Healthcare as a driver and casualty of antimicrobial resistance: Opportunities for interventions

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Abstract | Antimicrobial resistance (AMR) is a global health challenge that threatens human, animal and environmental conditions. Evidence is emerging for the role healthcare infrastructure, environments and patient pathways play in promoting and maintaining antimicrobial resistance via direct and indirect mechanisms. Advances in vaccination and monoclonal therapies alongside integrated surveillance, rapid diagnostics, targeted antimicrobial therapy and infection control measures offer opportunities to address healthcare-associated AMR risks more effectively. Additionally, innovations in AI, data linkage and intelligent systems can be employed as overarching methods to better predict and personalise the fight against AMR. In this review, we examine the mechanisms by which healthcare acts as a driver, reservoir and amplifier of AMR contextualised within a One Health framework, and the opportunities and innovative solutions that can be employed to combat AMR throughout the patient journey. We provide a perspective on the current evidence base for interventions designed to mitigate healthcare-associated AMR and promote healthcare resilience within high-income and resource limited settings, in conjunction with the challenges to their implementation.

Introduction

Antimicrobial resistance (AMR) constitutes a present and ongoing risk to human life and healthcare resilience, threatening the safe provision of clinical care with an associated economic and societal impact [1]. Various human, animal and environmental factors play a role in driving AMR [2], although, to date, the relative proportion of the global epidemiology of AMR attributed to each of these One Health sectors remains largely unknown. Variations in healthcare systems, structures, environments and processes, and their design and utilisation by staff and patients may promote the emergence and spread of AMR. The impact of these activities on AMR are seen beyond the frontiers of the healthcare system. For example, individuals acquiring resistant micro-organisms during their healthcare pathway serve as reservoirs for human-to-human transmission in healthcare and community settings [3,4], and antimicrobials and antibiotic-resistant organisms (AROs) released from healthcare facility sewage can potentiate the spread of AMR into environmental and animal compartments [5]. In this regard, healthcare can act as a powerful driver and amplifier of AMR globally, with setting-specific risks.

For over two decades, concerted efforts have been made globally to improve infection prevention, diagnostic, and treatment options to mitigate AMR in healthcare. Although these efforts have produced some effect, AMR persists and is even progressing amongst patient populations, hampering our ability to curtail the AMR crisis globally. It is therefore imperative that the key role healthcare plays in the maintenance and transmission of AMR is better appreciated, and interventions, innovations and opportunities to address AMR are considered which also protect the delivery of safe healthcare [6]. Within this review, using the patient pathway as a focus, we evaluate the mechanisms by which healthcare acts as a driver, reservoir and amplifier of AMR, and present areas for innovation, illustrating how these can be implemented to prevent AMR, both within healthcare, and beyond healthcare networks. We describe how advances in surveillance, diagnostics, preventative-therapies and targeted antimicrobials, combined with novel approaches to the delivery of care and individualised medicine technologies, can be integrated across the patient journey to protect individuals and populations from healthcare-associated AMR. Interventions need to be tailored for the variable contexts globally, and methods to make assesments of relevance and fit are included along with barriers to actions and future challenges. Lastly, we highlight how adoption of these systems and approaches would strengthen our ability to deliver safe healthcare and promote healthcare resilience.

[H1] The role of healthcare as a driver, reservoir and amplifier of AMR

Healthcare is delivered across a range of settings, from informal care/self-care, rural health centres, community and social care facilities to tertiary hospitals. The design of health systems and healthcare infrastructure (Bismark, Beveridge, single/multi-payer national insurance, out-of-pocket or pluralistic) and resulting capacity, differs globally, with variation in financing and care delivery having implications for public/patient health seeking, healthcare professional

motivations and behaviours and governance approaches [7]. Healthcare serves as a continuum of processes and activities along a patient journey and can drive AMR through several interlinked mechanisms, influenced by a variety of contributing factors (**Figure 1**).

By its nature, healthcare brings people together within shared spaces and along pathways that expose them to risks of AMR transmission, either from patients or staff colonised with AROs [8,9] or contaminated environments [10]. Particular healthcare settings and pathways provide enhanced risks, congregating the most vulnerable individuals together, often with increased antibiotic exposures and high levels of environmental contamination [11]. For example, immunosuppressed patients, such as those undergoing chemotherapy for cancer or haematological malignancies frequently require antibiotics for sensitive or resistant infections [12] promoting AMR colonisation [13]. Antibiotic-induced overgrowth of ARO (e.g., *Enterobacterales* in the gut microbiota) [14] associated with faecal incontinence and diarrhoea contribute to the subsequent dissemination of AMR into the healthcare environment [15]. Even short courses of antibiotics given to hospitalised patients can select for persistent gut colonisation of ARO over extended periods of time [4,16]. Once exposed to ARO, individual patient factors, such as those affecting the stability of their microbiome (e.g. severity of illness or immunosuppression) can trigger acquisition [17,18]. Modifications of antibiotic therapies (e.g., preferential use of narrower spectrum antibiotics) or therapies reducing the gastric acidity (e.g., avoidance of proton-pump inhibitors) may preserve the human microbiome [17]. Selective pressures exerted by antibiotics can drastically alter the ecological equilibrium of a patient's microbiota. By lowering the bacterial diversity they disrupt the resistance to colonisation of the microbiome [19]. This "dysbiosis" enables the colonisation by AMR organisms, with increased load, and dissemination of antimicrobial resistance genes (ARGs) (i.e., resistome). Antibiotic-resistant opportunistic pathogens and pathobionts can frequently persist asymptomatically within an individual's microbiota, including hard-to-treat pathogens such as carbapenemase-producing *Enterobacterales* (CPE) and vancomycin-resistant enterococci (VRE) [20,21]. This process of continuous pressure from healthcare-associated antibiotic exposures increases colonisation with ARO and amplifies resistance, leading to local outbreaks of AROs. Globally, neonatal units suffer a high burden from neonatal sepsis with resistant infections, particularly in resource-limited settings, and are increasingly recognised as hotspots for outbreaks of AROs [23]. Similarly, drug-resistant outbreaks are seen in intensive care units [10], where patients are regularly prescribed broad spectrum antibiotics and frequently colonised with drug-resistant organisms [24]. Nosocomial transmission in these locations further amplifies resistance, and can be associated with factors such as invasive procedures or indwelling devices, mechanical ventilation, levels of staffing and workforce education [25]. Antimicrobial stewardship programmes represent a core element for the overall and individual-level reduction of selective pressure in hospitals [22].

The proximity of individuals to ARO colonised patients represents a first exposure. In a study of patients treated in healthcare from across 41 European countries, 16.6% carried multi-drug resistant organisms (MDROs) varying from 12.1% to 38.1% [26]. Globaly, higher rates of extended-spectrum beta-lactamase (ESBL) *Enterobacterales* colonisation are generally found in healthcare

versus community settings [27], with some studies in low-income settings showing particularly high levels within hospital cohorts [28]. Thus, the exposure and risk of acquisition of ARO can increase once admitted in hospital, and vary according to the local epidemiology, the type of setting (i.e., a higher exposure in intensive care unit (ICU)), the type of care required, the severity of illness and the length of stay. Secondly, contamination of staff hands, gowns, gloves and equipment can potentially transmit ARO to patients [29]. Colonisation of healthcare workers (HCWs) with ESBL bacteria have been reported at rates between 4.6%–18.9%, likely to be equivalent to community exposure [30]. However, colonisation of staff with methicillin-resistant *Staphylococcus aureus* (MRSA) ranges from 17% to 20% in some settings and is recognised as a risk factor for patient acquisition. Thirdly, patients acquire bacteria from the environments in which they are situated, such as the hospital room during the first days of admission, and then transmit their own microbiota within the room during their stay [31]. Admission to a location which has previously been occupied by a patient infected or colonised with a specific pathogen therefore becomes a risk factor for acquisition [32]. Distinct ecological niches of microbes and antibiotic resistance genes co-exist, characterized by biofilm-forming and human-microbiome-influenced environments [33]. ARO can persist in hospitals for extended periods (>8 years), and opportunistically colonise and infect patients [33]. Some pathogens are predicated for the healthcare environment, colonising key surfaces (e.g., sinks/drains) [34,35] or hospital equipment [10], and provide an environmental reservoir for AROs with direct links to patient infections [34]. Colonised individuals and contaminated healthcare environments can then serve as reservoirs of ARO, and healthcare settings in turn, become distribution centres [36], amplifying ARO [37], that can be recycled within healthcare settings [3,10,34,36] or dispersed into the community [4,16].

Ineffectual or sub-optimal hygiene and infection control measures in healthcare settings provide human (i.e., hand-hygiene) and environmental (i.e., contaminated surfaces) factors that promote the exposure, transmission and acquisition of ARO / MDROs [32,34] and HCAIs [10,36]. In resource limited settings, underfunding, inadequate staffing, absent or ineffectual infrastructure and lack of access to water sanitation and hygiene (WASH) facilities pose significant challenges to controlling environmental contamination and maintaining IPC practices, increasing the risks of HCAIs [38,39]. HCAIs are also an important driver of antibiotic usage. Within European hospitals, 1 in 5 antibiotics are prescribed for infections directly acquired within healthcare premises [40]. HCAIs caused by bacteria or fungi, such as staphylococcal, pseudomonal or *Candida* spp. are often highly resistant [10,41], requiring the use of reserve antibiotics, longer hospital admissions [41,42] and are associated with increased mortality [42]. HCAIs from viral aetiologies such as SARS-CoV-2 or influenza are associated with increased antibiotic exposures [43], contributing to the generation of AMR through antibiotic-induced selection pressures [44].

The movement of people through healthcare settings and across international borders can promote the transmission of AMR [45]. Transferring patients between beds and wards within healthcare can drive nosocomial outbreaks [46]. Nursing home residents, who themselves have high rates of antibiotic usage [47] and colonisation with MDRO, including increasing important fungi such

as *Candida auris* [48,49] are frequently transferred between hospitals and community settings, and this process can potentiate or sustain epidemics across the healthcare network [3,48]. International human movement, whether related to short-term travel, migration or through forcible displacement can be associated with high rates of AMR and HCAIs [50]. Additionally, the operational aspects of healthcare systems can influence the spread of AMR within the healthcare network, especially when services designed to control AMR break down. This is impacted by a broad range of external drivers such as economic and human resource investment, conflict scenarios or the effects of climate change [45,51,52].

The physical architecture and utilisation of the healthcare environment also impacts the spread of resistance [53]. Single rooms can reduce cross-transmission, and temperature, humidity, and hospital water sources effect contamination levels with ARO [31]. Animals, such as flies, cockroaches, rodents or geckos that interact with hospital environments may act as reservoirs or vectors of AMR transmission [54]. Lastly, the dispersal of hospital waste may impact downstream AMR risks. Hospital wastewater provides an outflow of resistance-driving chemicals such as antibiotics, biocides, and ARGs and AROs into the broader environment [55]. The precise role that hospital effluent plays in the maintenance and promotion of human AMR is unclear. Nevertheless, the failure of hospital sewage treatment to eradicate resistance-driving chemicals, ARGs and ARO in high-income settings, and limited sewerage treatment in resource-limited settings enable AMR entry into the food chain and contamination of drinking water [55] which may pose risks for onward transmission [56].

[H1] Use of vaccines and immunotherapy to prevent healthcare-associated infections and minimise AMR.

[H2] Vaccines

Vaccines impact AMR through the prevention of infections associated with antimicrobial usage or the reduction in the incidence of disease by sensitive or resistant pathogens, via direct or indirect protection, without major side effects [57,58]. The most common cause for inappropriate antimicrobial prescribing comes from vaccine preventable respiratory diseases, such as influenza, COVID-19 or respiratory syncytial virus (RSV) [59]. In the recent pandemic, up to three-quarters of patients with COVID-19 received an antibiotic, despite the absence of data supporting a coexisting bacterial or fungal coinfection [43,60]. Pre-COVID-19 pandemic, RSV accounted for ~10% of antibiotic prescribing in primary care in the UK, amounting to >400,000 antibiotic prescriptions annually [61]. Optimisation of vaccination coverage can provide a simple method for preventing attributable deaths, and reducing unnecessary antibiotic use within patients situated in community and healthcare settings, with the largest impact felt in low-resource settings [62].

In low- and middle-income countries (LMICs), inappropriate healthcare-associated antimicrobial prescriptions are also commonly seen in the treatment of malaria, typhoid, and arboviral infections [63,64]. Large-scale campaigns for safe and efficacious typhoid conjugate vaccines, intelligent use of malaria and dengue vaccines are being considered to reduce AMR through inappropriate prescribing [65,66]. Gastrointestinal infections, which account for 29.3% of diarrhoea-related deaths in young children in resource-limited settings are of key importance [67]. Here, the implementation of rotavirus vaccination protects against severe disease [68] and its rollout is currently estimated to prevent 13.6 million episodes of antibiotic-treated illness annually among children <5 years old [69]. The rotavirus vaccine also provides an excellent example of how vaccines can prevent healthcare attendance and admissions, including indirect protection of non-vaccinated individuals within the community [70]. Vaccine-induced reduction in healthcare attendance has been seen for a range of vaccines and can limit exposure risks to HCAI and antibiotic usage, reduce AMR transmission in hospital and community settings, and improve healthcare functionality [59,71] (**Figure 2**).

Vaccines that target bacterial pathogens harbouring drug-resistant strains of global importance, such as *Streptococcus pneumoniae* and *S. aureus*, are also available. Pneumococcal conjugate vaccines (PCVs) rollout has been well evidenced to reduce antibiotic usage [72], lower rates of antibiotic-resistant invasive pneumococcal infections in children, and reduce non-susceptible invasive infections in populations in both high- and low-income countries [73]. However, the effect of PCVs on AMR has been complicated by the emergence of non-susceptible serotypes, and high residual carriage rates in low-resource settings [74]. Novel *Klebsiella pneumoniae* and *Neisseria gonorrhoeae* vaccines are in clinical trials [75], alongside vaccines in the development pipeline against gram-negative bacteria [75,76] or *Mycobacterium tuberculosis* [76]. For *Clostridium difficile*, the goal of obtaining a preventive vaccine seems to be near [77], and the results of large advanced phase trials will provide information on their effectiveness, cost and tolerance.

Vaccines offer an effective method to decrease the overall burden of HCAIs and associated use of antimicrobials, whether this is from viral (e.g., influenza and COVID-19), or bacterial (e.g., *C. difficile*, *S. aureus* and gram-negative pathogens) aetiologies [78]. Vaccination can take place pre-admission, throughout attendance or during periods of follow-up. Hospitalisation provides a unique opportunity to track unvaccinated cases [79], especially in vulnerable groups. Targeted vaccination could be incorporated with intelligently-designed surveillance systems, integrated with advances in diagnostic technologies to prevent AMR (**Figure 2**). Vaccines can also be used in surgical populations to reduce post-operative infections with sensitive or resistant *S. aureus* and associated antimicrobial usage. Whilst historical trial data on *S. aureus* vaccines has not yet shown efficacy in reducing *S. aureus* infections amongst surgical cohorts, the use of novel vaccine candidates (e.g., SA4Ag) in elective populations is still attractive, and ongoing trials of these candidates is warranted [80]. The pre-operative phase is critical, and intelligently designed pre-operative pathways that integrate screening and targeted-vaccination is needed. This period also

provides an opportunity to recover missed opportunities for SARS-CoV-2 [81], influenza virus and pneumococcal vaccinations in vulnerable populations, with pre-operative influenza vaccination shown to reduced episodes of pneumonia and in-hospital mortality [82]. Ultimately, improved vaccine uptake will assist with elective surgical system strengthening and surgical preparedness [83].

The recent COVID-19 pandemic highlighted how vaccines can limit stresses on a healthcare-resources and improve health system resilience. COVID-19 disruptions to antimicrobial stewardship and IPC services impacted the ability to control AMR and provide good clinical care [84]. Occupational exposures to infections lead to negative effects on the health and wellbeing of HCWs [85], and opportunities to optimise vaccination in this group could avoid preventable disease, avert transmission of HCAIs [86], and improve heath-system resilience via reduced staff absence [85,87]. Overall, innovations that prioritise and improve vaccination availability and uptake in HCWs, given the hesitancy amoungst HCWs, will enhance patient care, reduce HCAIs and associated antimicrobial usage, whilst simultaneously improving healthcare resilience via staff protection and economic efficiencies.

[H2] Immunotherapy

Preclinical pipelines for antimicrobials highlight a growing number of monoclonal antibody (mAb) programmes for infectious disease [88]. Reverse vaccinology technology is being used to discover therapeutic mAbs against AMR-bacteria [89], and more than 20 mAbs against bacterial pathogens are reaching efficacy evaluation [89], suggesting that mAb may provide a creative alternative in the future. Monoclonal antibodies currently in clinical development include those targeted against *S. aureus* and *Pseudomonas aeruginosa* for prevention or adjunctive treatment of pneumonia or adjunctive treatment of bloodstream infections [90]. Other antibodies have been approved for clinical use include those active against *Clostridium botulinum*, *C. difficile* [91] *and Bacillus anthracis* [90].

Like vaccination, mAbs have the potential to impact AMR via a reduction in HCAIs and the incidence and length of infectivity for diseases associated with antibiotic usage [92] alongside a reduction of ARO colonisation and disease [89,93] (**Figure. 2**). Monoclonal antibodies have the added benefit of being able to generate immediate immune responses, unlike vaccines which require time and competent immune systems; factors which are often lacking in hospitalised patients [94]. The targeted nature of their design also enables them to be less toxic to patients or disruptive to the microbiome than small molecules [93]. Therefore, their use as prophylactic or therapeutic treatment for bacterial infection, particularly in key vulnerable groups, provides an exciting avenue for reducing healthcare-associated AMR [31].

[H1] Combined advances in rapid diagnostics, screening and surveillance, and intelligently-targeted antimicrobial prophylaxis and therapy.

Point-of-care testing (POCT) and novel molecular diagnostics play a pivotal role in transforming how infections are diagnosed and treated. These technologies enable rapid identification of pathogens[95,96] and their antimicrobial resistance profiles [97], and offer the promise for healthcare providers to make timely, informed decisions at the bedside. By facilitating quick and accurate diagnoses, these tests contribute to reducing unnecessary antimicrobial usage and enhancing antimicrobial optimisation, thereby mitigating the selective pressure driving AMR [98,99]. POCTs which differentiate between viral and bacterial infections are an example of a proposed solution in combatting AMR, and the use of rapid-diagnostic tests (RDTs) is recommended by a number of authorities [100,101]. The introduction of rapid POCT for respiratory microbes has been shown to reduce prescriptions in viral respiratory illness [102]. Additionally, molecular tests targeting specific pathogens, like MRSA or *Streptococcus pyogenes*, enable precise identification and tailored treatment, avoiding unnecessary broad-spectrum antibiotics [103,104]. Antimicrobial stewardship is enhanced through the use of rapid POCTs for malaria [63] or arboviruses [105] in travellers and endemic settings. AI-guided analysis of radiological imaging can also be implemented to optimise infection diagnosis in low-resource settings [106], improving antimicrobial stewardship and surveillance. Lastly, the use of POCTs can reduce AMR through indirect mechanisms, and their uptake has been associated with prevention of hospital admissions, helping to control outbreaks and reducing healthcare costs [105,107–109].

Within laboratory settings, rapid AMR diagnostics can be used to augment traditional antimicrobial susceptibility testing, and ongoing research in this field is focused on novel techniques, such as microfluidics, spectroscopy, mass-spectrometry and WGS [97,110,111]. POCT and AMR diagnostics can also be fed back to clinical decision-makers through easy-to-interpret innovations, such as smartphone applications or data platforms, further optimising antimicrobial stewardship [112].

Advancements in precision medicine offer opportunities to optimise antimicrobial usage through tailored therapies and prophylaxis [113]. Tailored antimicrobial prescribing involves the selection of specific agents based on the patient's individual characteristics, including their microbiome, genetic makeup, and susceptibility patterns, and can be targeted at key AMR pathogens in hospital settings [114]. This approach ensures that the chosen antimicrobial is effective against the identified pathogen and minimises collateral damage to the patient's commensal flora. This process can also be dovetailed with diagnostic information to guide antimicrobial selection, dosing, and duration using intelligent data linkage systems.

Precision antimicrobial prescribing relies on the accurate identification of pathogens and their susceptibility patterns. However, challenges exist in rapidly determining antibiotic concentrations to enable dose optimisation, especially in critically ill or overweight patients [115]. Technological solutions, such as continuous monitoring of antibiotic levels in real-time, are needed to overcome these challenges [116]. Studies have shown that precision prescribing, involving selection, dosing and duration of antibiotic, may help prevent CPEs and associated hospital-acquired infections, and play a role in infection prevention and control strategies [114]. Additionally, innovations in wearable devices, sensors and smart technologies could provide a means to achieve this, ensuring that antibiotic doses are tailored to the patient's specific needs, thereby minimising the risk of under- or over-dosing [117]. Improved targeting of prophylaxis, particularly in pre-surgical settings, can contribute to AMR mitigation. Rather than administering broad-spectrum prophylactic antibiotics routinely, tailored prophylaxis considers the patient's individual risk factors and the anticipated pathogens associated with a specific surgical procedure. This strategy reduces unnecessary exposure to antibiotics and the subsequent risk of resistance development [118].

To maximize the impact of rapid diagnostics and screening, it is essential to integrate these technologies seamlessly along the patient pathway [11,119]. This integration spans pre-hospital attendance, inpatient treatment algorithms, and community-based screening and surveillance pathways. For instance, pre-hospital diagnostic tools can aid emergency medical personnel in identifying infectious agents promptly, influencing initial treatment decisions even before hospital admission [120]. In hospitals, the incorporation of rapid diagnostics into treatment algorithms ensures timely and targeted interventions [121]. Community-based screening and surveillance programs, supported by advanced molecular tests, enhance the early detection of infectious diseases, enabling proactive measures to contain their spread [122]. In LMICs, patient pathways informed by health and/or treatment seeking behaviours contribute to a repetitive cycle of antibiotic consumption, exacerbating AMR [123]. Within these settings, improved access to diagnostics and refinement of healthcare pathways are likely to be paramount to address the overuse of antibiotics [123]. Lastly, we should be mindful of the vulnerabilities in patient pathways, with regards to fragmented care structures and inefficient resource allocation, and future pathways should be developed that take a whole health economy approach that spans across health sector boundaries [11,124].

[H1] Opportunities to minimise reservoirs, improve IPC and limit environmental contamination.

The prevention and minimisation of AMR reservoirs among hospitalised patients is paramount. Antimicrobial stewardship which avoids unnecessary antimicrobial therapy, shortens antimicrobial duration as much as possible, and favours antibiotics with low anti-anaerobe activity can prevent dysbiosis, acquisition and overgrowth of ARO [125]. More personalised approaches can be used to emphasise these efforts, such as applying targeted drug delivery approaches to the

infected sites [126], pathogen or species-specific drugs [127], or drug combinations to antagonise the activity against commensal species. These evolutions are dependent on advances in rapid pathogen detection technologies and big data analytics. Antibiotic adsorbents or administration of enzymes (e.g., β-lactamase) represent interesting strategies to mitigate the collateral damages of antimicrobial therapy on the gut microbiota [128,129], and the targeted administration of live bacteria can preserve colonisation resistance, favour microbiota resilience or decolonise patients. Faecal microbiota transplantation (FMT) [130] or probiotics have been trialled, to variable effect [131,132]. These modalities have been evidenced to increase gut microbial diversity and improve sustained CPE eradication, although their effectiveness for intestinal decolonisation, applicability, and safety are still to be confirmed. Selective decontamination of the digestive (SDD) tract has shown benefits in lowering rates of ARO infections in low-prevalence settings [133]. The lack of evidence on SDD effectiveness and long-term side effects has led to its use not being recommended in gram-negative *Enterobacterales* carriers to control the AMR reservoir amongst hospitalised patients [134]. Early evidence exists for bacteriophage therapy providing sustained decolonisation with AROs, such as Carbapenemase-producing *Klebsiella pneumoniae* [135]. However, further research is needed to examine the role of bacteriophages in decolonisation, alongside the technical capacities and costs to develop these customised therapies. Safer and simpler, the patient diet with high-fibre nutrition seems promising in microbiome resilience, ARO implantation and expansion [136].

The hospital microbiome harbours a significant, uncharacterised diversity of ARG combinations and represents a fertile ground for the evolution of AMR. The microbiota community composition and ARO abundance on hospital surfaces is site-specific [137], dynamic according to patient occupancy, and subject to modifications of the built environment (e.g., renovations) [138]. Sink drains, for example, are a major reservoir for ARO with direct links to patient infections [139]. The rapid development of *P. aeruginosa* colonisation and its association with patient infections emphasises the need for future work to decrease the spread of AROs in hospital built-environments, complemented by efforts towards decolonising and eliminating sink drain AMR reservoirs [139]. Plasmid-mediated transmission accounts for 50% of CPE acquisition in hospitalised patients [140], and clonal and plasmid-mediated transmission may be differentially affected by existing infection prevention and control measures. Plasmid CPE transmission and persistent carbapenemase gene reservoirs in the hospital will need to be considered in future research. Developing and using anti-plasmid agents could be a complementary strategy to curb the spread of ARGs through hospital environments [141].

Compliance with environmental cleaning and disinfection processes and reprocessing measures of medical goods (e.g., bed pans) influences the level of environmental contamination [142]. Traditional cleaning methods are notoriously inefficient for decontamination [143], and innovative technologies such as disinfectants, steam, automated dispersal systems, and antimicrobial surfaces offer an alternative strategy for environmental hygiene purposes [144]. Hydrogen peroxide vapour or ultraviolet devices demonstrate effectiveness in reducing the incidence of *C. difficile*,

VRE and hospital-onset gram-negative bloodstream infections [145,146]. Aside from the costs of equipment, the wide variability of impact among hospitals highlights the need for clear implementation strategies that consider the training, management, personnel, and logistical complexities to maximise effectiveness [147]. The utility of antimicrobial surfaces needs urgent and considered attention including evaluation of the resources and economic investment required for installation, durability, possible toxicity, resistance, and allergenic properties, alongside which sites and surfaces to coat, and the relative contribution of self-disinfecting surfaces toward hand contamination. Systematic metagenomic surveys of the hospital microbiome providing detailed measures with reference maps and visualisation of variations in human influence scores may offer an opportunity to target resources and fine-tune cleaning practices.

Compliance of staff with standard precautions (mainly hand hygiene and excreta management) and personal hygiene by patients are universally applied to reduce a broad range of risks, including the hidden ARO reservoir [142]. The use of alcohol-based hand rub has been shown to improve HCW compliance, reducing HCAI rates and ARO transmission [148]. Despite significant improvements, innovative methods addressing both the quantitative and the qualitative aspects of hand hygiene are required [149]. Reduction in the burden of ARO present on patients' skin may reduce transmission by decreasing the contamination on health care workers' hands. Multiple large trials have shown that universal body surface decolonisation of patients with chlorhexidine bathing and nasal mupirocin can significantly reduce ARO prevalence in high-risk settings and long-term acute care facilities [150]. However, its widespread use over many decades, has raised questions about chlorhexidine resistance, coincident biocide resistance and clinically relevant antibiotic resistance [151]. Importantly, the implementation of standard precautions requires an adequate built environment with IPC and WASH factors providing complementary opportunities for interventions at health facilities, both during outbreaks and in non-outbreak situations[39].

Surveillance of ARO in healthcare facilities is complicated by the diffuse nature of AMR epidemiology, pathogen heterogeneity and predilection for particular subtypes transmitting and persisting within hospitals [152]. The real-time use of whole genome sequencing (WGS) in healthcare may allow IPC teams to identify transmission, target interventions, and provide surveillance and infection control benchmarking [153]. The use of patient-level microbiome or metabolome data to predict and assess an AMR reservoir in hospitals is of utmost importance. Functional metagenomics and long-read sequencing offer perspectives to better characterise the proliferation of mobile gene elements within (human) and across (human and environment) microbiomes, and presents new opportunities and challenges for pathogenome and resistome monitoring [154]. They are an invaluable resource as we move toward a future of microbiome-directed methods of identifying and preventing the spread of AMR and infection (e.g., routine assessment of patient's microbiome before antimicrobial therapies, abundance, and clearance of ARO carriage). Targeted screening, for example, in travellers and patients repatriated from endemic regions can be a beneficial strategy [155]. The prompt identification of these patients and rapid assessment of the risk of ARO carriage may prevent in-hospital transmission and

amplification of the AMR. Additionally, patients who acquire ARO during hospitalisation can contribute to onward spread in the community [156], with a high frequency of acquisition and transmission events occurring early after discharge. Educating ARO colonised patients and carers about key hygiene measures may prevent transmission in community settings. Equally, admission screening for patients known to have ARO colonised household or nursing home contacts should be considered, given intra-household community transmission [157]. The current gap in predicting ARO carriage at hospital admission may be solved by the availability of artificial intelligence (AI) and health data hubs [158].

New methods based on the microbiologic analysis of wastewater appear a promising option to accurately identify, quantify and describe the epidemiology of the AMR in healthcare settings [159]. Sewage monitoring represents a valuable modality for early warning of emerging ARO in low prevalence settings [160], and might be able to estimate the prevalence of ARO at a population level, simultaneously sampling healthcare, nursing homes and community-associated populations [161]; avoiding biases in current surveillance methods. Additionally, large amounts of antimicrobials and ARO are dispersed in wastewater and the broader environment. Whilst their contribution to the global ARO epidemiology still needs to be ascertained, innovative and cheap wastewater treatment processes should be developed to eliminate ARO from hospital effluents.

Finally, measures that assist in coordination of IPC measures alongside oversight and management of antibiotic use, healthcare facility connectivity and patient transfers at a regional scale are important avenues for innovation [162]. Coordinated responses in the prevention of ARO spread across interconnected healthcare facilities has been shown to reduce ARO acquisitions over time [163]. Mathematical models of healthcare networks may also serve to identify facilities which serve as reservoirs for the spread of ARO at a large scale [162], and inform decision-makers on priorities for the surveillance and IPC efforts.

[H1] Innovations in data linkage, intelligent systems and AI

Intelligent systems provide many avenues to benefiting AMR in healthcare (**Figure 3**). Access to healthcare data has dramatically increased with the use of electronic health record (EHR) systems and interconnected devices, giving rise to the age of “big data” [164]. The complex nature of AMR in healthcare requires linking data of drug-resistant pathogens, characteristics of patients, social demographic environments, and health systems and services contexts. At the patient level, routine EHRs can be linked with antimicrobial usage and AMR data for hospitalised inpatients. Population-level linkage of administrative data and EHRs have started to emerge [165], and more recently, whole genome sequencing data has been linked with laboratory and clinical data to form national-level integrated genomic surveillance of AMR [166]. These linked datasets not only allow genotypic and phenotypic characterisation of AMR, but also enable the assessment of emergence and transmission pathways, care quality and outcomes for drug-resistant infections, and social

and health-system determinants of AMR burden. Although data protection must be addressed, risk/benefit evaluations should be performed to ensure that data access and availability is preserved.

Ideally, AMR data would be integrated across settings of human health systems (i.e., primary, secondary, and social care), across One Health domains (i.e., human, animal, agricultural, and aquaculture), and across data types (i.e., isolate-based genomic and pathogen data, patient-based demographic and clinical data). Examples of data integration are seen in recent research methodologies [167] including the World Health Organisation-funded Tricycle project, which provides a holistic, multisectoral approach to monitor ESBL-producing *Escherichia coli* derived from human, food, and environmental sources using whole genome sequencing [168]. Research must be done to understand and develop the minimum dataset prior to implementation, and novel methods, such as simulation and systems dynamics modelling, allow the development and piloting of the minimum dataset in an iterative manner by engaging policy makers, data generators and users [169]. To overcome ethical issue regarding AMR data sharing, online platforms such as Trusted Research Environments (TREs) provide real-time feeds from local laboratories, patient and hospital operational data enabling the rapid reporting of AMR and HCAI trends to local IPC personnel [170]. TREs can access and analyse de-identified data, and benefit from AI-driven automated pseudonymisation processes, minimising time delays, and enabling cloud-based solutions for data storage and accessibility in low-resourced settings [171].

Optimal analysis and interpretation of complex health datasets can be enhanced by supervised or unsupervised machine learning (ML) tools [172] providing patient-specific assessments to better predict and prevent HCAI or to optimise antimicrobial treatment with personalised approaches for better individual outcomes and lesser impact from AMR [173]. Precision infection-prevention is the next frontier in infection prevention [174]. ML algorithms that incorporate EHRs and surveillance data can efficiently identify demographic data, select laboratory values, diagnoses, medications and vital signs, and help prioritise IPC interventions for patients at greatest risk of HCAI [175]. AI hand-hygiene applications can deliver behaviour change, though it requires further evaluation in different clinical settings [176]. ML tools using dynamic contact networks are able to identify patients who are most at risk of developing COVID-19 or *C. difficile* infections while in hospital [177]. In clinical practice, a ML-based tool could support prophylactic measures, earlier diagnosis, and timelier implementation of IPC measures [178]. In addition to improving effectiveness, the implementation of AI may significantly reduce the time spent by IPC team reviewing clinical records manually for HCAI surveillance [179].

Innovations in pathogen and genomic surveillance can be enhanced by ML systems [180], and their application in AMR surveillance is of vital importance [181]. ML systems have shown promise in analysing metagenomic data to predict antibiotic-resistant genes from humans and environmental sources, such as hospital wastewater [182], which could provide improved surveillance of ARG dissemination and transmission pathways. AI can provide source identification and early warning of AMR outbreaks in healthcare networks [183]. AI-assisted automated data mining of EHRs is able to detect hidden transmissions and outbreaks of AMR pathogens early and

cost-effectively [184]. These methods have even shown the resolution to identify a specific source, for example, a contaminated gastroscope in the case of an *Pseudomonas aeruginosa* outbreak [185]. These measures could be further explored to improve efficiencies and targeting of IPC services in healthcare.

The use of ML to improve pathogen identification and phenotypic or genotypic AMR profiles is attractive [186]. To date, a number of ML systems have been shown to predict antibiotic resistance from genomic and metagenomic data for a number of key bacterial species, such as *E. coli* and MRSA [182]. Additionally, ML technology has been linked with matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectra data in the laboratory to rapidly identify AMR in clinically important pathogens, accelerating timing of antimicrobial optimisation [187]. Low-resource options for AI integration into the laboratory also exist. This is exemplified by the use of AI-based mobile phone technology which enables automatic reading of disk diffusion antibiotic susceptibility testing, highlighting that AI technologies already have a global reach [188]. These systems can be integrated into cloud-based technologies, automatically forwarding to international systems of pathogen surveillance, enhancing the tracking of global AMR in healthcare.

ML-Clinical Decision Support Systems (ML-CDSS) have been trialled to improve choices of antimicrobials in sepsis [189] primary care prescriptions [190], and hospital AMS programs [191]. These systems are still in their infancy with limitations in their utility relating to the quality of information inputted (e.g, absence of clinical or therapeutic history, isolate antimicrobial susceptibility or local resistance epidemiology) and the outputs generated (e.g, need for dose, duration and allergy status). Nevertheless, their ability to identify inappropriate prescriptions compared to expert systems have been shown [191], and further trailing of newer ML-CDSS in real-world clinical settings should be explored, with reporting of clinical and/or microbiological outcomes and their impact on AMR in healthcare.

Recognizing that much of healthcare is delivered in environments without experts in infectious diseases, antimicrobial stewardship, microbiology and infection prevention, virtual platforms based on ML and AI may be leveraged to assist rural environments and low-resource settings through real-time, expert consultation [192].

[H1] Feasibility, tailoring to context, and prioritising

Health and wider systems present variable barriers and opportunities which decision-makers must assess through engagement with relevant stakeholders across One Health sectors, depending on the scale of implementation and innovation type [193] Most innovations require behavioural change or are behavioural in nature, and require trial and tailoring [194].

Defining and measuring impact must also be tested for feasibility and appropriate structures strengthened. Prioritisation of AMR outcomes of interest (e.g., AMR transmission, AMO,

morbidity, mortality, economic and ecological) is necessary to inform policy. Many AMR domains, such as antimicrobial optimisation require an interdisciplinary consensus to achieve equitable, scalable, economically viable and contextually appropriate interventions, that can utilise data across a range of healthcare settings [195]. Additionally, sub-optimal healthcare infrastructure, resources, staffing-levels, laboratory capabilities and data management systems preclude the generation of key AMR data needed to initiate, optimise or measure these outcomes of interventions. Such eonomic constraints can lead to further global inequalities, and international bodies have called for urgent improvements in access and infrastructure in LMIC settings, alongside advancements in data networks to improve the functionality and real-time evaluation of healthcare systems[194]. Opportunities for creative solutions in diagnostics, immunotherapy, intelligent-pathway development, laboratory surveillance and genomic sequencing may provide leapfrog technologies that can overcome key barriers in resource-limited settings [196]. Ethical and legal issues surrounding the regulation of AI and data privacy provide additional challenges to AMR interventions [197]. Improved international collaborations and the use of secure online platforms with user accountability may enhance regulation standards and dissuade negative public opinions [171].

At the national level, understanding the political context is important, but recent assessments have perhaps overlooked wider technological and economic factors needed to make informed decisions [198] However, there are number of frameworks that can help to prioritise and stagger innovations at the national level according to the maturity of AMR National Action Plans; notably the AMR Policy Accelerator *SMART CHOICE* process, a tool to help prioritise national level interventions through facilitated engagement with local stakeholders to identify 'Quick-wins, Best-buys, Game-changers, and Equity-drivers' [199]. From the health systems perspective the level of integration of infection prevention and control and antimicrobial stewardship across the system can be used as marker for readiness to adopt as well as informing roll out plans [124]. Specifically, the level of integration of IPC and AMS programmes within the wider health system along the dimensions of stewardship and governance, financing, planning, service delivery, monitoring and evaluation, demand generation [124]. The approach to governance needs to be politically and culturally acceptable and feasible and heterogeneity of approaches is found even within high income countries [200].

Lastly, future challenges to the resilience of healthcare may arise from global threats from pandemics or climate factors [52], and innovations should be designed and optimised to account for evolving threats.

[H1] Conclusion

In high-income and resource-limited settings, healthcare infrastructure, pathways, processes, and systems play a key role in maintaining and driving AMR transmission beyond the frontiers of healthcare via a range of modalities. In a vicious circle, the global acceleration of AMR is threatening the safe functioning of healthcare systems. To address this crisis, it is imperative we consider innovative solutions to combat the direct and indirect drivers of AMR in healthcare that span across the patient journey that can also promote healthcare resilience. Innovations should be tailored within a global context and able to adapt and respond to future challenges.

Uncertainty and knowledge gaps surround many AMR interventions. The feasibility and success of implementing putative interventions is further hampered by structural, economic, technological and behavioural barriers, compounded by challenges relating to local and national leadership, external policy environments and international barriers to action. International, transdisciplinary consensus on the desired impact of AMR interventions might enable cross-evaluation, prioritisation and resource allocation. Collaborations are required at all scales between experts and non-experts, in high- and low-income settings, to share knowledge and expertise and develop reciprocal, long-term partnerships built on principles of systems approaches and capacity strengthening.

Despite the challenges that exist, opportunities to develop integrated healthcare pathways that embed novel approaches to preventative therapies (e.g., vaccination), improved diagnostics, antimicrobial optimisation, IPC and surveillance methodologies should be implemented to minimise AMR risks to patients. Innovations in these areas should be urgently considered as research priorities to address the burden of AMR and enhance the protection of healthcare.

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[H1] Author contributions

D.C, G.B. J.R.M, N.Z, R.A and A.H contributed to the discussion, research, writing, reviewing/editing of this manuscript. K.J and A.S.L. contributed to discussion, writing and reviewing/editing the manuscript before submission.

Competing interests statement

The authors declare no competing interests.

[H1] Display Items

Figure 1| **Healthcare as a driver, reservoir and amplifier of antimicrobial resistance.**

Healthcare settings congregate people within shared spaces and along pathways exposing them to antibiotic-resistant organisms (AROs), selection pressures (i.e., antibiotic exposure) and healthcare-associated factors that promote AMR transmission. Colonised or infected individuals and contaminated healthcare environments serve as reservoirs of AMR organisms, and healthcare settings become distribution centres, amplifying AROs and antibiotic-resistant genes that are recycled within healthcare settings or dispersed into the community via people and wastewater; leading to onward cycles of AMR transmission before readmission into healthcare (Figure 1A).

A broad range of factors contribute to driving AMR in healthcare settings including patient and staff level characteristics such as co-morbidities, vaccination status, attitudes and behaviours and colonisation status (Figure 1B). AMR colonisation is influenced by antimicrobial usage, which is in turn influenced by antibiotic stewardship and antimicrobial optimisation measures. Here, suboptimal access to improved diagnostics, irregular supply chains, or the absence of clear antimicrobial prescribing policy can lead to inappropriate antimicrobial prescriptions, increasing AMR. Additionally, healthcare infrastructure, patient pathways and IPC practices play a key role

in AMR transmission events and environmental contaminated with AROs, illustrating their role in facilitating AMR in healthcare.

Healthcare-associated reservoirs of AMR include (i) the microbiota of medical staff and patients and animals present on healthcare grounds, and (ii) surface biofilms on key environments (e.g., sinks), especially in settings with high levels of ARO colonised patients (e.g., ITUs), medical equipment and hospital waste and wastewater.

Healthcare can amplify AMR via (i) patents pathways that congregate vulnerable patients with high levels of antimicrobials (ii) outbreaks of AROs within hospitals and care homes, (iii) the movement of colonised patients between locations and within healthcare networks and (iv) the dispersal of contaminated hospital wastewater into the environment.

Figure 2| **The use of vaccines and immunotherapy to reduce AMR and protect healthcare.**

Vaccines (or monoclonal antibodies) targeted at viral or bacterial aetiologies can limit disease and/or colonisation at an individuals and population level, preventing healthcare exposure, reducing unnecessary antibiotic usage, and limiting transmission outside of healthcare settings and reducing transmission events, HCAIs and outbreaks within healthcare settings. In turn, improved antimicrobial optimisation and a reduction in transmission events from vaccination and immunotherapies will limit the burden of AMR and improve healthcare resilience. These measures can be integrated with vaccination records, surveillance and diagnostic data through improved AI and data linkage systems to personalise and target therapies pre-admission and during healthcare attendance.

Figure 3| **Schematic illustrating the power of AI and data-linkage technology to reduce AMR and improve healthcare resilience.**

Different types of healthcare and non-healthcare data are available via a spectrum of data collection systems (A). Current advances in data technologies permits the integration of complex datasets and allows for AI-driven analysis (B). These methodologies can be utilised to provide a number of AMR specific applications (C), which can deliver data driven outputs to healthcare staff and regulators that protect individuals, populations and health systems (D).