Health Economics Review

REVIEW

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Economic costing methodologies for drug-resistant bacterial infections in humans in low- and middle-income countries: a systematic review

Edward Masoambeta[1*], Charity Mkwanda[1], Edna Ibrahim[1], Kenneth Chizani[1,2], Chikondi Chapuma[2], Priscilla Dzanja[2], Edson Mwinjiwa[1,2], Raphael Chanda[3], Mirfin Mpundu[4], Luigia Scudeller[5], Tomislav Kostyanev[6], Finola Leonard[7], Surbhi Malhotra-Kumar[8], Fiammetta Bozzani[9], Eric Umar[1], Rajab Mkakosya[1], Chantal Morel[10], Chisomo Msefula[1] and Jobiba Chinkhumba[1]

Abstract

Background This review examined methodologies used to cost the impact of antimicrobial resistance (AMR) infections in humans from household and health system perspectives. Although extensive research has been conducted on the clinical AMR burden in low- and middle-income countries (LMICs) in terms of prevalence and other drivers of antimicrobial resistance, there is increased misuse and overuse of antibiotics which increases the risk of AMR infections compared to high-income countries. Lack of comprehensive estimates on economic costs of AMR in LMICs due to lack of standard methodologies that incorporate time biases and inference for instance, may negatively affect accuracy and robustness of results needed for reliable and actionable policies.

Methods We conducted a systematic review of studies searched in PubMed and other electronic databases. Only studies from LMICs were included. Data were extracted via a modified Covidence template and a Joanna Briggs Institute (JBI) assessment tool for economic evaluations to assess the quality of the papers.

Results Using PRISMA, 2542 papers were screened at the title and abstract levels, of which 148 were retrieved for full-text review. Of these, 62 articles met the inclusion criteria. The articles had a quality assessment score averaging 85%, ranging from 63 to 100%. Most studies, 13, were from China (21%), followed by 8 from South Africa (13%). Tuberculosis (TB), general bacterial, and nosocomial infection costs are the most studied, accounting for 40%, 39%, and 6%, respectively with TB common in South Africa than the rest of the countries. The majority of the papers used a microcosting approach (71%), followed by gross costing (27%), while the remainder used both. Most studies analyzed costs descriptively (61%), followed by studies using regression-based techniques (17%) and propensity score matching (5%), among others.

*Correspondence:
Edward Masoambeta
masoambeta.edward@gmail.com

Full list of author information is available at the end of the article

Conclusion Overall, the use of descriptive statistics without justification, limited consideration for potential data challenges, including confounders, and short-term horizons suggest that the full AMR cost burden in humans in LMICs has not been well accounted for. Given the limited data available for these studies, the use of a combination of methodologies may help triangulate more accurate and policy-relevant estimates. While the resources to conduct such cost studies are limited, the use of modeling costs via regression techniques while adjusting for cofounding could help maximize robustness and better estimate the vast and varied burden derived directly and indirectly from AMR.

Keywords Antimicrobial resistance, Economic costs, Costing methodologies

Introduction

Antimicrobial resistance (AMR) occurs when microbes develop resistance to medicines to which they were previously susceptible and results in infections that are harder to treat with a high risk of severe illness and death [1]. AMR is a critical and persistent challenge to global health, modern healthcare, and sustainable development globally [2]. AMR poses a global risk beyond the capacity of any organization or nation to manage or mitigate alone, requiring concerted efforts from all stakeholders; however, in general, there is little awareness and proper accounting of the potential social, economic and financial impacts of drug resistance [1].

Globally, bacterial infections harboring AMR infections cause approximately 5 million deaths annually [3]. 4.3 million of these deaths are estimated to occur in low- and middle-income countries (LMICs) especially in Africa and Asia but the burden is believed to be much higher due to lack of comprehensive AMR surveillance than in developed countries [3, 4]. In LMICs, the impacts of AMR include higher health care costs, decreases in labor supply and productivity, household incomes, national income and tax revenues [1]. New evidence suggests that the AMR burden, if left unchecked, will be greater and more difficult to contain. For example, AMR was the leading cause of death in Africa in 2019, with a mortality rate approximately 49% higher than that of HIV, AIDS and malaria combined [2]. The problem of AMR is more pronounced in LMICs because of overuse and irresponsible antibiotics utilization across diverse contexts, predominantly in clinical treatment, agricultural practices, animal healthcare, war crisis and in food system which increases the risk of AMR infections compared to high-income countries [5].

The overuse is in part due to less-effective antibiotics, limited access to healthcare, and poor infection practices given the limited budgets available compared to high income countries [6]. The lack of effective antibiotics threatens routine medical procedures and could lead to millions of deaths annually if no actions are taken into consideration [5].

Cost estimates of antimicrobial resistance (AMR) are usually reported by multilateral organizations such as the World Health Organization (WHO) and the Centre for Disease Control (CDC). Despite increased efforts in improving stewardship of AMR to prevent a future with more resistant bacteria [6], national cost benchmark figures are lacking or underestimated [7]. One of the reasons for insufficient investment in AMR is that there are no proper estimates of the costs associated with it [7, 8].

Additionally, owing to the lack of data on the economic costs associated with AMR infections at the local level, governments have not prioritized investments to fight current AMR as much as they have in the fight against malaria and HIV, among other infections, at least in sub-Saharan Africa (SSA) [9]. This is not surprising, as resources are scarce; therefore, governments weigh the range of competing budgetary demands and prioritize investments with the apparently most promising rewards in the future [6]. This calls for proper costing with robust methodologies to contextualize the broad AMR economic burden at the local or national level for best-fit policies. Without proper methodologies to monetize the AMR burden in LMICs, which include a comprehensive set of economic costs, policy makers are less likely to gauge the magnitude and allocate optimal resources.

This study aimed to review the AMR costing methodologies used in LMICs to inform researchers on how well the literature matches established methodological standards.

Methods

Selection criteria and search strategy

We used a Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) model. The protocol was registered with the International Platform of Registered Systematic Reviews and Meta-Analysis Protocols (INPLASY) with registration number INPLASY202470004 [10].

We used five main aspects of the inclusion criteria: condition, context, population, type of study, and language. Under condition, we assessed the economic costing methodologies that have been used to identify and analyze patients' data related to drug-resistant bacterial infections.

The context of this systematic review was at all levels, which encompassed individuals, communities, facilities, nations, and regions, but in LMICs. For studies

conducted in more than one country, there needed to be at least one LMIC with its own results because we were then able to attribute the paper outcomes in the context of LMICs to avoid contamination of developed countries outcomes which could bias the review results. The review incorporated studies of the human population without consideration of age or sex. The studies included quantitative costing papers and economic evaluation studies that used primary or secondary cost data published or in gray literature to reduce publication bias, increase reviews' comprehensiveness and timeliness, foster a balanced picture of available evidence, and to fill in the gaps in information landscape outside scholarly publication. We targeted papers written or already translated into English.

The review excluded all systematic and scoping reviews and commentaries because the methodologies used in such studies (as original papers in themselves) do not match the economic costing this review is interested in.

The search for papers was conducted in June 2024 and updated between 1st and 5th March 2025. Social sciences and medical databases and libraries included PubMed, CINAHL, Embase, the Cochrane Library, regional databases, global journals online, global index medicus, and gray literature. These data bases were selected for comprehensiveness, subject focus, and potential for capturing diverse economic costing methodologies on AMR research from various journals and LMICs, thereby minimizing the risk of missing crucial studies and maximizing the accuracy of this review findings. Boolean operators (AND, OR, and NOT) were used to search for terms with a focus on the review. Studies conducted in LMICs focused on the cost of treating resistant bacterial infections with clear quantitative methodologies were identified.

The key words used included "antimicrobial resistance", "antibiotic resistance", "multidrug resistance", "economic costs", "cost evaluation", "cost analysis", "low- and middle-income countries", "developing countries", and "less developed countries". These terms were piloted in different databases to confirm their precise capture, relevance and comprehensiveness of economic costing methodology papers before finalizing. We did not restrict the search for papers by date to have a wider methodological capture.

Data extraction and quality

Data were extracted via the Covidence platform for systematic reviews which included study characteristics such as country, study design, sample size, costing methodology, and the level of costing (whether patient or provider, or societal perspective).

To eliminate bias, each paper was screened and extracted by two independent reviewers. All possible conflicts were resolved through discussion or a decision from a third reviewer.

We subjected each study to quality review using a modified JBI assessment tool for economic evaluation studies that uses key quality items or questions [11]. The excluded checklist items were those which could not add any value to the selected economic costing methodology papers for instance, checking whether effectiveness of clinical interventions discussed in those papers was established. The modification was based on economic cost measurement of key quality-related questions, which included but were not limited to whether costs and outcomes were measured accurately, valued credibly, adjusted for differential timing, or underwent incremental analysis. These items were scored based on "yes", "no", "unclear", and "inapplicable." The JBI tool has eight questions (see appendix 1). Each question has a maximum score of 2 if "yes", 1 if "unclear", and 0 if "no". If the question was answered "inapplicable", the paper was scored out of the remaining questions. All items on the checklist not related to costs as per this description were excluded. The scoring and the weighting further justified the relevance of all the papers for the final analysis as the quality was 63% and above indicating good papers for the objectives of this review.

The risk of bias in reaching consensus when screening papers was further checked by Cohen's kappa coefficient, which is a measure of agreement among independent reviewers.

Data analysis

First, we characterized the papers included in the review by study design and the frequency of types of AMR infections by country. The infection types reported include TB, urinary tract infections (UTIs), bloodstream infections (BSIs), nosocomial infections, intra-abdominal infections, and general infections.

We also analyzed the level of costing indicated in the papers on the basis of patient, provider, and societal (both patient and provider) perspectives together with cost variables. Finally, we analyzed the costing approaches and methodologies used and noted the justifications provided.

Results

Characteristics of the included studies

The initial search yielded 2542 articles, some of which were duplicates ($n = 184$). The duplicated papers were identified via the Covidence platform and were verified by the author. The title and abstract screening involved 2358 studies, some of which were excluded at this stage ($n = 2210$). The reasons for exclusion included lack of focus on AMR, qualitatively designed papers,

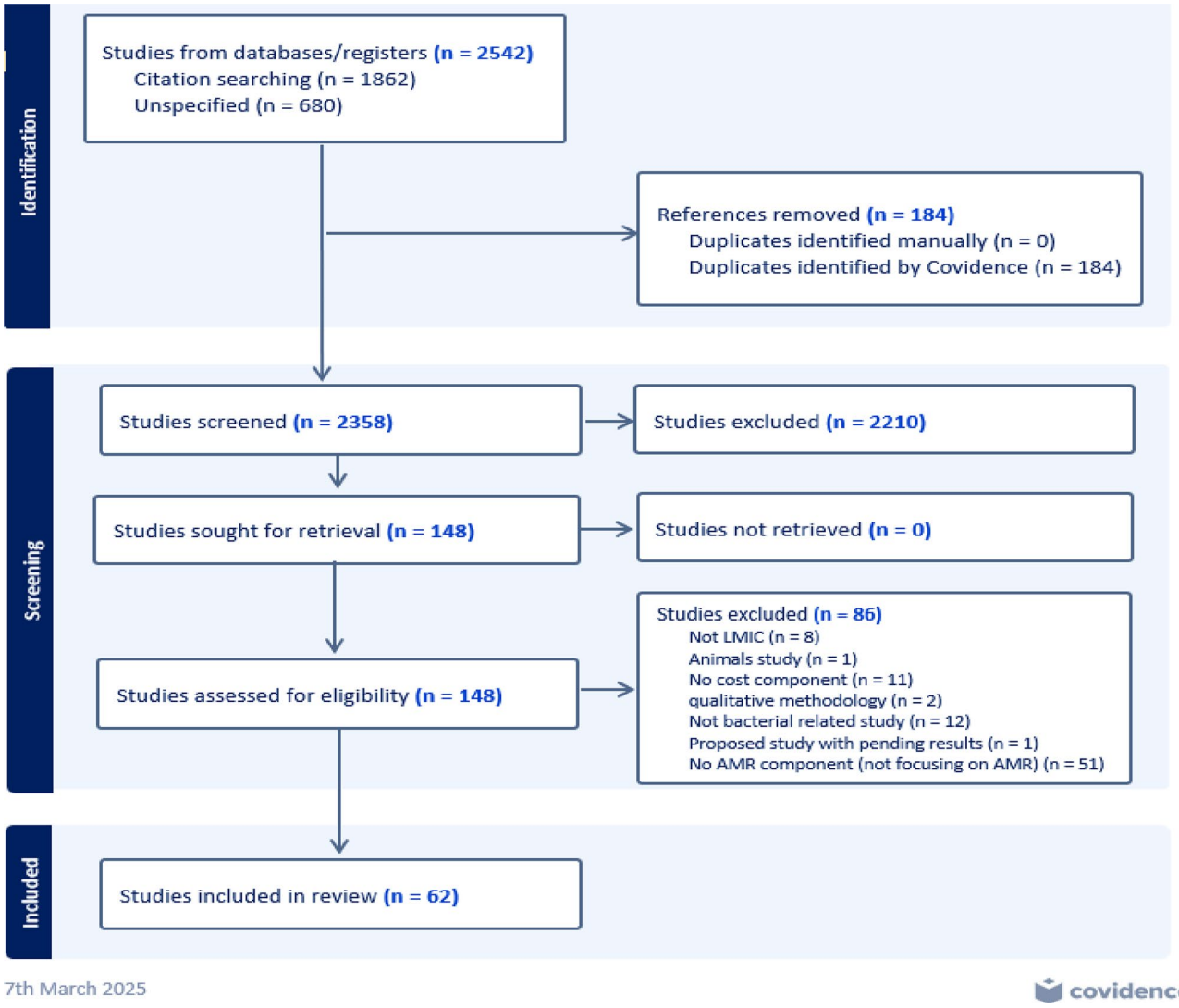

Fig. 1 Flow chart showing the identification, screening and inclusion of studies for a systematic review of economic costing methodologies for treating antibiotic-resistant infections in LMICs

not using costing methodology, systematic reviews and commentaries.

In total, 148 studies were retrieved for full-text review and appraisal of eligibility criteria. During this process, 86 papers were further excluded as follows: papers not focused on AMR ($n = 51$), no bacterial infection-related studies ($n = 12$), no cost component ($n = 11$), qualitative studies ($n = 2$), studies outside LMICs ($n = 1$), studies with pending results ($n = 1$), and animal-related studies ($n = 1$).

After the full-text review and eligibility criteria assessment, 62 studies were included in the review. Figure 1 below depicts the full study selection process.

Quality of included studies

In the Covidence platform, the Cohen's kappa coefficient for interrater reliability was 0.8, implying almost perfect agreement on the decision to include/exclude by the two independent reviewers before conflict resolution. The results of the quality assessment scoring are summarized in Table 1 below.

Table 1 Quality assessment score of papers

Number of Papers	Quality Assessment Score (%)
1	70
3	98
4	78
8	63
12	76
17	88
17	100

The results indicate that the majority of the papers (17) had an assessment score of 100%, for example, the high-cost burden and health consequences of AMR; the price to pay by Chandy et al. [12] and Penno et al. [13]

for cost effectiveness of blood stream infections for sepsis management in low-resource settings; cost analysis of GenoType® MTBDRplus and GenoType® MTBDRsl at the State Laboratory of São Paulo, Brazil [14]; and cost-effectiveness analysis of typhoid conjugate vaccines in an outbreak setting: a modeling study [15], among others, suggesting a good fit for inclusion as per the JBI quality assessment tool. These were seconded by another set of 17 papers with a score of 88%, which include the healthcare costs of AMR in Lebanon [16], enumerating the economic cost of AMR per antibiotic consumed to inform the evaluation of interventions affecting their use [17], determining the ideal prevention strategy for multidrug-resistant organisms in resource-limited countries [18], and pretreatment out-of-pocket expenses for presumptive multidrug-resistant tuberculosis patients [19].

Eight of the 62 papers had a minimum quality assessment score of 63%, including studies by Lester et al. [20], Zhen et al. [21], and Vallejo-Torres et al. [22]. Overall, 62 papers had an average quality assessment score of 85%, implying a good overall fit for inclusion.

Study designs of the reviewed papers

The studies used different approaches to achieve objectives and to limit or delimit desirable or even unintended outcomes. The majority of the studies included in this systematic review were cross-sectional studies (34%), such as Penno et al. [13], Figueredo et al. [14], and Rosu et al. [23], followed by cohort studies, such as Phillips et al. [15], Resch et al. [24], and Vargas-Alzate [25]; case control studies, which included Chen et al. [26], Jia et al. [27] and Liu et al. [28]; randomized control trials, such as Rosu et al. [29], Sweeney et al. [30] and Varon-Vega et al. [31]; and observational studies, such as Vallejo-Torres et al. [22] and Hu et al. [32], which were retrospective, whereas Lester et al. [20] was prospective. Figure 2 below summarizes the number of designs of the studies included.

Papers by country and infection type

The 62 studies included in the review were from at least 36 different LMICs. These countries are shown in Fig. 3 above. Five of the studies [13, 22, 23, 30, 33] were jointly conducted in more than two countries, whereas the remaining (57) were conducted in only single LMICs. China, with 13 papers, had the largest share of studies (21%), including Zhen et al. [21], who examined the effects of multidrug resistance on total medical costs among patients with intra-abdominal infection; Huang et al. [34], who investigated the in-hospital medical costs of infections caused by carbapenem-resistant *Klebsiella pneumoniae*; and the AMR economic burden [35], among many other studies. Papers from South Africa were the second most common, accounting for 13% of the total, and included studies such as the cost of the diagnosis and management of drug-resistant tuberculosis [36], the impact of reduced hospitalization on the cost of treatment for drug-resistant tuberculosis [37], the cost per patient of treatment for rifampicin-resistant tuberculosis in a community-based programme [38], and the cost-effectiveness of Xpert MTB/RIF for tuberculosis diagnosis in South Africa: a real-world cost analysis and economic evaluation [39]. Figure 4 shows the share of papers by country.

TB was the most common infection investigated (approximately 40%), with most of the studies conducted in South Africa (28%), followed by China and Ethiopia (12% each). General bacterial infections comprised

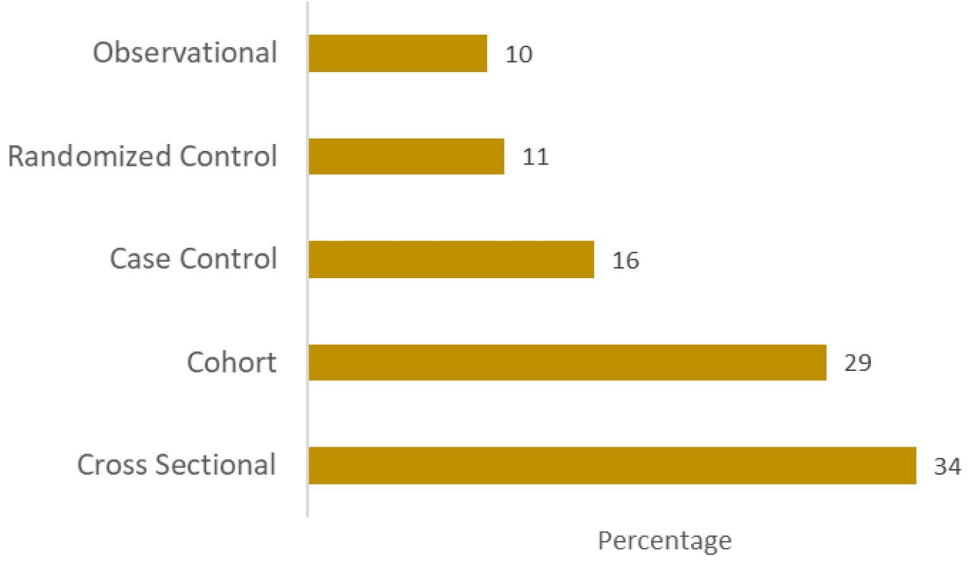

Fig. 2 Study designs

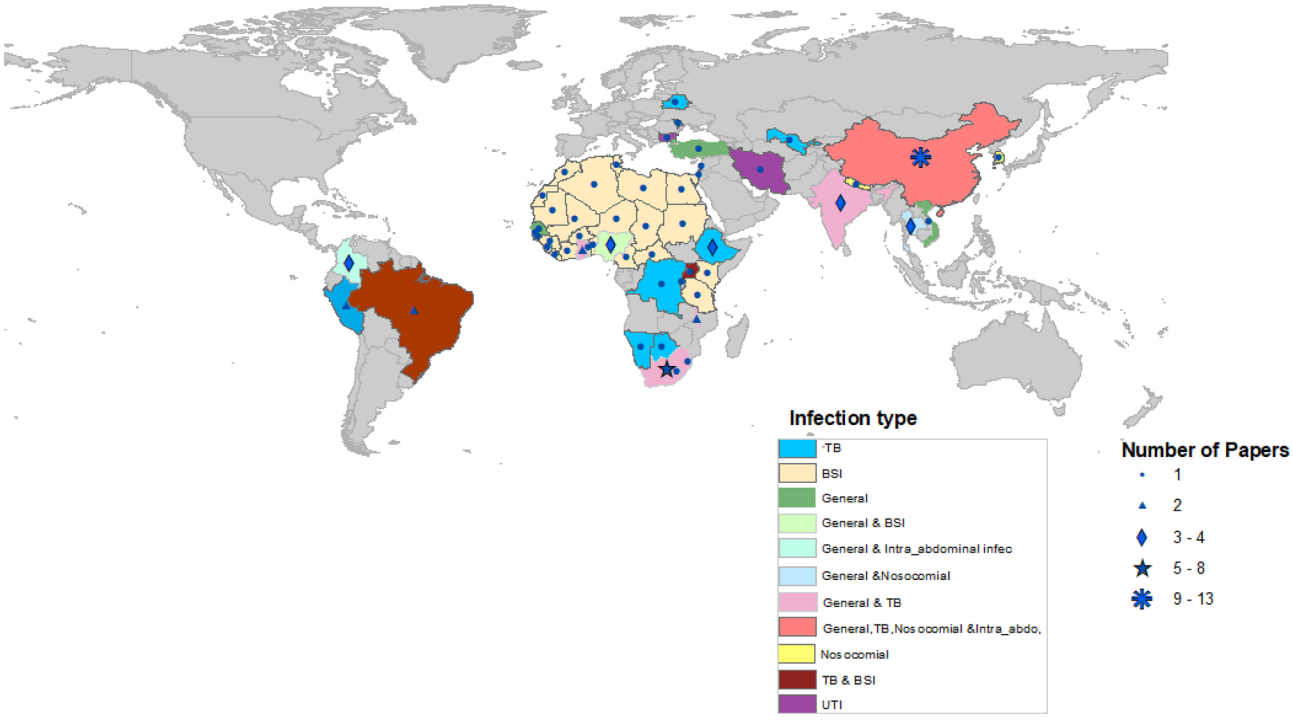

Fig. 3 Map showing countries and infection type

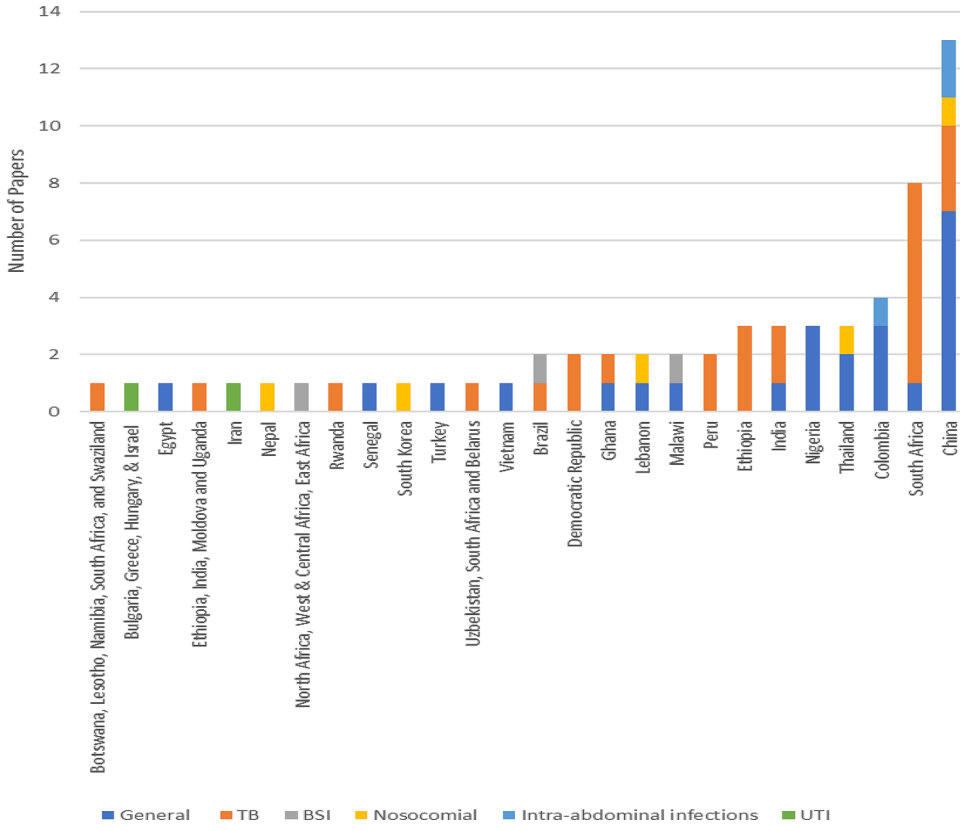

Fig. 4 Distribution of papers by country and infection type

the second highest category (approximately 39%), with most of the reports coming from China (29%), followed by Colombia and Nigeria (13% each). The costs of AMR in UTIs have been the least studied, with a share of only 3% in the papers in this review. China is the only country where studies covering 80% of the five categories of infections were included in the papers under review. The categorization of the infection type mostly follows the naming of AMR infections covered by the papers under this review. The Majority of the papers had indicated lack of necessary laboratory equipment to test BSIs than the rest of the infections due to monetary constraints and yet these infections are among those proving difficult to treat as a result of AMR [20, 40].

Perspective of cost analysis

Patient level perspective

Patients incurred costs whenever they went for treatment at health facilities. Overall, 23% of the 62 studies focused on the patient perspective. Some of the papers for this level included the epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on multidrug-resistant tuberculosis in India and China [41], the cost-effectiveness of treating multidrug-resistant tuberculosis [24], and the impact of a nationwide antibiotic restriction program on antibiotic usage and resistance against nosocomial pathogens in Turkey [42].

Provider perspective

These are the costs associated with health providers, such as hospitals or health centers.

These included treatment costs and resources used in managing or preventing AMR infections or related activities by the facilities.

Most (52%) of the 62 papers were from the health system perspective and included the AMR economic burden in China [43], cost analysis of GenoTypeÂ® MTBDRplus and GenoTypeÂ® MTBDRsl at a state laboratory [14], excess annual economic burdens from nosocomial infections caused by multidrug-resistant bacteria in Thailand [44], and the direct medical economic burden of healthcare-associated infections and antimicrobial resistance [45], among many others.

Societal perspective

Some papers covered costs at both the patient and health system levels. There were 25% of the papers whose cost of AMR-related infections covered both the patient and health system levels. The cost variables for such papers included direct medical costs, productivity losses, and indirect costs [26, 46–48], among others.

Overall, there is still a lack of studies on AMR economic cost burden in LMICs from the patient and societal perspectives compared with provider level in relation to primary care. This gap is attributable to lack of AMR surveillance data from (almost) entire population point of view in most LMICs.

Commonly used cost variables

Patient-level (or individualized) studies mostly included direct medical costs compared to indirect medical and non-medical costs. Some of the cost variables included treatment costs, visits, hospital stay, cost of antibiotics/drugs, impact of family employment and income, asset ownership, transport, nutritional supplements, communication/airtime, food and accommodation, for example, a study on high excess costs of infections caused by carbapenem-resistant gram-negative bacilli in an endemic region [49] and infections caused by extended-spectrum beta-lactamases producing *Enterobacteriaceae*: a clinical and economic impact of patients hospitalized in two teaching hospitals in Dakar, Senegal [50].

At the health system level, costs included drug use, hospital stay, clinic use and diagnostic/monitoring test use, the episode cost of managing patients, and the cost of performing each test at each site, which was recorded and included test-specific materials, personnel, and equipment costs. These studies included a cost analysis of GenoTypeÂ® MTBDRplus and GenoTypeÂ® MTBDRsl at the State Laboratory of Saint Paulo, Brazil [14], and a cost–utility analysis of ceftazidime–avibactam versus colistin–meropenem in the treatment of infections caused by carbapenem-resistant *Klebsiella pneumoniae* in Colombia [31].

Economic costing approaches

The economic costing approaches are typically in two categories: micro- or bottom-up costing and gross- or top-down costing. Microcosting captures the full extent of the individual resources used. The information is usually collected from sources that may include direct observation, clinical records, and laboratory and pharmacy records. Most papers (71%) in this review used a microcosting approach. These papers included those of Weerasuriya et al. [41], Rosu et al. [29], Kongnakorn et al. [48], and Otieku et al. [51].

Gross costing, on the other hand, uses aggregated cost data, for example, at the level of the hospital department, total costs from all the patients who received the service during a given time period.

In this review, 27% of the studies used a gross costing approach to estimate AMR-related costs. Some of the studies included Iskandar et al., [16], and Chittamany et al., [52].

Only 1 paper of valued costs used both micro- and gross costing approaches [53]. This paper analyzes the cost-effectiveness of bedaquiline versus injectable

standard-of-care agents for the treatment of drug-resistant tuberculosis (DR-TB) in Russia, India, and South Africa.

It is not surprising that most studies have used microcosting than macrocosting approach mainly because most LMICs do surveillance and laboratory testing to collect data from individual patients at a hospital setting to take advantage of the already existing structure. Therefore, aggregate data for macrocosting is mostly not available immediately for use.

The review is however not affected by use of any of these approaches in the papers it has covered.

Methodologies for analyzing costs

The studies used different approaches to analyze cost data. These included descriptive, regression, and Bayesian estimation.

The majority of the studies employed descriptive summary statistics to analyze data, which accounted for up to 61% of the full-text included studies. These descriptive methodologies to cost AMR related burden included papers by Kongnakorn et al., [48], Figueredo et al., [14], Otieku et al., [51], Kaswa et al., [54], Rupani et al., [55], Dat et al., [56], Bada et al., [57], Rathi et al., [19], Li et al., [58], Jia et al., [27], Mekonnen et al., [59], Chen et al., [26], Ionescu et al., [53], Pedrazzoli et al., [60], Vallejo-Torres et al., [22], Meng et al., [46], van den Hof et al., [61], Cox et al., [38], Sinanovic, Ramma et al., [37], Chandy et al., [12], Kim et al., [47], Wingfield et al., [62], Pooran et al., [36], Marra et al., [63], Girgis et al., [64].

All the papers that employed descriptive methodologies did not provide justification for the use of such a method. However, only 1 study by Ndir et al. [50] indicated failure to show individual cost components by mean values as a limitation of this methodology because this may lead to over- or underestimation of costs. Theoretically, however, descriptive statistics in LMICs are preferred given the limited data capture possible in these countries because such data are simple and easy to understand while still providing a summary of cost data to users.

In terms of regression-based techniques, 8% of the papers [16, 21, 44, 65, 66] employed linear regression models (either stepwise forward or backward depending on data entry), mostly to check and control for potential confounding factors while testing for statistical assumptions such as normality, homoscedasticity, and variable inclusion. No significant weakness pertaining to this costing methodology was reported. 6% of the papers [20, 32, 34, 52] used the logistic regression technique (with latent variables) for two main reasons: the first was to account for possible confounding among variables while testing if certain statistical assumptions were met for robust results, and the second was to allow small sample sizes to emulate large sample properties. There is confounding, for instance, if in a regression where total costs are the dependent variable while the type of antibiotics in use and length of treatment as independent variables affect each other but they also have separate influence on the dependent variable (total costs). Confounding requires proper estimation techniques such as instrumental variable (IV) regression.

Multivariate backward stepwise logistic regression with a multistate model and Cox proportional hazard model accounted for approximately 3% of the papers [16, 50] to account for time-dependent bias and to allow adjustment for independent effects of variables and confounders.

Generally, most purely descriptive-based methodologies are conducted at the health facility level using aggregate data. The cost variables were broad and from a provider rather than a patient or societal perspective. In contrast, regression-based techniques were used with patient-level data where the influence of separate variables was to be isolated in terms of effect or magnitude on the potential costs of AMR-related infections.

A summary of all the cost analysis approaches and corresponding justifications is shown in Table 2 below.

Discussion

In this review, the main focus was on economic costing approaches and methodologies that have been used to estimate costs related to resistant bacterial infections or burdens in LMICs, particularly in humans.

The reviewed papers show that among LMICs, countries with relatively higher per gross domestic product (GDP) like China and South Africa have contributed more papers than the rest. With respect to costing approaches, many papers have used microcosting over gross and mixed costing. In practice, microcosting in health offers policy and accountability edges because it allows accurate estimation of costs, especially for studies whose services are labor intensive [76]. Principally, microcosting is also very useful for evaluating the economic analysis of new interventions that lack established cost estimates [77–79]. However, microcosting mostly requires direct measurement, which can be costly and time-consuming to implement when generated from complex hospital-based services [80]. This point has direct implications for the study design used, which we discuss later. Additionally, microcosting is likely to miss important cost items, especially where it is necessary to determine fixed costs and overheads separately in analyses related to AMR infections, which renders it difficult and sometimes impossible [81]. The other drawback of microcosting is that it could be limited to the generalizability of the results, as it reflects only the attributable costs and socioeconomic composition of the local population [80].

Table 2 Costing methodology and its justification and limitations

Author(s)	Cost analyses	Justification	Limitation
[16], [50]	Multivariate backward stepwise logistic regression with multistate model and Cox proportional hazard model.	-Multistate model to account for time dependent bias -Cox proportional hazard to allow independent effect of variables and confounders adjustment.	Other nontime covariates might still be biassed
[33]	Bayesian estimation with Monte Carlo simulation.	Calibrating complex nonlinear models and for characterization of uncertainty in analysis results.	-depends on a number of fixed assumptions
[49]	Bivariate and multivariate generalized gamma distribution linear models.	Suitable for economic variables that do not comply with the assumption of normality of linear regression.	Not reported
[17], [42]	Correlation	Not reported.	Not reported
[12–14], [18], [19], [22–24], [26], [27], [29–31], [36–38], [46–48], [51], [53–60], [62–64], [67–72]	Descriptive	No justification provided	Mean values fail to capture individual circumstances costs which likely underestimates the costs
[16], [65], [44], [21], [66]	Linear stepwise regression models.	To control an array of potential confounding variables while testing a number of assumptions required to be met by the data set e.g. normality test, heteroskedasticity, and variable inclusion.	Not reported
[52], [20], [34], [32]	Logistic regression (with latent variable).	-To account for possible confounding among variables while testing a number of assumptions required to be met by the data set e.g. normality test, heteroskedasticity, and variable inclusion. - (To allow small samples to emulate large sample properties).	Not reported
[73]	Mathematical Operational model.	Allows comparison of two different interventions as if they had similar adherence and identical population characteristics.	Not reported
[45], [43], [35]	Propensity score matching (PSM).	To minimize bias and confounding by randomly assigning research subjects, e.g. inpatients, into case control groups by matching a set of covariates like gender, age, and diagnosis.	Not reported
[74]	Schulzer's Estimate.	To estimate the future burden of tuberculosis problem by taking into account various economic and medical forms.	Not reported
[15]	Stochastic transmission model.	To account for the probability of an event happening as new, or that it will continue to happen, or reoccur in the near future with associated costs. It takes care of all these three states.	Not reported
[25], [75]	Univariate and multivariate models.	To allow small samples emulate large sample properties.	Not reported

In terms of gross costing, the most significant practical determinant for its use is that it can be cheaper and faster than microcosting [80]. Thus, gross costing could be the only viable alternative when complex hospital services are included in the costing exercise. Additionally, several cost-of-illness studies use gross costing partly because detailed input data could be missing [79, 80, 82], in which aggregate cost data would help reduce such gaps in analysis.

Another advantage of using the gross costing approach is that it can be used where variation in resource use is reasonably small and/or when the level of aggregation is relatively high as well as where microcosting would be very expensive [80, 82]. Again, gross costing may be practically preferred when the generalization of results is a requirement, and most of the time, cost data are readily available (at least for the covered cost items and periods), which may help to respond promptly in expedited studies requiring quick evidence or policy action, for instance, during infection outbreaks [83].

The limitations of gross costing, however, include that first, the method may rely on several assumptions, such as randomness of data collection, to eliminate bias, which can significantly reduce the accuracy of the unit cost estimate if it is violated [80]. Similarly, the accuracy and reliability of the gross costing method depend on the quality of secondary data, which makes it unreliable when the data quality is not known [80, 84]. Furthermore, gross costing cannot be performed in such cases when no cost data are available in hospital or national databases or in the literature [85], for instance, where new technologies are implemented.

Finally, gross-costing is limited in that it cannot be used to measure small changes in resource consumption, for instance, inside hospitals, because costs are not distinguishable between patients via this costing approach [80, 82].

Therefore, a mixed method can be less expensive than using only a gross-costing approach, and it can be more accurate than using only microcosting by allowing researchers to tailor the cost measurement in line with the study objectives and decide where they will rely on microcosting and where to use macrocosting [80]. In other words, the mixed method of costing makes it possible to combine the accuracy of microcosting and the simplicity of gross costing [82].

The costing approach has a direct link with the study design, specifically prospective, retrospective, and direct observational, which could have a considerable impact on the accuracy of the unit cost estimate [79]. The costing approach can suffer the weakness of a particular study design. For example, direct observation better suits the microcosting approach, which could produce very accurate and precise data, as trained observers watch the intervention processes and consistently record the data on cost parameters. However, the research cost could be exorbitant since the observers would most likely require training and would need to be dedicated to research activities throughout the observation period to ensure that the observation recordings are consistent [80]. Additionally, staff or patients might find the presence of observers intrusive in some cases [80, 85]. This observation would also be true for randomized control trials and case studies that depend on primary data.

Prospective study designs can be ideal for a mixed costing approach to track all resources used in AMR interventions, but prioritizations need to be made in contexts where this approach might not be feasible for all cost categories owing to the limited research budget, time, and site buy-in [85]. In such cases, some costs might be more important to track in detail than others are. For example, interventions to prevent and manage chronic AMR tend to be heavily labor intensive; thus, labor cost is typically a key category for understanding AMR programme costs [85].

The quality and reliability of retrospective studies depend on the accuracy and availability of the original data recording system, similar to the macrocosting approach [80]. Thus, in general, prospective studies offer more detailed measurements and/or more flexibility than retrospective studies do [80].

In terms of analytical costing methodologies, the majority of the papers used descriptive statistics, which is not surprising given that they are simple, easy to use and easy to understand in identifying cost or population characteristics and trends [86]. Descriptive statistics are also widely used because they are less resource intensive in terms of data requirements, specifically in LMICs, regarding the complexity of cost variables related to the AMR phenomenon [79] but still suffice amid problems such as data gaps or unavailability. Studies such as [14, 48] and [51, 54] have used descriptive statistics, which are useful for establishing benchmark figures that render quick fix measures from the policy point. However, there is potential to misrepresent the cost structure of the health burden because a high proportion of this evidence could be unreliable, likely because of oversimplification of complex data and overlooking assumptions such as normality and the absence of outliers [81, 85, 87].

Otherwise, it is sensitive to small data changes, leading to unreliable conclusions [87]. Moreover, descriptive statistics may mask cost variability in the case of means and percentages, which tend to undermine other underlying factors that can influence costs, such as the time horizon, generalizability of results and prediction [80, 85]. Like descriptive statistics, correlations, which are used in only two papers [42, 88], lack the rigor to establish causation and prediction among AMR cost variables despite descriptions of conditions and relationships [80, 81].

Another commonly used analytical costing methodology in the papers under review is the regression technique. The form of these techniques varies from simple to multiple and from linear to nonlinear. Cost analyses, which are regression-based in nature, are useful for addressing specific data needs, such as checking and controlling for potential confounding factors while testing for statistical assumptions such as normality, homoscedasticity, and model fitness [16, 44, 65]. This is important, as AMR is usually associated with long hospital stays, increased expenditures, indirect costs such as productivity losses and many external factors that might affect each other as independent variables while affecting total costs as the dependent variable, requiring careful analysis [87]. Regression-based methodologies are advantageous for their ability to handle complex linear and nonlinear relationships (such as AMR, where direct medical costs, indirect costs, and productivity losses are involved at the provider, health systems, and society levels), have predictive power for future changes in cost drivers on the basis of past or current trends, can control for multiple factors, and can quantify the impact of each cost driver on total cost [76, 87, 89].

The limitations for using regression-based costing methodologies include reliance on so many statistical and numerical assumptions of cost data and samples that cannot always be met [78], where data surveillance and collection of AMR burdens are still not well developed, as in most LMICs. Additionally, regression methodologies are sensitive to data quality, including accuracy and completeness, which is a problem likely encountered in many

LMICs [85]. Additionally, regression-based methodologies are limited to quantitative data and require much expertise to use and interpret results [80, 82].

Clearly, various costing methodologies have strengths and weaknesses that may necessitate a combination of methodologies and costing approaches to capture the full scope of AMR costs. A combination of methodologies for acknowledging the complexities and challenges of AMR costs, which require reasonable investments to collect accurate data, and consideration of both direct and indirect societal costs, which will help in making a more comprehensive assessment of costs under a one health approach and expose challenges in LMICs for better policy decisions. There is thus a need for costing methodologies that account for these specific data concerns; to this end, a comprehensive and standardized approach to estimating the economic burden of AMR is needed.

Based on the findings of this study, which focus on costing approaches and methodologies for analyzing AMR cost burdens and when researchers have resources, including time to plan, future research should consider the following recommendations:

1. The costing approaches and analytical costing methodologies should be used with rationales that are clearly described. This may include health economics rationales, data problems expected or encountered, ease of checking or overcoming numerical or statistical or econometric assumptions, including time horizons such as whether the data are cross-sectional, time series or panel, and the study design. In addition, it is important to discuss how methodological assumptions, structural, heterogeneity and parameter uncertainty were addressed.
2. The data capture and/or variables should include wide societal costs to account for the full AMR cost burden. The cost categories should include, from a patient perspective, *direct costs* such as direct medical costs (e.g., antibiotics, investigations/laboratory testing charges, beds and nursing), direct nonmedical costs (such as travel costs, communication, lodging), and *indirect costs* such as the wage loss of patients and guardians, post illness, and years of life or disability lost. From the health system perspective, *variable costs* such as salaries of medical personnel, reagents, drugs, and building and equipment maintenance, among others, and *fixed costs* such as equipment, land and buildings, and utilities, among others, are needed.
3. The estimation of the healthcare system and economic impact costs, along with other covariates, should include an explanation of how these costs were measured and where alternative measurement methods exist to explain the suitability of the proposed method in this context. Again, if the costs occurred in significantly different time periods with the potential to have price differential impacts, attempts to discount the costs or use of appropriate matching methods should be made (especially on account of descriptive statistics).
4. The use of more analytical methodologies (for example, descriptive statistics and regression) should be encouraged if the context may allow in order to triangulate the results of the analysis.

Strengths and limitations

The strength of this paper stems from the fact that, first, there is a rigorous coverage of papers geographically across all LMICs globally that have attempted to capture and analyze costs related to AMR in humans. Second, the review was not limited by the period during which the studies were conducted. As a review of methodologies, all papers, regardless of the time of publication, that could fit the inclusion criteria were included in order to learn and support future analyses.

This review is not without limitations despite the strengths mentioned. First, it was outside the scope of this study to identify the factors that influenced the choice of the costing methodology other than the technical aspects. For example, it was not possible to determine whether data availability or unavailability determined the choice of a particular methodology within the studies. Second, any strengths or limitations reported in the papers included in this review that had no direct link with the technical methodology were not included in the assessment of the strength or weakness of the methodology used. Thus, the justification or weakness of costing methodologies should be understood in the pure sense of methodologies. We are not undermining studies that may have informed some policies without much information, as we acknowledge the need for fast action regarding AMR. In reality, AMR is extremely burdensome economically. Policymakers should not wait for "perfect" estimates before taking action on AMR. Clearly, our concern is that, in the absence of full assessments, we may risk underestimating the true cost and therefore not putting or advocating for sufficient resources toward tackling AMR. Third, the study did not attempt to establish a level of effort in combating AMR across countries to determine whether the availability of resources, political will and data would influence the methodology of costing. Another limitation in this paper is the restriction to search only papers written or already translated in English which has the potential of language bias in this review. The authors did not simply ignore such papers but successfully found English versions for the papers which had English title but with contents in another language

they could not understand. In addition, no date restrictions which has the potential to broaden the capture of papers may have resulted into inclusion of older studies that may not reflect contemporary costing practices as a limitation. Finally, the costing methodologies in LMICs were not compared with those in developed countries to determine whether there were any systematic differences and the likely causes, if any, involved.

Therefore, the findings of this review should be understood cautiously with these limitations in mind.

Conclusion

The findings suggest that the vast majority of studies concerning LMIC settings fail to capture or quantify the full AMR burden. While descriptive statistics are useful in estimating the economic burden of AMR in selected contexts, they cannot fully account for the complex nature of AMR. On the other hand, regression-based methodologies, which are uncommonly used in LMIC studies, could provide more plausible estimates but require significant data and resources.

The mixed costing approach that combines microcosting (e.g., for direct costs) with more macrocosting approaches (e.g., for indirect costs incurred with a longer-term time horizon) could be useful if time and other resources allow.

By strengthening the methodological costing approach, we can better capture the full costs associated with AMR and help policy makers better understand the nature and magnitude of the problem. While leaders should not wait for perfect, nationally derived economic evidence before addressing the problem of AMR, where these studies are undertaken, we should try to ensure that they are as broad and as robust as possible.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13561-025-00644-5.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We would like to sincerely thank Apatsa (Kamuzu University librarian) for support and advice during the literature search. We cannot be thankful enough without acknowledging Yanjanani Mapondera, Dan Bwanali and Stanley Azizi for their support in the initial phase of screening abstracts.

Author contributions

EM worked on the study design, data extraction, and data analysis, drafted the initial manuscript, and addressed comments from internal reviewers. CM, EI, CC, PD, KC, EMW, and RC contributed to the screening of papers as collaborators, resolving conflicts, quality assessments, and data extraction. MM, LS, TK, FL, FB, EU, RM, SMK, CM9, RM, CM2, and JC reviewed earlier versions of the manuscript and made substantial revisions. CM1 and JC supervised EM in the study design, data analysis, and manuscript writing and made substantial revisions to the manuscript. All the authors read and approved the final manuscript.

Funding

This study received financial support from the SIDA through the APHRC.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Systematic review protocol registration

This review was registered with the International Platform of Registered Systematic Reviews and Meta-Analysis Protocols (INPLASY) on 2nd July, 2024. The registration number is INPLASY202470004, and the DOI number is https://doi.org/10.37766/inplasy2024.7.0004.

Competing interests

The authors declare no competing interests.

Author details

[1]Kamuzu University of Health Sciences, P/Bag 360, Blantyre, Malawi
[2]Malawi Liverpool Wellcome Trust, P. O. Box 30096, Blantyre, Malawi
[3]University of Lusaka, Lusaka, Zambia
[4]ReAct Africa, Nairobi, Kenya
[5]Research and Innovation Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[6]Technical University of Denmark, Kongens Lyngby, Denmark
[7]School of Veterinary Medicine, University College Dublin, Dublin, Ireland
[8]Laboratory of Medical Microbiology, University of Antwerp, Antwerp, Belgium
[9]Department of Global Health and Development, London School of Hygiene and Tropical Medicine, University of Bern, London, United Kingdom
[10]University of Bern, Bern, Switzerland

Received: 7 October 2024 / Accepted: 28 May 2025
Published online: 05 June 2025

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