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JAC-Antimicrobial Resistance

A rapid evidence assessment exploring whether antimicrobial resistance complicates non-infectious health conditions and healthcare services, 2010–20

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Antimicrobial resistance (AMR) is one of the greatest public health threats at this time. While there is a good understanding of the impacts of AMR on infectious diseases, an area of less focus is the effects AMR may be having on non-communicable health conditions (such as cancer) and healthcare services (such as surgery). Therefore, this study aimed to explore what impact AMR is currently having on non-communicable health conditions, or areas of health services, where AMR could be a complicating factor impacting on the ability to treat the condition and/or health outcomes. To do this, a rapid evidence assessment of the literature was conducted, involving a systematic approach to searching and reviewing the evidence. In total, 101 studies were reviewed covering surgery, organ transplants, cancer, ICUs, diabetes, paediatric patients, immunodeficiency conditions, liver and kidney disease, and physical trauma. The results showed limited research in this area and studies often use a selective population, making the results difficult to generalize. However, the evidence showed that for all health conditions and healthcare service areas reviewed, at least one study demonstrated a higher risk of death for patients with resistant infections, compared with no or drug-susceptible infections. Poor health outcomes were also associated with resistant infections in some instances, such as severe sepsis and failure of treatments, as well as a greater need for invasive medical support. While there are gaps in the evidence base requiring further research, efforts are also needed within policy and practice to better understand and overcome these challenges.

Background

Antimicrobial resistance (AMR) is recognized as a major public health issue, threatening the ability to prevent and treat a large range of infectious diseases.[1,2] If action against AMR is not taken soon, there is the potential for 10 million deaths every year associated with AMR, alongside additional economic costs due to the inability to effectively treat infections.[1]

Antimicrobials have revolutionized modern medicine and are now vital in being able to prevent and treat potentially fatal infectious diseases. Part of the increase in life expectancy over the last century can be attributed to a reduction in infectious diseases, in part due to the development of new antimicrobial treatments.[3,4] For example, in the pre-antibiotic era, the mortality due to infectious diseases in the USA made up one-third of all deaths and the top three causes of deaths were all infectious diseases (pneumonia, TB and diarrhoeal-related illnesses), which we are now able to treat.[4,5]

Antimicrobials are also critical for supporting the treatment of non-communicable health conditions, and modern health systems and treatments rely heavily on these drugs.[1] For example, antimicrobials are given to patients as part of surgery to reduce the risk of post-operative infection. They have also supported the treatment of patients with health conditions affecting their immune system, such as cancer treatments and immunosuppressed patients.

Although antimicrobials offer effective treatment for infectious diseases, their greater use (and misuse) is resulting in an increase in drug resistance. This threatens the return of healthcare to a pre-antibiotic era, in which many of the most important medical treatments would become riskier or no longer possible due to increased risk of infection, complications and death, as well as subsequent higher healthcare costs and economic burdens.[1,6]

Despite the routine use of antimicrobials to support the treatment of non-communicable diseases and to care for patients in hospital, there is little research into the implications of AMR for these purposes. Therefore, given the enormous challenge posed by AMR to modern medicine, it is necessary to better understand the evidence on if and how AMR complicates non-communicable diseases and hospital care.

Objectives

The aim of this study was to conduct an exploratory review of the published literature on the impact of AMR on patients with non-communicable diseases, as well as particular areas of health services. The research question was: what impact is AMR currently having on non-communicable health conditions (e.g. cancer or diabetes), or areas of health services (e.g. surgery or the ICU), where AMR could be a complicating factor impacting on the ability to treat the condition and/or health outcomes?

Methods

To address the research question, a rapid evidence assessment (REA) of the literature was conducted. An REA is a literature search that implements a structured search of the academic literature within a short timeframe, using a specific set of search terms. This was intended to be exploratory in nature to understand which topics evidence is available for (and what this evidence suggests) and where there are gaps in the existing literature. As per standard REA stages, this review consisted of: (i) definition of the research questions and development of a literature search protocol; (ii) definition of inclusion and exclusion criteria; (iii) conducting the literature search; (iv) screening literature search results; and (v) extraction of information from included articles and analysis. This REA approach to synthesizing the literature has been used extensively elsewhere in relation to antimicrobial resistance (e.g. James *et al.*,[7] Hockenhull *et al.*[8] and Chambers *et al.*[9]).

The results summarized in this paper were part of a broader REA that explored the impact of AMR on communicable diseases, non-communicable diseases and patient care, as well as the future impact AMR could have in these areas. Only the key findings relevant to non-communicable diseases/health conditions and patient care in hospital have been discussed in this article given the limited existing synthesis of evidence on these topics.

Table 1 outlines the search terms used for this study. These terms were tailored to search PubMed, Web of Science and Embase for relevant literature published between January 2010 and April 2020. There were no restrictions on geography or type of non-communicable disease/area of healthcare services. Only papers published in English were included. The searches were run in the three databases and screened in EndNote against the inclusion/exclusion criteria and the relevant studies were extracted using an Excel template.

The impacts were analysed thematically and organized into the following categories: (i) risk of developing AMR; (ii) mortality; (iii) health outcomes (the wider impacts on health, such as sepsis or organ failure); (iv) treatment efficacy (impact on the ability to treat the patient, excluding direct treatment of the infection); (v) length of hospital stay, hospital admission and/or ICU admission; and (vi) treatment invasiveness (whether invasive medical support is required, such as mechanical ventilation).

The included studies were not individually assessed for quality; however the strength of the evidence base per condition/area of care for each of the above categories was assessed and ranked on a scale from weak to strong, based on the study design. Where 10 or more studies were identified for a particular category, including a systematic review and meta-analysis, the evidence was rated as strong. Evidence was categorized as weak where there were three or fewer studies reporting on an outcome, including no more than two empirical studies. These rankings were devised by the research team and were used to categorize the overall strength of evidence for each condition/healthcare area.

Limitations

This review included a large number of studies covering a range of different non-communicable health conditions, as well as certain areas of health services at greater risk of being impacted by AMR. To the best of the authors knowledge, there are few literature reviews covering a similar topic with such a broad focus as this one. However, there are some limitations to note.

Firstly, this REA was not a systematic review of the literature, and the nature of an REA means the inclusion criteria are fairly restrictive (e.g. this search was limited to studies published in the previous 10 years, only articles in English were reviewed). This means it is possible that relevant literature was not included in this review (particularly in relation to studies published more than 10 years ago) and a meta-analysis of the evidence was not conducted. Therefore, a systematic review on this topic, with broader inclusion criteria, may be of future benefit. In addition, while the overall strength of the evidence base was explored, the quality of each included study was not assessed in this review. Therefore, it is not possible to provide an overview of the quality of the evidence presented here in particular detail. The limited nature of the available evidence also meant the health conditions and healthcare services are presented as relatively broad categories when in reality there are many subgroups within these categories that may be impacted by AMR differently (e.g. different types of cancer or surgery). This also warrants further investigation in a systematic review.

Results

Overview of identified literature and strength of evidence

In total, 101 articles were included in the review. Figure 1 outlines the PRISMA diagram for the screening and extraction stages.

While the review was open to include any non-communicable health condition and healthcare service only a small number of these topics were identified in the reviewed literature. These were: surgery; organ transplants; cancer; patients in the ICU; diabetes; paediatric patients; immunodeficiency conditions; liver and kidney disease; and physical trauma. Literature on other health conditions or services was not identified in the reviewed literature.

The strength of evidence assessment for each health condition/area of care, by type of outcome, is presented in Figure 2.

A summary of the type of literature and key findings across all health conditions/area of care is provided in the supplementary material (Tables S1 and S2, available as Supplementary data at *JAC-AMR* Online).

Surgery

Overall, 11 studies were identified that discussed the impacts of AMR on surgery.[10–18] These studies explored the impact on mortality, health outcomes, surgical success and length of stay in hospital.

The literature suggests that patients undergoing surgery are at risk of death if an antimicrobial-resistant infection develops.[10–12] In addition, surgical patients who develop a drug-resistant infection are at an increased risk of developing post-operative complications compared with those with drug-susceptible infections (e.g. visual impairment after eye surgery, surgical site infection, internal bleeding, fever for long periods, cardiac issues).[10,11,13–17] The likelihood of the surgery having a successful outcome can also be negatively affected for surgical patients with resistant infections compared with those with drug-susceptible infections.[17,18] Finally, the one study found that patients undergoing orthopaedic surgery who develop a resistant infection require longer stays in hospital.[17]

Table 1. Search protocol (these terms were tailored to each of the three databases)

Search terms
Antimicrobial resistance OR AMR OR antibiotic resistance OR antiviral resistance OR antiparasitic resistance OR antifungal OR drug resistance OR drug resistant OR superbug*
AND
Cancer* OR chemotherapy OR oncology OR immunotherapy OR immunotherapies OR immunocompromised OR pregnancy OR pregnancies OR birth OR births OR postpartum OR abortion OR c-section OR cesarean section OR gynecology OR premature birth* OR pre-term birth* OR obstetrics OR pediatrics OR paediatrics OR neonatal OR endocrinology OR diabetes OR cardiovascular OR respiratory OR cystic fibrosis OR asthma OR stroke OR heart disease OR cardiology OR pulmonary disease OR dermatology OR gastroenterology OR ophthalmology OR orthopedics OR orthopaedics OR emergency medicine OR hematology OR nephrology OR rheumatology OR hepatology OR neurology OR urology OR trauma OR injury OR surgery OR surgeries OR transplant OR secondary care OR immunosuppressed OR Immunodeficient OR Autoimmune OR Common Variable Immune Deficiency OR CVID OR dental OR HIV OR human immunodeficiency virus* OR human immune deficiency virus* OR immune deficiency associated virus OR acquired immunodeficiency syndrome* OR acquired immune deficiency syndrome* OR AIDS OR sexually transmitted disease* OR sexually transmitted infection* OR STI OR STD OR urinary tract infection* OR bladder infection* OR UTI

This article does not cover all the health conditions in this search protocol as the review was part of a broader study. Only the key findings relevant to non-communicable diseases/health conditions and patient care in hospital have been discussed in this article.

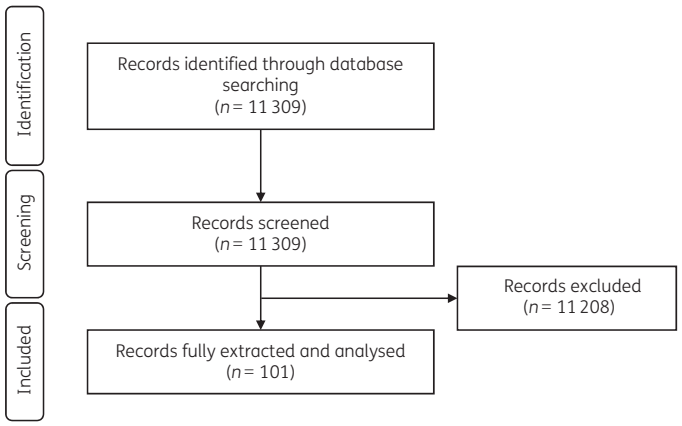

Figure 1. PRISMA diagram.

Organ transplant

Results from the literature on organ transplants was analysed separately to those of surgery due to the use of immunosuppressants and patients often requiring longer hospital stays after a transplant.[19] In total, 22 studies were identified that discussed the impact of AMR on patients undergoing organ transplants (both solid organ and tissue transplants).[19–40] The types of impacts explored include mortality, health outcomes, treatment efficacy, hospital and ICU admission, length of hospital stay, invasiveness of treatment, and risk of developing AMR.

For some of the impacts, the literature was unclear as to whether AMR caused a negative impact for those undergoing organ transplants due to mixed evidence across studies. This was the case for mortality,[21–30,38] the likelihood of success of the organ transplant[27,32–34] and hospitalization/ICU admission.[21,23,24,26,31,38]

Other outcomes were found to be negatively affected by AMR. Firstly, the literature identified solid organ transplantation as a risk factor for developing a resistant infection, particularly kidney transplants.[21,34–36,38] The literature suggests that organ transplant patients developing a resistant infection are more likely to suffer poor health outcomes (such as persistent sepsis, which may be due to the immunosuppressed state of the patient after a transplant, organ failure and kidney/urinary tract infections) than those with drug-susceptible infections.[19–21,24,31,38] In addition, these patients are more at risk of requiring invasive medical support, such as mechanical ventilation, with a drug-resistant infection compared with a drug-susceptible infection.[21,38]

Cancer

Overall, 10 studies explored the impacts of AMR on cancer patients, covering mortality, length of hospital stay, health outcomes and risk of AMR.[10,11,37,41–47]

The evidence indicates that the health impacts associated with cancer (e.g. gastrointestinal tract infection and use of multiple antibiotics) are a risk factor for developing a resistant infection.[37,44] The evidence suggests that cancer patients may be at a greater risk of mortality if a drug-resistant infection is developed, compared with patients without cancer (although the evidence was mixed across studies as to whether this was the case).[37,41–45] Additionally, cancer patients with resistant infections may face poorer health outcomes, particularly development of sepsis, as a result of a drug-resistant infection compared with patients without cancer.[46,47] The literature was inconclusive as to the impact of AMR on length of hospital stay for cancer patients.[10,45]

Patients in the ICU

Eleven studies explored the impacts of AMR on patients in the ICU,[40,48–57] covering mortality, health outcomes, length of hospital stay and risk of developing AMR. Multiple studies explored the specific impacts for children admitted to the ICU and these impacts will be described separately to adults where possible.

The literature suggests that both children and adults admitted to the ICU are at a higher risk of developing a drug-resistant infection.[49,50,54–57] For mortality, the literature identified that children admitted to the ICU are at a greater risk of death should they develop a resistant infection compared with children with drug-

	Mortality	Health outcomes	Effectiveness of treatment	Length of stay in hospital	Invasiveness of treatment	Risk of AMR
Cancer	Moderate	Weak		Weak		Weak
Diabetes	Weak	Strong				Moderate-strong
ICU	Moderate-strong			Weak		Moderate
Immunodeficiency	Weak	Weak				Weak
Liver or kidney disease	Weak	Weak	Weak	Weak		Weak
Newborns	Weak-moderate	Weak-moderate		Weak		
Organ transplant	Moderate-strong	Moderate	Moderate	Moderate-strong	Weak	Moderate
Physical trauma	Weak-moderate	Weak		Weak-moderate	Weak	
Surgery	Weak	Moderate	Weak-moderate	Weak		

Figure 2. Overall strength of evidence across conditions and impacts.

susceptible infections.[49,52] This risk may also extend to elderly patients; however the impact on adult mortality was less clear, with some studies not identifying an association between AMR and mortality for adult ICU patients while others did.[40,48,50,51,54] For length of hospital stay, the evidence from one study suggests that children admitted to the ICU with a resistant infection require longer stays than those with drug-susceptible infections.[52]

Diabetes

In total, 16 studies were identified that explored the impact of AMR on diabetic patients.[58–73] These impacts included risk of developing AMR, mortality and health outcomes (in this case, the risk of develop drug-resistant TB). However, while the strength of evidence was considered moderate-strong (as most data was from empirical studies, secondary analysis of health data and systematic reviews), the evidence was inconclusive for all of these. This uncertainty was due to conflicting conclusions arising from the 16 studies, with some studies finding no impact on the risk of AMR, mortality and health outcomes, whereas others identified negative outcomes for patients. Other studies also demonstrated a lower risk of developing resistant infections in diabetes patients compared with non-diabetics.[58,60]

Infant and paediatric patients

Eight studies explored the impact of AMR in young infants,[74–81] exploring mortality, health outcomes and length of hospital stay. The study populations were primarily neonates, with one study including children aged under 18 years. One study discussed the impacts of AMR on children broadly (in a review), two used healthy infants and the others explored the impact on children with other health conditions (extremely low birth weight and infants admitted to the neonatal ICU).

For mortality and length of hospital stay, the evidence was unclear as to whether these were negatively impacted as a result of AMR.[74–77] For health outcomes in children, findings across various disease processes are mixed. For example, infants with resistant infections may have a higher risk of sepsis, supporting the link between AMR and negative outcomes.[75,76,78] However, other studies have not demonstrated an association between AMR and negative outcomes, such as impaired neurodevelopmental outcomes after resistant neonatal candidiasis.[77]

Immunodeficiencies

In total, seven studies explored the impact of AMR on patients with immunodeficiencies,[37,57,82–86] covering risk of AMR, mortality and health outcomes. Unsurprisingly, the evidence suggests that patients with immunodeficiencies are at a greater risk of developing AMR infections than those with functional immune systems.[37,57,86] However, for mortality and health outcomes (such as sepsis, need for central line removal in children with cancer and spontaneous abortions in pregnant women), the evidence was unclear as to whether these patients were negatively affected as only narrative reviews without quantification of impacts were identified in the literature.

Liver and kidney disease

This review identified three studies exploring the impact of AMR on patients with liver and kidney disease,[6,87,88] covering mortality, treatment efficacy, health outcomes, hospital admission, length of hospital stay and risk of AMR.

The evidence suggests several risk factors for patients with liver cirrhosis (requiring a transplant) developing a resistant infection (e.g. long-term preventative antibiotic use, use of certain types of antibiotics, recent contact with healthcare services and recent infection with a resistant bacteria).[87] Patients with liver and kidney disease are at a risk of dying if a drug-resistant infection develops (although the evidence was unclear about how this risk compares to patients with drug-susceptible infections).[6,87,88] A resistant infection may also lead to poor health outcomes for liver and kidney disease patients, such as deterioration of organ function; however the strength of evidence was low for two out of three of these studies.[6,87,88] Patients with liver cirrhosis are at risk of requiring hospitalization and may need to face longer stays in hospital if a drug-resistant infection develops, although, again, the strength of evidence for this outcome was low.[87,88] Finally, the evidence was unclear as to the impact of AMR on the efficacy of treatment for the liver or kidney disease.[6,87]

Physical trauma

Five studies explored the impacts of AMR on patients presenting with physical trauma (e.g. burn injuries, military-related injuries).[89–93] These covered mortality, health outcomes, length of hospital stay, ICU admission and treatment invasiveness.

For mortality, length of hospital stay, ICU admissions and health outcomes (requirement of tracheostomy, long-term rehabilitation and sepsis), too little evidence was identified to come to a conclusion as to the impacts of these factors as a result of AMR.[89–93] However, one study identified that burn patients are at greater risk of developing sepsis should they have a drug-resistant infection.[91] For invasiveness of treatment, patients with both physical trauma and a resistant infection are more likely to require mechanical ventilation (and for a longer period of time) than patients with a drug-susceptible infection.[91,93]

Conclusions

This study implemented an REA to explore whether AMR complicates non-communicable diseases and areas of healthcare services. Development of a drug-resistant infection in patients with non-communicable health conditions and in certain areas of healthcare services can result in a variety of poor outcomes and has the risk of death in some situations.

The evidence from the reviewed literature indicates that, for all the types of health conditions and service areas we explored, at least one study demonstrated a higher risk of death for patients with a resistant infection (compared with either no infection or a drug-susceptible infection). While not as severe as death, but still highly important, a range of poor health outcomes were also associated with AMR. This includes, for example, severe sepsis in young infants and cancer patients and failure of surgery/transplants. The literature also indicates that AMR can sometimes lead to a need for additional medical support, such as hospitalization (and longer hospital stays), admission to the ICU and the need for invasive medical support. AMR may also lead to a lower likelihood of the surgery or treatment of the health condition being effective.

There are also important gaps in the existing literature that need to be addressed to better understand the impact of AMR on non-communicable diseases and healthcare services. Firstly, the REA had no restrictions on the type of non-communicable disease impacted by AMR. However, there are a number of health conditions included in the literature search terms where no relevant studies were identified. This includes childbirth; abortions; asthma; stroke; heart disease; dermatological conditions; rheumatological conditions; common variable immune deficiency; and dental health. Secondly, for some of the health conditions that were included in this review, five or fewer studies were identified, suggesting a need for further research (these were immunosuppression, physical trauma and liver and kidney disease). Thirdly, while other health conditions and areas of health services were the focus of a larger number of studies, the strength of this evidence was identified as being poor. This was, for example, due to different studies finding conflicting evidence or the evidence was from lower quality studies (e.g. narrative reviews). In addition, for the conditions/services with a larger number of papers, the studies often only focused on a subset of the condition or service (e.g. only cancer, eye and orthopaedic surgery were covered in studies relating to non-transplant surgery). Similarly, the majority of the literature explored the impacts relating to antibiotic resistance, with very little research on antivirals, antifungals or antiparasitics. Finally, further research needs to be conducted across countries and healthcare centres, as opposed to single hospitals, to obtain evidence that is generalizable to a larger population.

While exploring these evidence gaps is important to gain a fuller understanding of the broader impacts of AMR (beyond just the impact on preventing and treating infectious diseases), research of this kind can take time. Therefore, efforts should be made within both policy and practice, alongside additional research, to understand and tackle these wider effects of AMR. This includes the

need, for example, of improved surveillance data (and use of this data to inform policy and practice) relating to the impacts of AMR beyond infectious diseases alone.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC-AMR* Online.

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