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System-wide approaches to antimicrobial therapy and antimicrobial resistance in the UK: the AMR-X framework

AMR-X Collaborators

Antimicrobial resistance (AMR) threatens human, animal, and environmental health. Acknowledging the urgency of addressing AMR, an opportunity exists to extend AMR action-focused research beyond the confines of an isolated biomedical paradigm. An AMR learning system, AMR-X, envisions a national network of health systems creating and applying optimal use of antimicrobials on the basis of their data collected from the delivery of routine clinical care. AMR-X integrates traditional AMR discovery, experimental research, and applied research with continuous analysis of pathogens, antimicrobial uses, and clinical outcomes that are routinely disseminated to practitioners, policy makers, patients, and the public to drive changes in practice and outcomes. AMR-X uses connected data-to-action systems to underpin an evaluation framework embedded in routine care, continuously driving implementation of improvements in patient and population health, targeting investment, and incentivising innovation. All stakeholders co-create AMR-X, protecting the public from AMR by adapting to continuously evolving AMR threats and generating the information needed for precision patient and population care.

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Introduction

Antimicrobial resistance (AMR) makes antimicrobial therapy exceptionally challenging.[1] The rights of individuals to access safe and effective antimicrobial agents are intricately balanced with the long-term need to preserve these agents as strategically valuable societal assets. Antimicrobial agents contribute towards safeguarding human health and ensuring sustainable food production, while posing a challenge to environmental health (eg, residues in soil and water and agricultural run-off).[2] Therefore, the optimal use of antimicrobial agents constitutes a broad sociopolitical challenge. Within the context of such a challenge, health systems are particularly vulnerable to multidrug-resistant (MDR) and extremely drug-resistant (XDR) pathogens that are a consequence of factors such as international travel,[3] natural disasters,[4] wars,[5] climate change,[6] and geopolitical instability.[7] Addressing AMR requires an international perspective, necessitating multilateral thinking.[8]

Infection prevention and control, along with antimicrobial stewardship, are important tools to manage AMR. Nevertheless, the principal AMR-combating strategy for the past half-century has been, and largely continues to be, the discovery and development of antimicrobials. This approach involves the successive introduction of new classes as microbiological targets are progressively exploited. Despite the investment and establishment of public-private initiatives for development programmes such as CARB-X and the AMR Action Fund, current pipelines are dry.[9] Furthermore, although identifying novel antimicrobial compounds is an easily manageable task,[10] only a select few antimicrobials show properties required to effectively function as drugs.[11,12] Clinical development programmes are slow, expensive, and challenging, and enrolling and studying individuals with drug-resistant disease remains surprisingly difficult.[13] The current linear discovery-to-implementation translational pathways of separately funded disconnected segments are risky and inefficient. Therefore, new paradigms designed for agility, acuity, and practicality are urgently needed.

Multiple interventions were enacted to respond to the COVID-19 pandemic. Biomedical measures, such as the development of new vaccines, diagnostics, genomics, and antivirals, were complemented by public health measures, such as lockdowns,[14] physical distancing,[14] testing,[15] and mask wearing.[16] AMR is more complex because of extensive host–drug–pathogen combinational complexities, superimposed microbial transmission dynamics, complex social determinants of antimicrobial use,[17,18] and multiple potential beneficiaries of antimicrobial therapy (eg, the patient, the same patient with a different future health trajectory, distant individuals, health-care systems, and the pharmaceutical industry). Nevertheless, effective responses to the COVID-19 pandemic provide blueprints for better approaches to AMR, combining both biomedical and public health solutions. In this Personal View, we build on these insights to describe the case for AMR-X and its fundamental principles and illustrate how AMR-X can address the boom-bust cycles of antimicrobial development and AMR emergence.

AMR-X is a vision for a national learning health system (and potentially a blueprint for a global network) to develop and apply optimal use of antimicrobials based on data obtained from the delivery of routine clinical care. This framework recognises that the prevention and management of AMR involves both biomedical innovation and the use of informative data collected in real time for the benefit of patients and the broader health-care system. AMR-X builds on previous programmes of data integration for antimicrobial and disease surveillance (eg, WHO's global antimicrobial resistance and use surveillance system,[19] infectious diseases surveillance via the European Centre for Disease Prevention and Control,[20] and the surveillance efforts in the UK conducted by the UK Health Security

For **CARB-X** see https://carb-x.org/

For **the AMR Action Fund** see https://www.amractionfund.com

Agency[21]), while considering how collecting, linking, and curating data could enable a step change in tackling AMR via continuous knowledge generation, a progressive transition to precision care, and enhanced public health protection against AMR. AMR-X primarily focuses on human health but also recognises many of the challenges that are pertinent to antimicrobials and AMR in the context of environmental and animal health. Given the complexities and undeniable challenges associated with AMR-X, it is ideally constructed incrementally (eg, initial construction at the localised level, within integrated care systems in England), with a plan to progressively connect these nodes to form a single national network.

The case for AMR-X

AMR-X is a system-wide, engineering approach to AMR, optimising antimicrobial discovery, development, use, policy making, and implementation through a network of health systems that learn quickly from their data, ensuring that the clinical value of available antimicrobial agents is realised and sustained in clinical practice. Below, we consider the following underpinning arguments:

Coordinated scale-up of antimicrobial agents from registration trials to practice

Registration trials are designed conservatively to ensure feasibility and secure licensing. The evidence base stems from a restricted set of patient and pathogen phenotypes, consequently restraining the reach and accuracy of the evidence. Uncertainty over the clinical effectiveness and value of a new antimicrobial asset amplifies as its use extends across heterogenous clinical contexts. Without effective and timely feedback, learning from progressively complex settings (eg, multimorbidity, MDR infections, and XDR infections) is lost, and the care of the next patient requiring an intervention does not benefit from cumulative experiences. Evidence in post-licensure, real-world settings is often obtained opportunistically rather than strategically, increasing the risk of bias. In this context, AMR-X potentially enables supervised and strategically managed scale-up of new therapeutics, diagnostics, behaviour modification, and artificial intelligence, which can adapt to an evolving evidence base.

Dynamic data action for adaptive evidence generation of antimicrobial use

AMR is different from other therapeutic challenges in that there are continuously evolving threats: what is currently relevant might not be relevant in the future as threats emerge and recede. AMR-X is an efficient and agile system that generates new knowledge, assets, and interventions to minimise adverse outcomes associated with gaps in knowledge and imprecise antimicrobial therapy. Examples of new knowledge that might not be immediately available after licensing include activity against pathogens not included in registration trials (eg, ceftolozane–tazobactam activity against MDR or XDR *Pseudomonas aeruginosa*),[22] scarce activity in relevant organs such as the lung (eg, insufficient efficacy of daptomycin for pneumonia),[23] or evidence of activity of novel agents against emergent pathogens and diseases (eg, fosmanogepix for fungal meningitis caused by *Fusarium* spp).[24]

Slow, segmented discovery-to-implementation translational paradigms propelled by discordant funding schemes are suboptimal. Segmentation limits broad oversight of the entire AMR landscape, impairing downstream implementation due to inadequate engagement with end users and commissioners. Insufficient consideration of implementation means that new knowledge and assets might only deliver incremental or short-lived value, thereby risking producing products and knowledge that no one wanted or asked for. Agile, cyclical innovation and learning built around the needs of planners, prescribers, and patients could improve resilience and efficiency. In the UK, such an approach might enable linked strategically designed funding to provide end-to-end solutions rather than producing outputs that supply the next node along a translational pathway. Closing data-action loops offers an additional advantage by enabling continuous value estimations, an essential factor for antimicrobial subscription-based schemes (eg, the National Institute for Health and Care Excellence–National Health Service [NHS] England Pilot Project for ceftazidime–avibactam and cefiderocol).[25,26]

Precision antimicrobial prescribing to counter AMR-induced value erosion

In various clinical contexts, the precision of antimicrobial therapy is often compromised because of the paucity of relevant information, system pressures, time-delimited decision making, slow and incomplete diagnostics, and the relative safety and low cost of antibiotics.[27] AMR is frequently driven by use of the wrong antibiotic, used in the wrong regimen, for the wrong patient, the wrong indication, and at the wrong time. With system-wide coordination, advances in precision care could become much more common. Patient involvement could drive a greater scale and pace of precision antimicrobial therapy, with individuals participating in their own care and understanding the benefits and risks of antimicrobial agents and interventions. An opportunity exists to explore covenants between individuals and communities whereby data are used to both optimise individual care and maximise broader societal benefit.[28] AMR-X addresses the challenges in data science, evaluation, behaviour, and implementation that could enable precision care to emerge as a standard of care.[18,27]

A solution to AMR as a system-wide challenge: the AMR-X framework

The development of AMR-X emerged in December, 2021, from meetings hosted by the National Institute for Health and Care Research, the UK Department of Health and Social Care, and the Academy of Medical Sciences, where COVID-19 learning was being considered in the context of AMR. An AMR-X Steering Group coordinated a series of face-to-face meetings in 2022, that were attended by

stakeholders and public contributors. AMR-X is a vision developed by the AMR community of the UK and is not formally sanctioned by any official body or society.

AMR-X is a system-wide approach for AMR research, operational at a national level. Connected data-to-action systems are used to underpin an evaluation framework embedded in routine care, continuously driving implementation of improvements in patient and population health, facilitating investment, and incentivising innovation (panel 1).

AMR-X is delivered by three linked components driven by subject-matter experts and stakeholders in data science and informatics, evaluation and policy analysis, and implementation science (panel 2).

Panel 1: **Outputs and features of AMR-X**

AMR-X delivers three principal outputs:

- Continuous knowledge generation by integrating research and service intelligence.
- Delivery of precision care for individual patients and populations.
- Enhanced public health protection.

The AMR-X system will:

- Enable learning embedded within routine health-care delivery facilitated by routine randomisation steps to assess multiple interventions.
- Establish interoperable, regional learning systems with close-coupled AMR research and continuous service improvement. This integration might involve real-time changes in clinical treatment guidelines and formularies.
- Form a national grid of regional learning systems, drawing strength from each other for prediction, evaluation, and proportionate action.
- Attain a standard-of-care status so that activities are considered core components of the health system functioning rather than isolated within a silo of disconnected clinical research.
- Aim to address challenges and risks associated with antimicrobial use and AMR in environmental health, animal health, and food safety (eg, adopting a more comprehensive One Health approach).

AMR=antimicrobial resistance. AMR-X=AMR learning system.

Outputs of AMR-X

AMR-X delivers a step change in activity to advance precise and sustainable antimicrobial therapy. AMR-X will aid in the intelligent use of both novel and existing antimicrobial agents.

Continuous knowledge generation

AMR-X delivers continuous, rapid, system-embedded learning that addresses the ever-changing landscape of antimicrobial therapy and AMR. Outputs include new knowledge, development of new assets (diagnostics, therapeutics, and artificial intelligence algorithms), models, methods, and policies that are updated in real time. Continuous knowledge generation includes new information related to biomedical assets, alongside social and behavioural determinants of antimicrobial use such as social inequalities driving different health-seeking behaviours because of information disparity and barriers in accessing health care, AMR vulnerabilities, or varying trust in biomedical expertise.[29]

Additionally, AMR-X generates knowledge as a direct by-product of health care and leverages connected data flows that are efficient, inclusive, generalisable, and minimally disruptive to the delivery of care. Thus, new knowledge is more likely to be contemporary, locally implementable, and nationally and internationally scalable. Embedded multidisciplinary evaluations, including economics, enable decisions that deliver the best value under rapidly changing circumstances.

Precision care for patients and populations

Precision care contributes to mitigating AMR through optimised targeted antimicrobial therapy. This approach is relevant to health-care providers (by ensuring AMR does not disrupt core NHS business), payors (by preventing erosion of the value of new assets and supporting cost-effective care), practitioners (by underwriting safe and effective treatments for other diseases such as cancer), and patients. AMR-X promotes precision care using integrated and contemporaneous data from host–drug–pathogen combinations and clinical, social, and environmental contexts to build, curate, and implement decision support tools.

More precise use of antimicrobials will maximise effectiveness, minimise toxicity, and reduce the emergence of AMR during therapy. Precision also promotes the efficient use of resources at an individual and population level.

Enhanced public health protection from AMR

Continuous learning promotes resilience of health systems to emerging threats, which are characteristic of AMR. This cyclical learning also drives care quality improvement and generates new knowledge in tandem. With this approach, AMR-X can rapidly launch clinical studies to address a new AMR threat (eg, emergence of an MDR or XDR pathogen from travel, war, migration, climate change, or a health-care setting outbreak), assess planning for natural disasters or drug and diagnostic supply chain disruption, and model the spread of MDR and XDR pathogen resistance motifs with evaluation of appropriate mitigating strategies. Such an approach enables timely, cost-effective, and agile public health responses to mitigate the AMR threat.

Beneficiaries

AMR-X serves as a transformative framework, benefiting a wide range of entities, from individual patients to the more comprehensive health-care industry (table). Patients (individuals and groups) benefit from both active involvement (via citizen science through NHS and other app-based interaction and engagement activities) and passive participation via routine use of patient-level data for individual and broader societal benefit. Individual patients benefit through direct access to precision care tools that both guide their own health care and help fellow citizens.

Clinicians and broader health services benefit from the fact that AMR-X facilitates continuous quality improvement

Panel 2: **Components and features of AMR-X**

Data science and informatics

- Agreement on data types format and establishing core datasets.
- Continuously tuned data sharing, linkage, curation, and processing to transform data into actionable information.
  Addressing data-action gaps crucial for AMR action research in the following ways: (1) people-to-data, encouraging the public's and health professionals' active support in data capture and sharing as core business for health systems and best clinical practice; (2) data-to-analysis, capturing results from extensive natural experiments and mapping treatment pathways within and among health systems; (3) analysis-to-action, seamlessly providing feedback to clinical, laboratory, public health entities, policy organisations, and patients, without excessive alert fatigue.
- Regional secure data environments for integrated research, innovation, and care are used for networking AMR-X nodes with each other and overlapping data-action research areas embedded in health systems.
- National federated data services feeding national data flows into regional integrated record and intelligence systems, enabling connectivity among network AMR-X nodes.
- Publication of AMR-X's data processing methods and code books in a public repository, forming a national library of AMR learning system algorithms, applying findable, accessible, interoperable, reusable data principles to maximise reproducibility of evidence and transferability of learning.

Factors involved in evaluation and policy analysis

- An evaluation framework enabling participation in AMR research at a scale only achieved previously in the research response to COVID-19, embedding research in routine clinical care and capitalising on the increasing digital maturity and integration of health and care.
- Adaptive platforms using experimental and quasi-experimental designs to evaluate diagnostics, decision support tools, therapeutics, emergence of AMR, and infection prevention interventions (eg, vaccines, diagnostics, and other therapeutics).
- Data science-driven feasibility studies, target population definition, patient pathway characterisation, outcome measure identification, and routine randomisation when possible and appropriate.
- Data-driven quality improvement.
- Assessment of the burden of disease related to different conditions and AMR-related treatment failure and its contribution to health inequality, enabling appropriate prioritisation of investigation and research activity.
- Health economic analyses to support a range of policy decisions (eg, cost-effectiveness analyses to assess the value for money of new diagnostics, therapeutic pathways, and care pathways; assessments of the long-term value of commercial technologies to inform National Health Service delinked funding arrangements; assessments of the value of investment in research).

Implementation science

- Leveraging expertise in health services and implementation science.
- Co-production with practitioners, patients, and the public to ensure that knowledge, innovations, and interventions that are developed in AMR-X are useful for patients, health-care services, and other stakeholders.
  Implementation at scale facilitated by expertise on barriers and enablers of the implementation of core AMR-X building blocks (digital infrastructure and the evaluation framework), important constituent elements (eg, data sharing and routine randomisation), and products (eg, ensuring feedback of system learning to stakeholders).
- Conducting policy assessment and cost-effectiveness analysis of alternative implementation strategies—eg, information feedback loops, design of contract, and payment mechanisms within the health system.
- Participation of patients, public, practitioners, and providers in antimicrobial therapy and AMR.
- Mapping of new pathways for the developments of flexible and rapidly adaptable treatment guidelines, approval processes, and rapid reimbursement processes.

AMR=antimicrobial resistance. AMR-X=AMR learning system.

and value for money by providing health services with knowledge, therapeutics, diagnostics, formularies, and decision support tools to offer state-of-the-art care for patients.

The public benefit from AMR-X being a framework that promotes extensive debates on the complexities of AMR, encouraging collaborative problem solving from across diverse segments of society.

The benefits to industry is that AMR-X provides a streamlined approach to develop assets, especially in real-world settings. The closely coupled implementation and economic evaluation activities help to ensure that useful and valuable assets are developed, used, and appropriately reimbursed, which, in turn, guides further investment and innovation. AMR-X can supplement traditional registration trials and aid in post-approval activities that are required by regulatory authorities.

Researchers benefit because AMR-X provides infrastructure for AMR researchers in the discovery sciences and translational sciences. Researchers in the discovery sciences include those working on drug discovery programmes, novel diagnostic technologies, digital innovations, epidemiology, data sciences, and mathematical modelling. AMR-X disrupts slow, segmented, and linear translational pathways by integrating discovery science for patients, health-care providers, and health systems. The data and

	Current best practices and limitations	Advances enabled by AMR-X
Continuous knowledge generation	Knowledge generation can be slow because the research is not synchronised with increasingly detailed intelligence from increasing data capture, linkage, and curation across health-care systems. The translation of evidence into practice can be unpredictable and slow, even when supported by national guidance and current approaches for implementation. Unsupervised scale-up from initial clinical studies of new drugs and diagnostics to wide-scale use results in deficiency of evidence. The value of antimicrobial agents is uncertain, and estimates are not contemporaneous.	Observational and quasiexperimental study designs enable rapid and routine evaluation of the impact of interventions, with large-scale handling of systematic errors and duly cautious interpretation of results. Embedded adaptive platform trials with designs developed to reflect the complexity of antibiotic prescribing pathways, such as personalised randomised controlled trial,[30] multi-arm multi-stage, and sequential multiple assignment randomised trial designs, enable the evaluation of different types of intervention (diagnostics or decision support, therapeutics, and infection prevention interventions such as vaccines). Both individual patient-level and cluster-level randomised trials are embedded in routine care. Reduced burden approaches are used to facilitate inclusivity and generalisability in enrolment through intervention opt-out, deferred consent, proportionate consent, etc, as appropriate. Randomisation becomes routine in best practice antimicrobial prescribing and quality improvement. Intensive substudies allow detailed characterisation of patient subgroups or for outcomes requiring additional or invasive sampling (eg, for evaluating the effect of interventions on carriage of AMR).
	Licensing studies of new antimicrobial agents are based on strict inclusion criteria and homogeneous study populations and are often of marginal or incremental value initially.	Real-world data in increasingly heterogeneous clinical settings are collected as a standard of care and in a systematic manner; data are progressively acquired on special populations, allowing estimation of resistance liabilities and design of mitigation strategies.
	Study feasibility and power are difficult to estimate.	Feasibility is easy to establish, thus facilitating timely reporting of clinical study results.
	Recruitment of patients into clinical studies is slow.	Clinical trial workflows are embedded in care workflows, thus making recruitment easy and accommodating innovative designs with remote coordination and reduced administrative overheads for health-care systems.
Public health protection	Unlinked management of data, intelligence service development, and research widens the gap between data and action; aggregation of data before release restricts analysis. Surveillance programmes generally do not have inbuilt automatic corrective actions enabled through linkage between public health and clinical workflows. State-of-the-art molecular epidemiology generally do not consider effector arms for corrective or adaptive actions.	Public health and clinical digital workflows are combined, allowing health systems to adapt clinical actions to pathogen and resistance surveillance intelligence. Combined AMR and infection prevention and care intelligence across public health, care quality, and commissioning teams allows health systems to promptly respond to emerging threats.
Precision	Algorithms trained with isolated, poorly curated data show poor generalisability and unmanaged calibration drift or data shift. Precision is academically attractive but remains a long way from routine clinical care. Regulatory uncertainty arises in cases of any deviation from a one-size-fits-all solution.	Decision support tools and forecasting systems use cumulative data to maintain dynamic prediction models or algorithms. Uses of antimicrobial agents in precision medicine is a byproduct of learning health system methodology and technology. Continuous learning of precision antimicrobial therapy is a standard of care.

AMR=antimicrobial resistance. AMR-X=AMR learning system.

Table: **Advances enabled by AMR-X**

processes needed for this dynamic translational approach can also drive advances in implementation science and health economics. Through such an approach, the value of innovations to address AMR is easily maximised rather than searching for value and market positioning after lengthy and expensive development programmes.

Building AMR-X

Constitution and leadership

AMR-X requires representation from stakeholders (ie, health services, public health authorities responsible for AMR, health technology assessment agencies, industry, academics, funding bodies, regulatory authorities, the health insurance industry, patients, and public representatives). This consortium of stakeholders could leverage infrastructure to ensure AMR-X achieves its overarching goals of knowledge generation, precision, and public health protection. The costs of AMR-X could be offset by public sector and commercial funding. AMR-X could help to establish and deliver national priorities for AMR research.

Components of AMR-X

AMR-X requires three enabling components: data science and informatics (including data engineering, data

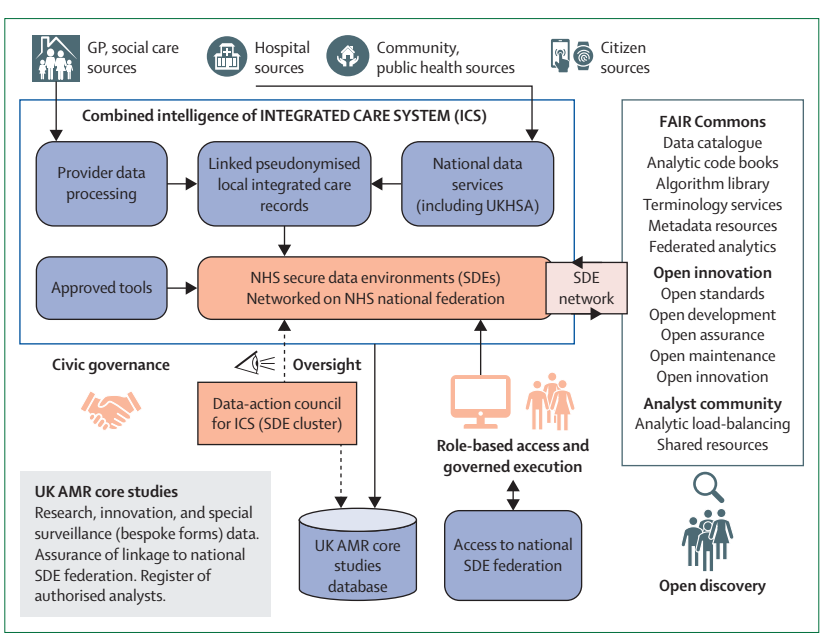

Figure: **Data infrastructure to enable a national (and potentially international) grid of responsive, research-embedded learning health-care system for AMR reduction and health-care resilience**

governance, and data science coupled with biostatistical, machine learning, health economics, and epidemiological approaches), evaluation and policy analysis, and implementation science. These components include core personnel and AMR-X networking of specific groups and communities.

The legal basis and operational arrangements for data processing are crucial considerations for AMR-X. Connecting data to address a public health emergency was a hallmark of the UK's response to the COVID-19 pandemic whereby a control of patient information notice allowed confidential data to be collected to control SARS-CoV-2. Similarly, AMR-X would require clarity over the legal, ethical, and operational conditions required for the optimal flow of data to support the best antimicrobial practice in the care of individuals and populations. The legal and regulatory prerequisites are available, but their interpretations can vary, leading to inconsistent implementation, which needs to be urgently clarified.

AMR-X requires the development of secure data environments (SDEs; figure), which are dynamic repositories of patient-level data and trusted, data analytical environments. Access to the SDE could occur routinely via the health service or from government agencies tasked with public health protection. The SDE also needs to be configured to enable regulated access by the research community, as different information governance might apply for academic-led research versus service-led (or action-led) research involving academics. The SDE can operate at various levels—the health system (closely coupled with an integrated care record), region (such as NHS England's sub-national SDE), or national. Data processing methods and code books will be made available via public repositories, supporting a national library of AMR learning system algorithms applying the findable, accessible, interoperable, and reusable principles to maximise reproducibility of evidence and transferability of learning. Methodological advances in biostatistical modelling and machine learning can be harnessed to tackle the extreme challenge that AMR poses to clinical prediction with minimal calibration drift (ie, ensuring models fitted to data in one context perform as expected when generalised), to adaptive observation, and to trial designs.

Enabling research

Connecting data from multiple health-care settings facilitates the creation of clinical trial platforms. Such platforms can, in turn, enable the continuous assessment of new interventions. Since the prescribing of antimicrobials is strongly influenced by local and regional guidance, a unique opportunity exists for system-wide randomisation to continuously evaluate antimicrobials in a real-world context (eg, ACORN trial[31]). AMR-X would require protocols for platform studies (similar to the RECOVERY trial, ISRCTN50189673, during the COVID-19 pandemic and protocols for MDR and XDR infections being developed by ADVANCE ID[32]) for the assessment of new therapeutics, diagnostics, and digital innovations and to understand the transmission patterns of resistant organisms to inform prevention interventions. Further capacity building and advancements are required in specific areas with uncertainty, such as innovations in health economic assessments for interventions that address AMR, and mapping of patient pathways to facilitate embedded studies of new interventions, novel endpoint definitions, and patient-reported outcomes.

Summary

AMR is an ever-present challenge that cannot be sustainably managed by solely relying on the discovery and development of new antimicrobial agents; therefore, new holistic and system-wide approaches are required. In this context, AMR-X provides a method to integrate multiple sources of contemporaneous data to improve the care of patients receiving antimicrobial therapy. AMR-X proposes linking routinely collected health-care and surveillance data to be used for the benefit of individual patients and the broader population. The cost of building and maintaining such a system is relatively modest compared with the cost of developing a new antimicrobial agent.

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Declaration of interests

JA reports being a shareholder of Pfizer, holding both stock and stock options, and is a full-time employee of Pfizer, Medical Affairs Department. DAJ reports payments from Gilead, patents for lung transplant diagnostics, participation in Grace Infection Biobank, and stock options in Pulmocide. SB reports being a shareholder of Pfizer, holding both stock and stock options, and is a full-time employee of Pfizer, Medical Affairs Department. GB reports receiving an honorarium and expenses for a talk on AMR: The current United Kingdom and global landscape at UCB Biopharma UK, Slough, 2022; support from Pfizer UK (pneumococcal vaccine policy), Biomerieux (new diagnostic tests for septic arthritis and bloodstream infections), and AvanzPharma (management of soft tissue infections); and honoraria for attending advisory boards of Pfizer UK (pneumococcal vaccine policy), Biomerieux (new diagnostic tests for septic arthritis and bloodstream infections), and AvanzPharma (management of soft tissue infections). VB reports receiving meeting and travel expenses from the NIHR for work as a public contributor. 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ADa reports acting as a paid consultant for the pharmaceutical and biotechnology industry—companies and institutions include Adagio, Amplyx, AN2, Bioscript, Bugworks, CARB-X, Closed Loop Medicine, Correvio, Davolterra, Destiny, Evopoint, F2G, Entasis, Gates, GSK, Humanigen, University of Liverpool, Kymab, Melinta, Modis, Orca, Phico, Quince, Roche, SFunga, Scynexis, Sinovent, SNIPR Biome, Spero, tranScrip, and VenatoRx; and has acted as an independent statistician on Data Safety Monitoring Boards for Aridis, Cerium, ContraFect, Egetis, Midatech, Pfizer, Pled, Rare Thyroid, Sanofi, and tranScrip. PD reports salary from serving as Deputy Medical Director, NIHR Clinical Research Network Coordinating Centre, Leeds and London, UK. 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