The Lancet Regional Health - Europe 000 (2021) 100161

Contents lists available at ScienceDirect

The Lancet Regional Health - Europe

journal homepage: www.elsevier.com/lanepe

Health Policy

Optimising antimicrobial use in humans – review of current evidence and an interdisciplinary consensus on key priorities for research

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A R T I C L E I N F O

Article History:
Received 6 May 2021
Revised 27 May 2021
Accepted 2 June 2021
Available online xxx

A B S T R A C T

Addressing the silent pandemic of antimicrobial resistance (AMR) is a focus of the 2021 G7 meeting. A major driver of AMR and poor clinical outcomes is suboptimal antimicrobial use. Current research in AMR is inequitably focused on new drug development. To achieve antimicrobial security we need to balance AMR research efforts between development of new agents and strategies to preserve the efficacy and maximise effectiveness of existing agents.
Combining a review of current evidence and multistage engagement with diverse international stakeholders (including those in healthcare, public health, research, patient advocacy and policy) we identified research priorities for optimising antimicrobial use in humans across four broad themes: policy and strategic planning; medicines management and prescribing systems; technology to optimise prescribing; and context, culture and behaviours. Sustainable progress depends on: developing economic and contextually appropriate

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https://doi.org/10.1016/j.lanepe.2021.100161

Please cite this article as: E. Charani et al., Optimising antimicrobial use in humans – review of current evidence and an interdisciplinary consensus on key priorities for research, The Lancet Regional Health - Europe (2021), https://doi.org/10.1016/j.lanepe.2021.100161

interventions; facilitating better use of data and prescribing systems across healthcare settings; supporting appropriate and scalable technological innovation. Implementing this strategy for AMR research on the optimisation of antimicrobial use in humans could contribute to equitable global health security.

1. Introduction

Antimicrobial resistance (AMR) is one of the leading threats to human health[1,2] requiring multifaceted activity embedded within a One Health agenda, that takes account of antimicrobial use in human health, animal health, agriculture, and environment.[3,4] In human health, action is needed in many areas, including underpinning efforts to prevent and reduce infectious diseases, for example through improved access to water, sanitation and hygiene, and to vaccination. Whilst the need for new antimicrobials through research and development (R&D) is widely acknowledged, [5−7] it is critical that AMR research should not be entirely dominated by the development of new agents, as these alone will not solve this silent pandemic.[3,4] More equitable investment in all the aforementioned elements is needed, as well as in research on optimising antimicrobial use, including the investigation of how the efficacy of existing and new antimicrobials can be maximised and how their effectiveness can be preserved.[8] The remarkable success of therapeutic trials and vaccine development in response to the COVID-19 pandemic shows what is possible if similar strategies were mobilised for other problems, including AMR.[9] While progress is being made in research initiatives addressing AMR, important research gaps remain.[4,10]

Optimisation of antimicrobial use as a means to tackle AMR and improve the treatment of infections, is a priority of the health agenda of the June 2021 G7 meeting.[11] Antimicrobial use, like much human behaviour, is complex and dynamic and is influenced by sociocultural contexts as well as changing population and individual characteristics, such as the increasing prevalence of multimorbidity.[12] Interventions developed in one setting may not necessarily work in another and interventions to optimise antimicrobial use need to extend beyond a narrow concept of antimicrobial stewardship (AMS)[13], and be based on a comprehensive and inclusive systems approach, informed by a broad research base.

In this paper we set out a research strategy for optimising antimicrobial use in human populations, developed from a review of current evidence and a multi-stage process of engagement with diverse international stakeholders, drawn from academia, clinical medicine, public health, patient advocacy, and non-governmental organisations who, together with the authors, include all G7 nations. We have taken a whole systems approach to the many issues that influence the use of antimicrobials in human populations,[14] arguing for a comprehensive research strategy that will allow us to understand the complexities of technology and innovation adoption and human behaviour and the many factors that influence them, within health systems and beyond.[15−17]

2. Search strategy and Selection criteria

In March 2020, an interdisciplinary team of stakeholders was convened, with extensive expertise in medicine (in general infectious diseases, microbiology, tuberculosis and HIV), surgery, pharmacy, clinical pharmacology, epidemiology, social science, economics, engineering, public health, patient safety, healthcare management and policy research, along with patient and public advocates and representatives, to identify the current research priorities in optimising antimicrobial use in human populations. Key stakeholders (32 members from 15 countries) were purposively selected based on track-record, expertise, and representation from all World Health Organization (WHO) Regions. Between March 2020 and November 2020, via a series of virtual round-table discussions organised and analysed by the core team, stakeholders contributed to the research process. Additional individual input was sought from several stakeholders who were not able to attend the round table discussions. There were three phases.

Phase 1 Review of existing research and generation of key themes

To provide an overview of current research on optimised antimicrobial use in humans a core team (9 of the listed co-authors) gathered evidence through a narrative review of published and selected grey literature. References were identified through searches on PubMed with the search terms “antimicrobial resistance”, “antibiotic resistance”, “national action plans”, “antimicrobial stewardship”, and “health services” from 1995 until 2020. Articles were also identified through searches of the authors’ own files. Only papers published in English were included. The global and national initiatives for funding and research, capacity building and infrastructure development in AMR were also reviewed using open resource material. Global policies, agreements and recommendations such as the Global Antimicrobial Resistance Surveillance System and national action plans (NAPs) for AMR were reviewed.[18] The gaps and opportunities for optimising antimicrobial use in human populations were identified in the narrative review and discussed in virtual round-table discussions amongst the core team to identify the key emerging themes. A thematic survey was developed based on these themes to identify potential barriers and opportunities in advancing research, together with open questions to capture broader concepts and ideas from local and national settings. From amongst the stakeholders identified, an expert panel of seven members was convened. The survey was disseminated via email to the expert panel. The panel members were requested to identify relevance to context, feasibility, urgency, and importance of the priority areas for each theme.

Phase 2 Evidence analysis and identification of key priority areas

The feedback from the first-round table, together with feedback from the expert panel, was used to refine the identified priority areas and the survey themes and questions. A matrix of emerging research priority areas and cross-cutting considerations was developed based on the phase 1 findings. The matrix was then validated via 1) a survey with open questions disseminated via email to the 32 stakeholders, and 2) three roundtable, and one-to-one virtual discussions with selected members of the full stakeholder team.

Phase 3 Validation of the roadmap

The stakeholder feedback elicited in phase two was used by the core team iteratively to refine the concepts in the roadmap. The evidence-base supporting the roadmap content was regularly updated by the core team with any emerging evidence (up until 31 January 2021) deemed relevant discussed by the core team before being included in the final matrix and roadmap. The final roadmap was discussed and validated with original seven stakeholders in a further virtual round-table discussion.

3. Four research themes

Our initial review identified four key research themes: policy and strategic planning, medicines management and prescribing systems, technology for optimised antimicrobial prescribing, and context, culture and behaviours. Broadly, there is imbalance in funding with emphasis on new drug R&D, and very limited funding for the identified themes (Figure 1). This creates inequalities in impact in terms of populations who will benefit from the research. In technology and

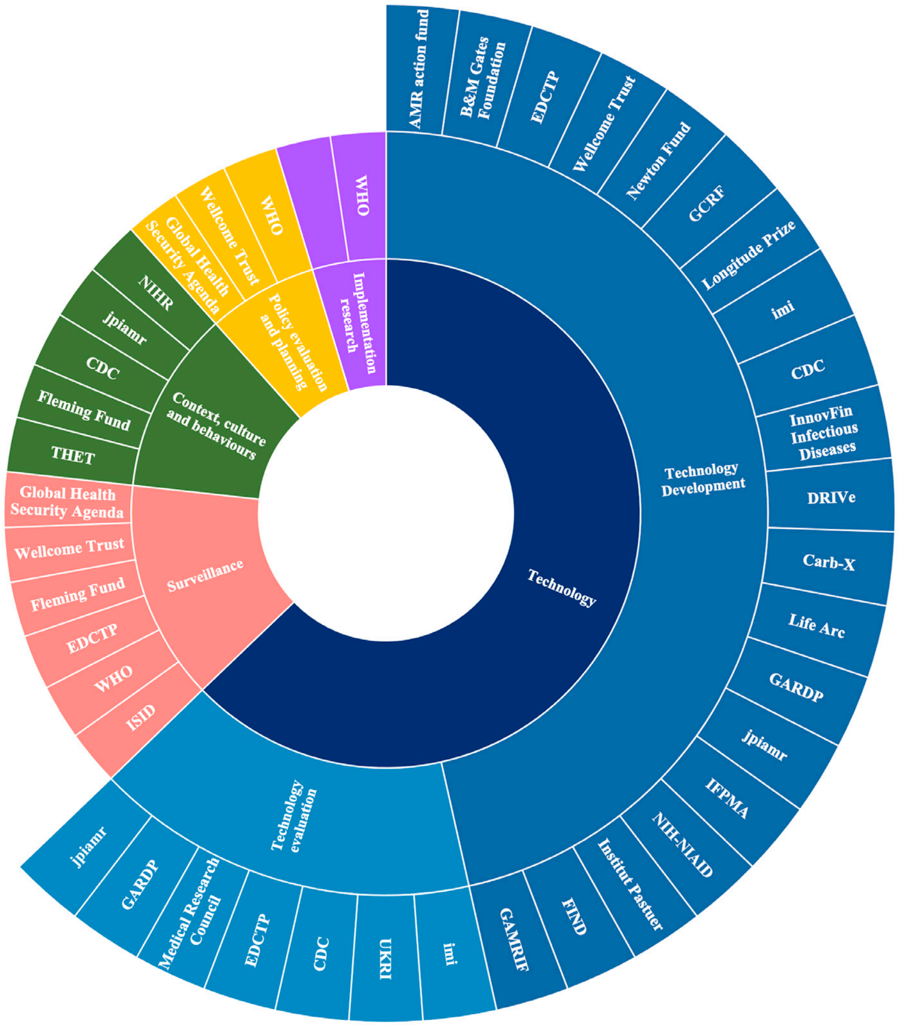

Figure 1. Current global funding bodies active in antimicrobial resistance research for humans and the broad themes under which funding is available

innovation there is a skew towards technology development rather than evaluation.

Whilst many of the research opportunities have global eligibility criteria, they are ultimately funded by high-income countries (HICs). We need greater accountability and scrutiny of how funding bodies apportion resources across the AMR agenda, particularly given the need for capacity building and strengthening.[19] It is imperative to balance research funding and allocate resources for cost-effective initiatives across the identified themes to achieve equity between R&D and optimisation in use of existing antimicrobials. The opportunities and gaps across these themes are discussed as follows.

3.1. Policy and strategic planning

Strategies and tools to support national interventions include the development and implementation of NAPs for AMR, based on best available evidence. The 2015 G7 summit in Germany explicitly committed to this in its Leaders' Declaration.[20] The process by which NAPs are developed is shaped by political forces as much as the scientific or technical evidence base.[21] Given the societal impact of AMR and the suite of interventions required to tackle the issue at individual, organisational and societal level, the research informing policy and management strategies requires a multidisciplinary approach that includes patient and public representation.

In 2011, the WHO initiated a situational analysis of country progress in addressing AMR against four objectives: (1) Improved awareness and understanding of AMR through effective communication, education, and training; (2) Strengthened knowledge and evidence base through surveillance and research; (3) Reduced incidence of infection through effective sanitation, hygiene, and infection prevention measures; and (4) Optimised use of antimicrobial medicines in human and animal health.[18] This has been important as an initial framework but the detail and quality of analyses of national and local strategies may benefit research that considers AMR as inextricably linked to other public health and health system level processes and outcomes.

Following global directives, 117 of 208 countries have government-approved AMR NAPs that reflect the WHO Global Action Plan objectives, but only 26 have identified funding sources.[22] The remaining 91 countries are still at the development stage. National situational analyses are underway in individual countries and as part of learning networks (e.g., the Global Antibiotic Resistance Development Partnership)[23] but they employ different frameworks and approaches that, whilst having local relevance, impede cross-country or global comparisons or benchmarking. Few, if any, have employed a strategic management framework[15] critical for enabling agile responses to macro-level environmental influences. Beyond review and development of plans, there is potential to conduct dedicated research to understand how disparate health systems within individual countries are equipped to adopt and implement NAPs. There is also potential to consider this from a regional perspective. For example, countries within the Southern and Eastern African Development

Communities could align their political and economic resources to harmonise strategies. Specific research needs for policy and strategic planning for AMR are summarised in Box 1.

Box 1 *Specific research needs in policy and strategic planning and the suggested frameworks*

Consideration of AMR as part of the wider policy agenda

While national efforts are critical, they are shaped by the wider political and economic global agenda. Considering antimicrobial resistance (AMR) as a global public health threat requires commitment at an international level in determining priorities and formulating policies. This international-level focus and agenda setting has been initiated through the United Nations General Assembly and the agreement on Sustainable Development Goals, however greater advocacy and representation at the international level is required for there to be effective and lasting change in policies and strategy. A key area where international policy can have impact is in legislation for access to antimicrobials, this includes improving access to quality-assured antibiotics and restricting unregulated and under the counter acces. The regulatory aspects of antimicrobials are important for AMR as they influence access, quality, and equality in relation to antimicrobials.

Investigation of health systems organisation and management

Health systems includes health and social care and the role of non-governmental organisations and civil society. Existing frameworks have facilitated the rapid appraisal of health interventinos at a health systems level. The Systematic Rapid Assessment toolkit,[90] for example has recently been applied to examine the extent of integration across the health economy in a review of the international literature.[91] There are also opportunities for learning from successful health system interventinos, e.g. the largely integrated health and social care responses to tuberculosis in the Eastern European settings.[90]

Health system level governance and accountability

The complex nature of system governance is important for AMR policy and has been analysed at the overall health system level, and if and how governance at these levels is aligned or divergent. Health system governance refers to processes, structures, and organisational traditions that determine how power is exercised, how stakeholders have their say, how decisions are taken, and how decision-makers are held to account.[92] Three main governance processes — setting priorities, monitoring performance against these priorities, and accountability of all actors within the system for their expected contribution[93] — have been examined, providing case studies of effectiveness in high-income countries.[94,95] A systematic review of the literature[96] provides a synthesis of frameworks for such analyses but these have yet to be applied to the context of addressing AMR in low-, and middle-income countries (LMICs).

Role of the private sector

The role of the wider private industry, including private healthcare providers and insurance companies, and how these sectors disrupt or align the goals for addressing AMR and antimicrobial optimisation is not fully explored or understood, particularly in the LMICs setting. The role of big pharma should not be ignored. Frameworks exist for assessing how significantly (positively/negatively) this sector may interact at the global and national level to initiate and sustain solutions to address AMR, including classic policy analysis models (e.g. Kingdon's model[97,98]) as well as systematic stakeholder analyses.[99]

Understanding pluralistic health systems

The role of pluralistic health systems comprising public, private, and non-governmental providers as well as the interactions within them, particularly in LMICs settings, is important in understanding whether the response to AMR is consistent across these settings. This is particularly important when there is open direct access to hospitals and other providers, resulting in care-seeking behaviours of switching among and between these domains of care.

3.2. Medicines management and prescribing systems

Medicines management refers to the processes, behaviours and systems that determine the way that medicines are used in clinical practice. How antimicrobials are made available in each country partly depends on how these drugs are classified legally and partly on the extent to which legislation is monitored and enforced. Non-prescription access to selected antimicrobials is still prevalent worldwide in both HICs as well as low-, and middle-income countries (LMICs), including provision via community pharmacies, online pharmacies and other retail vendors.[24,25] This is partly due to the significant lack of prescribers and the pressure of market forces. A balanced approach that includes some level of control aligned with incentivisation, training, and monitoring of the non-prescription access pathways, is likely to provide a more sustainable mechanism for access to effective antimicrobials. Mapping of the antimicrobial drug supply chain for human use revealed gaps in practice at each point of the R&D and supply chains (Figure 2), including poorly regulated access,[26,27] perverse economic incentives,[28–30] patient and public illicit access, access to black market and falsified agents, and public misbeliefs. There is, however, a need for balance between over-regulation and under-regulation, especially in places where lack of access to antimicrobials may result in increased morbidity and mortality.

The importance of timely access to antimicrobials is recognised internationally through their inclusion in country-specific essential medicines lists (EMLs); however, maintaining an up to date EML remains a challenge due in part to the number of medicines that though withdrawn from the market remain on EMLs.[31] In 2017 the WHO introduced the AWaRe (Access, Watch, Reserve) system in the EML, categorising antibiotics based on their activity against multi-drug resistant organisms.[32] The AWaRe system adds value to point-prevalence studies on antimicrobial consumption[33] and is being used to measure the change in proportion of AWaRe antimicrobials, with data reporting rapid increases in consumption in the Watch category, particularly in LMICs.[12] The system has been used to compare patterns of antimicrobial use between countries, advocating for more use from the access category (up to 60% of total consumption) by 2023 as part of initiatives to help countries reach their health related sustainable development goals.[8,34] A key research gap is understanding how different countries use and adapt the AWaRe system[35] and to what extent it will influence the design, implementation, and sustainability of strategies that balance timely access with reducing inappropriate use. Furthermore, in many LMICs, protracted shortages of Access antimicrobials result in use of broader spectrum agents; the AWaRe system could be enhanced to monitor availability of antimicrobials in different regions, countries, and healthcare systems.[33,36]

3.3. Technology for optimised antimicrobial prescribing

Effective medicines management requires data and technological advances can support and provide this. The lack of robust data on how to use antimicrobial agents correctly in different populations and in the context of multimorbidity, hinders appropriate use and drives AMR. For example, obesity, an increasing global health concern, is a significant contributor to multimorbidity. Despite this, and

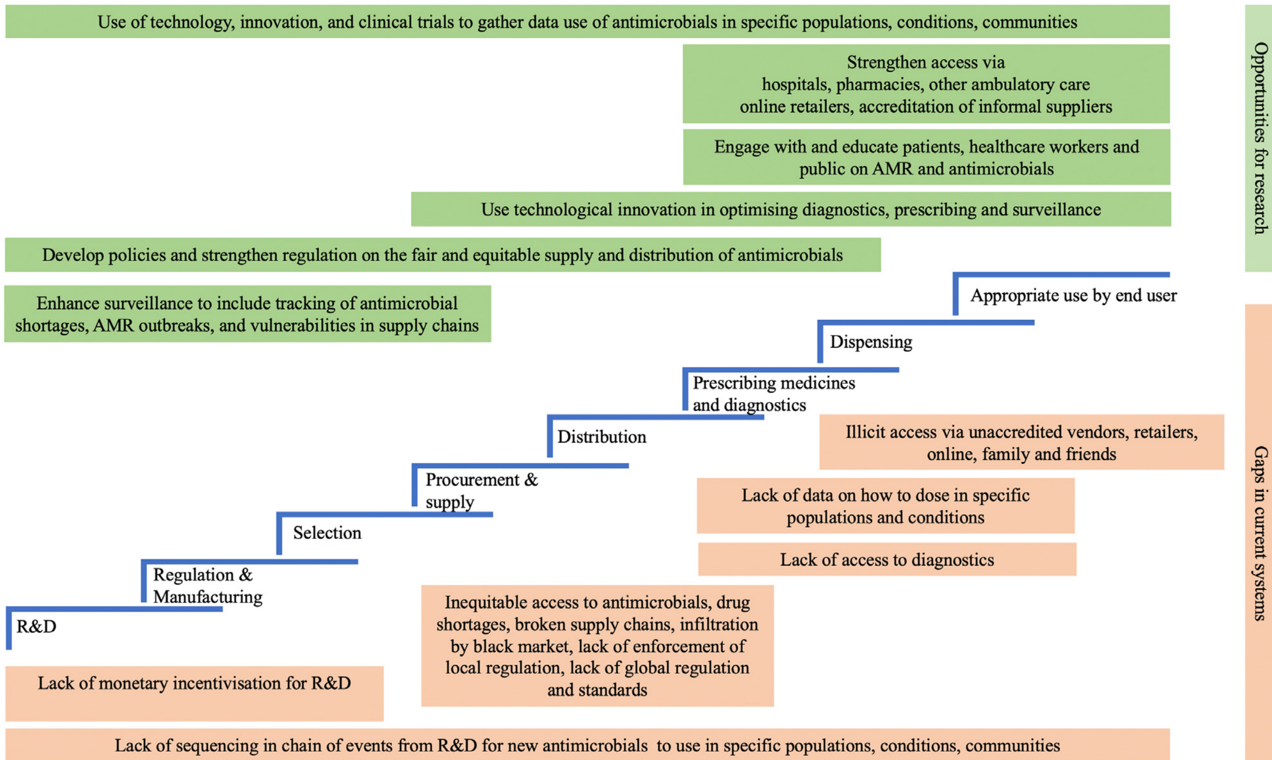

Figure 2. The antimicrobial drug supply chain indicating gaps in current systems and opportunities for research, adapted from the WHO framework for development and stewardship to combat antimicrobial resistance (AMR)[90]
R&D: research and development

despite complicated infection-related outcomes in obese patients, the bioavailability and efficacy of different antimicrobials in obese populations remains inadequately studied,[37] resulting in inappropriate dosing.[37,38] Multimorbidity and its associated polypharmacy further complicate antimicrobial dosing, increasing the risks of therapy failure and AMR.[38] Robust clinical data on the use of different antimicrobial agents and antimicrobial dosing in specific populations would facilitate their optimised use and reduce the risk of emergence of AMR through inappropriate therapy. Generation of such data requires strategic epidemiological trials in specific populations (e.g., in neonates and paediatrics, in pregnancy, in the obese, in multimorbidity). Decision support systems hold considerable potential and may accelerate antimicrobial optimisation through standardising mechanisms for large-scale clinical data curation and global data sharing. Additionally, data linkage across sectors (primary and secondary) including linkage of clinical indications with antimicrobial prescriptions is lacking. Enhanced decision support systems can facilitate data gathering and analysis at scale from different populations to support surveillance mechanisms.[39]

Rapid diagnostic devices, clinical decision support systems, wearable devices, and biosensor technologies are some of the existing technologies in use for infection-related clinical practice that can be readily applied to optimise antimicrobial use.[40–42] Artificial intelligence provides another potential for significantly enhancing the ability to gather robust data for surveillance as well as facilitating individualised real-time clinical decision-making.[43,44] Despite technological advances, research supporting the integration and sharing of information generated by individual technological solutions is lacking. Historically, the development and acceleration of technology has been concentrated in HICs, despite evidence of rapid adoption and application of such technologies in LMICs; for example, the use of drones for blood delivery to remote hospitals, and electronic surveillance of childhood bacterial infections in Bangladesh.[45,46]

Infrastructure and systems limitations can block innovation uptake. Limitations include the mismatch between available data and expertise, data being distributed across different entities (without being linked), and cultural and behavioural barriers to technology adoption. Technology developed in one setting cannot be assumed to be directly translatable to other settings. For example, in HICs, specific strategies focused on reducing antimicrobial prescribing may have the greatest impact on reducing AMR; however, in LMICs, vaccine technology may have a greater impact on reducing lower-respiratory tract infections and thus antimicrobial usage.[1,47] Frameworks for the funding, development, and evaluation of technology must take such differences into account to ensure that targeted interventions are developed and implemented in an appropriate way.

3.4. Context, culture and behaviours

AMR is a multifaceted issue and its drivers and consequences are manifested socially.[17,48,49] Recognising this, increasingly, social science methods have been applied in the study of antimicrobial use.[50,51] A qualitative study in Australia examined how hospital doctors balance competing concerns around antimicrobial use and AMR.[52] With a focus on individual care versus broader public health considerations, participants did not perceive AMR as central to clinical decision-making and clinical risk was prioritised over population risk. Under-prescribing was associated with legal and reputational risk, while overprescribing carried minimal risk to themselves or the patient. These findings demonstrate the inability of prescribers to associate their own behaviours with the emergence of AMR, while simultaneously tending towards over-prescription of antimicrobials to treat the patient in their care.[52]

Professional hierarchies as key determinants of antimicrobial decision-making in hospitals have been described using social science research.[48,53,54] Prescribing etiquette in hospitals means that hierarchy within and among professions can limit the involvement of junior members of teams and pharmacists and nurses in key decision-making, leading to gaps in care and lack of direct responsibility for actions.[48,53,55] Two studies emphasise how interprofessional relationships between non-infectious disease clinicians and infectious diseases (ID)/clinical microbiology shape prescribing practices.[17,55] Competing hierarchies result in limited consultation with ID/clinical microbiology, while negotiating clinical ownership and antimicrobial decisions are influenced by multiple competing authoritative figures. Antimicrobial decisions are caught between the tensions caused by evidence-based recommendations by ID/clinical microbiology and experiential-style learning – a skill passed on from senior doctors to junior doctors.[55] Antimicrobial prescribing decisions in this context are a balance between the specialists' advice and the clinicians' judgement.[55]

Little is also known regarding the impact and consequences of social constructs (e.g., gender, ethnicity, race) on AMR or on infection related behaviours of healthcare workers or the public. This gap in knowledge is critical as we collectively experience the evolving COVID-19 pandemic.[56] Paradoxically, over 70% of the world's healthcare providers and carers are female and are thus at greater risk of acquiring illness themselves while working. Additionally, previous epidemics have led to disastrous consequences for health and social well-being of women, e.g. rising maternal mortality during the West African Ebola outbreak, and increased domestic violence during the Wuhan lock-down in China in response to COVID-19.[57] The majority of the health workforce driving infection prevention and control (IPC) in healthcare facilities are female nurses, with the pharmacy workforce responsible for reviewing antibiotic prescriptions also predominantly female.[58] The differences in gender and class of those healthcare professionals who study medicine versus other healthcare professions can influence the power dynamics, with behaviours, roles, and opportunities based on different levels of power.[59]

Inequalities harm health and this is equally true for AMR. For example, in HICs, poverty is associated with drug-resistant infections.[60] In LMICs, a lack of formal education has been linked to resistant *Streptococcus pneumoniae* and *Escherichia coli* infection.[61] The intersection of socioeconomic factors and AMR and how it puts individuals at greater risk of poor outcomes needs to be better understood in order to bring about sustainable change for vulnerable populations.

4. Cross-cutting systems level considerations

Beyond the four research themes, the engagement with wider stakeholders and experts identified cross-cutting issues that need addressing as part of efforts to tackle AMR in human populations: engagement with the public and capacity building. It is also necessary to consider the implications of the COVID-19 pandemic that are likely to shape policies for years to come. These three cross-cutting themes are discussed below.

4.1. Public engagement

Popular knowledge about antimicrobials is poor and the scale of the threat of AMR is under appreciated.[62,63] National and international AMR responses fail to recognise the role of the public and wider society in efforts to tackle AMR and implement effective IPC.[64] Reducing popular demand for antimicrobials must be a key goal of any AMR strategy; however, research on how best to do this is limited.[2] Existing communication and engagement initiatives often leave behind the most vulnerable and those at most risk of the negative consequences of AMR. Within civil society and across systems there needs to be a greater engagement with and awareness of the threat of AMR to engender a culture of civil responsibility, activism and sustained accountability. The climate movement is an example of collective civil society and public engagement and activism to address a global threat. There is much to learn from the approaches applied by climate advocacy campaigns; including the provision of information that is accessible by citizens and the public, how that information is framed, and the efforts made to challenge the terms of political debate. It has been argued that climate campaigns' success has been in creating a space for open dialogue and discussion that emphasises values and focuses on grass-roots engagement.[65] Likewise, strategies for antimicrobial optimisation need to practice pragmatic reasoning that considers the interests of all stakeholders.

The Wellcome Trust report 'Reframing Resistance' encourages use of standard language for communication about AMR.[66] However, the language used must be consistent with local understanding of terminology. Dialogue and active engagement with informal vendors to drive local initiatives may help to address this gap. Research on public engagement in AMR needs to consider health literacy.[67,68] Enhancing health literacy across multiple generations and in different contexts, has the potential to facilitate patient and public understanding of when to seek healthcare, how to self-care when appropriate, and how to reduce inappropriate antimicrobial use. This includes use of context-specific language and communication styles alongside developing appropriate health literacy assessment tools.

The role of the public as consumers of healthcare is also important.[64] Communication and information provision within healthcare often fails to address the needs of the consumer and may be responsible for driving many misconceptions and the misuse of antimicrobials.[62,69,70] When technological solutions are co-designed with end users there is better patient knowledge and understanding of AMR.[71] Early engagement is vital to explore concerns and support development that will lead to adoption.[72] Strategies for the evaluation of the effectiveness of public health initiatives for AMR in relation to public perceptions, motivations, and behaviours around antimicrobial use are also needed.[73–76]

4.2. Capacity building

Significant disparities and inequalities between the capabilities of HICs and LMICs settings impede global collaboration and research in AMR. Building capacity in AMR research needs to be much wider and go beyond primary, secondary, and tertiary care settings across HICs and LMICs. The strategic capacity to implement the existing NAPs remains a major concern.[77] Gaps in mechanisms for effective surveillance of AMR and infections mean that in many LMICs the true scale of the problem is not known. The capacity for data gathering, analysis, and sharing needs to be developed to a minimum acceptable standard across HICs-LMICs to enable the evaluation and benchmarking of population and systems level data on AMR at a global scale. Accurate, contextually relevant, and timely data are crucial to enabling not only good science but also the public discourse and activism needed to tackle AMR.

Current initiatives and practices to address antimicrobial optimisation often leave many in the healthcare workforce behind.[78–80] The nursing workforce can make important contributions in IPC, AMS, and patient and public engagement.[81,82] The surgical specialty is often overlooked in AMS initiatives, and this is despite the high burden of infection in surgical populations, particularly in LMICs.[83,84] There must be much greater engagement with all healthcare professions, across specialties, with sustainable, agile training in AMS and IPC strategies. The Child Health Research Foundation in Bangladesh offers a model of capacity building to tackle AMR,[85] working with locally trained community healthcare workers who receive specific training not only in epidemiological data collection but also in recognition and referral of children with bacterial infectious diseases to qualified healthcare workers for diagnosis and treatment.[46]

4.3. Impact of the COVID-19 pandemic

Finally, we cannot ignore the consequences of COVID-19. There are concerns that the pandemic may have an adverse impact on AMR as many patients with COVID-19 have, often inappropriately, been treated with antibiotics. However, the situation is complex as whilst the widespread use of antibiotics in severely ill hospitalised patients may encourage AMR in acute care, the apparent reduction in infectious diseases seen in the community and reductions in community use of antibiotics may also have a significant impact.[86,87] Furthermore, disruption to research programmes may adversely impact AMR research. It will be important to harness the opportunities, including important lessons in reducing transmission of infection. The experience of the pandemic, and especially the nosocomial spread of COVID-19, could encourage IPC practices to be revisited. We need to rethink pandemic preparedness and response beyond just global health security and look at strengthening multisectoral (e.g., in One Health) and multilateral approaches (as has been done in other areas such as HIV), using AMR as the proof of principle.

The barriers that the global health community is facing in tackling the COVID-19 pandemic can be used as learning. Key areas to focus research on are the state of public health infrastructure at the local level (beyond national centres of excellence), public trust in government, long-term funding trends for public health (beyond recent or specialised budgets), and relative political autonomy of public health systems.

5. Moving forward: a roadmap

In developing this analysis of current evidence and expert consensus on optimising the use of antimicrobials in humans we have identified global research priorities. However, these now must be adapted to the situation in each country, as priorities for research are likely to differ as will the applicability of findings given the differing contexts. In Figure 3 we set out a possible roadmap, based on the four identified priority themes for research policy and implementation and with a timeline that we believe will be feasible.

Within countries, the focus should be on: developing economic and contextually appropriate AMR-specific policy interventions; facilitating better use of data and prescribing systems across healthcare settings; supporting appropriate and scalable technological innovation and data linkage and evaluation; and better understanding and accounting for sociocultural and behavioural factors. Following this research roadmap, within two years, countries should have achieved a detailed understanding of the challenges they face and be able to develop context appropriate policies and interventions appropriate to address these challenges. Within five years they should be implementing them, refining their approach where necessary, and incorporating emerging developments. By ten years they should be moving to a sustainable model, incorporating a sustainable system of research and evaluation.

Action is also needed at regional and global levels, building on existing structures. From a research policy perspective there are three broad roles to consider. The first is technical. While some countries will be able to implement necessary measures using their own resources, others will need assistance, either because they are small or because they have limited public health and research capacity. The public health role is traditionally undertaken by the WHO, and especially its regional offices. Increasingly, other regional organisations are entering this space, a process that is accelerating following the COVID-19 pandemic, exemplified by proposals for a European Health Union. While much less advanced, other regional groupings, such as the Association of Southeast Asian Nations (ASEAN) and the African Union, are developing a health role.[88] These regional groupings also have a role to play in harmonising legislation and policies, recognising that free trade facilitates movement of not only goods but also micro-organisms. The development of international norms and standards has traditionally rested with WHO, this time with its Headquarters, the Food and Agriculture Organisation (FAO), working together in certain areas such as through the Codex Alimentarius in

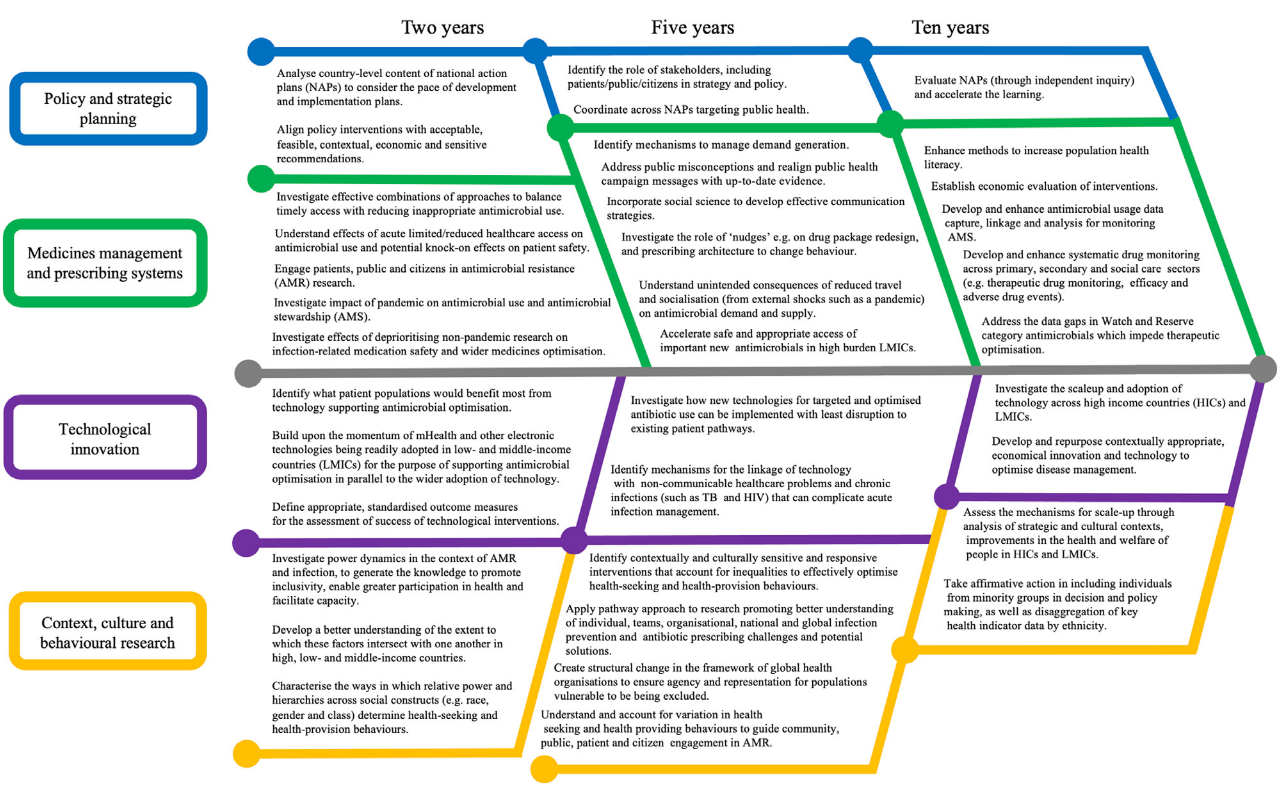

Figure 3. The proposed timeline for the identified research priorities in optimising antimicrobial use in human

relation to foodborne infections. However, given increasing understanding of role of agriculture and aquaculture in AMR, there is a case for stronger and closer alignment between all agencies with a direct interest in One Health, including WHO, FAO, the World Organisation for Animal Health (OIE) and the UN Environment Programme.[89]

The second role is financial. Again, many countries can implement a roadmap with domestic financial resources, but others cannot. For LMICs, Multilateral Development Banks and Development Finance Institutions can play a crucial role if they develop greater expertise in the investments needed to tackle AMR. Other international financial institutions, such as the International Monetary Fund, can play a role, adding progress in reducing the risk of AMR to their monitoring of environmental, social, and governance indicators that feature in their discussions with governments. However, many of the measures needed to combat AMR can be considered as global public goods, in that investments benefit the entire world.

A third role is foresight. The Intergovernmental Panel on Climate Change has done much to draw attention to the threats from global warning, convening leading scientists who can assemble the necessary evidence. As AMR also poses an existential threat to humanity, there seems a strong case for a similar organisation, such as an Intergovernmental Panel on Health Threats, that would include AMR in a broader portfolio of work that would include development and monitoring of appropriate indicators of the risks from AMR. We recognise that the challenges of achieving concerted international action are considerable. However, the experience in developing a response to the global financial crisis does suggest that progress is possible when there is political will and a structure to make things happen. The Financial Stability Board, established after the 2009 G20 summit, offers a model for what might be achieved in the health arena.

From a research perspective, population and geographical inequities among and within HICs and LMICs remain critical barriers to progress in sustainable research to tackle AMR. To address the gaps in AMR research in human populations and achieve antimicrobial security, it is essential to invest in capacity to conduct and apply research in all HICs and LMICs. Funding and research on AMR remains heavily skewed towards HICs while current priorities do not capture the full spectrum of issues relevant to AMR. Most funding is dedicated to surveillance and technology, and while this is necessary – especially in LMICs where availability of data is limited by underinvestment in digital laboratory and prescribing systems – little consideration has been given to building capacity for technology evaluation, implementation and management science, behavioural research, and understanding the influence of context on outcomes and sustainability of interventions. There is also a need for enhanced mechanisms to enable engagement with policymakers.

Responses to the threat posed by AMR have often been fragmentary, failing to recognise that the solution demands a systems approach that recognises the complexity unique to AMR which is influenced not only by the interactions of many different actors, but also the added complexity of evolution of microorganisms capable of undergoing rapid unpredictable change. These characteristics call for a dynamic response based on continuous learning, with close links between research and policy. We believe that our roadmap creates a means to achieve this.

6. Contributors

AH, EC, and RA conceived the project and gained funding. EC, RA, MMc, BDF, TMR, NZ, and AH coordinated the data collection. EC, RA, MMc, BDF, TMR, NZ, CB, and OM analysed findings from review and surveys. MM, M Mpundu, MB, AJML, CT, WH, and SS validated the survey tool and provided input into the key themes identified. EC, RA, M McK and MMc wrote the first draft, all co-authors contributed to subsequent versions and approved the final draft. AH had the final responsibility for the decision to submit for publication.

Data sharing

The data used to inform this policy paper can be made able, upon reasonable request from Esmita Charani, e.charani@imperial.ac.uk.

Declaration of interests

We declare no competing interests.

Acknowledgements

We thank the following expert panel group members for their valuable input: Adrian Brink (South Africa), Peter Borriello (UK), Peter Childs (UK), Nick Feasey (UK), Grant Hill-Cawthorne (UK), Steven J Hoffman (Canada), Izhar Hussain (Pakistan), Fran Husson (UK), Claas Kirchhelle (UK), Nathan Peiffer-Smadja (France), Mathieu Poirier (Canada), Michael Sharland (UK), Julia E Szymczak (USA), Karin Thursky (Australia), Paul Tambyah (Singapore), Charles Vincent (UK), Thomas G Weiser (USA), Yazdan Yazdanpanah (France), Shahidul Islam (Bnagladesh) and Samir Saha (Bangladesh).

This work was supported by the Wellcome Trust. RA, CB, EC, AH, MM, SS, OM, and NZ acknowledge funding from the Economic and Social Research Council (ESRC) and the National Institute for Health Research ASPIRES project (Antibiotic use across Surgical Pathways: Investigating, Redesigning and Evaluating Systems) (https://www.imperial.ac.uk/arc/aspires/). ASPIRES aims to address antimicrobial resistance and improve clinical outcomes optimising antibiotic usage along surgical pathways. The support of ESRC as part of the Antimicrobial Cross Council initiative supported by the seven UK research councils, and also the support of the Global Challenges Research Fund, is gratefully acknowledged. The funders had no role in the design and conduct of the study; collection, management, analysis, review, or approval of the manuscript; and decision to submit the manuscript for publication. RA, EC, AH, TMR and NZ acknowledge funding from the National Institute for Health Research, UK Department of Health [HPRU-2012-10047] in partnership with Public Health England. BDF and MMc acknowledge the NIHR Imperial Patient Safety Translational Research Centre. MMc is also supported by the ESRC. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, PHE or the Department of Health and Social Care.

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