Antimicrobial Resistance (AMR) development map: a conceptual map and a tool to support economic evaluation of AMR interventions

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**Statements and Declarations**

**Ethics approval**

Not applicable

**Consent to participate**

Not applicable

**Consent for publication (from patients/participants)**

Not applicable

**Code availability**

Not applicable

**Authors’ contributions**

KA: Conceptualisation; methodology and investigation; visualisation; writing – original draft; writing – review and editing. MS: Funding acquisition; methodology; supervision; writing – review and editing. CH: supervision; writing – review and editing. WH: methodology; writing – review and editing. JR: methodology; supervision; writing – review and editing. BWs: Funding acquisition; methodology; supervision; writing – review and editing.

**Competing Interests and Funding**

Beth Woods sits on the Board of Directors for the York Health Economics Consortium; this is an unpaid role. Authors have no competing interests to declare. This research was undertaken as part of a University of York studentship relating to the Policy Research Unit in Economic Methods of Evaluation in Health and Social Care Interventions (EEPRU).

**Disclaimers**

The views expressed are those of the author(s) and not necessarily those of the National Institute for Health Research or the Department of Health and Social Care. Any errors are the responsibility of the authors.

**Data availability statements**

Not applicable.

**Key Points for Decision Makers:**

1. Decisions on which types of AMR intervention effects to quantify/consider should be based on the biology and mechanisms of AMR development/spread.
2. Choice of the system of analysis and the spillovers considered should depend on the specific setting of interest and its connectivity with the wider ecosystem.
3. AMR intervention effects should be considered across the key AMR burden dimensions that include time, physical space, different sectors (One Health framework), and wider pathogen pool (types of pathogens). Considerations on which effects to capture across these dimensions depend on which AMR process drivers are addressed by the intervention and the connectivity of the setting of interest.
4. Limiting the system of analysis/scope of analysis may result in incomplete capture of AMR intervention effects and may hinder evidence-based decision-making. The types of effects that have and have not been quantified should be explicitly stated along with the analysis outcomes.

**Abstract**

**Introduction:** Antimicrobial resistance (AMR) is a complex, inter-sectoral and international problem. Economic evaluation (EE) methods offer systematic, evidence-driven approaches to inform policy decisions about which AMR interventions to fund. EE of AMR interventions is complicated due to diffuse effects, complex mechanics of the problem and high levels of uncertainty. The current AMR EE literature restricts the analytical scope, potentially resulting in omissions of effects that may limit the utility of EE to inform policy decisions. We aimed to systemise the key evolutionary and ecological processes of AMR to elucidate the paths through which AMR interventions impact population health and healthcare costs to support EE design and to support decision makers in understanding the limitations of EE evidence for decision-making.

**Methods:** A conceptual map and a corresponding tool were developed based on a literature review in consultation with experts across the relevant disciplines of molecular biology, infectious disease modelling, health economics and ecology.

**Results:** The AMR development map: (1) distils the key AMR processes and process drivers behind AMR development and maps the available types of AMR interventions to AMR process drivers; (2) proposes a way to conceptualise the spatial scope of analysis through considering the connectivity of the wider ecosystem; and (3) outlines the key dimensions that AMR burden and intervention effects could be measured across. An AMR development map tool was developed to support conceptual modelling, with the focus on the choice of scope in the EE of AMR interventions and an illustrative case study was provided.

**Discussion:** This work summarises the key underlying biological principles of AMR development to provide mechanistical grounding for considering the scope of effects of AMR interventions and the appropriate system of analysis to support conceptual modelling in EE of AMR interventions. This map can also facilitate identification of effects that cannot be considered or quantified, thus enabling transparency about these omissions within decision-making.

**Key words**: Antimicrobial resistance, antibiotic resistance, AMR, economic evaluation, narrative review, conceptual map, cost-effectiveness.

**1. Introduction**

Antimicrobial resistance (AMR) is a rapidly escalating and highly complex global health and economic problem. A recent comprehensive analysis of the AMR burden estimated that there were 4.95 million (95% uncertainty interval 3.62-6.57 million) deaths associated with AMR in 2019 (1) with the latest in-depth analysis forecasting 70% increase in deaths by 2050, compared to 2022 (2, 3). The complex and uncertain nature of the mechanics of AMR[[1]](#footnote-1) and the effects of available interventions, alongside heterogeneities across settings, regions and pathogens make evidence-driven policy responses challenging (4, 5).

Economic evaluation methods offer systematic, evidence-driven approaches to explicitly evaluate and compare outcomes and resource implications for alternative interventions of interest with the primary objective to inform policy decisions (6). There are several approaches to economic evaluation available, but the preferred approach for healthcare interventions in many settings is cost-utility analysis (7). One of the core tasks in economic evaluation is capturing the relevant health and cost consequences of the intervention(s) of interest and comparator interventions/treatment pathways. This is challenging for AMR interventions due to the complex and often poorly understood mechanics of the problem and intervention effects, the varied and diffuse effects of interventions and data limitations (8). Furthermore, the current economic evaluation framework is anchored in the non-communicable disease paradigm, focusing on the benefits to individuals receiving the intervention with little guidance on how to consider the additional indirect effects of AMR interventions amongst the wider population (6, 9, 10).

As a result, there is a lack of economic evaluation literature on AMR interventions with the available literature focusing on high income countries, hospital settings and interventions that aim to prevent and control infections in healthcare facilities and regulate antimicrobial use rather than reduce the probability of emergence (11) (12, 13). The available literature is also limited in the scope of analysis, types of analytical approaches used, and the types of effects quantified and considered (11)Hence the current/commonly used economic evaluation methods may not capture important consequences of AMR interventions, hindering well-informed decision making (8, 9). These limitations in the capture of intervention outcomes may also result in economic evaluations favouring interventions with short term effects designed to decrease the spread of the resistance rather than prevent its emergence and evolution (8).

This work aims to support a more structured and explicit approach for considering the effects associated with AMR interventions in the context of resource allocation decisions in the human health sector (however the key principles apply across all the sectors). Within the AMR development map, we systemize the key evolutionary and ecological processes of AMR to elucidate the paths through which AMR interventions might impact population health, healthcare costs and effects. We then present the AMR development map tool which is a series of questions and considerations intended to be used to support decisions about the scope of economic evaluations and the types of effects included. We hope that this will, in turn, enable the development of more transparent economic evaluations and better-informed decision-making.

**2. Approach to formulation of the AMR development map and tool**

AMR development refers to the system of biological mechanisms and anthropogenic factors underlying the emergence and spread of AMR, and changes in and/or accumulation of the associated resistance burden in the population. Summary and definitions of the key terms and concepts can be found in the *Supplementary material: information box*.

2.1. Development steps

The conceptual map was developed to summarise the mechanics of AMR development through a narrative review and synthesis of diverse literature on ecology and evolution of AMR, in consultation with experts across disciplines. The conceptual map was discussed with relevant research groups and presented to several conferences and meetings of different disciplines for input on its correctness, usability and usefulness [[2]](#footnote-2). The meetings included: (1) Scientific forum at the HCAI, Fungal, AMR, AMU & Sepsis Unit (Department of Clinical and Emerging Infections) at the UK Health Security Agency (May 2023; infectious disease modelling focus); (2) Health economics study group meeting (Oxford, UK; June 2023; focus on health economics); (3) Medical Research Foundation National PhD Training Programme in AMR Research meeting (Bristol, UK; August 2023; focus on molecular biology); (4) Centre for Health Economics annual conference, University of York (York, UK; September 2023; health economics audience); (5) One Health Antimicrobial Resistance Research (OHARP) workshop (Singapore; September 2023; interdisciplinary audience with AMR policy focus); (6) RESIST3 Antimicrobial Resistance Centre, Centre for Mathematical Modelling of Infectious Diseases conference (London, UK; April 2024; interdisciplinary AMR audience). After presenting the AMR development map, including the key mechanics captured, the principles and considerations, any feedback from these meetings was incorporated into the AMR development map over several iterations. The main feedback received was about how this could be translated to the economic evaluation context and that the tool was prepared in response to that.

2.2. Anchoring questions

The AMR development map (Figure 1) was anchored by the following questions (also used in the AMR development map tool) ): (1) What AMR process driver/-s does the intervention/-s of interest target? (2) What is the ecosystem connectivity of the setting of interest? (3) What are the anticipated intervention effects across the AMR burden dimensions (time, physical space, sector (One Health), wider pathogen pool)? (4) What should be the system of analysis[[3]](#footnote-3), given the AMR burden dimensions and connectivity/permeability considerations? (5) What are the likely sources of spillover from the wider ecosystem to the system of analysis?

2.3. AMR development map tool (Figure 2)

The AMR development map tool (Figure 2) was designed based on the AMR development map to support the process of conceptual modelling when developing economic evaluations of AMR interventions. The tool contains a series of questions to consider when formulating the scope of an economic evaluation of an AMR intervention. Supplementary Figure 1 presents an illustrative case study that summarises the use of the tool.

2.4. Generalisability of the map

The AMR development map is generalizable across settings, but the specific importance of different components of this map will vary across interventions investigated and the settings of interest. This work is not aiming to be comprehensive in the included biology or the specific features of varied settings but instead summarises the key mechanics of AMR development and proposes a structured approach to help outline the expected effects of AMR interventions on health and costs, using biological reasoning. This in turn will help guide the development of conceptual models that better support both the development of appropriate quantitative models and identify key effects of interventions that are not amenable to quantification, but which may represent important considerations for health care decision makers.

**3. The AMR Development map and tool**

The further sections summarise the elements of the AMR development map (Figure 1) and tool (Figure 2). The AMR development map tool (Figure 2) should be used in conjunction with the AMR development map (Figure 1).

3.1. Antimicrobial Resistance (AMR) development map

The AMR development map is presented in Figure 1 and the following sections summarise the knowledge underlying the formulation of the map. PART 1 of the map distils the key biological concepts in AMR development as a set of AMR processes and AMR process drivers (AMR burden) and maps the available types of AMR interventions on to the AMR process drivers they influence, helping to identify the key biological forces involved; PART 2 proposes an approach to consider the wider ecosystem connectivity in the spatial scope considerations; PART 3 outlines the dimensions that AMR burden could be measured across.

[Insert Figure 1]

3.2. Types of antimicrobial resistance

On a pathogen level, we can distinguish between intrinsic (also known as innate) and acquired resistance. Intrinsic resistance typically refers to microorganisms carrying resistance to specific types of exposure that is typical for their taxon[[4]](#footnote-4) (14). In some literature intrinsic resistance may also refer to microorganisms possessing the genetic code for the required machinery that under certain conditions could result in a resistant phenotype (proto-resistance) (15). In contrast, acquired resistance develops when pathogens adapt to treatments they were once susceptible to (15).

Acquired resistance emerges through genetic and epigenetic changes in individual pathogen cells, often accompanied by a form of selection pressure that helps amplify resistant subpopulations (16). These acquired changes can occur spontaneously[[5]](#footnote-5) (17, 18) and/or from uptake of mobile resistance elements (horizontal transfer[[6]](#footnote-6)) (19). The specific dynamics within pathogen populations are highly complex and heterogenous depending on the pathogen species and selective pressure induced by exposure. There is also increasing evidence to support the role of interactions between pathogens and the surrounding bacterial communities in the emergence of antibiotic resistance (20). Antimicrobial agents may also contribute to genetic changes within pathogens resulting in a wider range of variants that may confer resistance (21). Acquired resistance could result in development of a previously known resistant strain of the pathogen or a novel variant (22). Selection of resistant strains may happen through direct treatment of the pathogen species or from treatment targeting other species (bystander/collateral selection) (14, 20, 23).

Individuals (for example, patients) can be categorised to susceptible, colonised (asymptomatic) and infected (symptomatic) with respect to a pathogen. They can obtain the colonisations or infection with a resistant pathogen by emergence of resistance in a previously susceptible pathogen or through transmission from other colonised/infected hosts and/or external reservoirs. Asymptomatic colonisations may then progress to acute infections. Individual hosts can clear the infection/colonisation spontaneously[[7]](#footnote-7) or through successful treatment, which varies by specific pathogen and context, however, there are key knowledge gaps around this process. Spread/transmission of pathogens, progression from colonised to infected and clearance of susceptible/resistant pathogens will depend on within-host dynamics (how do the susceptible and resistant types of pathogens interact within an individual). The key within-host dynamics scenarios considered in mathematical modelling[[8]](#footnote-8) include replacement infection (one type of strain replaces/outcompetes the other), strain conversion (one strain becomes converted to the other) and superinfection of strains (co-existence of both susceptible and resistant strains within a host) (24). The ways resistant infections emerge and spread informs the AMR processes and AMR process driver categories described below.

3.3. PART 1: AMR development (Figure 1)

Overall, the development of AMR can be distilled to a set of AMR processes and AMR process drivers. The AMR processes include (1) emergence of resistance (existing and novel strains), (2) progression from colonised to acutely infected state, (3) spread of resistant pathogens/resistance elements, and (4) clearance (or reversal) of resistance or infection. These AMR processes govern the changes between individuals’ AMR health states. AMR process drivers determine the rate at which these movements occur.

In the AMR literature individuals are often categorized in a series of health states as susceptible (not infected or colonized with the pathogen of interest), colonized with either susceptible or resistant pathogen strain, and infected with susceptible or resistant pathogen strain (24, 25). The key possible transitions between health states and the attributable AMR processes (for a single drug-bug combination) are summarized in Table 1 below. The range of potential health states and transitions become more complex as additional pathogens and drugs are considered. Multiple AMR processes can contribute to each of the transitions between health states as listed in the cells. AMR process and AMR process drivers are mapped in part 1 of Figure 1.

*Table 1: Possible movement between health states and respective key processes that would result in each transition with respect to a single drug-bug combination; each of the transitions could result from multiple simultaneous/ sequential processes.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| TOFROM | Susceptible | Colonised S | Colonised R | Infected S | Infected R |
| Susceptible |  | Spread\*\* | Spread\*\* | Spread\*\* | Spread\*\* |
| Colonised S | Clearance\* |  | Emergence\*Spread\*\* | Progression\*  | Emergence\*Spread\*\* |
| Colonised R | Clearance\* | Reversal of resistance\* |  | Spread\*\* | Progression\*Spread\*\* |
| Infected S | Clearance\*Recovery\* | Clearance\*Recovery\* | Clearance\*Recovery\* (Combined with Emergence or Spread) |  | Emergence\*Spread\*\* |
| Infected R | Clearance\*Recovery\* | Clearance\*Recovery\* | Clearance\*Recovery\*  | Combination of multiple processes |  |

*Terms: S – susceptible; R – resistant; Progression as a process refers to progress from a colonisation to an active infection within an individual.*

*\* Process within individual; \*\* process between individuals*

*(i) Colonised R should be assumed to have a mixture of S & R strains; (ii) This transition matrix is with respect to a single pathogen-antimicrobial combination. (iii) Transition from colonised/infected health states to susceptible are included for completeness but is an unlikely event. (iv) Colonised S refers to carrying a susceptible version of a pathogen that could become resistant upon exposure; in many cases this will refer to a healthy phenotype (for example E. coli in a rectal swab), while with some pathogens, such as Stenotrophomonas would be considered an MDR/XDR pathogen. However, the table illustrates the overall principle.*

Emergence of resistance is driven by the overall infection and colonisation burden, the exerted selection pressure (itself determined by multiple forces which vary between settings, such as antibiotic exposure) (26) and the ecological context and wider pathogen community (20). Spread of resistance is dependent on presence of transmission pathways and the overall burden of resistance (27). Progression from colonised to acute infection depends on individual patient characteristics and environmental factors, however, drivers such as interaction between the pathogens and wider resistome (pathogens can acquire further genetic components) as well as selection pressure (such as antimicrobial exposure) play an important role (28-30). Spontaneous clearance of resistance depends on the competition between the resistant and sensitive strains and other host factors (23). Clearance due to treatment (or recovery) will also depend not only on the host and pathogen factors, but also pharmacokinetic and pharmacodynamic factors of the treatment used. Clinical recovery may not always be associated with clearance of pathogen.

The specifics of the process drivers of AMR are poorly understood, and the extent to which they contribute to the AMR burden in different sectors and settings has not been quantified (31-34). For example, the key drivers of AMR emergence include inappropriate and/or excessive use of antimicrobials across sectors (35-38), however, the specific relationship between antimicrobial consumption and AMR selection has not yet been established (39). The importance of different process drivers of resistance will also depend on the environmental factors and setting (32, 40).

*Overview of AMR interventions*

AMR can be addressed through a range of different interventions that target a range of AMR process drivers. We used categories of AMR interventions outlined by the WHO Global Action Plan (GAP) (41) (as they loosely correspond to how the interventions address AMR) to identify their impact on the AMR processes and the resulting potential methodological considerations. Intervention categories included both AMR-sensitive (interventions that indirectly address AMR burden, such as vaccinations and sanitation strategies) and AMR-specific (interventions that directly target AMR burden, such as treatments) interventions.

3.4. PART2: Considering wider ecosystem connectivity in the choice of system of analysis (Figure 1)

Antimicrobial resistance and infectious disease dynamics are governed by key ecological and evolutionary principles, including ecological spatial connectivity (42). Hence, when considering the spatial and inter-sectoral aspects of the economic evaluation, it should be considered that any selected system of analysis is embedded in a wider ecosystem. Spread can happen between individuals (including via external reservoirs, such as surfaces) within the system of analysis and between the system of analysis and its exterior. This can also happen between the One Health sectors, such as human health, agriculture, and environment. The spread of resistance between settings/system of analysis (often referred to as spillover) plays an important role in development of AMR burden (One World and One Health frameworks). This means that depending on the permeability (how easily can resistance elements move across the boundary of the system), the choice of the system of analysis would also require considerations of sources of the spillover, as it may affect the analysis outcomes. In summary, the decision of the system of analysis involves considering the complexity and feasibility of modelling alternative possible systems of analysis, the permeability of the system of analysis and the resulting sources of spillover.

3.5. PART 3: Measuring AMR burden across dimensions (Figure 1)

Four key dimensions of AMR burden can be highlighted that include time, physical space, different sectors (One Health) and wider pathogen pool effects. Quantifying intervention effects on AMR burden will involve choices about each of these dimensions that will affect the overall effects quantified. The extent to which each dimension should be considered will vary depending on which process(-es) are addressed by an intervention and the specific setting of interest.

The time dimension refers to how the AMR burden develops and what the effects would be over time. The physical space dimension captures how AMR will spread/develop through physical space. The different sectors dimension concerns the AMR burden across the wider ecosystem or One Health framework (explicitly considering the ecosystem connectivity and wider sources of spillover to/from multiple sectors). The wider pathogen pool dimension refers to which elements of the wider pathogen/resistome pool may be affected. For example, an analyst may choose to quantify effects over 20-year time horizon within the site of intervention or also consider effects to the wider community. Given the choice of time and space, the analyst might also consider effects across multiple sectors (One Health framework) or just choose to quantify effects to human health. Finally, the analyst may choose to focus on the pathogen targeted by an intervention or to consider broader effects on the pathogen pool. However, it is important to acknowledge when these effects may still be present. Knowledge of the underlying mechanics of the problem given the setting of interest will aid these decisions.

Understanding of the distribution of the intervention effects across the AMR burden dimensions enables us to outline the system of analysis. System of analysis represents the scope of analysis and includes the effects and system dynamics we are interested to model. The choice of system of analysis may be modified by the wider ecosystem connectivity considerations associated with the setting of interest described below.

*3.5.1. Reporting AMR burden*

Literature describing AMR burden, mostly reports health loss associated with the number of AMR infections, for example, estimated Disability-adjusted life years (DALYs) associated with the number of deaths due to AMR globally (1). Key AMR databases, such as GLASS, European Centre for Disease Prevention and Control (ECDC) and Centers for Disease Control and Prevention (CDC) AMR surveillance efforts report the number or proportion of resistant infections for pathogen-antimicrobial combinations of interest (43). Overall, estimating the global burden of human disease associated with AMR is highly challenging (44) [[9]](#footnote-9).

Further distinctions should be made between the concept of AMR burden used in epidemiological and clinical literature and the concept of “burden” in the health economics literature. The latter includes a wider concept of impact on population health and broader economic metrics, such as health care costs and productivity.

For this work, AMR burden refers to all components of resistance, including infections, colonisations, and associated resistance elements[[10]](#footnote-10).

3.6. Using the AMR development map in economic evaluation of AMR interventions

The AMR development map tool below (Figure 2) is designed to aid conceptual modelling in economic evaluation of AMR interventions. The tool is based on and is to be used in conjunction with the AMR development map (Figure 1) and accompanying text. The tool guides the reader through questions on the distribution of effects across AMR burden dimensions and considers the specifics of the setting of interest to consider the wider ecosystem connectivity and the resulting sources of spillover. The outcome of this working sheet is an outline for the system of analysis that represents the scope of the model and the effects of interest, along with potential sources of spillover beyond the system of analysis. The AMR development map tool uses a checklist to support readers to integrate these considerations when developing specific economic evaluations of AMR interventions. Supplementary Figure 1 provides an example case study of a hospital screening and isolation strategy using the tool.

[Insert Figure 2]

Due to the complex nature of AMR, substantial heterogeneities and a broad range of available interventions, these questions were designed for guidance and are not comprehensive in nature. Each unique decision problem will require critical reflection on these questions and further research specific to the context.

**4. Discussion**

The AMR development map frames the key biological concepts of AMR development to aid conceptual modelling in economic evaluation of AMR interventions and provide mechanistical grounding for considering potentially relevant effects in decision making. First, this work structures the key AMR processes and process drivers and maps the available types of AMR interventions to highlight how these interventions would affect these processes. Second, it supports consideration of the ecological connectivity of the setting of interest and potential spillovers when deciding on the spatial scope of analysis. Third, the map outlines the key dimensions across which to measure AMR burden effects dependant on which AMR processes/process drivers are targeted by the intervention and the setting of interest. The corresponding AMR development map tool was designed to assist readers to integrate these considerations when developing specific economic evaluations. This work addresses a current need in economic evaluation literature, where due to the inherent ambiguity and complexity of the AMR mechanics and diffuse nature of the intervention effects, comprehensive quantification and consideration of the effects is challenging. This work provides a biologically grounded systematic approach for the decisions on which effects to quantify and consider within resource allocation decisions.

Most of the available economic evaluation literature of AMR interventions restricts the scope of analyses, potentially omitting important effects of interventions, hindering well-informed decision making. For example, a recent systematic review found that most of the studies used short time horizons (1 year or less) in the evaluation of AMR interventions and none of the reviewed studies quantified the effects beyond the time horizon of the interventions (11) . However, there has been recognition of the additional effects of AMR interventions in the case of valuing novel antimicrobials. Proposed additional components of value of novel antimicrobials were identified that included diversity value (reduced selection pressure and preserved efficacy of the available antimicrobials due to a range of treatments), transmission value (reduced spread), enablement value (allowing a range of medical and surgical procedures), spectrum value (better targeted treatment) and insurance value (in case of increase in prevalence of certain resistant infections) (46, 47). However, these additional components of value lack a mechanistic grounding in the specific types of effects and their scope and have proved elusive as a target for quantitative modelling.

The purpose of the AMR development map is to ground discussions of pathways through which AMR interventions affect population health and healthcare costs in the biology of AMR development. More specifically, this map and tool could be used to 1) inform conceptual modelling stages of economic evaluation, 2) aid with critical assessment of the available economic evaluation evidence for decision making and 3) aid with data collection by highlighting potentially important effects of interventions on which further primary data collection or review and synthesis efforts could be targeted. The work also encourages analysts to use a more comprehensive approach to evaluation of different types of interventions. This work should be useful for analysts conducting economic evaluations of AMR interventions, intervention efficacy investigations and decision makers reviewing evidence to inform resource allocation decisions.

The AMR development map and tool forms the basis of initial considerations and the requirement for explicit reflection on these effects. However, questions of feasibility given the complexity of the system, available knowledge, data and the scope of the project will still need to be considered in consultation with the project stakeholders. While limitations in scope will inevitably be necessary in any intervention evaluation, it is important to highlight that computational, evidential or other challenges do not eliminate the need to be transparent about the anticipated effects of interventions of interest. Any exclusions of effects due to such challenges should be explicitly reflected on by those developing economic evaluations, and those using economic evaluations to support health care decision making. This map does not replace the research and considerations required in modelling the impact of interventions, but it proposes a systematic approach to working through the question of scope. To our knowledge, this is the first tool to support consideration of more explicit mechanics of AMR development in economic evaluation.

This map distilled the key features of AMR biology/ecology and, given the complexity of the field, cannot be comprehensive in its detail. However, it was designed to be sufficiently general to be applicable across settings and is not focused on any specific pathogen-drug combination. The importance of the specific components of the map will depend on the settings, pathogens, and interventions under study. We anticipate substantial heterogeneities across the specific decision problems, and hence analysts should consider the specifics associated with their investigation. Hence in addition to the conceptual map which structures and summarises the key concepts, this work also outlines a set of guiding questions to aid considerations of scope and methodology (summarised within the AMR development map tool). Further work could include a more in-depth investigation on the importance of these dimensions and pathways across different settings, geographical regions, and pathogens of interest to aid researchers. Conceptual modelling within future economic evaluations utilising the AMR development map and tool would help us understand its usability and make future improvements. Finally, we acknowledge the limitations of developing such a tool as a small team and welcome further iterations of this work.

Several key aspects central to this topic were not discussed in this work. To begin with, considerations of extended time horizon require consideration of discounting, which is not covered/discussed by the AMR development map. Extensions in scope and inter-sectoral considerations also raise questions of perspective, which have also not been further explored by this map. The modelling approaches used in decision modelling of AMR interventions are also outside the scope of this work, but using mechanistic transmission models would likely aid incorporating many of the considerations summarised in the AMR development map. The specific types of health effects and health care costs, and the ways in which these should be reflected are also outside the scope of this map and will be highly context specific.

This map provides an outline of the key biological aspects of AMR development, but it does not summarise the knowledge gaps and the further work required to understand and quantify the dynamics of the process. Further work summarising these gaps would both aid choices in economic evaluation and identify key research priorities in the field.

**5. Conclusion**

Currently there is a lack of economic evaluation literature on AMR interventions due to the high complexity of the problem, and the diffuse and uncertain effects of interventions. This AMR development map provides a biologically grounded conceptual map to aid explicit consideration of the potential effects of interventions, the appropriate scope for economic evaluation, and further considerations for decision makers. To guide this process, we also developed an accompanying tool presented with a case study. In this paper, we argue for the need to better consider and reflect the underlying mechanics of AMR when capturing AMR intervention effects. Where comprehensive capture of effects is not available, the potential omissions should be acknowledged explicitly to inform resource allocation decisions. We hope this work will aid economic evaluation in this field and encourage further analyses that better support health care decision making.

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1. Mechanics of AMR refers to the biological processes and other mechanisms (such as human activity and environmental conditions) through which microorganisms, such as bacteria, fungi, viruses, and parasites, acquire the ability to survive exposure to antimicrobial agents that would normally kill them or inhibit their growth. [↑](#footnote-ref-1)
2. This work was developed prior to the meetings, and then edited given the feedback. [↑](#footnote-ref-2)
3. System of analysis (or scope of analysis) – is outlined by the choice of AMR burden dimensions, and include choices across the physical space, different sectors of interest (and the relevant units/participants), choice of time horizon and types of pathogens. [↑](#footnote-ref-3)
4. To simplify, intrinsic resistance is when microorganisms naturally (common for their group) resist certain treatments due to inherent traits or genetic potential (proto-resistance). [↑](#footnote-ref-4)
5. A mutation refers to a heritable change in an organism’s genome sequence, and can include changes in individual nucleotides, small scale substitutions, inserts and deletions, as well as larger changes and rearrangements of the genome. Origin of mutations that result in resistance is a stochastic process, [↑](#footnote-ref-5)
6. Horizontal transfer is the movement of genetic information between organisms other than transfer of genetic material from parent to offspring (“vertical” transfer). [↑](#footnote-ref-6)
7. Spontaneous clearance does not imply a sudden process but rather refers to resolution without additional intervention. [↑](#footnote-ref-7)
8. Within-host dynamics are not considered routinely in mathematical models used in the policy and economic evaluation sphere, but there is increasing amount of modelling work trying to understand the impact of within-host dynamics on between-host dynamics. [↑](#footnote-ref-8)
9. It is important to highlight that the above information is focused on human health. AMR burden measurements in other sectors such as agriculture and environment are even more complicated and lack well established surveillance systems

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10. The components of resistance were not aggregated, but these components acknowledged. [↑](#footnote-ref-10)