



Review

Global knowledge gaps on antimicrobial resistance in the human health sector: A scoping review



Raph L. Hamers^{1,2,*}, Zlatina Dobрева³, Alessandro Cassini^{3,4,5}, Alice Tamara¹, Gilbert Lazarus¹, Koe Stella Asadinia¹, Stefano Burzo³, Ioana Diana Olaru^{6,7}, Daniele Dona^{3,8}, Fiona Emdin⁹, Kitty Van Weezenbeek³, Silvia Bertagnolio³

¹ Oxford University Clinical Research Unit Indonesia, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

² Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK

³ Antimicrobial Resistance Division, World Health Organization, Geneva, Switzerland

⁴ Public Health Department, Canton of Vaud, Lausanne, Switzerland

⁵ Infectious Diseases Service, Lausanne University Hospital, Lausanne, Switzerland

⁶ Institute of Medical Microbiology, University of Münster, Münster, Germany

⁷ Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

⁸ Division of Paediatric Infectious Diseases, Department for Women's and Children's Health, University of Padua, Padua, Italy

⁹ Global Strategy Lab, Toronto, Canada

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ABSTRACT

Objectives: To identify and summarize existing global knowledge gaps on antimicrobial resistance (AMR) in human health, focusing on the World Health Organization (WHO) bacterial priority pathogens, *Mycobacterium tuberculosis*, and selected fungi.

Methods: We conducted a scoping review of gray and peer-reviewed literature, published in English from January 2012 through December 2021, that reported on the prevention, diagnosis, treatment, and care of drug-resistant infections. We extracted relevant knowledge gaps and, through an iterative process, consolidated those into thematic research questions.

Results: Of 8409 publications screened, 1156 were included, including 225 (19.5%) from low- and middle-income countries. A total of 2340 knowledge gaps were extracted, in the following areas: antimicrobial research and development, AMR burden and drivers, resistant tuberculosis, antimicrobial stewardship, diagnostics, infection prevention and control, antimicrobial consumption and use data, immunization, sexually transmitted infections, AMR awareness and education, policies and regulations, fungi, water sanitation and hygiene, and foodborne diseases. The knowledge gaps were consolidated into 177 research questions, including 78 (44.1%) specifically relevant to low- and middle-income countries and 65 (36.7%) targeting vulnerable populations.

Conclusion: This scoping review presents the most comprehensive compilation of AMR-related knowledge gaps to date, informing a priority-setting exercise to develop the WHO Global AMR Research Agenda for the human health sector.

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Introduction

The global increase in antimicrobial resistance (AMR) is considered one of the greatest public health threats, with a disproportionate burden in low- and middle-income countries (LMICs) [1]. Antibiotic-resistant bacterial infections were estimated to

be directly responsible for 1.27 million deaths and associated with 4.95 million deaths in 2019 alone [2]. Globally, there were an estimated 450,000 incident cases of multi-drug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB), and 191,000 associated deaths in 2021, with increasing trends for several regions and high-burden countries [3]. Increasing trends of invasive fungal diseases constitute a growing concern worldwide, particularly among immunocompromised populations, although data on antifungal resistance patterns are lacking [4,5]. The main drivers of the emergence of AMR in micro-organisms include antimicrobial expo-

* Corresponding author: Tel: +62 811180912.

E-mail address: rhamers@oucru.org (R.L. Hamers).

sure; lack of access to clean water, sanitation and hygiene (WASH), poor infection prevention and control (IPC) in health care facilities; poor access to quality-assured medicines (including new and existing essential antimicrobials), vaccines and diagnostics; lack of awareness and knowledge; and lack of enforcement of legislation [6].

Concerted efforts have been made to develop strategies to mitigate the global impact of AMR. The World Health Organization (WHO) coordinated the development of a Global Action Plan (GAP) on AMR in 2015 [7]. The GAP identified targeted research as one of five strategic objectives, highlighting the importance of a solid evidence base for interventions to measure, prevent, diagnose, and manage drug-resistant infections. Despite progress, there is an urgent need to expand the evidence on the AMR burden and its drivers, on tools and interventions for AMR prevention, diagnosis, and treatment and care, also considering impact, prioritization, cost-effectiveness, financing, and how to deliver them at scale [8–11].

To accelerate a coordinated and effective global effort in line with the pressing timeline to attain the 2030 Sustainable Development Goals (SDGs), WHO has been mandated to develop a Global Research Agenda for AMR for the human health sector [12] that aims to provide an assessment and prioritization of knowledge gaps related to AMR in WHO bacterial priority pathogens [13], *Mycobacterium tuberculosis* and fungi of critical importance for AMR [4]. We conducted a comprehensive scoping review of the global gray and peer-reviewed literature that sought to identify existing knowledge gaps on the burden, drivers, technologies, tools, and interventions for the prevention, diagnosis, treatment, and care of infections with antimicrobial-resistant pathogens, and the best ways to deliver these. This scoping review will result in a set of consolidated, thematic research questions, which will provide a framework to inform the subsequent priority-setting exercise.

Methods

Study design

Scoping reviews are often defined as a process of summarizing (“mapping”) a range of evidence to convey the breadth and depth of a field and are an increasingly popular approach to reviewing health research evidence [14]. We adhered to the methods developed by Arksey and O'Malley [14], Levac et al. [15] and the Joanna Briggs Institute [16], following a six-stage process of defining the scope and main question of the scoping review; searching for relevant documents; document selection; data extraction; collating, summarizing and reporting results; and consulting stakeholders. The scoping review protocol has been previously published [17]. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) (Supplementary Material) [18]. The scoping review was conducted between November 01, 2021, and September 30, 2022.

Search strategy and selection criteria

The scope of the review is summarized in Table S1. Given that the scoping review aimed to identify and compile knowledge gaps rather than individual research findings, our search strategy mainly focused on reports, guidelines, and systematic reviews, and not on individual original research studies. We searched the following information sources of peer-reviewed and gray literature to identify relevant documents in areas relevant to AMR (Table S2):

- A systematic search of peer-reviewed systematic reviews in three bibliographic databases (PubMed, Embase, and Web of Science). The searches were jointly developed and conducted

by the core team and an experienced WHO librarian (full search terms in Tables S3, S4, S5);

- A hand search of WHO guidelines and other publications in relevant WHO repositories (WHO Institutional Repository for Data Sharing, Data Platform, The Global Health Observatory, and WHO Observatory for Health R&D);
- A hand search of the websites of 92 key organizations in the area of AMR, identified through a stakeholder mapping exercise (Table S6), supplemented with a Google search including the terms “filetype:pdf” and “antimicrobial resistance”.

The searches were restricted to the English language and the 10-year period from January 01, 2012, through December 31, 2021. The search results were reviewed by the WHO Core Steering Group on AMR, and any additional relevant publications suggested by its members were also considered. The scoping review involved only documents available in the public domain and did not include any personal information on individuals; therefore, ethical approval was not required.

Documents were included if they (1) described one or more knowledge gaps on AMR, including priorities, framework, components, elements, or steps for the description (i.e., epidemiology, burden, and drivers), delivery, development and/or discovery of tools, products, or interventions for AMR prevention, diagnosis and/or treatment and care; and (2) had a global or regional application and/or relevance for LMICs. Documents were excluded if they (1) only described original research studies or case reports; (2) were not related to bacteria included in the WHO bacterial priority pathogen list, *M. tuberculosis* or selected fungi (i.e., *Candida* spp. and *Aspergillus* spp.); (3) were related to the nonhuman sector; (4) had no identifiable authors, publisher and/or year of publication. The searches comprised an iterative process involving searching the literature, reviewing documents by the predefined eligibility criteria, and refining the search strategy as needed. All steps in the literature search were conducted using Mendeley reference manager. Two reviewers (KSA, EE, GL, RLH) separately screened all titles and abstracts. Full-text articles were independently evaluated by at least two reviewers (AT, GL, KSA, KS, FE, RT, RLH). We assessed the degree of agreement of document inclusion between the first and second reviewer (Tables S7, S8, S9). Any disagreement on document inclusion was resolved by a senior researcher (RLH). Duplicate documents were removed manually as well as by using automated tools (i.e., Mendeley for gray literature and Bramer method [19] for bibliographic databases). Superseded documents were excluded. We did not perform a formal assessment of the methodological quality of the included documents as the purpose was to achieve a broad description of existing knowledge gaps.

Extraction of knowledge gaps

Data elements were extracted using a data extraction form developed in Microsoft Excel, which was updated during the iterative extraction process. The content of the included documents was read to identify relevant knowledge gaps within the scope of the review. A single reviewer (RLH, AT, GL, KSA, KS, FE, RT) extracted explicitly stated knowledge gaps, as well as text extracts to formulate knowledge gaps, each in question format.

Each identified knowledge gap was classified according to a predefined “knowledge matrix”, comprising three people-centered themes (prevention, diagnosis, treatment, and care) [20] and four research domains from the Child Health and Nutrition Research Initiative (CHNRI) (description, delivery, development, and discovery research) [21,22] (Table S10). Each knowledge gap was annotated with relevant attributes, such as research discipline, AMR-relevant area, socio-economic context, sub-population, and target pathogen. At least two other team members (AT, GL, AC, RLH) of

the core team reviewed the extracted knowledge gaps and annotations and ensured data extraction was accurate and consistent with the defined scope. The whole exercise resulted in a database of annotated knowledge gaps.

Consolidation of research questions

In the first round of review, the knowledge gaps were consolidated into higher-level thematic research questions, by removing duplicates, merging overlapping knowledge gaps, and rejecting invalid knowledge gaps, where appropriate and feasible. In doing so, groups of knowledge gaps were curated and listed under the pertinent research question. Each research question was formulated as a statement in the PI/ECO (population, intervention/exposure, comparator, outcome) format, where possible, and annotated with relevant attributes (as above). In the second round of review, core team members (ZD, DD, IDO, SB), who had not been involved in the knowledge gap extraction and consolidation process, advised on further merging, rejecting, and/or rephrasing the research questions. In the third round of review, experts from the WHO Core Steering Group on AMR reviewed the research questions to improve clarity, remove redundant research questions, and propose new research questions to fill any remaining gaps.

Data collation and analysis

We used descriptive analytics to present numerical and thematic summaries of the key characteristics of included documents, knowledge gaps, and research questions. All analyses and visualizations were conducted in R version 4.2.1 and GraphPad Prism version 7.0a.

Results

Characteristics of included documents

The search gave 13,786 hits from peer-reviewed (12,897) and gray literature (889), of which after duplicate removal 8409 (7585 and 824, respectively) remained. After title and abstract screening, 3169 documents remained (Figure S1). After full-text screening, 1156 documents were included, comprising 979 from bibliographic databases; 108 through the websites of 92 key organizations; 29 WHO guidelines and other publications; and 40 documents additionally suggested by the WHO Core Steering Group on AMR. Document characteristics are summarized in Table S11. Included publications originated from 68 different countries and included 225 (19.5%) publications originating from LMICs (Table S11 and Figure S2). Most documents were systematic reviews or meta-analyses (749, 64.8%), followed by narrative reviews or editorials (294, 25.4%), reports (61, 5.3%), 39 (3.4%) guidelines or guidance documents, and other (13, 1.1%). Most documents were authored by a research organization (1030, 89.1%), followed by international technical agencies (56, 4.8%), governmental agencies (29, 2.5%), professional associations (17, 1.5%), nongovernmental organizations (14, 1.2%), funding agencies (6, 0.5%), and private for-profit organizations (4, 0.3%). In total, 1069 (92.5%) documents had a global scope, while 41 (3.5%) and 46 (4.0%) had a regional or national scope, respectively. The number of annual publications showed an increasing trend over time (2012–2021), particularly on WHO bacterial priority pathogens, selected fungi, and from LMICs (Figure S3).

Characteristics of extracted knowledge gaps

We extracted a total of 2340 knowledge gaps (Table 1) from documents identified through bibliographic databases (1229, 52.5%), key organizational websites (578, 24.7%), WHO publications (332, 14.2%), and from the WHO Core Steering Group on

AMR (201, 8.6%) (Figure S4). Pharmacological and clinical research (1658, 70.9%) was the predominant research discipline, followed by epidemiology (527, 22.5%), behavioral and social science (275, 11.8%), health economics (181, 7.7%), and legislation and regulation (76, 3.2%) (Figure S5). The knowledge gaps covered the three people-centered themes of prevention (747, 31.9%), diagnosis (283, 12.1%), and treatment and care (1310, 56.0%), across the four CHNRI domains of description (627, 26.8%), delivery (1035, 44.2%), development (349, 14.9%), and discovery (329, 14.1%) research (Figure 1).

Antimicrobials (including R&D) (800, 34.2%) were the most frequent AMR area, followed by AMR burden and drivers (526, 22.5%), resistant tuberculosis (505, 21.6%), antimicrobial stewardship (392, 16.8%), diagnostics (266, 11.4%), IPC (254, 10.9%), antimicrobial consumption and use data (175, 7.5%), immunization (79, 3.4%), sexually transmitted infections (75, 3.2%), AMR awareness and education (72, 3.1%), policies and regulations (53, 2.3%), fungi (30, 1.3%), water, sanitation and hygiene (WASH) (17, 0.7%), and foodborne diseases (13, 0.6%) (Figure 1). In total, 704 (30.1%) knowledge gaps specifically targeted WHO bacterial priority pathogens, 505 (21.6%) targeted resistant tuberculosis, and 30 (1.3%) targeted fungi. In total, 2246 (96.0%) knowledge gaps had a global focus, 184 (7.9%) knowledge gaps were specifically relevant to LMICs, and 407 (17.4%) knowledge gaps targeted vulnerable groups (such as neonates, children, pregnant women, or migrants).

Characteristics of the thematic research questions after consolidation

Through an iterative review process, we consolidated the 2340 knowledge gaps into 177 research questions (Table 1 and Figure S6). Pharmacological and clinical research (120, 67.8%) was the predominant discipline, followed by epidemiology (53, 29.9%), behavioral and social science (37, 20.9%), health economics (29, 16.4%), and legislation and regulation (11, 6.2%) (Figure S5). The research questions covered the three people-centered themes of prevention (63, 35.6%), diagnosis (24, 13.6%), and treatment and care (90, 50.8%), across the four CHNRI domains of description (52, 29.4%), delivery (65, 36.7%), development (24, 13.6%), and discovery (36, 20.3%) research (Figure 1).

Antimicrobial stewardship (33, 18.6%) was the most frequent AMR area, followed by antimicrobials (including R&D) (30, 16.9%), AMR burden and drivers (29, 16.4%), resistant tuberculosis (26, 14.7%), diagnosis/diagnostics (24, 13.6%), antimicrobial consumption and use data (22, 12.4%), IPC (19, 10.7%), policies and regulations (12, 6.8%), fungi (11, 6.2%), immunization (9, 5.1%), sexually transmitted infections (7, 4.0%), AMR awareness and education (4, 2.3%), foodborne diseases (2, 1.1%), and WASH (1, 0.6%) (Figure 1). In total, 29 (16.4%) research questions targeted one or more WHO bacterial priority pathogens, 26 (14.7%) targeted resistant tuberculosis, and 11 (6.2%) targeted fungi. All 177 research questions had a global scope, 78 (44.1%) research questions were specifically relevant to LMICs, and 65 (36.7%) targeted vulnerable groups (such as neonates, children, pregnant women, and migrants).

The full list of annotated knowledge gaps and research questions and their distribution by micro-organism group, socio-economic context, and sub-populations are included in Figures S7, S8, S9, and GitHub link.

Discussion

This scoping review presents the most comprehensive and novel compilation of AMR-related knowledge gaps in the public domain to date, published in the ten-year period from 2012 through 2021, covering the prevention, diagnosis, and treatment of infections caused by resistant WHO bacterial priority pathogens,

Table 1
Characteristics of knowledge gaps and research questions.

Characteristics	Knowledge gaps		Research questions	
	N = 2340	%	N = 177	%
Research discipline				
Pharmacological and clinical	1658	70.9	120	67.8
Epidemiology	527	22.5	53	29.9
Behavioral and social science	275	11.8	37	20.9
Health economics	181	7.7	29	16.4
Legislation and regulation	76	3.2	11	6.2
Antimicrobial resistance area				
Antimicrobials (including research and development)	800	34.2	30	16.9
AMR burden and drivers	526	22.5	29	16.4
Tuberculosis	505	21.6	26	14.7
Antimicrobial stewardship	392	16.8	33	18.6
Diagnosis/diagnostics	266	11.4	24	13.6
Infection prevention and control	254	10.9	19	10.7
Antimicrobial consumption and use data	175	7.5	22	12.4
Immunization	79	3.4	9	5.1
Sexually transmitted infections	75	3.2	7	4.0
Antimicrobial resistance awareness and education	72	3.1	4	2.3
Policies and regulations	53	2.3	12	6.8
Fungi	30	1.3	11	6.2
Water, sanitation, hygiene (WASH)	17	0.7	1	0.6
Food-borne diseases	13	0.6	2	1.1
Geographical scope/focus				
Global	2246	96.0	177	100.0
Regional ^a	105	4.5	7	4.0
Africa	41	1.8	0	0.0
Southeast Asia	29	1.2	0	0.0
Western Pacific	23	1.0	0	0.0
Americas	8	0.3	0	0.0
Eastern Mediterranean	6	0.3	0	0.0
Europe	5	0.2	0	0.0
National	99	4.2	11	6.2
Subnational/local	13	0.6	1	0.6
Socio-economic context				
General/Unspecified	2171	92.8	163	92.1
Low- and middle-income countries	184	7.9	78	44.1
Sub-populations				
General/Unspecified	2092	89.4	171	96.6
Children	201	8.6	21	11.9
Immunocompromised	96	4.1	21	11.9
Neonates	49	2.1	7	4.0
Pregnant women	33	1.4	13	7.3
Older persons	20	0.9	2	1.1
Migrants and displaced populations	8	0.3	1	0.6
Setting				
General/Unspecified	1774	75.8	21	11.9
Health care system	490	20.9	141	79.7
Acute-care hospitals	140	6.0	22	12.4
Intensive care unit	90	3.8	6	3.4
Primary care	56	2.4	8	4.5
Long-term care facilities	36	1.5	6	3.4
Community	109	4.7	65	36.7
Micro-organism				
General/Unspecified	1107	47.3	113	63.8
World Health Organization bacterial priority pathogens	704	30.1	29	16.4
Enterobacterales – carbapenem-resistant, ESBL-producing ^b	244	10.4	3	1.7
<i>Staphylococcus aureus</i> – methicillin, vancomycin-resistant	178	7.6	7	4.0
<i>Pseudomonas aeruginosa</i> – carbapenem-resistant	147	6.3	3	1.7
<i>Acinetobacter baumannii</i> – carbapenem-resistant	140	6.0	2	1.1
<i>Neisseria gonorrhoeae</i> – 3rd generation cephalosporin-resistant	78	3.3	7	4.0
<i>Helicobacter pylori</i> – clarithromycin-resistant	42	1.8	2	1.1
<i>Enterococcus faecium</i> – vancomycin-resistant	27	1.2	2	1.1
<i>Streptococcus pneumoniae</i> – penicillin-resistant	20	0.9	1	0.6
<i>Salmonella</i> spp. – fluoroquinolone-resistant	9	0.4	1	0.6
<i>Campylobacter</i> spp. – fluoroquinolone-resistant	4	0.2	0	0.0
<i>Shigella</i> spp. – fluoroquinolone-resistant	4	0.2	1	0.6
<i>Haemophilus influenzae</i> – ampicillin-resistant	3	0.1	0	0.0
<i>Mycobacterium tuberculosis</i>	505	21.6	26	14.7
Multidrug-resistant (MDR-TB)	460	19.7	26	14.7
Extensively drug-resistant (XDR-TB)	291	12.4	23	13.0
Rifampicin-resistant (RR-TB)	278	11.9	15	8.5
Isoniazid-resistant (Hr-TB)	267	11.4	15	8.5
Pre-extensively drug-resistant (Pre-XDR-TB)	240	10.3	15	8.5

(continued on next page)

Table 1 (continued)

Characteristics	Knowledge gaps		Research questions	
	N = 2340	%	N = 177	%
Fungi	30	1.3	11	6.2
<i>Candida</i> spp.	16	0.7	8	4.5
<i>Aspergillus</i> spp.	6	0.3	4	2.3

TB, tuberculosis.

Numbers in table represent number of knowledge gaps or research questions (percentage of column total). Numbers per category may not add up to the total N knowledge gaps or research questions, because they could be assigned to more than one category.

^a World Health Organization regions.

^b Includes *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., and *Morganella* spp.

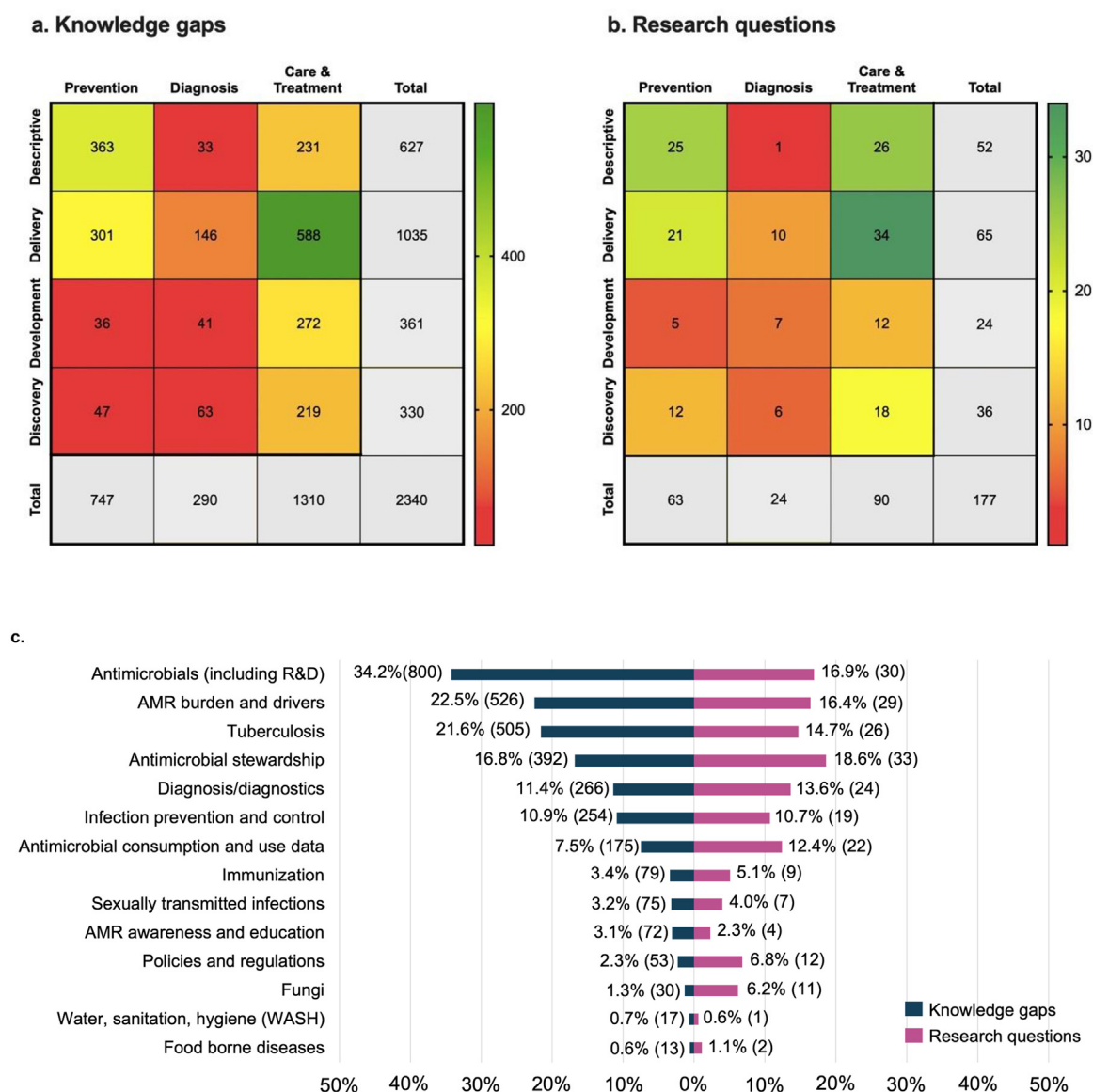


Figure 1. Distribution of the extracted knowledge gaps (a) and thematic research questions (b) across the “knowledge matrix” as well as across all AMR-related areas (c). Heatmaps showing the distribution of (a) extracted knowledge gaps (n = 2340) and (b) thematic research questions (n = 177) based on the “knowledge framework” by people-centered themes (prevention, diagnosis, care, and treatment) and Child Health and Nutrition Research Initiative-domains (descriptive, delivery, development, and discovery research). (c) Tornado plot showing the distribution of the 2340 knowledge gaps and 177 thematic research questions across the 14 areas related to AMR. Numbers (%) per category may not add up to the total N (100%) knowledge gaps and research questions, because each knowledge gap and research question could be assigned to more than one category.

Abbreviations: AMR, antimicrobial resistance; WASH, water, sanitation, and hygiene.

M. tuberculosis and selected fungi (i.e., *Aspergillus* spp. and *Candida* spp.), across all areas relevant to AMR, geographic regions, socio-economic contexts, and sub-populations. Overall, the increasing number of AMR-related publications during recent years seems to reflect the increasing AMR burden as well as a growing recognition of AMR in the global health agenda. Although still lagging behind high-income settings, the number of publications addressing AMR-related issues specifically relevant to LMICs has increased over time, especially those related to the WHO bacterial priority pathogens and the selected fungi. The publication of the GAP on AMR in 2015 [7] and the WHO bacterial priority pathogen list in 2017 [13] may have provided an impetus to producing an improved evidence base as well as highlighting remaining research gaps, although their direct influence on the scale of research funding, as well as the scope and impacts of ongoing and planned research programs, is difficult to ascertain.

The identified knowledge gaps on WHO bacterial priority pathogens and selected fungi mainly relate to the treatment and care and prevention of infections with drug-resistant pathogens, whereas significantly fewer knowledge gaps highlighted the need for further research on diagnostic tests and other tools for pathogen identification, AMR testing, and clinical decision-support tools. This finding reflects the neglected importance of quality-assured laboratory capacity and related innovations, especially in LMICs, where the lack of accessible, robust diagnostic processes results in poor patient outcomes, irrational antimicrobial use, and further emergence and spread of AMR. By contrast, we identified a substantial number of knowledge gaps related to diagnostic tests and related tools for resistant tuberculosis, which can be explained by decades of significant financial support for tuberculosis programs in LMICs (e.g., Global Fund).

Overall, the most frequently reported knowledge gaps concerned antimicrobial research and development, AMR burden and drivers, resistant tuberculosis, and antimicrobial stewardship followed by diagnostics, IPC, antimicrobial consumption and use data, immunization, sexually transmitted infections, AMR awareness and education. However, the following areas were found to be markedly less represented in the scoping results: WASH, foodborne diseases, fungi, and policies and regulations. The paucity of knowledge gaps on WASH and foodborne diseases could be explained by the fact that these areas lay at the interface of environmental, animal, plant, and human sectors (“One Health”), which was outside the scope of this review (and will be covered by the complementary WHO One Health Priority Research Agenda for AMR [12]). Fungal diseases remain a neglected topic by public health authorities and research funders, despite the increasing incidence of fungal diseases in both LMICs and high-income countries [4,5]. To ensure that these underrepresented areas receive sufficient consideration at the prioritization stage, we deliberately augmented policies and regulations and fungi among the consolidated 177 higher-level thematic research questions. The consolidation process also ensured that delivery and development questions are also being considered, which are particularly important to address current policy-practice gaps and inform specific interventions to mitigate the impact of AMR.

Although our scoping review captured a significant breadth and scope of knowledge gaps related to AMR, it is important to note that the frequency or “popularity” of certain knowledge gaps as reported in the global literature was not necessarily a proxy for areas of greatest research priority or impact. The current set of 177 research questions will be scored and prioritized by a group of independent experts in the field of AMR to develop the WHO Global Research Agenda for AMR in the human health sector in 2023. Supplementing existing research agendas from several key actors and funders in the area of AMR, for example, the European Commission Joint Programming Initiative on AMR [23] and the Well-

come Trust [24], this Agenda is expected to catalyze investment and scientific interest among the global scientific community, funders, and governments to address high-priority knowledge gaps to inform effective global, regional and national policies on AMR, particularly in LMICs, by 2030 [12]. Novel approaches that integrate the WHO bacterial and fungal priority pathogens and resistant tuberculosis are expected to stimulate shared political momentum, advocacy, funding frameworks, and cross-disciplinary research and innovation.

Several previous initiatives have attempted to list research gaps related to AMR. In February 1999, the first WHO consultation identified research needs across the areas of prescriber behavior, patient/public behavior, laws and regulations, pharmaceutical industry (including promotional activities and R&D), pharmacological and clinical issues, microbial genetics and ecology, detection and surveillance of AMR, and nonhuman use of antimicrobials [25]. The GAP on AMR (2015) listed important knowledge gaps, including the epidemiology, development, and spread of AMR; the ability to rapidly characterize and elucidate mechanisms of newly emerged AMR; effective antimicrobial stewardship programs; optimal treatments and prevention of common bacterial infections, especially in LMICs; development of new treatments, diagnostic tools, vaccines, and other interventions; and the cost of AMR [7]. A recent scoping review of the literature from 2015–2019, although somewhat limited in its scope and methodology (e.g., did not include gray literature, tuberculosis, or fungi), highlighted the need for a better understanding of the magnitude and transmission of AMR across human, environmental, and agricultural reservoirs, interventions to mitigate drug-resistant infections, particularly in LMICs, and research investigating awareness and behavior related to AMR [26]. Further previous initiatives have focused on specific areas in AMR, for example, interventions to reduce antibiotic prescribing in LMICs [27]; prevention of AMR healthcare-associated infections [28]; government policy interventions to reduce human antimicrobial use [29]; and the programmatic management of resistant tuberculosis [30]. Our scoping review has considered all abovementioned publications in the knowledge gap identification process.

Scoping reviews are an increasingly important method of knowledge synthesis and were deemed the most suitable design for our purpose. In doing so, we expanded the standard CHNRI approach, which is typically based on research ideas submitted by invited experts [21,22]. Nonetheless, there are some study limitations. First, we cannot rule out the possibility that we missed any relevant knowledge gaps, and further expert consultations will ensure that any omissions are identified and supplemented. Second, although the consolidation of extracted knowledge gaps into thematic research questions was conducted through several iterations with the core study team and WHO Core Steering Group on AMR, there is a possibility that personal views and knowledge of the investigators may have influenced the selection and phrasing of the research questions. Lastly, this scoping review was restricted to English language documents, which could have biased the overall result to be more representative of high-income, English-speaking countries. We have made a deliberate effort to account for this bias by formulating research questions that targeted AMR issues specifically relevant to LMICs (representing 44% of the total).

In conclusion, our study is the most comprehensive compilation of existing knowledge gaps and research questions related to AMR in the human health sector to date. The results of this review will provide a framework to inform a priority-setting exercise, toward the development of a WHO Global AMR Research Agenda for the human health sector, to catalyze evidence-based interventions and research investments with the highest impact to mitigate the global burden of AMR by 2030.

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Ethical approval

The scoping review involved only documents available in the public domain, and did not include any personal information on individuals; therefore, ethical approval was not required.

Declaration of Competing Interest

ZD, KvW, and SBe are World Health Organization (WHO) employees. AC was a WHO employee. SBU and DD are consultants to WHO. RLH was a consultant to WHO and is also supported by the Wellcome Trust (106680/Z/14/Z). The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of WHO or any of the institutions mentioned.

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Author contributions

SBe is the project leader. RLH, AC, and SBe conceptualized the project. RLH, AC, KSA, and SBe developed the protocol and search strategies. RLH, KSA, and AC designed and tested the data extraction tools. RLH, AT, AC, GL, KSA, and FE conducted the literature searches, extracted the data and formulated the knowledge gaps. RLH, ZD, AC, AT, GL, SBU, IDO, DD, FE, and SBe consolidated the knowledge gaps into thematic research questions. RLH, AT, and GL performed the data analysis and visualization, with input from ZD, SBU, IDO, and SBe. RLH drafted the manuscript, with critical input from AT, ZD, SBU, IDO, DD, KvW, and SBe. All authors critically reviewed the paper for important intellectual content and approved the final version of the manuscript.

Data availability statement

All data relevant to the study are included in the article or supplemental material. The complete annotated database of the included documents, knowledge gaps, and research questions can be downloaded from: <https://github.com/gilbertlrus/AMR-scoping-review/tree/8439c474899238b9b27ef3eb1ea2429a53c94301>

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijid.2023.06.004](https://doi.org/10.1016/j.ijid.2023.06.004).

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