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Antimicrobial Treatment Imprecision: An Outcome-Based Model to Close the Data-To-Action Loop

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Summary

Healthcare systems, food supply chains, and society in general are threatened by the inexorable rise of antimicrobial resistance. This threat is driven by many factors, one of which is inappropriate antimicrobial treatment. The ability of policymakers and leaders in healthcare, public health, regulatory agencies, and research and development to deliver frameworks for appropriate, sustainable antimicrobial treatment is hampered by a lack of tangible outcome-based measures of the damage it causes. In this review, a mathematically grounded, outcome-based measure of antimicrobial treatment appropriateness, 'imprecision', is proposed. We outline a framework for policymakers and healthcare leaders to use this metric to deliver more effective antimicrobial stewardship interventions into future patient pathways. This will be achieved using 'learning antimicrobial systems' built on public and practitioner engagement, solid implementation science, advances in artificial intelligence, and changes to regulation, research, and development. The outcomes of this framework would be more ecologically and organisationally sustainable patterns of antimicrobial development, regulation, and prescribing. We discuss practical, ethical, and regulatory considerations involved in delivery of novel antimicrobial drug development, policy and patient pathways built on artificial intelligence-augmented measures of antimicrobial treatment imprecision.

1. Introduction

Antimicrobial agents underpin healthcare systems, sustainable food production, and safe, prosperous societies world-wide.[1,2] These benefits, however, are threatened by rising antimicrobial resistance (AMR). Inappropriate antimicrobial treatment in healthcare is an important driver of AMR, helping to perpetuate ecologically unsustainable cycles of 'boom-and-bust' between AMR emergence and antimicrobial discovery and development (Figure 1).[3,4]

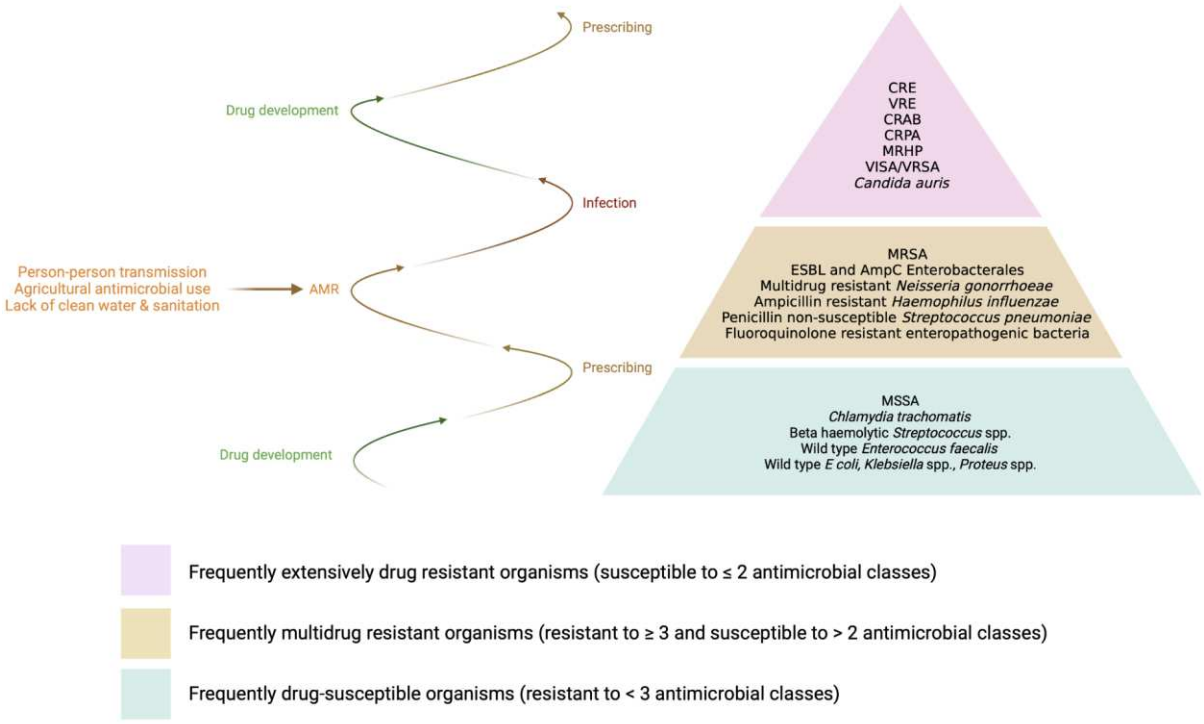

Figure 1: 'Boom-and-bust' cycles of antimicrobial discovery, development, prescribing and AMR as a contributor and response to the emergence of increasingly antimicrobial-resistant organisms. CRE: Carbapenem resistant Enterobacterales, VRE: Vancomycin resistant *Enterococcus*, CRAB: Carbapenem resistant *Acinetobacter baumannii,* CRPA: Carbapenem resistant *Pseudomonas aeruginosa*, MRHP: Macrolide resistant *Helicobacter pylori,* VRSA/VISA: Vancomycin resistant/intermediate *Staphylococcus aureus,* MRSA: Methicillin resistant *Staphylococcus aureus*, ESBL: Extended-spectrum beta-lactamase, MSSA: Methicillin-resistant *Staphylococcus aureus*[5,6]

Antimicrobial stewardship (AMS) aims to improve the appropriateness of antimicrobial treatment using frameworks such as The World Health Organisation's (WHO) Access, Watch, Reserve (AWaRe) classification.[7,8] These frameworks, however, do not necessarily quantify the imprecision of antimicrobial treatment in terms of its full individual and population costs in healthcare. These costs may include:

- Suboptimal outcomes caused by treatment failure and/or unanticipated toxicity (e.g., *Clostridioides difficile* diarrhoea, drug toxicity).[9]
- Emergence of multidrug resistant (MDR)/extensively drug resistant (XDR) organisms leading to treatment failure and creating the potential for their horizontal spread.[10,11]
- Financial costs incurred by poorly targeted use of expensive new drugs.[12]

Failure to routinely consider and capture the full cost of antimicrobial therapy hinders the design of policy in multiple sectors including healthcare, public health, regulation, and research and development (R&D). Integrated data from digitisation of healthcare records, new

diagnostics, and One Health AMR studies (e.g., in agricultural antimicrobial use, water cleanliness) could help better quantify the true impact of antimicrobial therapy. However, this opportunity is lost because of fragmented dataflows within and between global healthcare settings.[13]

Here, we propose an outcome-based model for policymakers and healthcare leaders worldwide to deliver better antimicrobial treatment outcomes for their citizens. This model is built on quantification of 'imprecision', which we define as the difference between the total effect of antimicrobial treatment and the effect that is required to provide the best overall (individual and societal) outcome. We outline an approach for reducing imprecision in patient pathways via:

1. Developing a quantitative model of imprecision based on individual and population-based outcome measures, biologically plausible covariates, and artificial intelligence (AI) techniques.
2. Identifying and understanding systemic and behavioural drivers of imprecision in healthcare that can be used to parameterise and calibrate models of imprecision and design a range of interventions to improve precision.
3. Outlining the improvements in data inputs, interpretation, and actionability required for collaborations of policymakers and healthcare leaders to build 'learning antimicrobial systems' (LASs) that will deliver the individual and societal benefits of more precise antimicrobial therapy. We consider the role of healthcare providers, R&D, patient/practitioner/public engagement, data stewardship, implementation science, and regulatory bodies in the delivery of these systems.

1.1 Search strategy and selection criteria

For major topics/concepts, advanced searches of Google Scholar for articles from the last 25 years utilised combinations of the terms "antimicrobial", "resistance", "prescribing", "stewardship", "artificial intelligence", "machine learning", "bayesian", "epidemiology", "drug development", "decision", "outcome", "data", "diagnostics", "public health", "health economics", "policy", and "regulation". Searches for minor topics/concepts (e.g., "pill-in-pocket") and known documents (e.g., WHO AWaRe) utilised relevant targeted search terms. Manual result searches determined sources for inclusion based on relevance.

2. Imprecision: a measure of antimicrobial treatment inappropriateness

Measures of the appropriateness of antimicrobial therapy monitored by AMS programmes and public health agencies are often based on the volume of antimicrobial use and adherence to population-level guidelines. The consequences of antimicrobial use are often inferred from aggregate-level trends (e.g., local AMR rates).

Optimally precise antimicrobial use requires a conceptual framework that uses an outcome-based model to capture and quantify the total impact of antimicrobial treatment. Table 1 summarises important concepts that will be introduced and used here in developing this model.

Term	Definition
Antimicrobial treatment imprecision	The difference between the total effect of antimicrobial treatment and the effect which is required to provide the greatest benefit, i.e., the best outcome once individual and societal needs are considered.

Artificial intelligence (AI)	The ability of algorithms to perform cognitive functions typical of human brains (e.g., perception, reasoning, learning, interacting with the environment, problem solving, and decision making).
Decision node	A time point in an individual's healthcare journey (pathway) where a decision is made that affects their ongoing antimicrobial treatment. There are three decision nodes, which correspond to starting, changing, and stopping treatment.
Deficit imprecision	An antimicrobial is not exerting enough intended effect to provide the greatest overall benefit in terms of 'total effect of antimicrobial treatment' (see below).
Excess imprecision	An antimicrobial is exerting non-intended effects which reduce overall benefit in terms of 'total effect of antimicrobial treatment' (see below).
Explainable artificial intelligence	Model frameworks that enable machine learning algorithm predictions to be understood and interpreted.
Learning antimicrobial system (LAS)	A set of processes built on integration of real-time dataflows and prediction techniques that enables continuous learning from, and reduction of, antimicrobial treatment imprecision.
Machine learning (ML)	A subdiscipline of artificial intelligence in which computer systems develop statistical models and predictions by making inferences from data.
Neural network	A set of artificial intelligence algorithms that aim to interpret data in a way that mimics the processes of a human brain.
Supervised learning	A subdiscipline of machine learning where algorithms map predictions between data labelled as inputs (covariates) and outputs (outcomes).
Total effect of antimicrobial treatment	An overall measure of all individual and population effects of antimicrobial treatment.
Unsupervised learning	A subdiscipline of machine learning where algorithms infer clusters and/or patterns in data not labelled as inputs (covariates) or outputs (outcomes).

Table 1: A glossary of important concepts introduced and used here in developing and considering implementation of a model of antimicrobial treatment imprecision[14–17]

2.1 Outcome measure: defining, detecting and quantifying imprecision

The potential effects of imprecision (I_t) can be considered in terms of deficit and excess (See Figure 2), which align with 'benefit and risk' in antimicrobial prescribing decisions:

- Deficit (I_d): antimicrobial treatment is exerting insufficient effect to provide the greatest overall individual and population benefit (e.g., inadequate treatment response).
- Excess (I_e): antimicrobial treatment is exerting non-intended effects that reduce overall individual and population benefit (e.g., nephrotoxicity, *C. difficile* diarrhoea, AMR emergence, subsequent person-to-person transmission of AMR).[18]

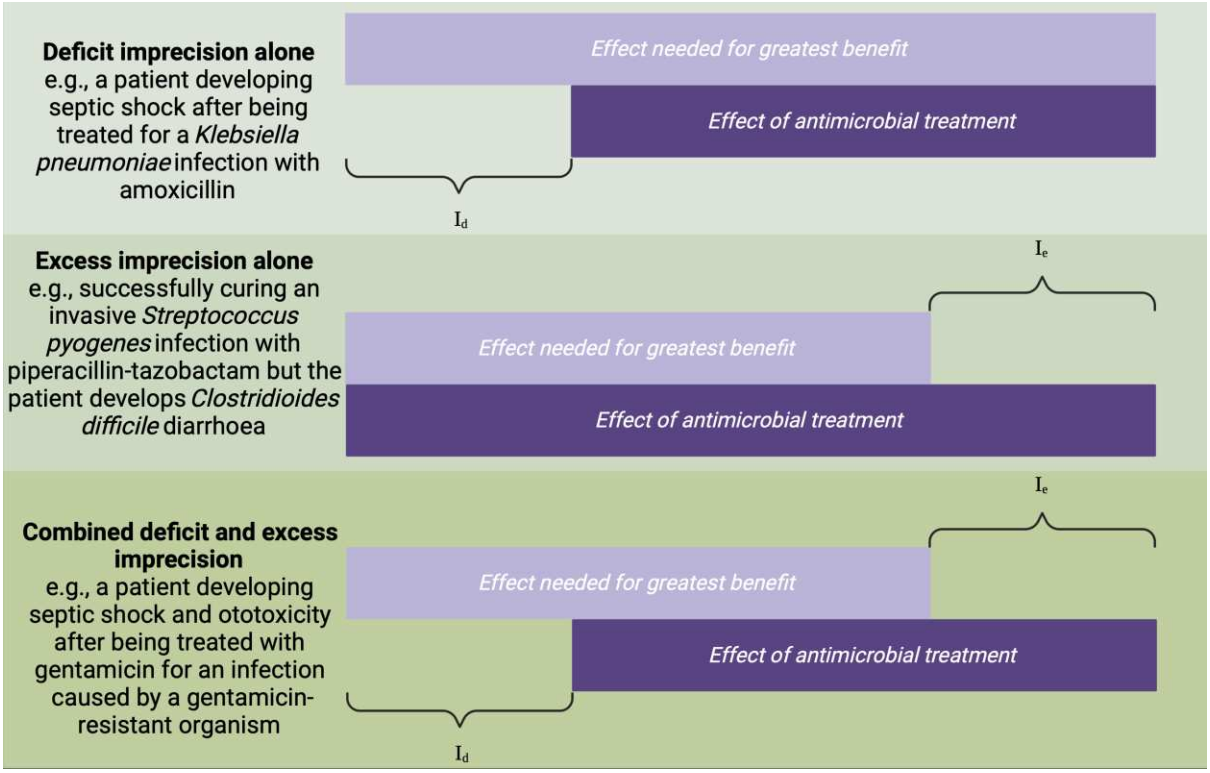

Figure 2: A conceptual model of antimicrobial therapy imprecision as a directional measure of difference in alignment between the effect of an antimicrobial and the effect needed to achieve the 'greatest benefit', i.e., the best overall outcome when both individual and societal needs are considered. I_d = deficit imprecision, I_e = excess imprecision.

Quantifying imprecision with this directional model presents four problems:

1. Analysing scenarios with coexisting deficit and excess imprecision demonstrates that they can be difficult to demarcate. For example, both uncontrolled sepsis and aminoglycoside therapy can cause nephrotoxicity.
2. Some forms of excess and deficit are difficult to detect (e.g., AMR emergence in an individual patient), particularly in terms of the impact on populations and 'distant others'.
3. Clinical scenarios are too complex to precisely determine the minimum effect required to avoid deficit imprecision and vice versa.
4. Plausible biological outcomes of excess and deficit do not necessarily result in impact that is meaningful for patients. For example, the impact of nephrotoxicity could range from a transient rise in serum creatinine to a lifetime of haemodialysis.

Measures of deficit and excess could therefore be used to screen for scenarios where antimicrobial imprecision may be present. For example, carbapenem treatment of bacteraemia caused by a carbapenem-resistant organism could plausibly be linked to prior carbapenem use (potential excess) and death from the bacteraemia (potential deficit). Employment of new scientific techniques (e.g., 'microbiomics', molecular epidemiology, ambient sensor tracking of movement in healthcare environments) will be key to detecting hidden imprecision events such as selection pressure, mutational events, and transmission.[48]

Imprecision modelling cannot not make subjective assessments about 'quality' of prescribing decisions. It could instead use Bayesian modelling of clinical covariates (as discussed in Section 2.2) to objectively estimate the most plausible probabilities of different outcomes following different prescribing decisions. These outcomes should be meaningful for patients in terms of how they 'feel, function, and survive' (e.g., patient-reported outcome measures and all-cause mortality). Aggregate population health perspective (APHP) health economic

analyses could then model the effects on society and 'distant others' (i.e., people whom the patient does not come into direct contact with) using combined health outcome measures (e.g., quality-adjusted life years [QALYs], disability adjusted life years [DALYs]).

2.2 Covariates: predictors of imprecision in patient pathways

Imprecision outcomes are influenced by a diverse range of (unmeasured and/or causally unlinked) covariates individual to patient, infection, organism, microbiome, and population. Mixed effects Bayesian logistic regression models could contain and weight such effects as random coefficients ($_r$) with multiple mechanistically plausible measures of potential deficit and/or excess imprecision ($I_t = \alpha + \alpha_r + \beta_r\beta_1 I_1 + \beta_r\beta_2 I_2 + ...$). Examples of mechanistically plausible factors influencing clinical response (potential deficit) and AMR generation (potential excess) that may be appropriate for inclusion in such models are summarised in Table 2.

Clinical Response (potential deficit)	AMR Generation (potential excess)	Clinical Response & AMR Generation (potential excess and deficit)
Time to initiation of therapy	Mechanistic liability of antimicrobial agent to generate mutational resistance (e.g., drugs affecting multiple microbiological targets may be less liable to generate resistance)	Length of antimicrobial treatment course
Age	Liability of infecting organism species to develop new mutational resistance (e.g., penicillins for ß haemolytic streptococci vs *Pseudomonas* species)	Microbial burden of disease in terms of the likely number of infecting organisms (e.g., abscess vs urinary tract infection)
Illness severity (e.g., APACHE II)	..	Adjunctive treatments (e.g., surgical source control)
Pharmacogenetic determinants of toxicity	..	Penetration of antimicrobial agent into site of infection in adequate concentrations to achieve logarithmic killing (e.g., intra-abdominal abscess, central nervous system, or intra-ocular infection)
Allergy history affecting use of first-line agents	..	Comorbidities including persistently impaired host immunity (e.g., profound prolonged neutropenia)
Drug-drug interactions	..	Microbial spectrum of coverage of antimicrobial agent
Pharmacokinetic properties of agent (e.g., action based on peak concentration vs time over minimum inhibitory concentration)	..	Number of antimicrobial agents used with activity against the infecting organism
Virulence factors of infecting organism species (e.g., ß haemolytic streptococci vs coagulase-negative staphylococci)	..	..

Table 2: Examples of mechanistically plausible factors that could be associated with clinical response (potential deficit), AMR generation (potential excess), or both clinical response and AMR generation (potential excess and deficit), that could be used to parameterise Bayesian predictive models of imprecision in antimicrobial treatment.[19–27]

Interdisciplinary statistical and microbiological expertise and counterfactual (sensitivity) analysis gives the best chance of selecting mechanistically plausible covariates. However, their predictive value may still be overwhelmed by statistical 'noise' from factors that are measurable and predictive but not causally intuitive.

Advances in computing power and statistical methods have led to statistical machine learning (ML) that is causally principled and capable of being grounded by clinical counterfactual scenarios. There is uncertainty as to whether ML models should extend to 'unsupervised' modelling techniques that do not incorporate biological causative mechanisms. Such causation-agnostic, unsupervised learning could surface complex associations in causally unlabelled patient pathway data. These algorithms may recognise and predict causally counter-intuitive 'fingerprints' of imprecision by forming complex and opaque deep learning neural networks to navigate sequences (and timing) of events in patient pathways. Such 'black box' approaches have challenges to overcome including lack of principled transferability between healthcare settings, and lack of patient/public/practitioner trust in non-explainable models. Unsupervised ML algorithms could theoretically screen for imprecision, but the 'label-free explainability' techniques required to create a meaningful, actionable unified model do not (yet) exist. Currently, mixed algorithmic approaches combining supervised and unsupervised ML are likely to be the most implementable.

3. Key drivers of imprecision in healthcare pathways

Imprecision is driven by complex, interacting psychological, sociological, biological, and system factors. Healthcare data which policymakers and healthcare leaders could use to detect and manage these factors is currently insufficient, unlinked, unvalued, and insufficiently actionable (Figure 3).

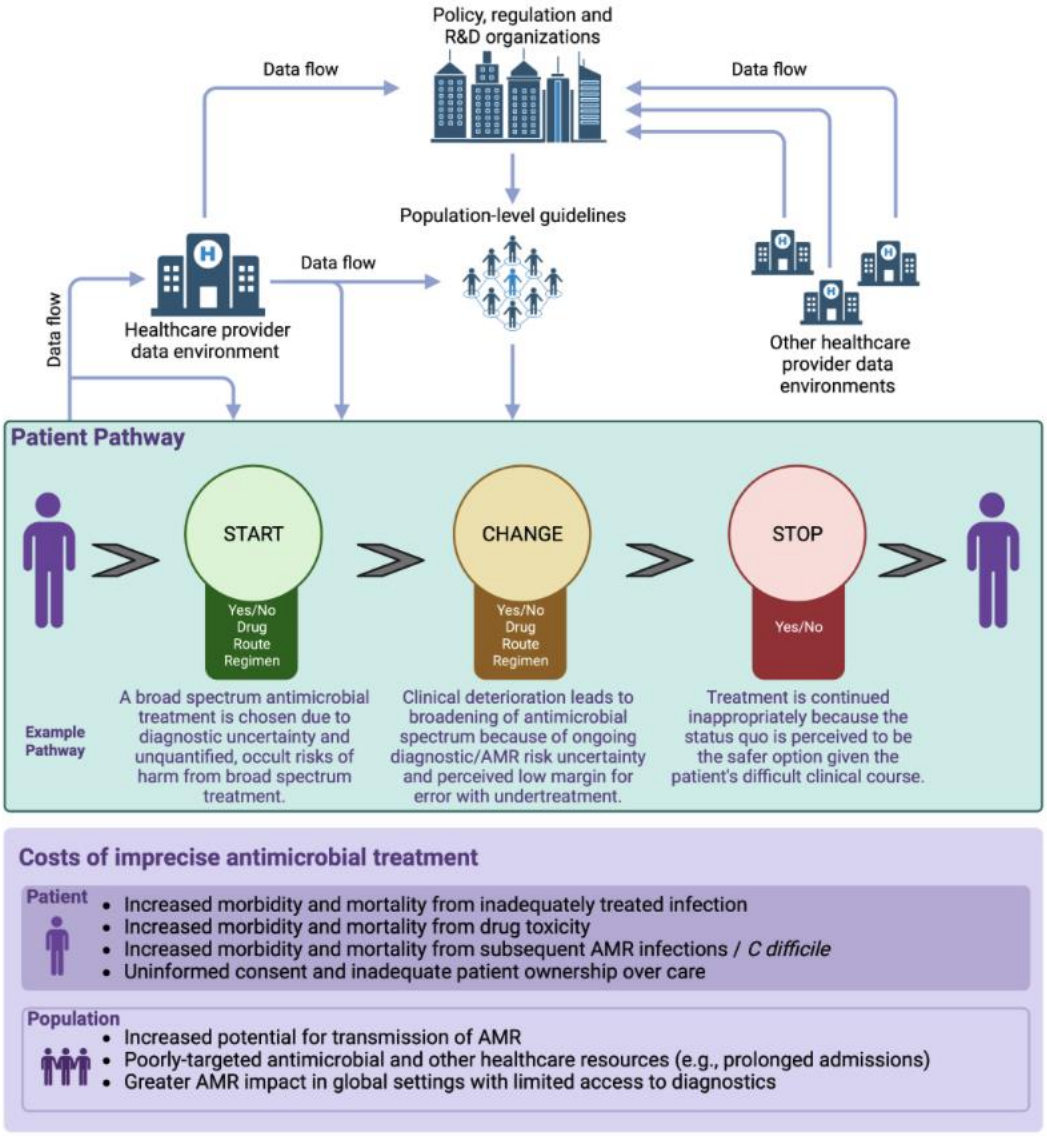

Figure 3: The current imprecise approach to healthcare data flows in patient pathways. Antimicrobial decision nodes in existing antimicrobial treatment pathways fed by clinical, diagnostic, R&D, and policy data. Imprecision is exacerbated by fragmented dataflows from multiple sources that are used to inform attending clinicians, population-level guidelines, policymakers, regulatory bodies, and R&D stakeholders. These dataflows fail to feed personalised, precise information back into the patient pathway, resulting in unnecessary costs to patients and populations.

3.1 Data inputs: insufficient, unlinked, and unvalued

Data inputs in many healthcare pathways globally are:

- Insufficient: electronic healthcare records and diagnostic innovations reduce diagnostic uncertainty by improving data availability, accuracy, and timeliness for decision makers. Leveraging these technologies to reduce treatment imprecision is affected by incomplete uptake and variations in availability globally. Some traditional data inputs are being eroded (e.g., telemedicine depriving clinicians of face-to-face sensory information).[28]
- Unlinked: fragmentation of healthcare economies often results in poorly integrated dataflows to, from, and between healthcare providers (Figure 3). Decisions are therefore often made based on incomplete information.[29]

- Undervalued: the information provided by data and analytics is often poorly understood and valued by clinicians, patients, and policymakers. New diagnostic tests are deployed in disconnected tendering, procuring, contracting and implementation processes. Their potential impact is therefore not realised, and their potential value not recognised. Undervalued, untargeted data collection also risks harming public trust in how their data are used.[30]

3.2 Data actionability: decision making in healthcare

To understand prescriber drivers (and therefore intervention targets) of antimicrobial treatment imprecision in patient pathways, it is informative to consider the component parts of three prescribing decision nodes: starting, changing, and stopping antimicrobial treatment.

3.2.1 Decision node 1: starting antimicrobial treatment

Starting antimicrobial treatment comprises four decisions:

1. Whether to commence treatment: where infections are part of differential diagnoses, empirical treatments bridge early uncertainty in patient pathways. Crucial new technologies, diagnostics, biomarkers, and therapeutic drug monitoring (TDM) cannot resolve this uncertainty alone because their impact in the context of human and healthcare system factors is incompletely understood – healthcare workers are under unprecedented time pressure and increasing administrative burden.[31] Perceived small margins of error and prior experience (e.g., previous death of a patient following insufficient antimicrobial treatment) can skew perceptions of risks, benefits and loss.[32] Antimicrobial treatment is therefore often perceived as the 'safe' option.[33,34] Biases towards heuristic, imprecise prescribing decisions result, which can become embedded in organisational practices and become culturally engrained.[35] Patients are rarely counselled as to the consequences of imprecision, exacerbating behavioural patterns of antimicrobial-seeking particularly in primary care.
2. Agent choice: the range of available agents is determined by drug development processes and frameworks that incentivise imprecision – broader organism spectrum coverage broadens the range of potential licensed clinical indications. Empirical treatment of infection syndromes (e.g., urinary tract infection) is predominantly directed by guidelines/formularies based on population-level data. Working diagnoses in periods of diagnostic uncertainty (e.g., 'sepsis of unknown origin' at initial presentation to healthcare) are often treated with broad-spectrum antimicrobial treatment. Colonisation status, comorbidities and risk of specific pathogens may facilitate more targeted therapy. However, their application is inconsistent in clinical practice, and their predictive value is not always understood.[36] Infection severity is often highest at initial presentation, increasing the likelihood of imprecise treatment in the face of perceived narrow margins of error.[37] Decision aids based on snapshots of context-specific observational data are often used to direct agent choice (e.g., CURB-65 in pneumonia). These are useful methods for leveraging evidence-based medicine in patient pathways. However, they may generalise inadequately beyond original populations and lack evidence-based implementation approaches.[38]
3. Route of administration: patients may receive parenteral antimicrobial therapy for practical reasons (e.g., swallowing difficulties) or to achieve high drug exposure, though highly-bioavailable oral therapy is increasingly used.[39]
4. Regimen: recommended dosing regimens are chosen in early clinical trials to maximise chances of efficacy or establish non-inferiority with minimum expenditure – additional time/resource input to identify occult harms of antimicrobial over- and/or under-exposure are not incentivised. Initial dosages can only be individualised using

readily observed values (e.g., weight, renal function). Other relevant information (e.g., pharmacogenetics) are often either not available in clinical practice due to a poor evidence base and lack of well-designed trials, or too slow to be clinically useful.[40,41] There is therefore variability in antimicrobial regimen imprecision ranging from routine TDM for some agents to 'one-size-fits-all' solutions for others.[42] Resource pressures can endanger precise regimens by shifting or distorting the goal of therapy (e.g., a six-hourly intravenous infusion regimen may be sacrificed for a more convenient but broad spectrum once-daily regimen to facilitate discharge from hospital).[43]

3.2.2 Decision node 2: changing antimicrobial treatment

Changing treatment also comprises four decisions:

1. Whether to change treatment: clinicians have high thresholds to challenge legacy diagnoses made at initial presentation, meaning opportunities to reduce treatment imprecision are lost. Many clinicians are uncertain how long treatment response should take, what constitutes adequate response, and what other clinical factors are relevant.[44]
2. Changing antimicrobial agent: diagnostic results may reduce treatment imprecision in several ways – examples of the potential effects of microbiology tests on diagnostic uncertainty are summarised in Figure 4. Discordance between susceptibility results and clinical response is common, however, reflecting the importance of clinical covariates, laboratory measurement and susceptibility breakpoint definitions.[45,46]

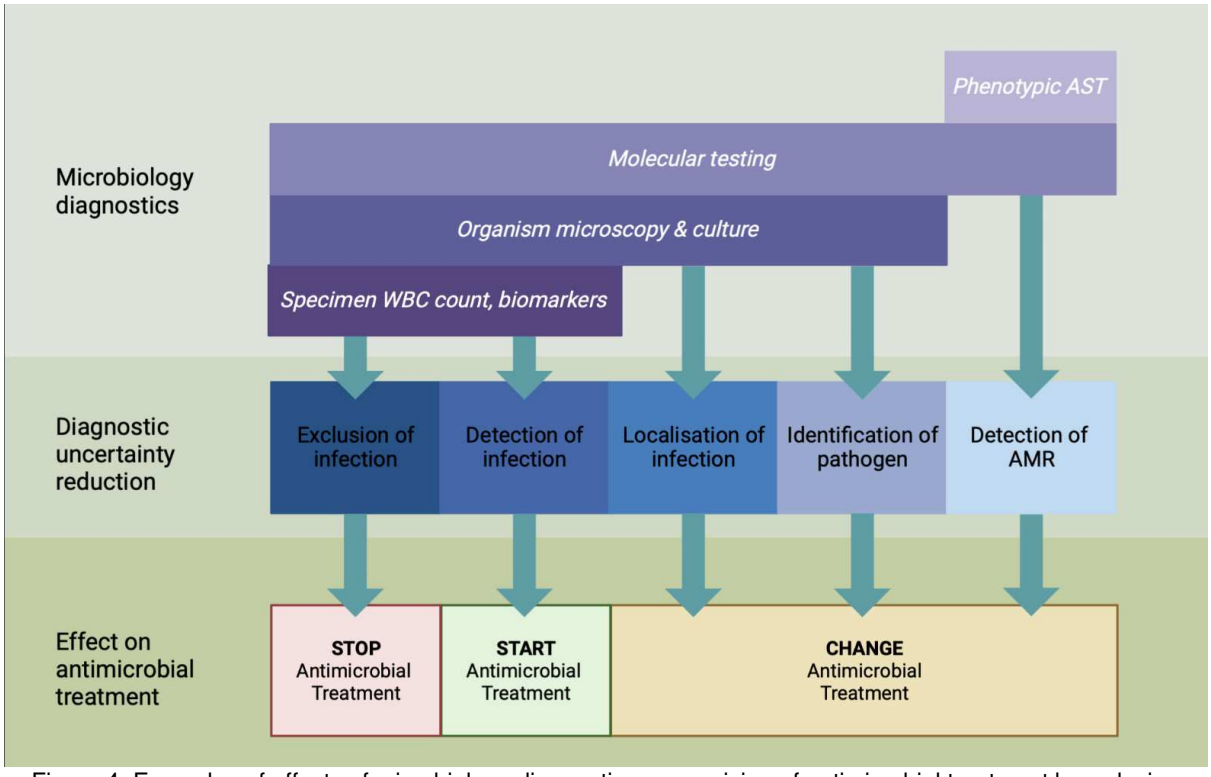

Figure 4: Examples of effects of microbiology diagnostics on precision of antimicrobial treatment by reducing diagnostic uncertainty. AST: Antimicrobial susceptibility testing, AMR: Antimicrobial resistance, WBC: White blood cell.

3. Changing route of administration: ‘step-down’ to similar spectrum agents with routes of administration facilitating discharge is common.[47] ‘Escalation’ from oral to intravenous agents in response to severity is often accompanied by broadening of antimicrobial spectrum, though like-for-like escalation can occur to increase drug exposure.[48,49]
4. Changing regimen: TDM is a powerful precision tool to maximise effect and minimise toxicity, but its targets may not always reflect biological variability and organism susceptibility is not always quantified.[50] Pharmacogenetic tests and treatment effect biomarkers are available but uptake in clinical care is poor and interpretation remains problematic (e.g., gentamicin *MT-RNR1* variant and hearing loss).[51] Resistance-suppressing drug exposure targets are have been identified, but their use carries ethical ramifications where individual patient and population benefits/risks are in tension (e.g., where exposure targets for resistance suppression increase likelihood of toxicity).[52,53]

3.2.3 Decision node 3: stopping antimicrobial treatment

Guideline-recommended durations of therapy often adhere to multiples of 5-day or 7-day units and are imprecise in many individual situations. Easy-to-remember durations prompt clinicians to think about length of treatment but maintaining the status quo and continuing treatment is often perceived as the ‘safe’ option. For decades, prevailing teaching has been that 'completing the course' reduces resistance generation, but this has recently been challenged.[54] Understanding the imprecision of flexible treatment durations adopted in the best interests of patients with recurrent or resistant infections (e.g., suppressive, prophylactic, or ‘pill-in-pocket’ antimicrobial plans) is difficult due to their relative rarity.[55–58]

4. Implementing precision modelling to close data-to-action loops in healthcare

4.1 Improving data inputs: connected dataflows and new technologies

Accurate, actionable models of imprecision will require ‘big’, real-world, contemporaneous clinical data.[59] This will necessitate new dataflows into continuously updated repositories with significant storage capacity and data engineering resource. These repositories will combine publicly accessible stores of antimicrobial study data with anonymised individual and aggregate-level electronic health records. They will form platforms for enhanced, continuously tuned systems for real-time data sharing, linkage, curation, and processing. Their encryption and governance processes will permit regulated access to Trusted/Secure Data Environments (TREs/SDEs) for researchers, practitioners, policymakers, and managers. Within healthcare, adoption of commodity AIs for tasks such as natural language processing will improve data structure and availability.[60]

Given that AMR is a global problem, expansion of connected dataflows beyond national borders should be the ultimate objective – this will undoubtedly be a significant legislative and technical challenge. Regional/national dataflow networks should be seen as achievable medium-term steppingstones towards that goal. Open-source sharing of algorithms and metadata will help nations to converge on the same goal. For R&D data, international hubs could be built for regulated cross-border access to preclinical data to inform global drug and device development programmes. The way in which encrypted data storage infrastructure can be sustainably funded and built in a range of global income settings (e.g., through cloud data storage and affordable hardware) will be another key consideration.

Traditional epidemiological techniques (e.g., population screening) combined with advances in genomic, proteomic, and ambient/wearable biometric technology will fill critical gaps for detecting and quantifying microbiome and transmission outcomes. Integration of healthcare

dataflows with One Health agriculture and clean water research will further enhance understanding of the transmission of AMR between people, animals, and the environment. Innovative data inputs with AI-informed R&D pathways will also be required to parameterise predictive models of imprecision (e.g., a wearable or in-line therapeutic drug monitor that models the effect of serum drug levels on treatment imprecision).[61] Advances in molecular diagnostics could improve timeliness of diagnostic information, improving precision and moving antimicrobial decision nodes closer to the start of the patient pathway.[62] Improved qualitative data collection techniques will help understand and predict human factor drivers of imprecision at decision nodes.

4.2 Improving data interpretation: learning antimicrobial systems

Systems built on integrated dataflows have already demonstrated an ability to formulate and effect policy by learning from population-level data.[63] Improved data inputs combined with accurate imprecision AI models that link causally-intuitive covariates to aggregative outcome measures of mortality and morbidity (outlined in Section 2) could enable leaders and policymakers to build 'learning antimicrobial systems' (LASs). The running and governance of these systems would incorporate health and social care, public health, regulatory and R&D stakeholders, and continuously adapt to real-time, real-world data, enabling R&D, policy, and patient pathways to be mapped, analysed, simulated, and controlled.[64]

Examples of the interpretive applications of an LAS in healthcare provider organisations, policymaking/regulatory agencies, and R&D include:

- Understanding the impact of diagnostic tests in both point-of-care and laboratory/diagnostic support settings.
- Assessing the performance of new diagnostics (e.g., turnaround time, accuracy).
- Auditing clinical services at multiple levels including individual clinicians, teams, units, and organisations.
- Assessing barriers to implementation and scalability of new interventions/drugs.
- Incorporating structured qualitative experiential data from patients and communities.
- Networking with different healthcare systems to borrow strength from each other through shared programming algorithms and digital connections.

4.3 Improving data actionability: the role of policymakers and healthcare leaders

LASs will be built, run, and governed by collaborations of policymakers and leaders across health and social care, public health, R&D and regulatory bodies (Figure 5). Their effective and safe implementation will require careful consideration of patient/practitioner/public engagement, data stewardship, implementation science, and regulation.

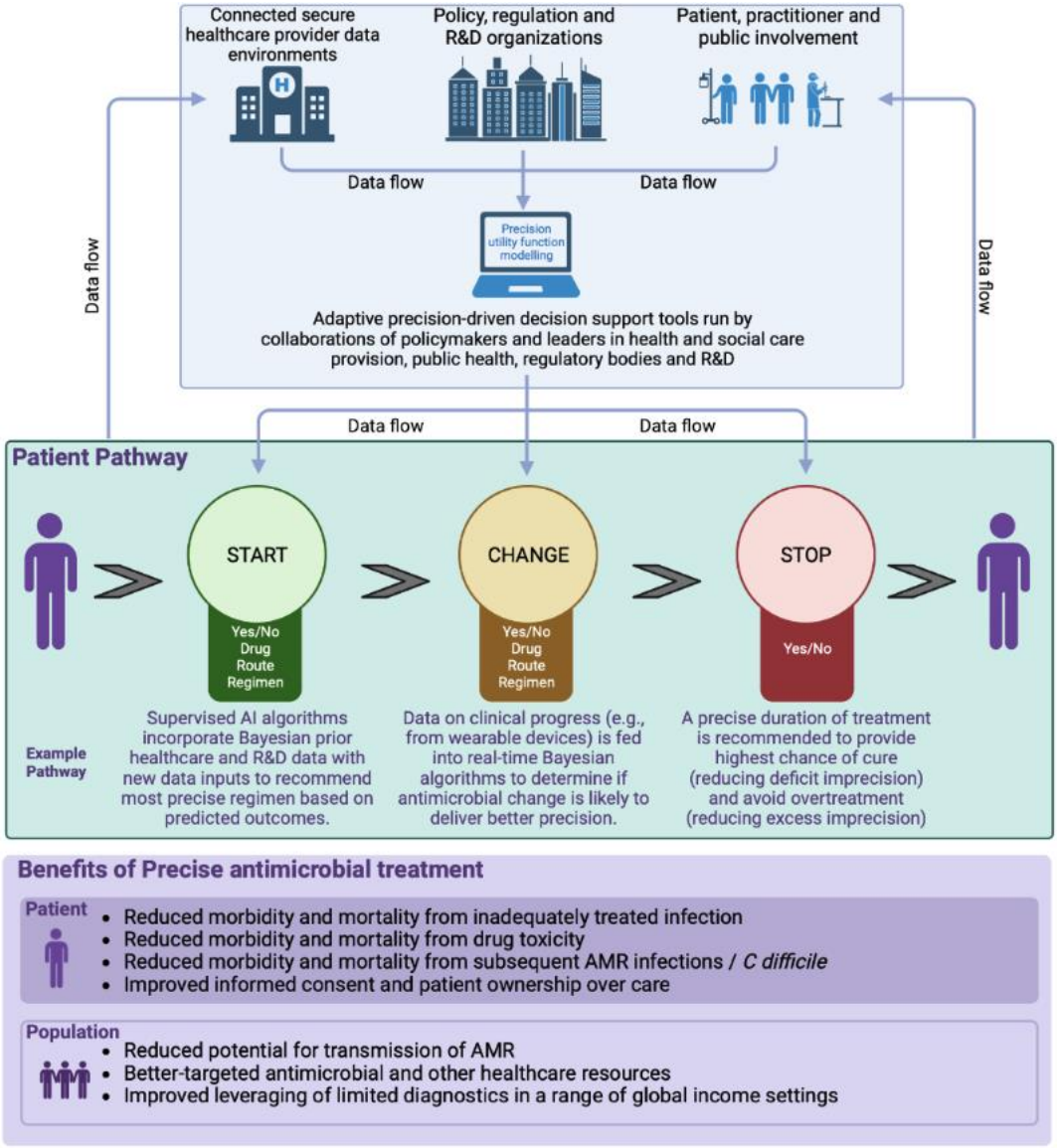

Figure 5: An AI model-informed precise approach to healthcare data flows in patient pathways. A schematic for the delivery and monitoring of precision antimicrobial treatment in the patient pathway by collaborations of policymakers and leaders in healthcare provision, public health, regulatory bodies, and R&D. This will be achieved by 'learning antimicrobial systems' built on connected dataflows. Improvements in patient and population care are driven by AI modelling of imprecision as a utility function, and fragmented dataflows (see Figure 3) have been replaced by integrated data-to-action loops.

4.3.1 Actioning models of imprecision in real-time patient and population pathways

Embedding real-time modelling of imprecision into decision support interfaces within LASs would better inform clinicians of the impact of antimicrobial treatment. Ambient, wearable and in-line biometric devices would provide real-time data inputs.[65,66] Diagnostic and R&D laboratories embedded in the LAS would target test implementation towards reducing imprecision. Valuation of diagnostics based on their ability to reduce imprecision would better target R&D and healthcare resources. Clinician- and patient-directed implementation science would help determine how LAS-embedded decision aids could insert into the patient pathway. In cases where the overall benefit of an intervention is debatable because individual and societal impact exists in tension, this increased burden of knowledge will bring with it difficult ethical decisions. These decisions cannot and must not be made by algorithms. User interfaces built around 'moral' AI, however, could help clinicians and policymakers navigate these complexities.[67]

Integrating patient-level data with traditional, readily available aggregate data metrics (e.g., hospital-level AMR data) would help model and reduce antimicrobial treatment imprecision on a larger scale. These models could complement or replace procedural markers such as defined daily doses (DDDs). Unsupervised neural network models would form early warning systems for AMS teams that sensitively detect imprecision. These areas would then be explored through further data gathering and causation-based imprecision modelling. The health consequences and resource impact of subsequent policies could then be simulated based on modelling of imprecision.[68]

4.3.2 Actioning models of imprecision in research and development

The impact of LASs would be continually assessed by teams of healthcare data scientists using system-wide statistical analysis. Clinical trial endpoints could be adapted from models of imprecision that enable ongoing questions about drugs and regimens to be addressed. A traditional evidence base of interventional trials of LAS-embedded decision aids would be continuously updated. An evaluation framework would facilitate participation in LAS-embedded research at scale. Low-burden, adaptive platform trials would be embedded in routine clinical care. State-of-the-art TREs with data engineering capacity would facilitate storage of clean, secure, externally validated R&D data.

Valuation, research, development, regulation, and reimbursement based on imprecision could incentivise the development of more targeted agents with useful characteristics (e.g., once daily administration). Health technology appraisals would leverage LAS data to develop more equitable measures of allocating resource for new drugs and diagnostics. The impact and value of delinked funding arrangements, contracts, and payment mechanisms within and between health systems could be better assessed.

4.3.3 Data stewardship and implementation science

LASs would apply FAIR (find, access, interoperate, reuse) procedures. They would prioritise data stewardship (including privacy, transparency, security, and governance), reproducibility of evidence, and transferability of learning.[69] Embedding human-driven implementation science (e.g., process evaluation, resource monitoring, qualitative methodology) and governance in LASs will provide accountability that AI cannot fulfil.

Chronic system stress risks embedding organisational cultural psychologies of inertia and impaired learning that may adapt poorly to the system changes required for LASs.[70,71] Experienced healthcare and public health organisational experts will therefore help facilitate LAS adoption, implementation and maintenance.[72] Clear lines of responsibility and communication will ensure that learning from the system is fed back to stakeholders. These measures will help sustain public trust, resource-efficiency, and feasibility of the system's ongoing operation in a range of global settings.

4.3.4 Patient and public involvement

Given the social impact of AMR, co-production of LASs with practitioners, patients, and the public is essential to ensure their operation is transparent, useful, and trustworthy. LAS data must inform patients how they might maximally benefit from an antimicrobial treatment. This will facilitate their role as decision makers in their own care. They must have access to their own clinical information and understand how they can opt out of data collection. Involving the public as stakeholders in LASs must drive a social conversation about the use of antimicrobial agents as critical societal assets.

4.3.5 Regulation and legislation of learning antimicrobial systems

Regulatory agencies (e.g., Food and Drug Administration), lawmakers, and expert bodies will need to develop positions on more flexible precision-based antimicrobial regimens. Clarity about regulatory pathways will be required for AI-based decision support algorithms (e.g., model-informed precision dosing). Legal positions must be clarified on data sharing and data protection impact assessment that reflect the public health impact of AMR.

Preserving public trust in healthcare institutions and medical research will be a priority for LASs. Legislating, vetting, monitoring, and regulating private companies' access to healthcare data will be essential to ensure transparency and data security. Code/algorithms/standard operating procedures must be open-source and not monetised, enabling LASs across the globe to learn from one another.

5. Conclusions

Reducing antimicrobial treatment imprecision requires an adaptive, integrative, and actionable representation of the evolving impacts of antimicrobial treatment on individuals and society globally. Revolutions in availability of electronic healthcare data, computing, and data science increasingly bring such intelligence within reach – clinically and scientifically guided use of AI-based imprecision modelling could play a key role in improving our understanding and uses of antimicrobial treatments. Better integrated dataflows will allow these technologies to be embedded in LASs run by policymakers and leaders in healthcare, public health, R&D, and regulatory bodies. The safe, practical, ethical, and sustainable operation of LASs will be informed by state-of-the-art implementation science incorporating clinician, patient, and public involvement. LASs built on models of imprecision could help dampen 'boom and bust' cycles of antimicrobial development and AMR with globally inclusive, ecologically, and organisationally sustainable models of infection management.

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AH – writing, editing, diagrams; NR – diagrams; SA – comments, editing; BW – comments, editing; AG – comments, editing; IB – comments, editing; WH – comments, editing; AGM – writing, comments, editing.

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AH declares consulting work for Pfizer outside the submitted work, NR/AG/SA have no interests to declare, BW sits on the board of the York Health Economics Consortium, IB holds a senior investigator award with NIHR, personal fees and other from AstraZeneca outside the submitted work, WH holds or has held research grants with UKRI, EU, F2G, Spero Therapeutics, Antabio, Pfizer, Bugworks, Phico Therapeutics, BioVersys, Global Antibiotic Research & Development Partnership (GARDP), and NAEJA-RGM. WH is or has been a consultant for Appili Therapeutics, F2G, Spero Therapeutics, NAEJA-RGM, Centauri, Pfizer, Phico Therapeutics, Pulmocide, Amplyx, Mundipharma Research, and VenatoRx. WH is a member of the Specialist Advisory Committee for GARDP and the Specialty National co-lead for Infectious Diseases for the National Institute of Health Research.

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