis of contextual determinants and outcomes; specifically, antimicrobial use (AMU) and AMR burden c. Interactive dashboard development to allow visualisation and comparison of context and components of AMR interventions in the case countries.

a. Textual analysis

A textual qualitative approach is used to enable an in-depth appraisal of all policy and intervention types. Deductive analysis is used to ensure a systematic approach to coding. Textual analysis of peer-reviewed literature (Pubmed, Medline, Embase, Global Health), policy documents, global, national and state level progress reports with validation by global and in-country experts. All-language article search conducted for years 2000–2024, using search terms: 'Antimicrobial resistance policies', 'national action plan', 'surveillance', 'AMR systems', 'drug resistant infections', 'antibiotic resistance', 'infection, prevention and control', 'antimicrobial stewardship', 'treatment guidelines', 'one health', 'animal health', 'zoonotic disease', 'livestock', 'agriculture', 'environmental health'. Deductive analysis using multi-disciplinary framework including the Expert Consensus for Implementation Research (ERIC).

Sampling. Purposive sampling starting with 17 countries, to represent each of the WHO world regions and emerging economies. The countries selected for the case studies (shown in country groupings) are **BRICS:** Brazil, Russia, India, China, South Africa; **Latin America**: Brazil, Columbia; **Asia:** Bangladesh, China, India, Indonesia, Pakistan, Philippines;

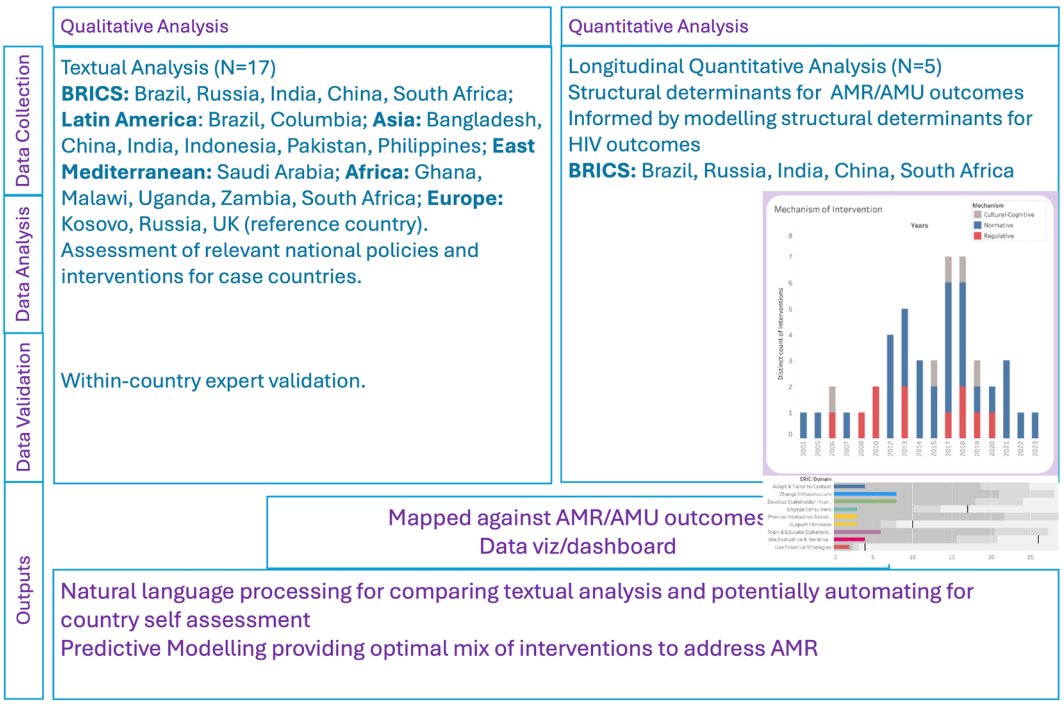

Figure 1. Overview of study methodology.

East Mediterranean: Saudi Arabia; **Africa:** Ghana, Malawi, Uganda, Zambia, South Africa; **Europe:** Kosovo, Russia-U.K.

Data sources. To map policy interventions for the period 2000–2024, we purposefully sampled secondary data sources from peer-reviewed and grey literature. Peer-reviewed articles in all languages are identified from the following databases: Pubmed, Medline, Embase, Global Health. Grey literature including policy documents, global, national and state level progress reports, guidelines, and legislation are sourced using search terms and hand search from: websites of case-country's health bodies/agencies, and global pan-national websites.

The search terms used are: 'Antimicrobial resistance policies', 'national action plan', 'surveillance', 'AMR systems', 'drug resistant infections', 'antibiotic resistance', 'infection, prevention and control', 'antimicrobial stewardship', 'treatment guidelines', 'one health', 'animal health', 'zoonotic disease', 'livestock', 'agriculture', 'environmental health'. Input was also sought from the global expert panel to identify any further within-country or global data sources and documents.

Data Extraction & Analysis. A deductive approach is being used with a range of multi-disciplinary frameworks to extract and code textual data. First the documentary sources are used to extract all interventions which address AMR, AMU, and Infection, Prevention & Control (IPC), and mapped to a timeline for each country. Interventions include all policies, regulations, recommendations, guidelines, plans, monitoring surveillance, campaigns, and activities.

Each intervention is then coded (Table 1) according to level of implementation (macro, meso, micro), maturity of implementation (developed, implemented, and evaluated), the Expert Consensus for Implementation Research (ERIC) Framework, the PESTELI (Political, Economic, Sociological, Technological, Environmental, Legislative, Industry) Framework, determinants of implementation (barriers, facilitators), setting (secondary, tertiary, specialist care, community and primary care, social care), target/audience (organisations, healthcare professionals and professional groups, patients/patient groups, general public), theme (AMR & AMU surveillance, Antimicrobial Stewardship (AMS), public education and awareness campaign, technology, and Research and Development (R&D), health industry and workforce) pathogen (fungi, bacteria, virus), elements to drive organisational change (Regulative: laws, policies, and contracts, Normative: work norms, habits, cultural-cognitive: beliefs, values).

The ERIC framework is a set of 73 discrete strategies for implementation, organised within 9 broader domains (adapt and tailor to context, change infrastructure, develop stakeholder interrelationships, engage consumers, provide interactive assistance, support clinicians, train and educate stakeholders, use evaluative and iterative strategies, utilise financial strategies), which can help with planning implementation and evaluating what has been done, in a structured way (Powell *et al.*, 2015) The PESTELI framework draws attention to the following domains: Political factors, Economic influences, Sociological trends, Technological innovations, Environmental factors, Legislative requirements, Industry analysis to assess the macro-enviornment (Ahmad *et al.*, 2019).

Coding is carried out in Excel by selecting sub-domains (Yes/No), if articulated in the intervention description. Coding is conducted independently and systematically by three researchers, with 10% of the sample looked at by all three and any disagreements are solved by group discussion and consensus. Final validation by a fourth reviewer, the within-country expert, who validates coding of 30% of the identified interventions (adapted from (Mizuno *et al.*, 2018)).

The peer-reviewed articles are additionally coded for barriers and enablers to addressing AMR.

An inductive thematic analysis is used (Thomas & Harden, 2008), informed by theoretical approaches from the field of health systems strengthening and from institutional theory (Kyratsis *et al.*, 2019).

b. Longitudinal analysis

Longitudinal analysis assessing potential impact of contextual structural determinants and AMR interventions on the two dependent variables: AMU and AMR. Data from repositories of global health indicators and international and national AMU and AMR surveillance networks are analysed using econometrics and machine learning approaches.

Sampling. The BRICS countries (Brazil, Russia, India, China, South Africa) are selected as they collectively encompass 45% of the global population and 33% of the global Gross Domestic Product (GDP) (Henley & Partners, 2024). Mitigating productivity losses due to AMR morbidity and mortality, in these five emerging world economies could allow them to reach their full economic potential with substantial global impact. Each have fully developed AMR NAPs but with varying levels of implementation. Analysing these countries with diverse structural, cultural, and health system contexts provides a means for benchmarking "within-region" countries as well as the future key economies (Mexico, Indonesia, Nigeria, Turkey (MINT)) (Coque *et al.*, 2023; O'Neill, 2016).

Data sources. We identified a collection of candidate-independent variables for each of the BRICS countries from multiple global health data repositories, including the Global Health Observatory (GHO), World Bank Open Data, and the Organisation for Economic Co-operation and Development (OECD) data. These global health databases (Table 2) collate evidence and statistics by country, to describe public health contexts and track country progress towards SDGs, which provide the most comprehensive collection of social determinants of health.

Table 1. Coding framework for deductive analysis.

	Dimension	Codes
A	ERIC strategy	• Adapt and tailor to context • Change infrastructure • Develop stakeholder interrelationships • Engage consumers • Provide interactive assistance • Support clinicians • Train and educate stakeholders • Use evaluative and iterative strategies • Utilize financial strategies
B1	Level of Implementation	• Macro (international, regional, national) • Meso (organisational) • Micro (individual)
B2	Maturity of implementation	• Developed • Implemented • Evaluated • Evaluation methods: indicators to measure uptake and effectiveness; frequency of review and update
B3	Determinants of implementation	• Barriers • Facilitators
C	Setting	• Secondary, tertiary, and specialist care • Community and primary care • Social care
D	Target / audience	• Organisations • Healthcare professionals and professional groups • Patients / patient groups • General public
E	Theme	• AMR and AMU surveillance • Antimicrobial stewardship (AMS) • Public education and awareness campaign • Technology and R&D • Health industry and workforce • Infection, prevention and control (IPC)
F	Pathogen	Fungi, Bacteria, Virus
G	PESTELI domain	Political, Economic, Social, Technological, Environmental, Legal, Industry
H	Elements to drive organisational change (optional)	• Regulative: laws, policies, and contracts • Normative: work norms, habits • Cultural-cognitive: beliefs, values

Data extraction & analysis: Regional and national surveillance systems and dashboards were searched to develop a panel dataset of AMR levels and AMU for each of the BRICS countries for a minimum of 20 years. We measured country-level AMU using total Defined Daily Dosage (DDD) of antibiotics dispensed to the human population. We considered how variation in data sources might influence the AMU data, so the data from monitoring hospital and community prescribing and dispensing, versus data from monitoring retailers, or import/export of antimicrobials. We are likely to under estimate AMU at global level. Each country's AMR burden was measured using the reported percentage of resistant isolates for the critical and high priority therapy-pathogen combinations defined by the WHO (WHO, 2024), including enterobacterales resistant to

Table 2. Data sources for AMR and AMU.

Country	AMR	AMU
International	WHO Glass Report 2014, 2021, 2022 One Health Trust ResistanceMap	WHO GLASS-Implementation Report 2016–17, 2017–18, 2020 One Health Trust ResistanceMap
Brazil	ReLAVRA: 2011–2014 (Spanish) report ReLAVRA: 2014–2016 report	
Russia	AMRmap national dashboard: 2011–2021 https://amrmap.net	As AMR
India	NCDC NARS-Net report: 2017–2023 report	
China	CHINET: 2011–2023 http://www.chinets.com CARSS: 2011–2023 http://www.carss.cn/	NHC中国抗菌药物临床应用管理和细菌耐药现状 2016 (2010–2015 data): report 2018 (2011–2017 data): report 2021, 2022 report available in hard copy
South Africa	NICD dashboard: 2012–2023: https://mstrweb.nicd.ac.za DoH: 2021 report	

carbapenems (meropenem, ertapenem, imipenem, and in rare cases, doripenem, panipenem/betamipron, biapenem, and tebipenem), enterobacterales resistant to 3rd generation cephalosporins (cefotaxime, ceftazidime, and ceftriaxone), and methicillin-resistant *Staphylococcus aureus* (MRSA). The worst-case scenario was taken if multiple antibiotic agents were tested for one pathogen (i.e., enterobacterales isolates 12% resistant to imipenem, 10% resistant to ertapenem, a resistance level of 12% is used). We are likely to have a skewed picture or only partial capture of the true burden of AMR since most countries report AMR data from secondary or tertiary care levels.

The candidate contextual-independent variables extracted from the global health data repositories were reviewed by the study advisory group panel of experts to generate consensus on which categories of these variables should be the initial focus of the longitudinal analysis, considering prior knowledge of potential impact of these variables on AMR. For instance, variables measuring the process and outcomes of other public health interventions considered less relevant to AMR (e.g., Resources for Substance Use Disorders), were excluded from the analysis. The variables included for analysis are organised under three categories: health system financing, health technologies, and health workforce. The variables within each of the included category are reviewed to identify duplication and the measures of the same objects with different units (e.g., crude number vs density), and the variables included are ones that are adjusted for country variation (i.e., age-standardised percentage is preferred over crude numbers) and with a minimum of 10 years of data. Multicollinearity between independent variables will be quantified using Pearson correlation coefficients (Sedgwick, 2012), principal component analysis (PCA), and Variance Inflation Factor (VIF) (Kherif & Latypova, 2020).

To assess the potential country-level impact from the independent variables and AMR interventions on the two dependent variables (AMR and AMU), we employed both econometric models and Machine Learning (ML) causal inference to maximise the validity of this analysis. We developed multivariate beta regression models (Ferrari & Cribari-Neto, 2004) for each pathogen-therapy combination, estimating parameters by maximum likelihood. Extreme Bounds Analysis (EBA) was performed to assess the robustness of independent variables and Bayesian Model Averaging (BMA) to address model uncertainty. EBA incorporates prior knowledge and attempts to determine the most extreme possible estimates for a fixed subset of coefficients (Leamer, 2010). It is a type of sensitivity analysis that provides upper and lower limits for the outcome variable for any possible set of determinants so that the determinants robustly associated with the outcomes across many possible scenarios can be identified. It is particularly useful when dealing with a large number of possible explanatory variables and enables testing for whether minor changes in the examined determinants can significantly alter the outcome variables. If the association between a determinant and the outcomes does not vary much across regressions, it is considered robust. EBA supports empirical research by demonstrating the inferential sturdiness of hypotheses (i.e. the robustness of the inclusion or exclusion of a variety of plausible explanation of an observation) (Hauck *et al.*, 2016). BMA is a statistical technique that addresses model uncertainty by averaging over a set of plausible models rather than selecting a single "best" model (Wasserman, 2000). BMA assigns probabilities to each plausible model using Bayes' theorem by averaging the parameter estimates from each model weighted by their posterior probabilities. The results from the EBA and BMA analysis will provide insights in how reliable the beta regression model is in capturing the association between the AMU and

AMR outcomes and the contextual independent variables. Bayesian networks, a machine learning based tool, are increasingly used for causal inference, decision support and understanding complex probabilistic relationships between variables (Teles *et al.*, 2014) (Pérez *et al.*, 2021). A Bayesian network consists of nodes representing variables (e.g. percentage of enterobacterales isolates resistant to carbapenems) and directed edges (e.g. connection between percentage of enterobacterales isolates resistant to carbapenems and population mobility/international travel) representing probabilistic dependencies between variables that contribute to the development and emergence of AMR. Each node has a conditional probability distribution that quantifies the effects of the parent nodes on the node. By analysing the network (the directed acyclic graph (DAG)), key risk factors and pathways leading to the changes in AMU and AMR can be identified, and predicted given certain conditions or interventions. To guide decision makers in terms of policy mix, we use the two modelling approaches to predict how the identified interventions (single or in combination, and sensitivity analysis based on varied level of implementation from partial to complete) would affect a country's AMU and AMR level, in combination with the contextual independent determinants. Anticipating that the AMR data would be generally less comprehensive and consistent across countries, we used HIV/AIDS prevalence as the outcome measure for model training and development in parallel with AMR and AMU data collection.

This study will be conducted in phases, in phase 1, the study will assess interventions and determinants in the human health sector and their potential impact on AMU and AMR outcomes in BRICS countries. Phase 2 will expand the quantitative assessment to include the environmental and animal health sectors in a different set of case countries.

c. Interactive dashboard development

Interactive Dynamic Dashboard development to display insights from A. & B., using Tableau to allow visualisation and comparison of context and components of AMR interventions in the case countries.

Using data visualisation, the aim is to present the output of the analysis of interventions so that geographically or economically close countries can compare and reflect on alternative approaches and actionable insights (Kim & Huang, 2021). The data and results visualised include country demographic profiles, socioeconomic status, AMU and AMR levels, the implementation of AMU and AMR surveillance, participation in surveillance networks, as well as AMR interventions implemented in human health and across One Health.

The benefits of interactive dashboards include the ability to display aggregated data and complex visual analytics embedded in a user-friendly platform (Thoma *et al.*, 2020). The intended users (policy makers, planners, and commissioners of funding) can navigate through curated visualisations, filter specific details, make comparisons, and uncover insights that are useful for decision-making.

In developing the dashboard, through stakeholder engagement, design-based approach will be adopted to ensure a user-need-informed design.

The dashboard development follows a participatory iterative process including: 1) Desk review of existing AMR policy dashboards to understand structure, functionality, define data sources, data preparation, analysis approach definition, etc. 2) Roundtable discussions with the study advisory group members and stakeholders from the Wellcome Trust and Fleming Fund to understand user needs and applicability in LMIC, HIC, utility within their respective programs of work, 3) Design, construction, and validation with project team and end users, 4) Launch and dissemination through SEDRIC and its peripheral network. Detailed steps in Dashboard Development:

Platform Selection: Desk-review of existing AMR policy dashboards to understand structure, functionality, define data sources, data preparation, analysis approach definition, etc. e.g., UKHSA COVID-19 data dashboard, IHME Global Burden of Disease Dashboard, WHO GLASS, CDC AR&PSP, EARS-Net, AMRSNET, AURA, PAHO/WHO Regional AMR, WPRO AMR surveillance, etc.

Multiple data visualisation software were considered (Power BI, Tableau, Data-flo, Pathogen Watch, Echarts, Vizhub) against five main criteria: publicly accessible, flexibility for broader applications outside domain, pre-built functionalities, drag and-drop interfaces, and extent of domain-specific knowledge required, and ease of local adoption.

The generic framework tableau was selected through a pragmatic approach to create the dashboard.

Data Sourcing: Outcomes from the deductive structured qualitative analysis which are categorical data variables including those generated from the ERIC coding, geographic/countries, and years. From the quantitative longitudinal analysis, the AMR and AMU indicators at country level and the underlying contextual determinants.

Data Processing: Normalisation of data in a structured and readable format for the platform.

Data Analysis: Visual analytics composed by temporal analysis, exploratory data analysis, comparative analysis, and geographical visualisation. Temporal analysis aims to discover the trends that can be derived from the data. Exploratory data analysis is focused on analysing the distribution and relation between relevant features (e.g. yearly distribution, focus of intervention). Comparative analysis seek to highlight multiple variable differences effectively. Geographical visualisation facilitates a simple representation of the data to identify and explore trends geographically.

Testing and Validation: Presentation and agreement with stakeholders on quality assurance, layout and colour, visual

balance, filters, intuitive navigation, and interactive elements (Bach *et al.*, 2022).

Discussion

This manuscript provides a detailed protocol including rationale for the research and methods for data collection and analysis. This work is conducted by an international multi-disciplinary team. The advisory team provide input periodically (every 3 months) to ensure relevance of the work.

While the Global Research on Antimicrobial Resistance (GRAM) study has provided much needed quantification of AMR burden and a renewed call to action, comprehensive insight of interventions in different country contexts is needed to inform decision making and enable evaluation (Murray *et al.*, 2022; Naghavi *et al.*, 2024).

The research approach is timely given the recent Lancet commission (The Lancet, 2024), and the United Nations General Assembly (UNGA) high level meeting (United Nations General Assembly, 2024) adding to the suite of tools available to follow through with recommendations from these activities (Wellcome, 2024).

Major strengths of the study include use of the ERIC framework to sensitise decision makers to the full compendium of options that are available to address AMR. Additionally, the outputs on the dashboards will include: (1) Display of time analysis visualisations to present the yearly distribution of interventions, highlighting trends and changes over time; (2) Display of the distribution and allocation of ERIC strategies across different countries and years, allowing for detailed comparison and analysis of implementation strategies; (3) Visualising of multiple dimensions that describe characteristics of the interventions and their implementation process, which helps understanding of the diverse landscape of AMR efforts; (4) Enablement of comparisons between different countries, different periods of time, or different parameters of implementation, allowing users alternatives to analyse and evaluate the impact of different strategies.

Study Limitations: There are gaps in AMR data and structural determinants at country level for any quantitative study because of inconsistency in AMR data collection across different regions and healthcare settings since many countries lack standardized protocols for collecting and reporting AMR data. The sample does not include countries of conflict which have unique challenges and required interventions (Pallett *et al.*, 2023; Rizk *et al.*, 2021). These countries would provide a different 'grouping' or filter in the data visualisation dashboard as the work progresses further. Limitations of the study also include the constraints of customisation options in Tableau but this is balanced by expense to maintain and expand the dashboard.

The outputs from this study will be shared early with the WHO, The Fleming Initiative, and other organisations that have a strong convening power which can help build local consensus, promoting development and uptake of recommendations. These will include The Fleming Fund as it progresses through Phase 2 of implementation, and the Second Trinity Challenge, both aimed at reducing the impact of AMR with data-driven approaches focusing on low- and middle-income communities.

Overall, this protocol provides a systematic and transparent approach for countries to benchmark their own strategies to address AMR while understanding context. The interactive dashboard will allow comparisons between country clusters by geography or economy, helping policy makers and planners. The interactive dashboards will enable rapid knowledge mobilisation among strategic and operational stakeholders. This protocol enables others to engage with this structured assessment approach and nominate their country for the next wave of analysis.

By looking across systems and sectors, there may be an emergent value proposition which resonates with national level stakeholders. Effective and efficient policy change might be achieved, if the solutions and arguments presented to solve the problem are credible, relevant, and feasible.

The systematic, comprehensive approaches employed in this analysis can also serve as a template to develop tools for decision-making and health planning to address other public health issues.

Ethics and consent

Ethical approval and consent were not required.

Data availability

Underlying data

No data associated with this article.

Extended data

Repository name: Systems Policy Analysis for Antimicrobial Resistance Targeted Action (SPAARTA): A Research Protocol, https://doi.org/10.6084/m9.figshare.27008017.v1 (Ahmad, 2024)

This project contains the following underlying data:

Supplementary 1 - Search Strategy

Supplementary 2 - AMU AMR Global Data Availability (Global/Regional Surveillance)

Supplementary 3 - National Surveillance

Supplementary 4 - Identified data from global/regional surveillance programmes/reports from case countries - year of reporting

Supplementary 5 - Expert Consensus for Implementation Research (ERIC) Framework

Supplementary 6 - SPAARTA Protocol ICROMS Quality Criteria

Author contribution

Conceptualization & Funding Acquisition: RAh, JJ, MM, RA.

Methodology, Formal Analysis & Validation: RAh, NZ, RJ.

Data Curation: RAh, NZ, RJ, PA & the SPAARTA Research Group

Visualisation: NZ, PA, TW & MLM

Project Administration: RAh, NZ, RJ

Writing – Original draft: RAh, NZ & RJ.

All authors contributed to revisions of the manuscript. RAh is the guarantor of the study. The corresponding author attests that all listed authors meet the ICMJE criteria for authorship and that no other meeting the criteria have been omitted.

Acknowledgements

Authors gratefully acknowledge the support of the esteemed global expert panel: Dr Ghada Zoubiane (International Center for Antimicrobial Resistance Surveillance (ICARS)), Dr Raphael Chanda (React Africa), Dr Izhar Hussain (Dow University of Health Sciences), Dr Patrick Oyibo (City, University of London).

We acknowledge the support of the SPAARTA Group – Agwah Nadeem Butt, Ashton Matthews, Ekaterina Mishareva, Malay Diwanji, Morteza Layegh Mirhosseini, Nilangi Patil, Pirabin Sivakunathasan, Zoecencia Rak-Sakyi. We thank Ben Gorst for the Plain Language Summary.

The study received funding from The Wellcome Trust (Grant No. 228072/Z/23/Z).

References

Ahmad R: **Supplementary file - SPAARTA protocol.** *figshare.* Dataset. 2024.
http://www.doi.org/10.6084/m9.figshare.27008017.v1

Ahmad R, Atun RA, Birgand G, *et al.*: **Macro level influences on strategic responses to the COVID-19 pandemic – an international survey and tool for national assessments.** *J Glob Health.* 2021; **11**: 05011.
PubMed Abstract | Publisher Full Text | Free Full Text

Ahmad R, Zhu NJ, Leather AJM, *et al.*: **Strengthening strategic management approaches to address Antimicrobial Resistance in global human health: a scoping review.** *BMJ Glob Health.* 2019; **4**(5): e001730.
PubMed Abstract | Publisher Full Text | Free Full Text

Bach B, Freeman E, Abdul-Rahman A, *et al.*: **Dashboard design patterns**. 2022.
Reference Source

Birgand G, Ahmad R, Bulabula ANH, *et al.*: **Innovation for Infection Prevention and Control—revisiting Pasteur's vision.** *Lancet.* 2022; **400**(10369): 2250–2260.
PubMed Abstract | Publisher Full Text | Free Full Text

Charani E, McKee M, Ahmad R, *et al.*: **Optimising Antimicrobial Use in humans – review of current evidence and an interdisciplinary consensus on key priorities for research.** *Lancet Reg Health Eur.* 2021; **7**: 100161.
PubMed Abstract | Publisher Full Text | Free Full Text

Charani E, Mendelson M, Pallett SJC, *et al.*: **An analysis of existing National Action Plans for Antimicrobial Resistance—gaps and opportunities in strategies optimising antibiotic use in human populations.** *Lancet Glob Health.* 2023; **11**(3): e466–e474.
PubMed Abstract | Publisher Full Text

Cocker D, Birgand G, Zhu N, *et al.*: **Healthcare as a driver, reservoir and amplifier of Antimicrobial Resistance: opportunities for interventions.** *Nat Rev Microbiol.* 2024; **22**(10): 636–649.
PubMed Abstract | Publisher Full Text

Coque TM, Cantón R, Pérez-Cobas AE, *et al.*: **Antimicrobial Resistance in the global health network: known unknowns and challenges for efficient responses in the 21st century.** *Microorganisms.* 2023; **11**(4): 1050.
PubMed Abstract | Publisher Full Text | Free Full Text

Ferrari S, Cribari-Neto F: **Beta regression for modelling rates and proportions.** *J Appl Stat.* 2004; **31**(7): 799–815.
Publisher Full Text

Global database for tracking Antimicrobial Resistance (AMR) Country Self-Assessment Survey (TRACSS). 2024.
Reference Source

Greenhalgh T, Wherton J, Papoutsi C, *et al.*: **Beyond adoption: a new framework for theorizing and evaluating nonadoption, abandonment, and challenges to the scale-up, spread, and sustainability of health and care technologies.** *J Med Internet Res.* 2017; **19**(11): e367.
PubMed Abstract | Publisher Full Text | Free Full Text

Hauck K, Martin S, Smith PC: **Priorities for action on the social determinants of health: empirical evidence on the strongest associations with life expectancy in 54 low-income countries, 1990–2012.** *Soc Sci Med.* 2016; **167**: 88–98.
PubMed Abstract | Publisher Full Text

Henley & Partners: **The BRICS wealth report: challenging the global economic order**. 2024.
Reference Source

Jasovský D, Littmann J, Zorzet A, *et al.*: **Antimicrobial Resistance—a threat to the world's sustainable development.** *Ups J Med Sci.* 2016; **121**(3): 159–164.
PubMed Abstract | Publisher Full Text | Free Full Text

Kherif F, Latypova A: **Principal component analysis**. In: *Machine Learning.* Elsevier, 2020; 209–225.
Publisher Full Text

Khurana MP, Essack S, Zoubiane G, *et al.*: **Mitigating Antimicrobial Resistance (AMR) using implementation research: a development funder's approach.** *JAC Antimicrob Resist.* 2023; **5**(2): dlad031.
PubMed Abstract | Publisher Full Text | Free Full Text

Kim E, Huang CY: **Visual analytics in effects of Gross Domestic Product to human immunodeficiency virus using tableau.** *Int J Mach Learn Comput.* 2021; **11**(3): 219–223.
Publisher Full Text

Kyratsis Y, Ahmad R, Iwami M, *et al.*: **A multilevel neo-institutional analysis of Infection Prevention and Control in English hospitals: coerced safety culture change?** *Sociol Health Illn.* 2019; **41**(6): 1138–1158.
PubMed Abstract | Publisher Full Text

Leamer EE: **Extreme bounds analysis**. In: *Microeconometrics*. Palgrave Macmillan UK, 2010; 49–52.
Publisher Full Text

Majumder MAA, Rahman S, Cohall D, *et al.*: **Antimicrobial Stewardship: fighting Antimicrobial Resistance and protecting global public health.** *Infect Drug Resist.* 2020; **13**: 4713–4738.
PubMed Abstract | Publisher Full Text | Free Full Text

Mizuno S, Iwami M, Kunisawa S, *et al.*: **Comparison of national strategies to reduce meticillin-resistant *Staphylococcus aureus* infections in Japan and England.** *J Hosp Infect.* 2018; **100**(3): 280–298.
PubMed Abstract | Publisher Full Text

Mounier-Jack S, Mayhew SH, Mays N: **Integrated care: learning between high-income, and Low- and Middle-Income Country health systems.** *Health Policy Plan.* 2017; **32**(suppl_4): iv6–iv12.
PubMed Abstract | Publisher Full Text | Free Full Text

Murray CJL, Ikuta KS, Sharara F, *et al.*: **Global burden of bacterial Antimicrobial Resistance in 2019: a systematic analysis.** *Lancet.* 2022; **399**(10325): 629–655.
PubMed Abstract | Publisher Full Text | Free Full Text

Naghavi M, Vollset SE, Ikuta KS, *et al.*: **Global burden of bacterial**

Antimicrobial Resistance 1990–2021: a systematic analysis with forecasts to 2050. *Lancet.* 2024; **404**(10459): 1199–1226.
PubMed Abstract | Publisher Full Text

O'Neill J: **Tackling drug-resistant infections globally: final report and recommendations the review on Antimicrobial Resistance chaired by Jim O'Neill**. 2016.
Reference Source

Pallett SJC, Boyd SE, O'Shea MK, *et al.*: **The contribution of human conflict to the development of Antimicrobial Resistance.** *Commun Med (Lond).* 2023; **3**(1): 153.
PubMed Abstract | Publisher Full Text | Free Full Text

Patel J, Harant A, Fernandes G, *et al.*: **Measuring the global response to Antimicrobial Resistance, 2020-21: a systematic governance analysis of 114 countries.** *Lancet Infect Dis.* 2023; **23**(6): 706–718.
PubMed Abstract | Publisher Full Text

Pérez S, German-Labaume C, Mathiot S, *et al.*: **Using Bayesian networks for environmental health risk assessment.** *Environ Res.* 2021; **204**: 112059.
Publisher Full Text

Pitchforth E, Smith E, Taylor J, *et al.*: **Global action on Antimicrobial Resistance: lessons from the history of climate change and tobacco control policy.** *BMJ Glob Health.* 2022; **7**(7): e009283.
PubMed Abstract | Publisher Full Text | Free Full Text

Powell BJ, Waltz TJ, Chinman MJ, *et al.*: **A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project.** *Implement Sci.* 2015; **10**(1): 21.
PubMed Abstract | Publisher Full Text | Free Full Text

Rizk NA, Moghnieh R, Haddad N, *et al.*: **Challenges to Antimicrobial Stewardship in the countries of the Arab league: concerns of worsening resistance during the COVID-19 pandemic and proposed solutions.** *Antibiotics (Basel).* 2021; **10**(11): 1320.
PubMed Abstract | Publisher Full Text | Free Full Text

Sedgwick P: **Pearson's correlation coefficient.** *BMJ.* 2012; **345**: e4483.
Publisher Full Text

Teles G, Oliveira C, Braga R, *et al.*: **Using Bayesian networks to improve the decision-making process in public health systems.** *2014 IEEE 16th International Conference on E-Health Networking, Applications and Services (Healthcom).* 2014; 565–570.
Publisher Full Text

The Lancet: **Antimicrobial Resistance: an agenda for all.** *Lancet.* 2024; **403**(10442): 2349.
PubMed Abstract | Publisher Full Text

Thoma B, Bandi V, Carey R, *et al.*: **Developing a dashboard to meet Competence Committee needs: a design-based research project.** *Can Med Educ J.* 2020; **11**(1): e16–e34.
PubMed Abstract | Publisher Full Text | Free Full Text

Thomas J, Harden A: **Methods for the thematic synthesis of qualitative research in systematic reviews.** *BMC Med Res Methodol.* 2008; **8**(1): 45.
PubMed Abstract | Publisher Full Text | Free Full Text

UNGA: **Interactive multi-stakeholder hearing as part of the preparatory process for the 2024 High-level Meeting on Antimicrobial Resistance**. 2024.
Reference Source

Wasserman L: **Bayesian model selection and model averaging.** *J Math Psychol.* 2000; **44**(1): 92–107.
Publisher Full Text

Wellcome: **Driving action on Antimicrobial Resistance (AMR) in 2024**. 2024.
Reference Source

WHO: **WHO Library cataloguing-in-publication data global action plan on Antimicrobial Resistance**. 2015.
Reference Source

WHO: **Turning plans into action for Antimicrobial Resistance (AMR) working paper 2.0: implementation and coordination**. 2019a.
Reference Source

WHO: **Tripartite AMR Country Self-assessment Survey (TrACSS) deadline for submission: 31 May, 2021**. 2021.
Reference Source

WHO: **WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent control of AMR**. 2024.
Reference Source

WHO, FO: **Monitoring and evaluation of the global action plan on Antimicrobial Resistance framework and recommended indicators**. 2019b.
Reference Source

Zhu NJ, Ferlie EB, Castro-Sánchez E, *et al.*: **Macro level factors influencing strategic responses to emergent pandemics: a scoping review.** *J Glob Health.* 2021; **11**: 05012.
PubMed Abstract | Publisher Full Text | Free Full Text

Zingg W, Castro-Sanchez E, Secci FV, *et al.*: **Innovative tools for quality assessment: Integrated quality Criteria for Review of Multiple Study designs (ICROMS).** *Public Health.* 2016; **133**: 19–37.
PubMed Abstract | Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 07 August 2025

https://doi.org/10.21956/wellcomeopenres.27049.r127912

✔ **Anand Balachandran**
World Health Organisation, Geneva, Switzerland
Zlatina Dobreva
AMR Surveillance, Prevention and Control Department, World Health Organization, Geneva, Geneva, Switzerland

The revisions address many of the comments raised in Version .1.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Implementation and assessment of national action plans on AMR; Integration of AMR interventions into PHC; People-centred approach to address AMR in human health; Monitoring and evaluation of AMR national action plans; Gender, equity and disability inclusion dimensions of AMR.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 01 April 2025

https://doi.org/10.21956/wellcomeopenres.25240.r119600

?

Anand Balachandran
[1] World Health Organisation, Geneva, Switzerland
[2] World Health Organisation, Geneva, Switzerland
Zlatina Dobreva
[1] AMR Surveillance, Prevention and Control Department, World Health Organization, Geneva, Geneva, Switzerland
[2] AMR Surveillance, Prevention and Control Department, World Health Organization, Geneva, Geneva, Switzerland

Background/ Context:

- The authors might wish to consider de-linking the lack of funding for interventions to the need for more systematic approach to select the most appropriate interventions that can predict progress**.** The identification of effective interventions to address AMU and AMR does not necessarily mean that it leads to funding for those activities – especially in the context of limited national budgets for public health, decline in ODA, and impact of geopolitical instability.

- The authors might wish to update their figures based on TrACSS 2024 data. 88% of WHO Member States (170/ 194) reported having developed a national action plan on AMR. In addition, 64% of WHO Member States are implementing their national action plans on AMR – in an ad-hoc manner. Data portal: www.new.amrcountryprogress.org

- The authors could consider initially reviewing the existing "packages of effective interventions" to address AMR developed by various international bodies based on existing evidence, estimations, modelling and expert opinions from countries, regions and at the global level. Some of the packages, that include cost effectiveness considerations, return on investment, technical feasibility etc.. are noted below.

- The authors could review and reflect upon many "best buy" packages of interventions proposed by the OECD – both for public health, and for One Health (OECD (2018), *Stemming the Superbug Tide: Just A Few Dollars More*, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/9789264307599-en; OECD (2023), *Embracing a One Health Framework to Fight Antimicrobial Resistance*, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/ce44c755-en)

- The authors could also review the package of 20 interventions proposed by the World Bank recently - Rupasinghe, N., C. Machalaba, T. Muthee, and A. Mazimba. Stopping the Grand Pandemic: A Framework for Action. Addressing Antimicrobial Resistance through World Bank Operations. Washington, DC: World Bank; 2024. License: CC BY 3.0 IGO. https://hdl.handle.net/10986/41533

- The authors could also review the WHO people-centred approach to address AMR in human health and core package of interventions to support national action plans. The core focus is on addressing inequities, was endorsed by the World Health Assembly in 2024, highlights the interdependence of interventions, highlights the need to address critical broader health system gaps, and barriers faced by people and vulnerable populations, and provides guidance for specific actions at each levels of the health system.

https://iris.who.int/bitstream/handle/10665/373458/9789240082496-eng.pdf

- The authors also may wish to review the "Smart Choice Process" developed by the AMR Policy Accelerator at York University, Canada that is currently being piloted in many countries in Africa to identify effective package of interventions across the One Health sectors.

Study Design:

- It will be useful to clarify if this research is purely for human health or as stated in the methods section, to address AMR at country level across One Health.

- For the textual analysis, it will be critical to expand the search terms. It could include different ways of referring to AMR such as: "drug resistant infections", "anti-bacterial/anti-fungal/anti-infective resistance", "antibiotic resistance" and their variations.

- The search terms are also missing important interventions such as "stewardship", "national treatment guidelines" "immunization", "infection prevention and control" "bacteriology laboratory systems"

- If the study is applying a One Health approach then consider including search terms that would cover interventions in other sectors related to animal health, agriculture, the environment. This is missing at this point.

- The list of 17 countries seem very ambitious. While many of the large countries like India have a "National Action Plan", health interventions are primarily implemented by the States, and so identifying interventions at the national level might not be helpful or drive actions in States. It might be useful to identify a smaller group of countries whose NAP on AMR is expiring or has expired, and are currently at the stage of conducting an assessment of their implementation. The proposed research design could then help provide valuable evidence-based policy guidance to countries to help develop new NAPs and cost the most essential interventions as part of developing an operational plan.

- In many of the selected countries conducting a literature search only to identify historically AMR interventions and the level of their implementation in that country will not be enough because the general literature is normally biased towards the Global North and not all interventions will be well documented.

- Having the preferred intervention in the country' NAP on AMR in turn is not a guarantee that it was implemented in practice and would not give an indication of the extent of its implementation. Pairing this with i) quantitative data from TrACSS and national/regional monitoring reports and with ii) national key informant interviews (beyond just one national expert especially in the case of countries of the size and administrative arrangement like China and Brazil) will be key.

- The authors could clarify how the deductive analysis of AMR interventions will be converted to a quantitative variable that can be used in the longitudinal modelling analysis. Will there be an overall score assigned for the level of implementation of a given intervention in a given year for a given country?

- It would be beneficial to include “Infection Prevention and control”, “ Diagnosis and Bacteriology / Mycology laboratory systems” under Theme “E” in the coding framework for deductive analysis.

- Will Gender and other social stratifiers that impact equitable access be included in the determinants of implementation.

- The authors can clarify how data from quantitative sources will be incorporated at the coding stage for each intervention.

- A major challenge for the longitudinal analysis of the impact of AMR interventions and independent variables on the two AMR outcomes will be the quality of the AMR and AMU data, and in particular changes in the quality of the data over the study period for a given country.

    - For example, the latest WHO GLASS report found that percentage of AMR infections was lower in countries that have high testing coverage (number of bacteriologically confirmed infections per million population) within the top 75th percentile. If there are significant changes in testing coverage or other factors affecting the quality of the data longitudinally in each of the countries then that can introduce bias in the effect estimates. The authors could consider observing the patterns of AMR/AMU data over time and if there are significant unexpected changes year on year, which would warrant including additional independent variable in the model to control for data quality.

- Another consideration for the Longitudinal analysis would be for the authors to identify a different indicator rather than HIV/AIDS prevalence for each country as an alternative independent variable. Significant systems have already been established for HIV/AIDs in many countries based on single disease financing mechanisms, and this might not be comparable for a complex phenomenon like AMR.

- The use of both Extreme Bounds Analysis (EBA) and ML-based the Bayesian networks as the two modelling approaches would be very beneficial to guide decision-makers at national, as well as regional and global levels. This, at the core, is a very innovative element of the protocol and in comparison to some other existing prioritization processes. The paper would benefit from additional details on the use of the two modelling approaches, including some examples and sample visualization.

- For the Visualization dashboard, the authors may wish to review the new TrACSS website that includes data comparison across countries, regions, across income levels, has global benchmarks for various indicators (across all One health Sectors), as well as a WHO AMR M&E portal (to be ready in April 2025) that will include the human health indicators as recommended in the Global Action plan M&E Framework and recommended indicators.

References

1. Data portal. Reference Source
2. Herzler M, Abedini J, Allen DG, Germolec D, et al.: Use of human predictive patch test (HPPT)

data for the classification of skin sensitization hazard and potency.*Arch Toxicol*. 2024; **98** (5): 1253-1269 PubMed Abstract | Publisher Full Text
3. OECD: Embracing a One Health Framework to Fight Antimicrobial Resistance. Publisher Full Text
4. *World Bank Group*. Reference Source
5. People-centred approach to addressing antimicrobial resistance in human health. Reference Source

Is the rationale for, and objectives of, the study clearly described?
Partly

Is the study design appropriate for the research question?
Partly

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Implementation and assessment of national action plans on AMR; Integration of AMR interventions into PHC; People-centred approach to address AMR in human health; Monitoring and evaluation of AMR national action plans; Gender, equity and disability inclusion dimensions of AMR.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 11 Jun 2025

Raheelah Ahmad

We would like to thank the reviewers for their constructive, insightful, and supportive feedback, which has been carefully considered and addressed in the revised version of the manuscript. No. Reviewer Comments

Author Comments 1. The authors might wish to consider de-linking the lack of funding for interventions to the need for more systematic approach to select the most appropriate interventions that can predict progress. The identification of effective interventions to address AMU and AMR does not necessarily mean that it leads to funding for those activities – especially in the context of limited national budgets for public health, decline in ODA, and impact of geopolitical instability. We agree and acknowledge the need for political and system level factors to progress implementation even when the financial/business case has been made. The need for data-driven evidence to inform policy is critical particularly because of constraints on funding. Completely delinking this conversation would be

counter to the aims of this study.

2. The authors might wish to update their figures based on TrACSS 2024 data. 88% of WHO Member States (170/ 194) reported having developed a national action plan on AMR. In addition, 64% of WHO Member States are implementing their national action plans on AMR – in an ad-hoc manner. Data portal: www.new.amrcountryprogress.org Thank you for your valuable feedback and for highlighting the updated TrACSS 2024 data. We have incorporated the most recent figures in the updated version.

3. The authors could consider initially reviewing the existing "packages of effective interventions" to address AMR developed by various international bodies based on existing evidence, estimations, modelling and expert opinions from countries, regions and at the global level. Some of the packages, that include cost effectiveness considerations, return on investment, technical feasibility etc. are noted below. Thank you for the valuable feedback. The recommendations of interventions have been referenced but we can now include a more comprehensive compendium. In addition to this we have created a column against these saying what the limitations and strengths of the underpinning methodology that was used in making these recommendations. To provide further rationale for the work we are undertaking in the current study, we agree that by doing so decision makers will be better informed and will not then be conflicted as to which recommendations to consider. The mentioned frameworks (OECD) are largely designed for high-income countries, our study focuses on high, low- and middle-income countries, allowing consideration of context and challenges. In our first empirical paper assessing the BRICS nations, we have indeed used the WHO core package of interventions to provide decision makers/readers with insights about alignment and wider scope. We have taken the 'Smart Choice Process' into consideration. This will allow us to assess its relevance in different contexts and further strengthen our analysis.

4. The authors could review and reflect upon many "best buy" packages of interventions proposed by the OECD – both for public health, and for One Health (OECD (2018), Stemming the Superbug Tide: Just A Few Dollars More, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/9789264307599-en; OECD (2023), Embracing a One Health Framework to Fight Antimicrobial Resistance, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/ce44c755-en)

5. The authors could also review the package of 20 interventions proposed by the World Bank recently - Rupasinghe, N., C. Machalaba, T. Muthee, and A. Mazimba. Stopping the Grand Pandemic: A Framework for Action. Addressing Antimicrobial Resistance through World Bank Operations. Washington, DC: World Bank; 2024. License: CC BY 3.0 IGO. https://hdl.handle.net/10986/41533

6. The authors could also review the WHO people-centred approach to address AMR in human health and core package of interventions to support national action plans. The core focus is on addressing inequities, was endorsed by the World Health Assembly in 2024, highlights the interdependence of interventions, highlights the need to address critical broader health system gaps, and barriers faced by people and vulnerable populations, and

provides guidance for specific actions at each levels of the health system.
https://iris.who.int/bitstream/handle/10665/373458/9789240082496-eng.pdf

7. The authors also may wish to review the "Smart Choice Process" developed by the AMR Policy Accelerator at York University, Canada that is currently being piloted in many countries in Africa to identify effective package of interventions across the One Health sectors.

8. It will be useful to clarify if this research is purely for human health or as stated in the methods section, to address AMR at country level across One Health. This research is focused on a One Health approach as stated in the methods "AMR interventions implemented in human health and across One Health". In phase 1, we focus on assessment of intervention and determinants in human health and the potential impact on AMU and AMR outcomes in BRICS countries. Particularly, we have chosen the determinants from 3 key domains of human health: health systems finance, medical technology, and health workforce. This is timely given the WHO's repositioning of AMR within the health systems division. In Phase 2, we will expand the quantitative assessment to the environmental and animal sector for a different group of case countries. This has now been made explicit in the updated version.

9. For the textual analysis, it will be critical to expand the search terms. It could include different ways of referring to AMR such as: "drug resistant infections", "anti-bacterial/anti-fungal/anti-infective resistance", "antibiotic resistance" and their variations. We acknowledge the importance of expanding the search terms to capture different ways of referring to AMR. We will incorporate these terms into our textual analysis to ensure comprehensive coverage. We have made these changes in the updated version of the protocol.

10. The search terms are also missing important interventions such as "stewardship", "national treatment guidelines" "immunization", "infection prevention and control" "bacteriology laboratory systems"

11. If the study is applying a One Health approach then consider including search terms that would cover interventions in other sectors related to animal health, agriculture, the environment. This is missing at this point.

12. The list of 17 countries seem very ambitious. While many of the large countries like India have a "National Action Plan", health interventions are primarily implemented by the States, and so identifying interventions at the national level might not be helpful or drive actions in States. It might be useful to identify a smaller group of countries whose NAP on AMR is expiring or has expired, and are currently at the stage of conducting an assessment of their implementation. The proposed research design could then help provide valuable evidence- based policy guidance to countries to help develop new NAPs and cost the most essential interventions as part of developing an operational plan. Thank you for your comment. Given the urgency of the global AMR response, including the development of the Global Action Plan (GAP) for 2026 and the UNGA targets, we believe that assessing 17 countries is both necessary and feasible. This work is now supported by the Fleming

Initiative, further reinforcing its significance and urgency, and we would ideally aim to expand this effort further to include more countries. We are in active dialogue to facilitate other countries to perform this structured assessment or nominate their country for the next wave of analysis. We understand that some interventions are implemented at the national level, particularly in countries where health interventions are primarily implemented at the state level. Our assessment extends beyond NAPs to include all relevant national and state-level policies pertaining to AMR. This has been made explicit in the updated version.

13. In many of the selected countries conducting a literature search only to identify historically AMR interventions and the level of their implementation in that country will not be enough because the general literature is normally biased towards the Global North and not all interventions will be well documented. We recognise the limitations of relying solely on published literature, as it often skews towards the Global North and may not comprehensively capture AMR interventions in many LMICs. To address this, we have carefully selected countries where we have strong collaborations with field experts. These experts provide critical contextual understanding, help access country-specific data (including local language) and policies and ensure that our research reflects on-the-ground realities beyond what is available in the literature. As stated in the protocol, "Final validation by a fourth reviewer, the within-country expert, who validates coding of 30% of the identified interventions".

14. Having the preferred intervention in the country' NAP on AMR in turn is not a guarantee that it was implemented in practice and would not give an indication of the extent of its implementation. Pairing this with i) quantitative data from TrACSS and national/regional monitoring reports and with ii) national key informant interviews (beyond just one national expert especially in the case of countries of the size and administrative arrangement like China and Brazil) will be key. Thank you for your valuable feedback. We acknowledge that the presence of a preferred intervention in a country's NAP on AMR does not guarantee its implementation. Therefore, we are also reviewing research studies evaluating interventions. Additionally, we plan to corroborate our findings with national and regional monitoring reports, assessing AMR/AMU data for the case countries as stated in the methodology "Regional and national surveillance systems and dashboards were searched to develop a time-series of AMR prevalence and AMU volume for each of the BRICS countries for a minimum of 20 years". As stated in the current version, we have a process of within-country validation.

15. The authors could clarify how the deductive analysis of AMR interventions will be converted to a quantitative variable that can be used in the longitudinal modelling analysis. Will there be an overall score assigned for the level of implementation of a given intervention in a given year for a given country? For the longitudinal modelling analysis, we assess the impact of AMR interventions on AMU and AMR levels using econometric and machine learning approaches. We also know that any of the following can happen - a time-lag between implementation and effect; increased impact after time; a waning of effect; and interventions which work together to reinforce – our analysis will allow inspection of these potential explanations. The temporal accuracy of any such analysis is always limited. The interventions were systematically categorised and coded based on

implementation coverage, strategy, and maturity so that the potential impact on AMU and AMR outcomes can be assessed quantitatively.

16. It would be beneficial to include “Infection Prevention and control”, “Diagnosis and Bacteriology / Mycology laboratory systems” under Theme “E” in the coding framework for deductive analysis. Thank you for this helpful suggestion. The 'Technology and R&D' theme in our coding framework includes diagnostics. We acknowledge the omission of IPC in the presented table, and this has now been corrected in the updated protocol.

17. Will Gender and other social stratifiers that impact equitable access be included in the determinants of implementation. We are using the PESTELI framework to identify barriers and facilitators for AMR policies. Gender is included under the “S” (sociological – norms, culture and practices, gendered roles) and “E” (ecological -epidemiology and disparities of infection risks) We have now made this more explicit and referenced the WHO publication Addressing Gender Inequalities in National Action Plans on Antimicrobial Resistance.

18. The authors can clarify how data from quantitative sources will be incorporated at the coding stage for each intervention. Findings from the analysis of interventions will be systematically coded, and these coded variables will be integrated into the quantitative analysis to inform model specification and assessment of intervention effects. As stated in the protocol: “To assess the potential country-level impact from the contextual independent variables and AMR interventions on the two dependent variables (AMR and AMU), we employed both conventional econometric models and Machine Learning (ML) causal inference to maximise the validity of this analysis.” The findings from the intervention assessment, including codings of implementation coverage, strategy, and maturity, will be included in the model as categorical variables along with other contextual determinants to assess their potential impact on the AMU and AMR outcomes, we employ both econometric and machine learning methods in data processing and analysis to maximise the methodological robustness and capability to accommodate a wider range of independent variables in our subsequent empirical piece.

19. A major challenge for the longitudinal analysis of the impact of AMR interventions and independent variables on the two AMR outcomes will be the quality of the AMR and AMU data, and in particular changes in the quality of the data over the study period for a given country. For example, the latest WHO GLASS report found that percentage of AMR infections was lower in countries that have high testing coverage (number of bacteriologically confirmed infections per million population) within the top 75th percentile. If there are significant changes in testing coverage or other factors affecting the quality of the data longitudinally in each of the countries then that can introduce bias in the effect estimates. The authors could consider observing the patterns of AMR/AMU data over time and if there are significant unexpected changes year on year, which would warrant including additional independent variable in the model to control for data quality. As stated in the protocol as one of the limitations: “There are gaps in AMR data and structural determinants at country level for any quantitative study because of inconsistency in AMR data collection across different regions and healthcare settings since many countries lack standardized protocols for collecting and reporting AMR data.” We are assessing the robustness of our findings to variations in data completeness and reliability. We are

visualising patterns of AMR/AMU over time, as stated in the protocol: “The dependent variables of this analysis are individual country’s AMR and AMU levels. Regional and national surveillance systems and dashboards were searched to develop a time-series of AMR prevalence and AMU volume for each of the BRICS countries for a minimum of 20 years.” All the caveats including changes in testing methods, laboratory coverage, case definitions were captured in the quantitative analysis.

20. Another consideration for the Longitudinal analysis would be for the authors to identify a different indicator rather than HIV/AIDS prevalence for each country as an alternative independent variable. Significant systems have already been established for HIV/AIDs in many countries based on single disease financing mechanisms, and this might not be comparable for a complex phenomenon like AMR. Thank you. We selected HIV prevalence as the outcome measure for model training as this data was readily available, while AMR-related outcome measures were generally less comprehensive and consistent across countries. The model development and training using HIV outcomes were conducted in parallel with the AMR outcome data collection. The intention is that the model structure developed using HIV prevalence can be mobilised for AMR-related outcomes once the data collection was completed. We therefore have amended the main text for further clarity.

21. The use of both Extreme Bounds Analysis (EBA) and ML-based the Bayesian networks as the two modelling approaches would be very beneficial to guide decision-makers at national, as well as regional and global levels. This, at the core, is a very innovative element of the protocol and in comparison to some other existing prioritization processes. The paper would benefit from additional details on the use of the two modelling approaches, including some examples and sample visualization. Thank you for your positive feedback. Besides the conventional econometric approach (Extreme Bound Analysis (EMA)), we used Bayesian Model Averaging (BMA) to improve the robustness of regression estimates, considering the situation where model uncertainty existed in our analysis. BMA is a statistically rigorous approach that explicitly handles model uncertainty through probabilities, whereas EBA provides a more intuitive and simpler option to assess the global sensitivity of estimates. We also employed Bayesian network analysis for causal inference. While we are able to quantify the potential association between the AMU and AMR outcome measures and the contextual and intervention determinants through statistical modelling, EBA and BMA improve the overall confidence in the modelling outputs. BMA addresses model uncertainty by averaging over a set of plausible models rather than selecting a single best model to provide a holistic, more realistic / less optimistic estimates compared to a single model. EBA quantifies the extent to which the estimated impact of a determinant on the model outcome remains valid. For instance, in our scenario, if a selected linear regression model suggests that increasing current health expenditure (CHE) by 1% would decrease the level of AMR by 15% (the estimated coefficient of the variable CHE predicted by this model is -0.15), the BMA will estimate the averaged coefficient of CHE of all plausible models, and EBA predicts whether this -0.15 coefficient can still hold if the variable CHE has more extreme values.

22. For the Visualization dashboard, the authors may wish to review the new TrACSS website that includes data comparison across countries, regions, across income levels, has global benchmarks for various indicators (across all One health Sectors), as well as a WHO

AMR M&E portal (to be ready in April 2025) that will include the human health indicators as recommended in the Global Action plan M&E Framework and recommended indicators. Thank you for your feedback. The visualisation created through our protocol also includes data comparison across countries, specifically focusing on AMR interventions/policies rather than just NAP or AMR/AMU data. Decision makers will be able to use the visualisations as part of a suite in order to make comparisons and have some insights to alternative approaches at intervention level.

Competing Interests: No competing interests were disclosed.

Reviewer Report 26 March 2025

https://doi.org/10.21956/wellcomeopenres.25240.r120264

Olga Perovic
[1] Centre for HAI, AMR and mycosis, University of Witwatersrand, Johannesburg, South Africa
[2] Centre for HAI, AMR and mycosis, University of Witwatersrand, Johannesburg, South Africa

I wish to thank Wellcome for asking me to review this SPAARTA protocol. Overall, it is well described innovative approach to NAPs analysis. Mixed method included textual analysis, longitudinal quantitative analysis, and interactive dashboard to allow visualization of deductive analysis, econometrics and machine learning. LMICs have additional issue and that is a severe lack of funding for AMR program. Also, majority of countries rely on external funding for most of their programs and sustainability of them is questionable.

The development of interactive dashboards is of a great value to create Geo Map for AMR and possibility to monitor development of resistance.

It is very useful to promote standardized way of consensus approach in development of AMR data repository.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical microbiology, public health, diagnostic stewardship, AMR surveillance, infectious diseases.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.