



How is modern medicine being affected by drug-resistant infections?

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Preface

Antimicrobial resistance (AMR) is a major public health issue. AMR is the ability of microbes (e.g. bacteria, fungi, viruses, parasites) to resist the effects of medications that were once able to successfully kill them or inhibit their growth. Increasing drug resistance threatens the ability of modern health systems to treat both infectious and non-infectious diseases and health conditions (i.e. those where there is an increased risk of a detrimental effect occurring as a result of an infection, such as cancer or diabetes). This report provides a review of the impacts of AMR for non-infectious health conditions and types of health services, e.g. ICU. The review presents evidence on: (1) the impact AMR is currently having on modern medicine for non-infectious diseases and health conditions; and (2) the impact AMR could have on non-infectious diseases and health conditions in the future, demonstrated by modelling studies, for these health conditions. The report provides a summary of the existing evidence and gaps in the evidence. The study was commissioned by Wellcome and was delivered by RAND Europe.

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Summary

Antimicrobial resistance (AMR) is the ability of microbes (e.g. bacteria, fungi, viruses, parasites) to resist the effects of medications that were once successfully able to kill them or inhibit their growth. This major public health issue could have significant impacts on modern medicine, rendering previously effective treatments no longer useable. Already, we see AMR impacting on our ability to treat certain conditions, but this is projected to grow significantly over the next 20-30 years [1]. The aim of this study is to understand the evidence base regarding the impact of AMR on modern medicine for non-infectious diseases and health conditions. The work consisted of a Rapid Evidence Assessment, which is a standardised and structured approach to searching the literature but has a narrow focus on a topic and is not intended to be a complete systematic review of the evidence-base. This report will be useful for patient advocacy groups, policymakers, health and healthcare research funders and the wider research community.

We looked at academic publications related to impacts of AMR on non-infectious diseases and health conditions published in the last 10 years, identifying a total of 135 articles for inclusion in the review.

Reflection on key findings

Development of a drug resistant infection in patients with non-infectious health conditions can result in a wide variety of other poor outcomes and in some cases can be life-threatening.

- The evidence demonstrates that for all the health conditions we reviewed¹, at least one study found that patients are at a higher risk of death than patients without infection or with non-resistant infections.
- In addition, a wide range of poor health outcomes have been associated with health conditions predisposed to the development of drug resistant infections, such as postoperative complications in surgical patients, severe sepsis in infants and development of drug resistant TB in diabetic patients.
- We have also found evidence that patients with drug resistant infections and other health conditions need additional medical support which is reflected in longer stays in the ICU or hospital (e.g. for liver cirrhosis and surgical patients), the need for more invasive medical support (e.g. organ transplant patients) and less effective treatment options (e.g. patients with STIs and diabetic patients).

¹ Except for STIs and autoimmune conditions in which no evidence on mortality was provided.

The evidence we have collected suggests that AMR is likely to have important impacts across a range of conditions. Table 1 provides a summary of our key findings across a range of different conditions.

We also identify several important gaps in the existing evidence base, summarised below.

- There are several health conditions which we included in the literature search, but for which no studies were identified. These include childbirth; abortions; asthma; stroke; heart disease; dermatological conditions; rheumatological conditions; Common Variable Immune Deficiency; and dental health.
- In addition, there are several health conditions for which fewer than 5 studies were identified, including autoimmune conditions, immunosuppressed patients, liver cirrhosis and kidney disease.
- We identified a larger number of studies for some conditions, but the strength of evidence was still poor. For example, treatment efficacy in transplant patients, mortality in diabetic and trauma patients, risk of AMR in diabetic patients and hospital/ICU stay in neonates and trauma patients.
- Also within scope of this review was the modelling of the future impact of AMR on non-infectious health conditions. However, we did not identify any studies directly addressing this issue at the level of individual conditions or patient groups. A brief review of the wider literature on models and datasets for AMR finds that not only are more disease specific analyses required, but also there is a need for better data and model validation, and improved incorporation of the wider context in which AMR occurs (e.g. uncertainty in incidence of infections).

While this REA included a broad search protocol across three different databases to ensure that as much of the relevant literature was identified as possible, it was not intended to be a systematic review of the literature. The nature of an REA means the focus is narrower than it would be for a systematic review. This means it is highly probable that some relevant literature was not included in this study and expert reviewers of this report also noted this limitation. Therefore, a more in-depth, systematic review on these topics will be required, drawing on input from experts in specific fields to identify more specific and nuanced criteria to draw out the full range of literature.

Areas for future research

The evidence we have collected suggests that more research is needed to understand the impacts of AMR on non-infectious health conditions, and to seek ways forward to mitigate and reduce the impacts of AMR on modern medicine in the future. Areas for which further research and evidence is needed include:

- Good quality evidence on the impacts of AMR on a wider range of health conditions, e.g. childbirth; abortions; asthma; stroke; heart disease; dermatological conditions; rheumatological conditions; Common Variable Immune Deficiency; autoimmune conditions; immunosuppressed patients; liver cirrhosis and dental health.
- Better evidence on the effectiveness and invasiveness of treatments where drug resistant infections are present.
- More data on the prevalence of AMR in relation to different health conditions.

- Evidence on the impact of wider types of AMR beyond bacterial infections (i.e. viruses, fungi and parasites).
- Better quality modelling studies to understand the likely future trends and implications of AMR, drawing on higher quality prevalence and impact data.
- Ongoing synthesis and review of the evidence to inform future research directions.

Table 1: Summary of key findings.

Health condition/ area	Overall strength of evidence ²	Key findings*
Surgery	Weak-moderate	Patients having undergone surgery (in this case, the literature focuses on cancer, eye and orthopaedic related surgery) and who develop drug resistant infections are at risk of death. Surgical patients with drug resistant and face longer hospital stays than those with non-resistant infections.
Organ transplant	Moderate	Organ transplants are a risk factor for the development of drug resistant infections and kidney transplants may be more likely to lead to drug resistant infection compared to other types of transplant. The evidence is unclear as to whether organ transplant patients with drug resistant infections are at a greater risk of death compared to patients with non-resistant infections. However, patients undergoing stem cell transplants who develop a drug resistant infection appear to be at a higher risk of death than those with non-resistant infections. Transplant patients who develop a drug resistant infection are at a greater risk of negative health outcomes (e.g. kidney failure and sepsis). The evidence is mixed as to whether transplant patient with drug resistant infections are at a greater risk of transplant failure, ICU admission or hospital admission compared to patients with non-resistant infections. However, organ transplant patients with cystic fibrosis who acquire a drug-resistant infection are more likely to require longer ICU stays than those with non-resistant infections or no infection. Organ transplant patients who acquire a drug-resistant infection are more likely to require mechanical ventilation than those with non-resistant infections.
Cancer	Weak-moderate	Patients with cancer may have a greater risk of developing drug resistant infections than non-cancer patients. Those who do develop drug resistant infections are more likely to develop sepsis. The evidence is mixed as to whether patients with cancer are at greater risk of death if they develop a resistant infection. Cancer patients with drug resistant infections may need to spend longer periods in hospital than those with non-resistant infections, although these studies did not provide comparative data for patients with a non-resistant infection.

² We first awarded strength of evidence ratings to each combination of health condition and impact (e.g. surgery and risk of AMR) based on the volume and type of evidence that we identified about each. In cases where we identified ten or more studies exploring a particular impact in a particular condition, including a systematic review and meta-analysis, we rated the evidence as 'strong'. At the other end of the spectrum, we rated the strength of the evidence as 'weak' for combinations of health condition and impact for which we identified three or fewer studies, including no more than two empirical studies. Based on these ratings, we were able to look across the evidence available on each condition's AMR-related impacts, and to award an overall strength of evidence rating for the full body of evidence available for each health condition.

Health condition/ area	Overall strength of evidence ²	Key findings*
ICU patients	Moderate	Admission to the ICU is associated with development of drug resistant infections. Children in the ICU who develop drug resistant infections are at a greater risk of death compared to those with non-resistant infections. The evidence for mortality in adult patients is less clear, although the studies indicate that elderly patients may be more at risk of death if they develop a drug resistant infection compared to a non-resistant one. Patients who develop drug resistant infections require longer stays in hospital. These results are particularly relevant given the COVID-19 pandemic which is still ongoing at the time of writing and had led to an increase in ICU admissions and use of invasive medical support, such as mechanical ventilation.
Diabetes	Moderate-strong	The evidence is unclear as to whether patients with diabetes have a greater risk of developing drug resistant infections than non-diabetic patients, are at a greater risk of death or show a higher risk of developing drug resistant TB.
Human immunodeficiency virus (HIV)	Moderate	People living with HIV are more likely to develop drug resistant TB than those without HIV, and for those co-infected with HIV and drug resistant TB, they are at a greater risk of death and are less likely to successfully treat their drug resistant TB. HIV patients infected with drug resistant bacteria may need to spend longer in hospital, ICU admission or more invasive medical treatment. The link between the impact of treatment for drug resistant TB is unclear and further research is needed. The strength of the evidence for the impact of resistance on STIs is low; however, the limited evidence does indicate that resistance leads to reduced treatment options for patients and increases the risk of contracting and transmitting HIV.
Infants and children	Weak-moderate	It is unclear whether infants who develop drug resistant infections are at an increased risk of death or require longer lengths in hospital than patients with non-resistant infections. However, they do appear to have a higher risk of developing sepsis than those with non-resistant infections.
Immunodeficiency	Weak	Patients with deficiencies in their immune systems may be at a greater risk of developing a drug resistant infection than patients with fully functioning immune systems. Those patients who develop resistance are at a greater risk of death and poor health outcomes (in pregnant women) than those with non-resistant infections, although the evidence base for this condition is fairly weak.
Liver and kidney disease	Weak	Patients with diseases of the liver and kidney may be at a greater risk of death and poor health outcomes (e.g. poor liver and kidney function or sepsis), treatment failure (e.g. transplant rejection), require hospitalisation or longer stays in hospital if they acquire a drug resistant infection compared to patients with a non-resistant infection. However, the evidence for these outcomes is fairly weak as most are based on narrative review.
Physical trauma	Weak-moderate	Clear conclusions on the impact of drug resistant infections on mortality, length of hospital stay, ICU admissions and health outcomes could not be made due to the differing results from the studies. However, the evidence does suggest that trauma patients with drug resistant infections are more likely to need mechanical ventilation and require this support for longer periods than those with non-resistant infections.

**Note that the comparison group of relevance here is those with a non-resistant infection. However, some of the studies included in the review also make comparisons to no infection. This is specified in detail in the main body of the report for each finding.*

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Abbreviations

AIDS	Acquired immune deficiency syndrome
AMR	Antimicrobial resistance
CDDEP	Centre for Disease Dynamics Economics & Policy
CI	Confidence interval
EARS	European Antimicrobial Resistance Surveillance network
ESKAPE	<i>Enterococcus faecium</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella pneumoniae</i> , <i>Acinetobacter baumannii</i> , <i>Pseudomonas aeruginosa</i> , and <i>Enterobacter</i> spp.
G-CSF	G-CSF (Granulocyte-colony stimulating factor)
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
ICU	Intensive care unit
IQR	Interquartile range
MDR	Multi-drug resistance
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NICU	Neonatal intensive care unit
PRISMA	Preferred reporting items for systematic reviews
REA	Rapid Evidence Assessment
STI	Sexually transmitted infection
TB	Tuberculosis
UK	United Kingdom
USA	United States of America

Glossary

Aneurysm	Enlargement of part of an artery due to weakening of the vessel wall.
Antimicrobial resistance (AMR)	When a microbe (bacteria, virus, fungus or parasite) becomes resistant to a drug used to treat it, such as antibiotics.
Abdominal hysterectomy	The surgical removal of the uterus through the lower abdomen.
Acute	In medical terms, a condition that occurs and progresses very quickly and requires urgent care.
Anaemia	A health condition affecting the red blood cells, in which the patient does not have enough red blood cells, or the cells lack haemoglobin to transport oxygen around the body.
Antimicrobial	A drug used to treat an infection. These can be antibiotics (to treat bacterial infections), antivirals (to treat viral infections), antifungals (to treat fungal infections) and antiparasitic (to treat parasites).
Appendectomy	The surgical process of removing the appendix.
Arrhythmia	A heartbeat that is irregular, too fast or too slow.
Bacteraemia	Presence of bacteria in the bloodstream.
Biopsy	The procedure of removing a small piece of tissue for medical tests.
Broad-spectrum antibiotic	An antibiotic that is not specific for treating one type of bacteria, but can kill or inhibit the growth of a large range of bacterial species
Candidemia	The presence of the fungal genus <i>Candida</i> in the bloodstream.
Candidiasis	Infection caused by the fungal genus <i>Candida</i> .
Cardiac infarction/ischemia	A lack of blood flow to the heart, causing a lack of oxygen for the organ (also called heart attack).
Central venous catheter/central line	A tube placed into a large vein to provide fluids or medications, or to undertake urgent medical tests.
Chronic obstructive pulmonary disease	A group of lung conditions which develop slowly and cause difficulty breathing, such as emphysema and chronic bronchitis. It leads to symptoms such as breathlessness, cough, risk of chest infection and wheezing.
Deep vein thrombosis	Blood clots that develop within deep veins, often in the leg.
Delayed gastric emptying	Condition in which the stomach empties food too slowly.

Dialysis	A procedure used on patients with kidney problems to help remove waste and excess fluid from the blood.
Drug susceptible/sensitive	When a microbe (bacteria, virus, fungus or parasite) is not able to grow or is killed in the presence of a drug (i.e. it is not drug resistant).
Empirical study	Primary data collection based on experiments or observations, rather than secondary analysis of existing data.
Enterobacteriaceae	Family of gram-negative bacteria, a large part of which are present in the human intestinal tract.
ESKAPE bacteria	A group of bacteria that are showing increasing antibiotic resistance and illness severity: <i>Enterococcus faecium</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella pneumoniae</i> , <i>Acinetobacter baumannii</i> , <i>Pseudomonas aeruginosa</i> , and <i>Enterobacter</i> spp.
G-CSF (Granulocyte-colony stimulating factor)	A treatment used to stimulate the production of white blood cells to support the immune system.
Glaucoma	A condition of the eye which causes damage to the optic nerve.
Gram-negative/positive bacteria	Gram-positive bacteria have thick, robust cell walls whereas gram-negative bacteria have thinner, more porous cell walls. In addition, gram-negative bacteria have an additional outer membrane which is not present in gram positive.
Haematological	Relating to the blood and blood forming tissues.
Immunocompromised	The state of having a weakened immune system.
Intestinal ischemia	Blood flow to the intestines is reduced or blocked completely.
Intraluminal or extraluminal bleeding	Bleeding within organs (intraluminal) or in the space between organs (extraluminal)
Intraocular lens implantation	The implantation of a lens into the eye to treat conditions in which the lens has been damaged, e.g. cataracts.
Intravitreal injection	An injection provided in the eye.
Intubation	The presence a tube into the airways to assist with breathing.
Keratoplasty	Surgery conducted on the cornea
Mechanical ventilation	The presence of a tube in the airway to act as an artificial airway and a machine breaths for the patient.
Neutropenia	A condition in which a person has a low number of white blood cells, making them susceptible to infection.
Odds ratio (OR)	A statistic that is used to demonstrate the strength of the association between two events. If an OR is greater than 1, this suggests the intervention is better than the control group.
Organ failure	A condition where one or more organs are unable to perform their normal functions.
Orthopaedic implant	A metal device used to replace a missing joint or bone, or used to support damaged bone.

Percutaneous ablation	A method of treating tumours using radio waves using a probe inserted through the skin. The radio waves create heat which destroys the tissue in a small surrounding area.
Pleural effusion	The build-up of fluid on the lungs, causing difficulty breathing.
Pneumonia	Infection of one or both lungs causing inflammation, making breathing difficult.
Prophylaxis	Use of a drug to prevent an infection developing.
Pulmonary embolism	A blood clot that develops in the bloodstream and moves to the lungs.
P-value	A p-value is used to demonstrate the probability that a result occurred by random. A value of <0.05 indicates a significant association, suggesting that there is a relationship between two events.
Respiratory failure	The lungs are unable to perform effective exchange of oxygen and carbon dioxide, leading to less oxygen transported around the body.
Sepsis	Infection of the bloodstream.
Septic shock	The development of severe sepsis which leads to extremely low blood pressure that can be fatal.
Stem cell/bone marrow transplant	Procedure used to replace damaged stem cells or blood cells in cases of blood cancers or other conditions affecting the blood, immune system or metabolic system.
Tracheostomy	The creation of an opening in the neck to insert a tube directly into the windpipe to assist in breathing.
Ventilator-associated pneumonia	An infection of the lungs associated with the use of a mechanical ventilator
Vitrectomy	A surgical procedure to remove vitreous humour (the gel-like tissue within the eyeball) from the eye.
Wound dehiscence	The re-opening of a surgical incision.

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1. Introduction and methods

1.1. Background and context

AMR is the ability of microbes (e.g. bacteria, fungi, viruses and parasites) to resist the effects of medications that were previously effective against them. Today AMR is recognised as a major public health issue, which is projected to severely undermine modern health systems that rely heavily on antimicrobial drugs to treat infections [2]. In the absence of mitigating action, by 2050, AMR is expected to account for 10 million deaths a year, with considerable associated economic costs [2].

Antimicrobial drugs, such as antibiotics³, have revolutionised modern medicine. Antibiotics are necessary for the treatment of bacterial infectious diseases (e.g. tuberculosis (TB) and sexually transmitted infections). Before the discovery of antibiotics, deaths due to infections, such as pneumonia and TB, were very high and part of the increase in life expectancy over the last century can be attributed to a reduction in infectious diseases, in part due to antimicrobial treatments [3, 4]. For example, in the US in 1900 (pre-antibiotics), the mortality due to infectious diseases made up one third of all deaths and the top three causes of deaths were all infectious diseases (pneumonia, TB and diarrheal-related illnesses) which we are now able to treat [4, 5]. Antibiotics are also critical for non-infectious diseases and health conditions (i.e. where antibiotics reduce the risk of a post-treatment infection), and modern health systems and treatments rely heavily on antibiotics [2]. For example, antibiotics are given to patients as part of routine surgery to reduce the risk of infection. They have also reduced the risks from childbirth (e.g. caesarean sections) and made cancer treatments possible. These procedures are dependent upon the availability of effective antibiotics to make them comparatively low risk.

As a result of AMR, infections are becoming drug resistant⁴, meaning that antibiotics and other antimicrobial drugs no longer work to treat them. Increasing drug resistance threatens the return to a pre-antibiotic era, in which many of the most important medical advances would become riskier or no longer possible [2]. For example, routine surgery (e.g. hip replacements) and other important medical advances (e.g. cancer treatment) would no longer be possible due to increased risk of infection, complications and death. Compared to infections caused by antibiotic-susceptible bacteria, those caused by antibiotic-resistant bacteria are associated with significantly higher mortality, longer hospital stays and greater healthcare costs and

³ Antibiotics are one type of antimicrobial that target bacteria. Others target other microorganisms (e.g. parasites, fungi and viruses).

⁴ Drug resistant infections are infections that no longer respond to the drugs designed to kill them. A drug-susceptible infection is an infection that is able to be treated with a drug (i.e. it is not resistant).

economic burden [6]. For mortality, estimates from the Review on Antimicrobial Resistance, commissioned by the UK Prime Minister in 2014, suggests that 300 million people could die as a result of drug resistance by 2050 [7].

Despite increasing evidence on the secondary health effects of AMR, and risks this poses to modern medicine, there is comparatively little research in this area. There are relatively few studies that have investigated the secondary health impacts of AMR (e.g. on surgery and organ transplantation). Moreover, evidence suggests that the general public consider the threat posed by AMR as being less than other threats such as cancer, HIV/AIDS and air pollution [8]. Therefore, given the enormous challenge posed by AMR and drug resistant infections to modern medicine, it is necessary to better understand the evidence on the impacts of AMR for non-infectious diseases and health conditions.

1.2. Research aims and approach

This study had two primary research questions:

1. What impact is AMR currently having on non-infectious health conditions (e.g. cancer or diabetes), or areas of health services (e.g. ICU), where AMR could be a complicating factor impacting on the ability to treat the condition and/or health outcomes?
2. What impact, demonstrated by modelling studies, could AMR have on modern medicine in the future for non-infectious health conditions or areas of health services?

To address these research questions, the study team conducted a Rapid Evidence Assessment (REA). An REA involves a structured and rigorous search of evidence on a particular topic in a short timeframe. They are useful in situations where evidence is uncertain and provide an overview of the 'breadth, depth and comprehensiveness' of evidence on a topic [9, 10]. This approach is suitable to answer these two research questions for these reasons, i.e. the evidence based for the impact of AMR on non-infectious diseases and health conditions is unclear. However, after conducting the screening it became clear that there was no study conducted to specifically understand the future impacts of AMR (answering question 2). As a result, the research team conducted an additional, small-scale literature search which used broader search terms and identified articles over a longer period. The summary of the findings of this additional search can be found in Chapter 2.

This REA followed the standard steps for the type of literature search⁵:

1. Define research questions and develop robust search protocol.
2. Define inclusion and exclusion criteria (see Table 2 below).
3. Conduct literature search.
4. Screening.

⁵ REAs can include quality appraisals of the included studies. This was not undertaken for this study as no other reviews of evidence on the topic of AMR in non-infectious health conditions had been identified. Therefore, the study aimed to gain an understanding of the extent and type of evidence available on this topic, rather than the quality. However, a high-level assessment of the quality of the literature is provided in each chapter.

5. Extraction and analysis.

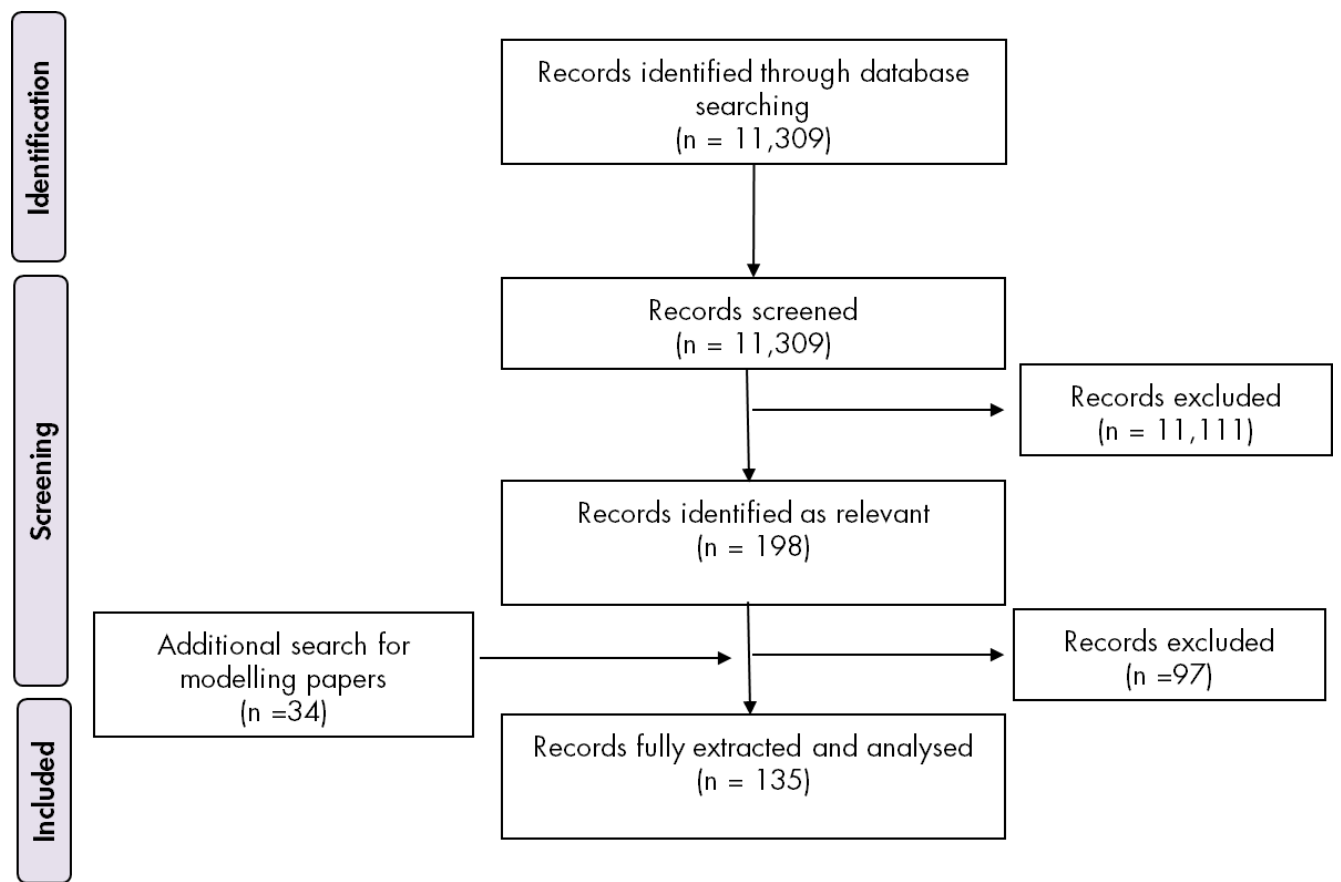
Table 2: Inclusion and exclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
Publication date	Published 2010-2020	Published before 2010
Location	All countries	N/A
Language	English	Non-English
Study type	Peer-reviewed journal publications presenting empirical evidence, review papers, grey literature with clear authorship, book chapter, theses, conference proceedings.	Documents without clear organisational authorship, theoretical work, letters, editorials, comments or opinion pieces, book reviews.
Diseases	Any non-infectious health conditions or type of health service, including (but not limited to) cancer, cardiovascular disease, stroke, surgery, trauma, pregnancy and birth, neonatal and child health conditions, immunocompromising conditions, cystic fibrosis, respiratory conditions, diabetes, obesity, TB, HIV/AIDS, STIs, UTIs, conditions of the liver, eyes, skin, kidneys, circulation, musculoskeletal system, digestive system, and dentistry. Also include: Direct resistance in STIs	Any infectious diseases/pathogens (except STI and HIV). In particular, we are focusing on secondary conditions affected by AMR rather than conditions where the primary pathogen itself becomes drug resistant. Direct resistance to STIs does not include HIV
Study participants	Humans	Animals and plants

Each of these is discussed in detail in Annex A on page 89 of this document. In Annex A you can find a full list of the search terms and criteria for including studies in this assessment.

After progressing through each of these steps, a total of 135 articles were included in the study and fully extracted (101 from the main literature search and 34 from the additional search for AMR modelling studies). The flow of articles and numbers included/excluded at each stage is provided in Figure 1.

Figure 1: Preferred reporting items for systematic reviews (PRISMA) diagram



Adapted from: Adapted from Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G., The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*, 6(7), e1000097. <https://doi.org/10.1371/journal.pmed.1000097>.

Table 3 provides an overview of the number of studies identified for each health condition/health service area and the number of studies for each type of resistance (antibacterial, antiviral, antifungal and antiparasitic).

Table 3: Number of studies covering the diseases/health areas of interest and the number of papers focusing on the different types of resistance⁶

General disease/condition	No. Papers	Antibacteria l	Antivira l	Antifunga l	Antiparasiti c
Organ transplant	22	18	4		
Diabetes	16	14		2	
HIV	15	15	1		
ICU	11	10		1	
Surgery	11	11			
Cancer	10	9		1	
Infant and paediatric infection	8	7		1	
Immunodeficiency	7	6	1	1	1
Physical trauma	5	5			
Liver and kidney disease	3	3			

Through the analysis of the literature, we created six categories for the types of impacts identified. Our definition of these are the following:

- Mortality: Any impact on the risk of a patient dying.
- Health outcomes: Wider health impacts associated with a drug resistant infection, such as organ failure, sepsis or vision loss.
- Effectiveness of treatment: The effects on treatment efficacy associated with a drug resistant infection, including any changes to the way the infection responds to treatment or the ability to treat the health condition of focus, e.g. diabetes or cancer.
- Length of stay in hospital: The impact on the length of time a patient needs to stay in hospital. We also include ICU admission and length of ICU stay in this category. These are important both for patient experience and because longer ICU/hospital stay (and ICU admission) are associated with higher costs for the hospital.
- Invasiveness of treatment: Whether additional, invasive methods of medical support are required, such as mechanical ventilation, intubation or central venous catheters, which may make patients susceptible to contracting a drug-resistant infection or are required as a result of contracting a drug-resistant infection.

⁶ The total number of papers more than the number of papers extracted as some covered multiple disease conditions. The number of papers covering the different types of resistance does not always equal the total number of papers as some studies researched more than one type of resistance.

- Risk of AMR: Whether the presence of a non-infectious health condition (e.g. cancer, immunodeficiency) or area of health service (e.g. surgery, ICU) lead to a higher risk that a patient will develop a drug resistant infection.

While we did not conduct a quality assessment of each included study, we do provide reflections on the strength of the evidence base for each health condition based on a scale of strong to weak. We began our high-level assessment by awarding strength of evidence ratings to each combination of health condition and impact (e.g. surgery and risk of AMR) based on the volume and type of evidence that we identified about each. In cases where we identified ten or more studies exploring a particular impact in a particular condition, including a systematic review and meta-analysis, we rated the evidence as 'strong'. This was the case for two combinations: HIV and mortality, and diabetes and health outcomes. At the other end of the spectrum, we rated the strength of the evidence as 'weak' for 22 combinations of health condition and impact for which we identified three or fewer studies, including no more than two empirical studies. Some examples of these are HIV and length of stay in hospital, and organ transplant and invasiveness of treatment. A full description of the strength of evidence rating criteria and the ratings awarded to each combination of condition and impact are provided Section 13.2. Based on these ratings, we were able to look across the evidence available on each condition's AMR-related impacts, and to award an overall strength of evidence rating for the full body of evidence available for each health condition. These overall ratings are presented in the summary boxes included at the beginning of each chapter.

1.2.1. Strengths and limitations

The strengths of this REA lie in the robust and broad search protocol and the searching across three different databases. This ensured that as much of the relevant literature was identified as possible. The inclusion of a pilot screening task with the research team is also a strength and ensured that a standardised approach to screening was taken across the team and any queries were answered among the researchers.

As with all studies, there are still some limitations to this approach. Firstly, while the search was made as broad as possible within the resources available, the nature of a REA means it is unable to identify all possible relevant studies and may have meant some possible associations between AMR and the health conditions of interest were not identified. In this case, articles published before 2010 (which may have impacted the collection of evidence differently for the health conditions of focus, depending on the availability of literature and progress of research for the health condition, for example) or not in English were not included and some relevant articles may only be indexed in databases that were not searched. HIV and cancer expert reviewers for this report also noted this limitation, suggesting that a systematic review which includes more specific terms relating to AMR (such as the names of specific drugs) and/or extending the publication date of included literature to include earlier years is the next step required for this research to obtain a more in-depth and comprehensive understanding of the issue for HIV and cancer (and it is likely that experts in the other health condition fields would have provided similar feedback). This study shows that there are no such existing reviews emerging from the literature and that conducting a search across such a broad range of disease areas and conditions runs into challenges since some of the literature in particular fields is not identified through the search terms used. Consulting with subject matter experts, condition-by-condition, would enable a more extensive search to be conducted

and having syntheses by condition would add significant value given the absence of existing reviews of this nature.

A quality appraisal of the included studies was out of scope for this REA. While the research team provides high-level reflections of the quality of the evidence for each disease/health conditions, a standardised approach to assess the quality of each article was not conducted. Therefore, the quality of the evidence reviewed cannot be commented on in detail. However, where possible we have indicated the strength of the evidence, considering factors such as the number of studies, the types of methods used (empirical data collection, systematic review etc.) and whether results are consistent across studies.

Note that this study intended to look at non-infectious diseases and areas of health services where AMR could be a complicating factor impacting on the ability to treat the condition and health outcomes. However, we also included HIV to expand the study, again looking at AMR risks and complications for people living with HIV (rather than focusing on primary resistance in those cases) due to the issues with the immune system these individuals face.

1.3. Structure of the report

This report provides an overview of each health conditions/area of health service identified in this review by chapter. We first provide an overview of the search we conducted into the evidence on AMR modelling (Chapter 2). In subsequent chapters we then provide evidence on the impact of AMR on different health conditions and services. As outlined in Annex A, the search protocol was wide to account for all types of non-infectious health conditions, as well as searching for specific areas of health services which may be impacted by drug resistant infections. The areas in which we identified literature, and our definition for these, are:

- Surgery (Chapter 3): Patients undergoing non-organ transplant surgical procedures.
- Organ transplant⁷ (Chapter 4): Patients undergoing a solid organ or tissue transplant.
- Cancer (Chapter 5): Patients diagnosed with cancer.
- Intensive care unit patients (Chapter 6): Patients admitted to the ICU or neonatal ICU for reasons other than surgery or organ transplants.
- Diabetes (Chapter 7): Patients diagnosed with type I or II diabetes.
- HIV infection⁸ (Chapter 8): Patients living with HIV.
- Infant and paediatric patients (Chapter 9): Infections occurring in children (younger than 18) and infants/newborns.
- Immunodeficiency (Chapter 10): Patients diagnosed with immunodeficiency for reasons other than organ transplant, cancer or HIV.

⁷ Due to the large number of studies focusing specifically on organ transplants, and the added risk of developing infections this patient population faces due to being on immunosuppressant drugs, this was analysed independently of the studies on surgery.

⁸ HIV infection was analysed separately to the studies on immunodeficiency due to the larger number of papers that focused specifically on HIV (particularly with TB co-infection) which was deemed important enough to be analysed separately from the immunodeficiency studies.

- Liver and kidney disease (Chapter 11): Patients with diagnosed conditions of the liver or kidney.
- Physical trauma (Chapter 12): Patients with serious injury to the body caused by an external force, such as falls, physical violence or road accidents.

We then reflect on the key findings from across the evidence and identify areas for future research in Chapter 12. Annex A provides additional detail on the methods.

2. Overview of evidence on models and datasets about AMR, and cost estimates of AMR

2.1. Introduction

This chapter is aimed at providing a high-level overview of the evidence on models and datasets about AMR and estimates of economic and healthcare costs of AMR. The intent is to provide a snapshot of current trends regarding the modelling approaches being used, bacterial pathogens being investigated, and known limitations of the models and datasets. The methods used to identify this literature are outlined in Annex A. The findings described here are representative of the evidence short-listed and intended to provide an overview of the evidence regarding models, datasets, and cost estimates about AMR. Since the focus was on high-level overview, important relevant studies may have been overlooked due to the highly targeted nature of the searches. To gain a thorough understanding of the data and modelling approaches for AMR, a more in-depth, structured evidence review would be necessary.

Box 1: Key findings on models and datasets about AMR, and cost estimates of AMR

Types of microbes:

- *E. coli*, MRSA, and *S. pneumoniae* appear to be the most commonly studied types of bacteria in modelling studies.
- Additional modelling studies are needed to better understand the potential future impacts of other important microbes, including fungi, parasites and non-influenza viruses.

Modelling approaches:

- Predictive mathematical modelling approaches based on historical healthcare and economic data currently appear to be the most commonly used approach to model AMR.
- There is also some evidence of innovative 'big data'-led approaches such as membrane computing or machine learning models in the literature.

Limitations of AMR models:

- The type and quality of the data underpinning AMR models appears to vary significantly.
- AMR incidence data is not yet recorded universally, and so important gaps exist in the data currently used for any AMR-related models and estimates.
- Current models for the future impact on AMR may not be sufficiently useful for informing policy and practice.

2.2. Findings

2.2.1. Specific types of microbes and antibiotics appear to be more frequently modelled

The types of microbes and diseases covered in modelling studies appear to differ based on whether the study refers to a hospital or community setting. Microbes such as *Mycobacterium tuberculosis* (which causes TB), HIV, influenza viruses, the plasmodium parasite (which causes malaria), and methicillin-resistant *Staphylococcus aureus* (MRSA) appear to be more frequently modelled as these diseases have historically had significant negative health outcomes and high mortality rates globally, and there is also better availability of epidemiological and surveillance data [11, 12].⁹ *Escherichia coli* (*E. coli*, which can lead to diarrhoea and food poisoning), MRSA, and *Streptococcus pneumoniae* (which can cause pneumonia) appear to be the most commonly studied types of bacteria [11, 13-15]. *Neisseria gonorrhoea* (causing the STI gonorrhoea), *Haemophilus influenzae* (causing a range of mild-moderate infections throughout the body) and *Klebsiella pneumoniae* (which can cause serious infections across the body in people who are already unwell) are other commonly studied bacteria in mathematical models on AMR (see [16-18]). It has been suggested that antibiotics are being overused to treat infections acquired in a hospital setting. Infections

⁹ The availability of data also likely played a key role in the selection of *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* as part of the analysis presented in the 2014 KPMG report. Although we did not consider the KPMG report in the analysis here, it is the source of the oft-quoted figure of 10 million deaths due to AMR by 2050.

acquired in a hospital setting are therefore likely to be a key source of potential future increases in rates of AMR [17].

In terms of specific antibiotics, cephalosporin, penicillin, carbapenem, and methicillin appear to be frequently mentioned in modelling studies [15, 19]. This is likely linked to the type of bacterial infections studied since MRSA, penicillin-resistant *S. pneumoniae*, and tetracycline-resistant *E. coli* appear to be frequently mentioned in the studies [15, 19]. In particular, increased penicillin resistance by *S. pneumoniae* is highlighted as being of critical importance since this could result in a three- to four-fold increase in mortality in future influenza pandemics due to secondary infections¹⁰ by *S. pneumoniae* [20].

2.2.2. Deterministic mathematical modelling appears to be the most common approach to modelling of AMR

Modelling helps researchers and others to better understand an infectious disease. For this review of evidence on AMR modelling and datasets, we have focused on models that aim to understand the impacts of AMR and what may happen if antimicrobials no longer work.

Systematic reviews of the literature on modelling of AMR¹¹ suggest that mathematical modelling techniques are most commonly used to analyse and explore the impact of AMR [11, 13, 15, 18, 21-23]. A systematic review of AMR modelling literature states that due to the increased importance of AMR, mathematical modelling is on the rise in epidemiological studies of AMR [24]. For example, one study examines epidemiological models for resistance diagnostics and also includes a simple mathematical model that could enable public health officials to develop tailored approaches for the treatment and transmission control of antibiotic resistance [19].

Predictive modelling approaches¹² based on historical healthcare and economic data currently appear to be the mainstay of the literature on AMR-related modelling (see also [11, 24]). Predictive models are most likely to be either deterministic or stochastic. Deterministic models are models which are designed to produce the same output for a specific starting point or input data by using known relationships and not including any random variation. Stochastic models are models which allow random variation in one or more inputs over time. Due to the variations in inputs, stochastic models will produce different outputs and better reflect what may happen in actuality.

A review of 60 studies about AMR modelling found that more than 80% used deterministic modelling [15]. However, of these, only very few used stochastic approaches (6 in the 60 they reviewed) or both deterministic and stochastic approaches (5 in the 60 they reviewed) [25]. There is emerging evidence of alternative and innovative approaches, including computational approaches such as agent-based modelling¹³ (for example, see [26, 27]), 'big data'-led

¹⁰ Secondary infections occur when a patient already has another type of infection.

¹¹ Such as Birkegård et al. (2018), Niewiadomska et al. (2019), Ramsay et al. (2018) and others.

¹² Predictive models are models that use data and statistics to predict specific outcomes (i.e. what is likely to happen).

¹³ Agent-based models are computational models which simulate actions and interactions between autonomous agents to understand their effects on a system.

approaches, such as membrane computing [16]¹⁴ or machine learning models [28-30].¹⁵ However, mathematical modelling combining health economic and epidemiological knowledge are more common. In this context, a different perspective is available in the form of a causal inference model of AMR transmission based on a system dynamics approach [31].

2.2.3. The quality of available data varies, and the models may not be comparable as a result

The quality of the data underpinning the AMR models appears to vary significantly, which makes it challenging to compare the findings across studies. A number of studies appear to rely on data based on hospital admissions, microbiological laboratory and pharmacy databases, and surveys of hospitals and medical centres to understand prevalence of specific bacterial infections [31, 32]. The European Antimicrobial Resistance Surveillance Network (EARS-Net) is used as a data source in multiple studies for understanding high-level infection rates in European countries [14]. Electronic health records can be used to collect data on patient demographics, clinical data (type of infection, outcome, and antimicrobial treatment regimen and doses), number of antibiotic prescriptions, and the proportion of patients treated with antibiotics as the basis for modelling AMR [16, 33]. The ResistanceMap¹⁶ which was developed and openly shared by the Centre for Disease Dynamics Economics & Policy (CDDEP) is a potential source to estimate the economic cost of antibiotic use [34].

A systematic review of AMR modelling studies highlights that less than half of the models appear to be calibrated¹⁷ against epidemiological data [11]. Precise, real world data on antibiotic consumption rates in humans and animals does not seem to be publicly available in most countries and is especially difficult in low- and middle-income countries [11, 14]. Therefore, authors often calibrate model outputs with available empirical data which makes them less accurate [15]. Published literature and/or expert opinion are also cited as potential sources of data for the models [15]. This suggests that estimates of the economic and healthcare costs of AMR need to be understood in the context of underlying assumptions and limitations of the data sources used.

It has been suggested that data collection at regional and national levels often differs in the level of detail and is not comparable across regions/countries [36, 37]. Therefore, AMR estimates at national levels are more likely to be reliable only when these are based on recorded incidence rates of AMR [14]. However, since such AMR incidence data is not yet recorded universally, the AMR estimate models are likely to overestimate the problem [11, 14]. In contrast, some suggest that the relative lack of data indicates that the current worst-case scenarios for the economic cost of AMR are underestimations [36, 37]. Despite the different perceptions of viability of current models and any estimates provided, available

¹⁴ Membrane computing refers to computing approaches which draw on the study of biological cells, specifically cellular membranes to devise new computational models.

¹⁵ Machine learning models are a set of computational models in which the algorithms 'learn' from the data captured to influence the outputs produced.

¹⁶ <https://resistancemap.cddep.org/> (accessed 24 June 2020)

¹⁷ Calibration is the process of validating a model, whereby the model is compared to real world systems and data and then refined until it produces valid results 35. Bucknell. *Calibration and Validation of Models*. 2002; Available from: <https://www.eg.bucknell.edu/~xmeng/Course/CS6337/Note/master/node70.html..>

evidence suggests that important gaps exist in the data currently collected and used for any AMR-related models and estimates.

2.2.4. Further research and systemic changes are needed to improve the current models, data sources, and cost estimates on AMR

Systematic reviews highlight several limitations of the AMR modelling literature in relation to the use of data and the underlying assumptions of the modelling approaches (see, for example, [11, 13, 14, 38]). Although the current literature often presents implications of AMR in real-life situations, more rigorous assessment of the underlying data is necessary to assess their usefulness [13]. Some have emphasised that model validation and inclusion of real-world observational data are needed to support the assumptions that guide the model development. Some have suggested that estimates of economic or healthcare costs of AMR need to acknowledge associated uncertainties regarding the incidence of infections, the prevalence of resistance, and the death rate that can be directly attributed to the infection being modelled [14]. Some authors appear critical of the models of AMR burden published after the 2014 AMR review. They suggest that there are strong limitations to any cost estimates of the impact of AMR on human health since the available AMR data, particularly in low- and middle-income countries, are insufficiently informative. Similarly, some indicate the need to routinely inform and calibrate any AMR models to ensure that any trend predictions on economic and healthcare costs of AMR are consistent with known or available epidemiological data on the evolution of the antimicrobial resistance [39]. Ramsay et al. (2018) suggest that to ensure transparency of reporting the models need to be tested for deterministic or probabilistic sensitivity analyses [15].¹⁸

Most of the reviewed studies focus on deterministic mathematical models that use predictive analysis, and one study presents a causal inference model focusing on the conditions due to which AMR is likely to become a problem [31]. A key gap and limitation of current models is that they are likely to assume that the problem of antibiotic resistance would be recognised in a timely fashion, its severity properly assessed, and that appropriate goals for behavioural change would be set [31]. In order to inform policy decisions, further studies are needed to understand likely outcomes when these hypotheses (such as timely recognition of the problems posed by AMR, the severity of AMR being properly assessed, and the required behavioural change for AMR taking place) cannot be established in terms of available evidence [39].

2.3. Discussion

This chapter provides a highly targeted snapshot of the current evidence on models, datasets, and estimates regarding AMR. The findings present a mixed picture – highlighting an emerging, highly active sub-field of AMR-related modelling studies on the one hand, and on the other hand, a need to ensure a more comprehensive process for collection of AMR data. Current AMR estimates offer useful indicators of the scale of the problem; however, in the absence of sufficiently granular data on population demographics such as gender- and age-

¹⁸ Sensitivity analysis is an analysis of how the outputs of a model are affected by changes to the input variables to the model.

based antibiotic consumption rates, and AMR-related data on mortality and health outcomes, they may not be sufficiently useful for actionable policy changes. As 'big data' approaches become more prominent, currently prevalent deterministic predictive mathematical models are likely to be used alongside machine learning-led, and more dynamic, feedback-loop based models. In particular, to understand the evidence on modelling and estimates related to specific secondary diseases or conditions such as cancer or surgery, further research is necessary. Depending on the extent to which the datasets on antibiotic use, resistance transmission, and patient demographics improve, AMR modelling literature can be expected to play an important role in informing AMR-related policy and decision-making.

3. Surgery

According to one estimate, 266.1 million surgical procedures were undertaken worldwide in 2015 [40]. In the UK, 10 million surgeries are performed each year [41]. Before the discovery of antibiotics, thousands of people died from bacterial infections, such as pneumonia, following surgery and antibiotics are now routinely used to prevent this [3, 42]. For example, one analysis suggests that surgery patients receiving antibiotics to prevent infections have an infection rate of 4%, compared with 11% for patients not receiving antibiotics [42].¹⁹ Increasing antibiotic resistance undermines the efficacy of these preventive measures and could lead to a return to a pre-antibiotic era in which surgery would no longer be possible due to the risk of infection, subsequent complications and death [42].

This section will describe the impacts of antimicrobial resistance on patients undergoing surgery. The literature we reviewed covered three main types of surgery: cancer-associated surgery, orthopaedic implants, and eye surgery. Box 2 summarises the identified impacts from resistant infections and Box 3 summarises the available literature on this population.

¹⁹ The overall surgical site infection rate for patients receiving prophylactic antibiotics for the ten surgeries reported in the meta-analyses.

Box 2: Key findings on patients undergoing surgery

Key findings on impacts:

- **Mortality:** Surgery patients are at **risk of death** if they acquire a drug-resistant infection. For example, patients with pancreatic cancer who undergo pancreatic surgery are 6 times more likely to die if they acquire a resistant infection compared to patients with non-resistant infections.
- **Health outcomes:** Surgery patients are at **increased risk of developing complications** if they contract a drug-resistant infection compared to those with a non-resistant infection. For example, patients with colorectal cancer undergoing surgical biopsies of the prostate are 7 times more likely to develop complications after surgery if they acquire a resistant infection compared to patients with a non-resistant infection.
- **Effectiveness of treatment:** Surgery patients who acquire a drug-resistant infection are **more likely to experience treatment failure – in terms of the surgery itself and in terms of antibiotic treatment** to prevent and to treat a resistant infection – compared to patients with a non-resistant infection.
- **Length of stay in hospital:** Orthopaedic surgery patients who acquire a drug-resistant infection experience **longer hospital stays**. For example, patients receiving orthopaedic surgery who are infected with drug-resistant bacteria face hospital stays of up to a third longer than patients with a non-resistant infection.

Box 3: Summary of the range and nature of studies on patients undergoing surgery

Number of studies: 11

Study types: 5 empirical studies (3 collecting primary data and 2 conducting secondary analysis of existing patient data); 4 reviews (3 narrative reviews, 1 modelling study); 1 case report.

Strength of evidence: **Moderate. Reasonable number of studies**, many studies use empirical research and most results across studies come to similar conclusions. However, half of the studies provide weaker evidence (narrative reviews and case reports).

Geography: Italy, Spain, France, South Korea, USA. The location was global in one study and was not specified in 5 studies.

Specific conditions: Patients undergoing three main types of surgery: cancer-associated surgery; orthopaedic implants; cataract surgery.

Type of resistance: Antibacterial.

Study populations: 7 studies focus on all types of surgical patients and 3 studies on adults only.

Impacts assessed: Mortality, health outcomes, effectiveness of treatment and length of hospital stay.

3.1. Mortality

Three articles investigated the impacts on mortality. These comprised two empirical studies and one modelling study. One article found that patients who acquire resistant infections following surgery are at **increased risk of death compared to patients with non-resistant infections**. Two articles, including the modelling study, found that drug-resistant infections

may be associated with increased risk of death, but two do not provide adequate comparator groups to be able to determine this.

Patients undergoing surgery are at risk of death if they acquire a drug resistant infection

An empirical study of 517 adult patients receiving pancreatic surgery for cancer found that the death rate was 12% in patients with infections resistant to more than one drug compared to 2% in patients with a non-resistant infection[43].²⁰

A modelling study estimating the impact of antibiotic resistance on the ten most common surgical procedures, such as hip surgery and C-sections,²¹ calculated that if 30% of available antibiotics prescribed to surgical patients were no longer able to treat infections due to drug resistance, it could result in 6300 additional infection-related deaths per year in the US [42]. However, it should be noted that these results are estimates based on secondary analysis of existing data.

An empirical study of 106 adult patients receiving general surgery who had infections resistant to more than one type of antibiotic reported a 15% death rate overall [44]. However, the study does not provide information on mortality in patients with non-resistant infections. In this study, the risk factors for mortality due to drug resistant infections in general surgery are older age and the presence of other health conditions such as malnutrition, chronic digestive conditions, and chronic obstructive pulmonary disease.

3.2. Health outcomes

Of the reviewed literature, seven articles explored the impacts on complications following surgery for patients who acquire a resistant infection. These comprised four empirical studies, two narrative reviews and one modelling study. Six studies reported that patients are **more likely to suffer from infectious and non-infectious complications** following different types of surgery if they acquire a resistant infection compared to patients with non-resistant infections. One study found that drug-resistant infections may be associated with increased complications following surgery but is based on an estimate.

The evidence is unclear whether drug resistance leads to additional surgical site infections and complications after surgery

A modelling study estimating the impact of antibiotic resistance on the ten most common surgical procedures (e.g. hip replacements and caesarean sections)²² stated that increasing drug resistance potentially threatens the safety and efficacy of surgical procedures. The study calculated that if 30% of available antibiotics prescribed to surgical patients were no longer able to treat infections due to drug resistance, it could result in 120,000 additional surgical site infections per year in the US, which could result in adverse clinical outcomes, including complications and amputation [42].

²⁰ P = 0.054 for drug resistance compared to no infection

²¹ Hip fracture surgery, pacemaker implantation, spinal surgery, total hip replacement, caesarean section, transrectal prostate biopsy, appendectomy, abdominal hysterectomy and colorectal surgery

²² Hip fracture surgery, pacemaker implantation, spinal surgery, total hip replacement, caesarean section, transrectal prostate biopsy, appendectomy, abdominal hysterectomy, colorectal surgery

Patients undergoing eye surgery who acquire a drug resistant infection are more likely to suffer from poorer vision

Three studies focused on all types of patients receiving eye surgery who acquired a post-surgical eye infection. The articles showed that patients who acquire resistant eye infections following eye surgery²³ have poorer visual outcomes (e.g. vision loss and blindness) than patients with non-resistant infections [45-47]. For example, out of 31 patients treated for an eye infection who had poor visual outcomes, 63% of patients had a drug resistant infections compared to 33% of patients who had a non-resistant infection [47].

A variety of risk factors were associated with acquiring a resistant infection following eye surgery, including: older age, diabetes, lack of visibility of the inside of the eye [46], initial clearness of vision and timing of interventions to treat the infection²⁴ [47].

Cancer patients undergoing surgery have a greater chance of suffering from post-surgical complications if they acquire a drug-resistant infection

In total, two articles focused on cancer patients undergoing surgery. One narrative review focused on all types of colorectal cancer patients receiving antibiotic treatment to prevent surgical site infections from surgery (e.g. prostate biopsies and liver transplants). The review reported that colorectal cancer patients undergoing surgical biopsies of the prostate and cancer-related liver transplants who acquire a resistant infection pre-operatively have a higher rate of post-operative infections compared to patients with a non-resistant infection [48]. For example, in patients receiving surgical biopsies of the prostate, those that acquired a resistant bacterial infection pre-operatively had a post-surgical infection rate of 7% compared to 1% in patients with a non-resistant infection. In patients receiving a liver transplant, those that acquired a resistant bacterial infection pre-operatively had a post-surgical infection rate of 45% compared to 4% in patients with a non-resistant infection.

One empirical study focused on adult cancer patients receiving pancreatic surgery and found that patients who acquired infections resistant to more than one type of drug were four times more likely to have major non-infectious complications, e.g. internal bleeding and heart problems,²⁵ than patients with non-resistant infections or patients without infections, which led to longer hospital stays [43]. The study found that specific surgical procedures²⁶ were associated with a 2.5 times increased risk of having resistant infections after pancreatic surgery.

Patients undergoing orthopaedic surgery are more likely to suffer poorer outcomes from surgery if they acquire a resistant infection

²³ This includes the following types of surgeries: cataract surgery, intravitreal injection, glaucoma surgery, phakic or secondary intraocular lens implantation, vitrectomy, vitrectomy combined with cataract surgery, and keratoplasty.

²⁴ In this case, an early vitrectomy, which is a surgical procedure to remove vitreous humour from the eye.

²⁵ Complications included: coagulopathy, intraluminal or extraluminal bleeding, deep vein thrombosis, pulmonary embolism, pleural effusion needing drainage, cardiac infarction/ischemia, arrhythmia needing pharmacologic conversion or percutaneous ablation, wound dehiscence, neurological disorders, delirium, intestinal ischemia, delayed gastric emptying, and any single or multiple organ dysfunction/failure requiring intensive care treatment.

²⁶ In this case, biliary stenting, a procedure to remove blockages in the bile duct of the pancreas.

One narrative review focusing on all types of patients receiving an orthopaedic implant infected with a resistant bacterial infection reported that these patients had substantially poorer clinical outcomes compared to patients infected with a non-resistant bacterial infection [49]. These patients also had more surgical procedures compared to those infected with non-resistant bacteria [49]. Similarly, children with bone and joint infections due to drug-resistant bacteria had complications, including a substantially longer duration of fever compared to those infected with non-resistant bacteria. The review did not provide any data to quantify these negative health outcomes.

3.3. Effectiveness of treatment

Four articles explored the impact of drug resistance on the effectiveness of treatment in patients receiving surgery who acquire resistant infections. These comprised an empirical study and three narrative reviews. One narrative review reported that patients with resistant infections have **a higher risk of failure** of the surgical procedure compared to patients with non-resistant infections. Three articles indicated that drug resistant infections may be associated with reduced effectiveness of treatment. However, two consist of narrative reviews that did not report a comparator group, and so further research is needed before firm conclusions can be reached. One article also highlights that the use of antibiotics to prevent infections is less likely to be effective in patients who acquire a drug resistant infection compared to patients who have a non-resistant infection [45].

Surgery is more likely to fail in patients with a drug resistant infection

Two articles focused on patients receiving orthopaedic implant surgery. One narrative review of all types of patients receiving an orthopaedic implant reported that patients who had a resistant bacterial infection had a higher rate of failure of the surgical procedure compared to those infected with non-resistant bacteria [49]. For example, among patients receiving a hip and knee replacement, only 48% and 18%, respectively, of patients who had a resistant infection were treated successfully compared to 81% and 89% of patients with a non-resistant infection. Children with bone and joint infections caused by drug-resistant bacteria had a longer duration of antibiotic treatment²⁷ compared to those infected with non-resistant bacteria. Older patients (aged 60 and over) receiving an orthopaedic implant appear to be at higher risk of acquiring a drug-resistant infection than younger patients, and more frequently carry the resistant forms of bacteria compared to younger patients [49]. For example, in a study of 163 patients with orthopaedic implant-associated infections, 91% of older patients had a drug-resistant infection compared to 66% of younger patients. One study focused on 131 adult patients from 10 countries receiving prosthetic joint surgery who acquired prosthetic joint infections that were resistant to more than one type of antibiotic. The study found that certain surgical procedures had a greater probability of failure compared with other types of procedures, both in late and early prosthetic joint infections. However, the study reported that this finding was independent of the level of resistance and did not provide information on the rate of failure in patients with a non-resistant infection[50].

²⁷ The review does not provide information on the length of antibiotic treatment.

One review estimating the impact of antibiotic resistance on the ten most common surgical procedures²⁸ stated that increasing antibiotic resistance potentially threatens the efficacy of surgical procedures [42]. The analysis found that if 30% of available antibiotics prescribed to surgical patients were no longer able to treat infections due to drug resistance, it could result in over 6,300 additional infection-related deaths per year in the US.²⁹

3.4. Length of stay in hospital

One narrative review explored the impact of resistant infections in surgical patients on length of stay in hospital.

Orthopaedic surgical patients who acquire a resistant infection experience longer hospital stays

The narrative review described the impact of antibiotic resistance on the length of stay in hospital following surgery. The review reported that among 43 adult patients receiving orthopaedic surgery, those who acquired a drug-resistant infection had substantially longer hospital stays compared to those infected with non-resistant bacteria (15 days compared to 10, respectively) [49]. Similarly, children with bone and joint infections from drug-resistant bacteria had a longer length of hospital stays compared to those infected with non-resistant bacteria (13 days compared to 8, respectively).

²⁸ Hip fracture surgery, pacemaker implantation, spinal surgery, total hip replacement, caesarean section, transrectal prostate biopsy, appendectomy, abdominal hysterectomy, colorectal surgery

²⁹ For the seven procedures for which mortality data were available.

4. Organ transplant

An organ transplant consists of a surgical procedure to transfer tissues or organs from one person to another to treat organ damage or failure [51]. In 2015, more than 126,600 solid organ transplants³⁰ were performed worldwide [52]. Infectious complications (e.g. bloodstream infections and pneumonia) are a major cause of poor health outcomes and death in organ transplant patients [53, 54]. Long hospital (and ICU) stays, alongside an immunosuppressed status, make this population of patients particularly vulnerable to infection [55]. Effective antibiotic treatment is crucial in the management of organ transplant recipients, without which transplantation would lead to poor outcomes, including rejection of the transplant and death [56]. Therefore, without effective antibiotics, the emergence of infections due to drug resistant bacteria poses a significant therapeutic challenge [56].

This section will describe the impacts of antimicrobial resistance on patients receiving an organ transplant. The literature covered solid organ transplants (kidney, heart, liver and lung) and tissue transplants (eye, stem cell). Box 4 summarises the identified impacts from resistant infections and Box 5 summarises the literature on this population.

³⁰ A solid organ transplant is a transplant of major solid organs including the kidney, liver, pancreas, small intestine, heart and lung. Other types of transplants, amongst others, are tissue and cell transplants.

Box 4: Key findings on patients undergoing organ transplant

Key findings

- **Mortality:** It is unclear from the evidence whether solid organ transplant patients are at increased risk of dying if they acquire a drug-resistant infection. However, two studies found that adult patients receiving a solid organ transplant (liver, heart or kidney) who acquired a bloodstream infection with drug resistant bacteria were more than twice as likely to die than patients infected with non-resistant bacteria.
- **Health outcomes:** Organ transplant patients are more likely to suffer **negative health outcomes** (e.g. persistent bloodstream infections and organ failure) if they acquire a drug-resistant infection compared to patients with a non-resistant infection.
- **Effectiveness of treatment: It is unclear from the evidence whether** organ transplant patients who acquire a drug-resistant infection suffer from **reduced effectiveness of treatment** (e.g. rejection of the transplant and reduced efficacy of antimicrobial drugs to treat the patient). Two studies found that drug-resistant infections reduced the effectiveness of treatment (e.g. requiring a repeat transplant) in transplant patients. However, some studies find no difference in the effectiveness of treatment between patients with and without a drug-resistant infection.
- **Hospital and ICU admission, and length of stay:** There is mixed evidence as to whether organ transplant patients who acquire a drug-resistant infection are more likely to **require ICU admission (or longer admission)** and to **require hospitalisation compared to patients with non-resistant infections**. In one study, kidney transplant patients with a resistant infection were 1.5 times more likely to require hospital admission compared to patients with non-resistant infections.
- **Invasiveness of treatment:** Organ transplant patients who acquire a drug-resistant infection are **more likely to require invasive treatment** (e.g. mechanical ventilation) compared to patients with non-resistant infections. For example, patients who received a liver, heart or kidney transplant and who acquired a bloodstream infection caused by drug-resistant bacteria were twice as likely to require invasive mechanical ventilation compared to transplant patients infected by non-resistant bacteria
- **Increased risk of AMR:** Organ transplant patients are at **increased risk of developing drug-resistant infections compared to patients not receiving an organ transplant**. For example, among patients with a urinary tract infection, those who had received a kidney transplant were more likely to have a resistant infection.

Box 5: Summary of the range and nature of studies on patients undergoing organ transplant

Number of studies: 22

Study types: 16 empirical studies (10 collecting primary data, 6 conducting secondary analysis of existing patient data); 3 case reports; 2 narrative reviews; 1 case report and review of the literature.

Strength of evidence: Moderate. Large number of studies, most evidence is from empirical studies and is consistent, but several do not provide adequate control groups to reach firm conclusions.

Geography: Spain, France, Greece, Italy, Germany, Brazil, Canada, China, South Korea and the US. The location was not specified in 2 studies.

Specific conditions: Patients undergoing solid organ transplants (kidney, heart, liver and lung) and tissue transplants (eye and stem cell). The specific organ was not provided in some studies.

Type of resistance: Antibacterial and antiviral.

Study populations: 11 studies focus on all types of patients, 9 on adults, 1 on children, and 1 on elderly patients.

Impacts assessed: Mortality, health outcomes, effectiveness of treatment, hospital and ICU admissions, length of hospital stay, invasiveness of treatment, and risk of developing AMR.

4.1. Mortality

Ten empirical studies explored the impact on mortality in organ transplant patients who acquire a drug-resistant infection. Five of these found that solid organ and stem cell transplant patients who acquire a resistant infection have a **higher rate of mortality compared to patients with non-resistant infections**. Two empirical studies found no difference in mortality between solid organ transplant patients with a resistant infection and those with a non-resistant infection. Three articles report a higher risk of death in solid organ transplant patients with resistant infections but do not provide adequate control groups to reach firm conclusions.

It is unclear from the evidence whether solid organ transplant patients are at increased risk of dying if they acquire a drug-resistant infection

Two empirical studies found that adult patients receiving a solid organ transplant (liver, heart or kidney) who acquired a bloodstream infection with drug resistant bacteria were more than twice as likely to die³¹ than patients infected with non-resistant bacteria [53]. Causes of death in patients infected with resistant bacteria were due to shock/multiorgan failure, including respiratory failure, liver shock and shock as a result of sepsis [56].

An empirical study of 69 solid organ transplant patients in the US who acquired a drug resistant infection found that 54% (22 out of 41) died in hospital three months after the transplant [57]. Patients receiving heart and lung transplants were twice as likely to acquire a drug resistant infection compared to those receiving abdominal transplants.³² Lung transplant recipients were at particularly high risk of respiratory tract infections (e.g. pneumonia) from drug resistant

³¹ Bodro et al 2015: 38% vs 16%; P=0.009. Bodro et al 2013: 35.2% vs 14.4%; P= 0.001.

³² Heart and lung (2.6%) vs abdominal [intestine, kidney, liver, multivisceral, and pancreas] (0.9%); P = 0.0004.

bacteria because of their need for prolonged mechanical ventilation. However, this study does not provide information on the number of deaths in transplant patients with no infection or with non-resistant infections, and so firm conclusions cannot be reached.

Three empirical studies specifically focused on adult patients who received a liver transplant. Two studies found that liver transplant patients who had drug-resistant bacteria present in the body were more likely to develop a drug-resistant infection after the transplant, and as a result were more than twice as likely to die compared to non-infected patients (30% of patients versus up to 17% of patients) [58, 59].³³ However, these studies do not provide information on the death rate in transplant patients with a non-resistant infection. In another study, the presence of bacteria resistant to the majority of commonly used antibiotics led to severe bloodstream infections with a high death rate [60]. A total of 25 (49%) liver recipients died due to infection within one-month post-transplantation, after being diagnosed with a resistant bloodstream infection. There was no information on the number of deaths in transplant patients without infection or with drug-susceptible infections as a comparison to these results.

In contrast, two studies found no difference in mortality between transplant patients with a resistant infection and those with a non-resistant infection. For example, there was no difference in death rate between paediatric and adult patients with cystic fibrosis who underwent lung transplantation who were chronically infected with drug resistant bacteria and patients infected with non-resistant bacteria [61].³⁴ In adult patients receiving a solid organ transplant, there were no differences in mortality between patients with a viral infection with genetic mutations associated with resistance and those without [62].

Given the mixed evidence from studies, with some identifying a link between drug resistance and death in organ transplant patients but others not finding this association, further research is needed to better understand whether this association exists and, if it does, the risk posed to this patient group from drug resistant infections.

Stem cell transplant patients are at increased risk of dying if they acquire a drug-resistant infection

Three empirical studies focused on patients receiving a stem cell transplant. In a study of adults and children in blood stem cell transplant centres from 25 countries in Europe, Australia, and Asia, those who acquired a drug-resistant bacterial infection had a higher rate of death than patients with infections caused by non-resistant bacteria [63].^{35,36} In a study based in Brazil of adults who received a blood stem cell transplant and who acquired a bloodstream infection, 13 patients died and 10 out of these had an infection caused by drug-resistant bacteria [64]. Older age, previous infection by drug-resistant bacteria, and feeding via a drip

³³ Colonised patients (30%) compared to non-colonised patients (11.76%), (P = .2); colonised patients (42.8%) compared to non-colonised patients (16.6%)

³⁴ The study investigated differences between patients chronically infected with pan-resistant *P aeruginosa*, polymyxin-sensitive only, or sensitive to 2 antibiotic classes (polymyxin plus one other) vs patients with more susceptible *P aeruginosa* or no *P aeruginosa* who were part of the control cohort. Differences in patient mortality (16% vs 5%, P = .487) were not statistically significant. The authors noted that this study had a small sample size and so may have been underpowered to detect a difference.

³⁵ 9% vs 2% in episodes caused by non-carbapenem resistant vs sensitive GNRs; 18% vs 4% in those carbapenem resistant vs sensitive; and 11% vs 4% in MDR vs non-MDR.

³⁶ Noncarbapenem resistant vs sensitive: p=0.002; Carbapenem resistant vs sensitive: p<0.001; MDR Vs non-MDR: p = 0.002.

were found to be risk factors for acquiring bloodstream infections caused by drug-resistant bacteria. In a study based in South Korea of 56 children who received a blood stem cell transplant and who acquired a drug-resistant viral infection, the rate of death was 2% (1 out of 49) [65]. There was no information on the number of deaths in transplant patients without infection or with non-resistant infections as a comparison to these results.

4.2. Health outcomes

Six studies investigated the impact on health outcomes in adult solid organ transplant patients who acquired a resistant infection. These comprised five empirical studies and one case report. All studies found that resistant infections are associated with **poor health outcomes** in transplant patients.

Solid organ transplant patients are more likely to suffer negative health outcomes if they acquire a drug-resistant infection

Two empirical studies based in Spain of adult patients receiving a solid organ transplant (liver, heart and kidney) who acquired a drug resistant bacterial infection found that they are twice as likely to develop persistent bloodstream infections and respiratory failure, and 1.5 times more likely to develop kidney failure compared to organ transplant patients infected by non-resistant bacteria [53, 56].³⁷

In one case report of a 60-year-old male patient with diabetes who received an emergency heart transplant, infection with a drug resistant bacterial infection led to rapid deterioration with sepsis and kidney failure [55]. After 4 days of unsuccessful treatment, severe anaemia developed. The authors suggest that the immunosuppressed status of the patient due to the transplant likely contributed to the persistence of the bloodstream infection. However, it is important to note that these results are based on a case report from one patient and therefore cannot be generalised to the wider heart transplant population.

Kidney transplant patients are more likely to suffer negative health outcomes if they acquire a drug-resistant infection

Two empirical studies found increased negative health outcomes in kidney transplant patients who acquired a resistant urinary tract infection compared to patients with a non-resistant infection. In a study of 147 kidney transplant patients, those who acquired drug-resistant bacterial infections were more likely to have a symptomatic urinary tract infection and kidney infection compared to patients infected with non-resistant bacteria (51% of infections were symptomatic compared with 35%) [66].³⁸ The strongest risk factor for acquiring a resistant bacterial infection was exposure to specific types of antibiotics in the six months before the presence of bacteria in the urine. Other risk factors included diabetes pre- and/or post-transplantation³⁹ and bacteria in the urine occurring in the first year post-transplantation.⁴⁰ In

³⁷ Bodro et al 2015: Persistent bacteraemia: 20.7% vs 7.7%, P= 0.03; Renal impairment: 56.7% vs 36.6%, P=0.04; Respiratory insufficiency: 36.7% vs 13%, P=0.002; Bodro et al 2013: Persistent bacteraemia: n.s.; Renal impairment: n.s.; Respiratory insufficiency: 33.3% vs 14%, P=0.002.

³⁸ More likely to be symptomatic: "29% vs 21% for cystitis, and 22% vs 14% for pyelonephritis; P=.004" (comparing resistant and sensitive strains).

³⁹ OR: 2.29; 95% CI: 1.11- 4.74.

⁴⁰ OR: 2.88; 95% CI: 1.36- 6.09.

another study based in Spain, patients who received a kidney transplant and who acquired a drug resistant urinary tract infection were more likely to have a recurrent infection (60% of patients) than patients with an infection caused by non-resistant bacteria [67]. Recurrent drug resistant urinary tract infections were more common in patients over 60⁴¹ and those needing re-operation.⁴²

Liver transplant patients may suffer negative health outcomes if they acquire a drug-resistant infection

An empirical study of 26 liver transplant patients found that those who did not have drug-resistant bacteria present in their body before the transplant had fewer complications than patients who did [59]. Fourteen out of 26 patients (54%) had drug-resistant bacteria present in the body pre-operatively, with 2 out of 14 (14% per cent) developing a serious infection as a result. The study does not indicate whether the control group had non-resistant bacteria present in the body, which means that firm conclusions about the impact of drug resistance on negative health outcomes in this study population cannot be made.

4.3. Effectiveness of treatment

Five empirical studies investigated the impact on effectiveness of treatment in organ transplant patients who acquire a resistant infection. Three studies found that resistant infections reduced the effectiveness of treatment, including a rejection of the transplant and reduced efficacy of antimicrobial drugs to treat the patient. In contrast, two other studies did not report a difference in the effectiveness of treatment between patients with and without a drug-resistant infection.

There is mixed evidence concerning the impact of drug resistant infections on the effectiveness of treatment in patients receiving transplants

Two studies found that drug-resistant infections reduced the effectiveness of treatment in transplant patients. In one study of patients receiving an eye transplant, out of 38 patients with infections caused by a pathogen resistant to more than one type of drug, 22 patients required a repeat transplant, and 1 patient had the contents of their eye removed [68].⁴³ There was no information on the effectiveness of treatment in transplant patients without infection or with drug-susceptible infections as a comparison to these results.

Drug resistant viral infection can also lead to negative outcomes in transplant patients. A study of five cases investigating the effectiveness of an antimalarial drug to treat a drug resistant viral infection in lung and kidney transplant patients found that the drug led to favourable outcomes in patients with a mild infection but was not effective in patients with a more severe infection [69]. However, care should be taken in generalising these results to the wider transplant patient population as these results are based on case reports of five patients.

In contrast, two studies found that resistant infections did not reduce the effectiveness of treatment in solid organ transplant patients. In a study based in Spain of 39 adult kidney and liver transplant patients, there were no differences between patients with viral resistance

⁴¹ OR: 3; 95% CI 1.4–6.5.

⁴² OR: 3; 95% CI, 1.3–7.1.

⁴³ This evidence is based on limited abstract information only due to the full-text being unavailable to the project team.

mutations and those without in the development of transplant rejection [62]. Similarly, in another study based in Spain of 1,057 adult kidney, heart, pancreas and liver transplant patients, complications (e.g. transplant rejection and need for re-intervention) were not associated with resistant infections [70].

4.4. Length of stay in hospital

Eight empirical studies reported on the impact on admission to hospital, the ICU and length of stay in solid organ transplant patients who acquired a resistant infection.

It is unclear from the evidence whether organ transplant patients who acquire a drug-resistant infection are more likely to require ICU admission

Two empirical studies based in Spain of liver, heart or kidney transplant patients with resistant infections reported that they were twice as likely to be admitted to the ICU compared to transplant patients infected by non-resistant bacteria (50-60% of patients admitted compared with 25%) [53, 56].⁴⁴

Two empirical studies based in Greece found that adult liver transplant patients with drug-resistant bacteria had a length of stay in the intensive care unit that was on average three times as long compared to patients with no drug-resistant bacteria (an average of 12-15 days compared with 4, respectively) [58, 59]. The studies do not indicate whether the control groups had non-resistant bacteria present in the body, which means that firm conclusions about the impact of drug resistance on length of hospital stay in this study population cannot be made.

There is mixed evidence concerning the impact of drug resistant infections on hospital admissions for patients undergoing organ transplants

An empirical study based in Canada of 147 adult kidney transplant patients with bacteria in the urine found that resistant infections were associated with a higher likelihood of hospitalisation compared to non-resistant infections (22% for resistant vs 14% for non-resistant) [66].⁴⁵ The strongest risk factor for resistant infections was exposure to specific antibiotics in the six months before the presence of bacteria in the urine. Other risk factors included having diabetes before and/or after the transplant and the presence of bacteria in the urine occurring in the first year after the transplant.

In contrast, in a study based in the US of 44 child and adult patients with cystic fibrosis who received a lung transplant, readmissions to hospital for infection were more frequent in patients with non-resistant infections or with no infection than in patients with drug-resistant infections [61]. The authors suggested that this could be due to the small sample size, and also that the patients with drug resistant infections were hospitalised for longer periods 6 to 12-months after the transplant, therefore getting discharged and readmitted less frequently.

Organ transplant patients with cystic fibrosis who acquire a drug-resistant infection are more likely to require longer ICU stays

One study investigated the impact on length of stay in the ICU in all types of patients receiving a solid organ transplant who acquired a resistant infection [61]. The study found that child and

⁴⁴ Infection with resistant *Pseudomonas aeruginosa*: $p < 0.001$; ESKAPE: $P = < 0.001$.

⁴⁵ 22% for resistant vs 14% for sensitive strains; $P = 0.04$.

adult lung transplant patients with cystic fibrosis chronically infected with drug resistant bacteria spent more time in the ICU compared to patients with a non-resistant infection or with no infection (10 versus 6 days), despite not having significantly more time on mechanical ventilation.⁴⁶

4.5. Invasiveness of treatment

Two empirical studies investigated the impact on invasiveness of treatment (i.e. the need for invasive medical support, such as mechanical ventilation) in adult solid organ transplant patients who acquired a resistant infection.

Organ transplant patients who acquire a drug-resistant infection are more likely to require invasive treatment

Two studies based in Spain of patients who received a liver, heart or kidney transplant and who acquired a bloodstream infection caused by drug-resistant bacteria found that they were twice as likely to require invasive mechanical ventilation compared to transplant patients infected by non-resistant bacteria [53, 56].⁴⁷

4.6. Risk of AMR

Six studies reported on the risk factors associated with developing a resistant infection following an organ transplant. These comprised five empirical studies and one narrative review. All studies found that organ transplant patients are at **increased risk of developing a resistant infection** due to several risk factors associated with this patient population.

Solid organ transplantation is a risk factor for developing a drug resistant infection

An empirical study in Spain of adult liver, kidney, and heart transplant recipients, reported that in this patient population, bloodstream infections due to drug resistant bacteria are frequent, and risk factors included previous transplantation before the current transplant⁴⁸ [56]. Another empirical study based in Spain in a similar patient population found that previous organ transplantation, hospital-acquired infection, and septic shock are associated with the development of bloodstream infections caused by drug-resistant bacteria [53]. In a study based in France of 346 organ transplant patients, those with existing infections (in particular viral infections) were three times more likely to develop a resistant infection compared to a non-resistant infection – 34% of patients with a drug resistant infection had a viral infection compared to 9% of patients with non-resistant infections. Viral drug resistance was found to be frequent in all types of solid organ transplant patients failing antiviral therapy [71].

Kidney transplant patients are more likely to develop a drug-resistant infection than other types of transplants

In one study in Germany of 137 patients (adults and children) who had a urinary tract infection, those who had undergone a kidney transplant were significantly more likely to develop an

⁴⁶ The resistant cohort spent significantly more days in the ICU than the control cohort (9.80 vs 6.16, P = 0.035).

⁴⁷ Infection with resistant *Pseudomonas aeruginosa*: p=0.006; ESKAPE: P= 0.001

⁴⁸ P=0.05

antibiotic resistant urinary tract infection [72]. The study did not provide any quantitative data on the increased risk. In the second study of 92 transplant patients (adults and children) based in Spain, resistant bacteria were 1.5, 1.8 and 2 times more common in kidney transplant patients (11% of patients) compared to liver (7%), double kidney-pancreas (6%), and heart (5%) transplant patients, respectively. Patients who required post-transplant dialysis had a higher risk of acquiring a drug-resistant infection, which the authors suggest may be linked to a more complicated post-operative period and longer hospital stays [70]. It was suggested that the high rate of resistant bacteria in kidney transplant patients may be due to the high incidence of urinary tract infections in this patient population.

It is unclear from the evidence whether stem cell transplant patients are at greater risk of acquiring drug-resistant infections

One narrative review reported that all types of patients receiving a stem cell transplant from another donor are at risk of acquiring a drug-resistant bacterial infection, particularly those patients who develop a gastrointestinal immune response to the transplant [73]. However, this study does not provide information on the likelihood of acquiring a drug-resistant infection in patients with other types of transplants.

5. Cancer

In 2018, there were 17 million new cases of cancer and 9.6 million deaths from cancer worldwide [74]. In the UK, between 2015 and 2017, there were 367,167 new cases of cancer and 164,901 deaths from cancer [75]. Patients with cancer may be amongst the most vulnerable to antimicrobial resistance because they potentially combine many other characteristics – such as being immunocompromised or immunodeficient, being hospitalised in the ICU, having another condition such as cystic fibrosis, or having breaks in the normal body barriers, e.g. the skin, which allows pathogens to enter [76]. Patients with cancer are often at risk of fungal infections⁴⁹[77], and immunosuppressed cancer patients undergoing chemotherapy and stem cell transplant recipients are at high risk of life-threatening infections [78]. The global spread of antimicrobial-resistant pathogens threatens to increase the mortality of cancer patients [79].

This section will describe the impacts of antimicrobial resistance on cancer patients. Some of the literature covered specific types of cancer, including pancreatic cancer, leukaemia and other haematological malignancies⁵⁰, while other articles looked at cancer more generally in which the type was not specified. Box 6 provides an overview of the key findings for cancer patients and Box 7 summarises the literature on cancer.

⁴⁹ A fungal infection caused by the fungal species *Candida*. Cancer patients are at risk of candidemia because of the greater use of catheters, abdominal surgery, use of cytotoxic chemotherapy, parenteral nutrition, antibacterial drugs and corticosteroids **Error! Reference source not found.**

⁵⁰ Cancer of the blood-forming tissue, such as bone marrow, or the immune system.

Box 6: Key findings on cancer patients

Key findings on impacts:

- **Mortality:** Patients with cancer may be at **increased risk of dying** if they acquire a drug-resistant infection compared to non-cancer patients, although the evidence is mixed. In one study, resistance to antifungal treatment was associated with increased mortality within 28 days, and 75% of patients with drug-resistant infections died compared with 25% of patients with drug-susceptible infections.
- **Health outcomes:** Patients with cancer who acquire a resistant infection may have an **increased risk of poorer health outcomes** compared to non-cancer patients, and specifically have a greater risk of sepsis. For instance, one study found that cancer patients who acquire a drug resistant infection were more likely to suffer from persistent sepsis compared to patients with infections due to other bacteria.
- **Length of stay:** It is unclear if patients with cancer need to spend longer in hospital if they acquire a resistant infection. However, one study found that the average length of hospital stay progressively increased according to the level of antibiotic resistance.
- **Risk of AMR:** Hospital stays, inflammation of the gastrointestinal tract, and use of multiple antibiotics **increase the risk of patients with cancer acquiring a drug resistant infection.**

Box 7: Summary of the range and nature of studies on cancer patients

Number of studies: 10

Study types: 7 empirical studies (4 collecting primary data and 3 conducting secondary analysis of existing data); 3 reviews (2 narrative and 1 qualitative).

Strength of evidence: Weak-moderate. Reasonable number of studies, most of which are empirical, but mortality is the only impact for which the volume and type of evidence is of reasonable (moderate) strength. Evidence for other impacts is weak.

Geography: Italy, South Korea, Greece, USA, Brazil, Spain, Egypt. The location was not specified in three studies.

Specific conditions: Solid tumour, pancreatic cancer surgery, paediatric cancer, haematological malignancy, acute myeloid leukaemia, haematological patients and hematopoietic stem cell transplantation (HSCT) patients, chemotherapy.

Type of resistance: Antibacterial and antifungal.

Study populations: 4 studies focus on all cancer patients, 4 on adults and 2 on children.

Impacts assessed: Mortality, length of stay, health outcomes and increased risk of AMR

5.1. Mortality

Six articles investigated the impact of a resistant infection on mortality in cancer patients. Most articles found that cancer patients who acquire a resistant infection are at **increased risk of death**, but a narrative review finds that this association is weak in some cases.

The evidence is mixed as to whether patients with cancer are at increased risk of dying if they acquire a drug-resistant infection

A study from Brazil found that drug resistant blood infections are associated with high mortality among cancer patients [80]. Another study, conducted in Greece, found that cancer patients who acquired a multi-drug resistant infection had a higher rate of death than patients who had a non-resistant infection (64% died compared with 32%, respectively) [76]. Specific factors associated with mortality in this study included the use of specific treatments⁵¹, septic shock, blood infection and infection due to the extensive drug resistant bacteria.⁵² Another empirical study focused on antifungal resistance in cancer patients in the USA. It found that resistance to antifungal treatment was associated with increased mortality within 28 days (75% of patients with drug-resistant infections died compared with 25% of patients with non-resistant infections) [77].⁵³ An empirical study conducted in Egypt found a higher mortality rate in children with resistant infections compared to those with non-resistant infections [81]⁵⁴, but the research team was unable to access the full-text of the study to identify the quantitative data. A narrative review found that the 14-day mortality rate associated with bloodstream infections is higher with resistant bacteria compared to susceptible bacteria (33% vs 11%, respectively) [73].⁵⁵

A narrative review of antibiotic resistance in cancer patients found that many studies show that a failure to treat drug resistant infections impairs outcomes in cancer patients, increasing mortality. However, the study also notes that these outcomes seem to vary depending on the specific type of resistant bacteria [82].⁵⁶ Similarly, another narrative review found that there was a lack of a robust association between preventative antibacterial treatment, the presence of resistant bacteria in the gastrointestinal tract, and increased mortality in cancer patients with low numbers of white blood cells [73]. For example, one study in the review found that there was no impact of a drug resistant bloodstream infection on the 28-day mortality in this patient group.⁵⁷ A study from Japan in this narrative review examined the effect of reducing the preventative uses of antibiotics on bloodstream infection rates and found that there was no impact upon mortality in the cancer patient group.⁵⁸

⁵¹ In this case, treatment with G-CSF (a treatment used to stimulate the production of white blood cells to increase a patient's immune response) and corticosteroids.

⁵² G-CSF administration $p = 0.01$; use of corticosteroids infection $p = 0.006$; septic shock: $p < 0.001$; bacteraemia $p < 0.001$; extensive drug resistant bacteria $p = 0.008$

⁵³ The 28-day all-cause mortality rate was 39.7% (58/146) among all patients, and 32.3% (30/93) among those who received echinocandins. Among patients who received echinocandins, the association between caspofungin minimum inhibitory concentration and all-cause mortality rates was significant (adjusted hazards ratio for minimum inhibitory concentration ≥ 0.5 mg/L = 2.59, 95% CI 1.08–6.19, $p = 0.033$)

⁵⁴ $P < 0.001$

⁵⁵ This was linked independently to an underlying diagnosis of haematological malignancy.

⁵⁶ The association between antibiotic resistance and prolonged hospital stay appears to be weaker in studies around vancomycin-resistant enterococcus infections and some other resistant Gram-negative pathogens, such as carbapenem-resistant Enterobacteriaceae and non-fermenting gram-negative bacilli.

⁵⁷ Whilst the majority of bloodstream infections among neutropenic ciprofloxacin prophylaxis recipients were fluoroquinolone-resistant compared to those not receiving ciprofloxacin, there was no impact upon the 28-day mortality (17.4 versus 22.6%, respectively)

⁵⁸ 13.8 and 3.8%, and 13.7 and 3.8%, respectively

5.2. Health outcomes

Two articles looked at the impacts of a resistant infection on the risk of poor health outcomes in cancer patients. Both found that cancer patients who acquire resistant infections are at **increased risk of sepsis**.

Patients with cancer who acquire a drug resistant infection are at increased risk of sepsis

An empirical study conducted in Spain found that cancer patients who acquire a drug resistant infection were more likely to suffer from persistent sepsis⁵⁹ compared to patients with infections due to other bacteria (25% with resistance caused by ESKAPE pathogens compared to 10% caused by other bacteria) [78]. A narrative review found similar results, noting that drug-resistant bacterial infections in cancer patients are likely to progress to severe sepsis and septic shock [83].

5.3. Length of stay in hospital

Of the reviewed literature, two articles explored the impact on the length of stay in hospital for cancer patients who acquired a resistant infection. Both studies reported that **cancer patients who acquire a resistant infection are more likely to spend longer in hospital**.

It is unclear whether patients with cancer need to spend longer in hospital if they acquire a resistant infection.

An empirical study conducted in Italy looking at the consequences of antibiotic resistance for the outcome of pancreatic surgery for cancer found that the length of hospital stay progressively increased according to the number of drugs the bacteria were resistant to [43].⁶⁰ In this study population, patients with bacteria that were resistant to three or more antibiotics had an average hospital stay of 24 days compared with 9 days for patients with no infection. However, a comparison to patients with a non-resistant infection was not provided. Similarly, a qualitative review of antibiotic resistance in cancer patients reported that many studies show that a failure to treat drug resistant infections have a substantive negative impact on outcomes in cancer patients, prolonging hospitalisation. The review does not provide data on the length of hospital stay reported in individual studies. The review also notes that these outcomes seem to vary depending on the specific type of resistant bacteria [82].⁶¹

⁵⁹ 25 % vs. 9.7 %

⁶⁰ Patients with no infection had an average hospital stay of 9 days. Patients who were multi-drug sensitive had an average hospital stay of 15 days, those with multi-drug-resistant infection had an average hospital stay of 18 days, and those with extensive drug resistance had an average hospital stay of 24 days **Error! Reference source not found.**

⁶¹ The association between antibiotic resistance and prolonged hospital stay appears to be weaker in studies around vancomycin-resistant enterococcus infections and some other resistant Gram-negative pathogens, such as carbapenem-resistant Enterobacteriaceae and non-fermenting gram-negative bacilli.

5.4. Risk of AMR

Two articles investigated the risk of developing a resistant infection in cancer patients. Both articles found that cancer patients are at **increased risk of AMR**.

Hospital stays, inflammation of the gastrointestinal tract, and use of multiple antibiotics increase the risk of patients with cancer acquiring a drug resistant infection

A narrative review reported that in cancer patients with blood cancer, development of a fever and a low white blood cell count, inflammation of the lining of the digestive system, severe illness, or receiving multiple antibacterial therapies are risk factors for developing a drug resistant infection. The severity of the inflammation of the lining of the digestive system appears to contribute to the risk of developing drug resistant infections in these patients. This review also found that having white blood cell cancer that progressed quickly increased the risk of developing a drug resistant infection [73]. The review did not provide quantitative data on the infection rate in these patients or information on other types of cancer patients.

An empirical study found that hospitalised cancer patients were more likely to develop a resistant infection than outpatients as they face prolonged exposure to hospital environment and antibiotics [81]. In this study population, 48% of hospitalised patients developed a resistant infection compared to 32% of outpatients, respectively. They were more likely to acquire different bacterial infections as well as antibiotic resistant infections. Cancer patients with longer durations of fever and low white blood cell counts were more likely to develop a drug resistant infection than those with shorter episodes (62% of patients with prolonged episodes developed a resistant infection).

6. Intensive care unit patients

Intensive care units (ICUs), also called critical care units, are hospital wards that are specialised in treating patients who are very ill, e.g. due to road accident, heart attack, serious infection, or surgery [84]. In the past 50 years (in the wake of World War II and Denmark's polio epidemic in the 1950s), critical care have spread to almost every country and most developed countries have dedicated specialist units for treating patients in critical condition [85]. In 2018-19, 175,000 adults were treated in ICUs across England, Wales and Northern Ireland [86]. While the effects of the COVID-19 pandemic are still ongoing at the time of writing this report, the number of patients requiring ICU admission in the UK due to the virus increased substantially between April and June 2020. At its peak in early April, over 3,300 patients in the UK were admitted to an ICU ward due to COVID-19 [87].

Antimicrobials, such as antibiotics, are an important part of treatment for ICU patients, with estimates indicating that up to 70% of ICU patients require antibiotics on any one day [88]. These patients are at particular risk of developing infections due to frequent close contact with healthcare professionals and the use of medical devices requiring entry into the body, such as mechanical ventilation and catheters [88]. In addition to a higher risk of contracting a resistant infection, ICU patients are also at greater risk of this infection being more severe due to the invasive medical equipment used, such as mechanical ventilation entering deep into the airways, leading to ventilator-associated pneumonia [88]. Drug-resistant infections are more likely to develop due to the use of broad-spectrum antibiotics, which allow resistant pathogens to thrive, particularly in the gut and lungs [88].

This section will focus on patients admitted to the ICU, primarily patients already in the ICU who develop drug resistant infections but also patients admitted to the ICU because of a drug resistant infection. Box 8 summarises the identified impacts from resistant infections and Box 9 summarises the available literature on this population.

Box 8: Key findings on ICU patients

Mortality: Infants and children in the ICU who develop drug resistant infections are at a **greater risk of mortality**. For example, one study found that children with drug resistant pneumonia were over four times more likely to die compared to children with non-resistant infections. The evidence is less clear for the impact on adult mortality, with some studies identifying no association between drug resistant infections and death, although the evidence does indicate that the elderly with drug resistant infections may be at a higher risk of mortality.

Length of hospital stay: Infants and adults on the ICU showing drug resistance to antibiotics require longer hospital/ICU stays.

Developing AMR: ICU admission is associated with development of drug resistant infections in children and adults, particularly with the use of invasive medical support, such as mechanical intervention and catheters inserted into a vein, and the presence of co-morbidities. For example, one study of 160 children already admitted to a Chinese paediatric ICU who developed drug resistant pneumonia found that for intubation (insertion of a tube into the airways to aid in breathing), 49% of children requiring this support developed drug resistant pneumonia compared to 22% of patients who did not need intubation.

Box 9: Summary of the range and nature of studies on ICU patients

Number of studies: 11

Study types: 1 narrative review and 10 empirical studies (5 collecting primary data and 5 conducting secondary analysis of existing patient data).

Strength of evidence: Moderate. Reasonable number of studies, most are empirical studies and the results across studies are generally consistent. However, the evidence for the impact on deaths rates in adults is weaker.

Geography: Turkey, Vietnam, Lithuania, South Korea, Brazil, China, Saudi Arabia, the USA, Thailand and the Netherlands. The location was not specified in 2 studies.

Specific conditions: Patients admitted to the ICU or neonatal ICU (NICU).

Type of resistance: Antibacterial and (for one study) antifungal.

Study populations: 3 studies focus on all types of ICU patients, four study neonates/children admitted to the ICU and 5 study adults admitted to the ICU.

Impacts assessed: Mortality, health outcomes, length of hospital/ICU stay and risk of developing AMR.

6.1. Mortality

Eight studies explored the impact on death rate as a result of ICU patients contracting drug resistant infections [54, 89-95]. All studies found a higher risk of mortality in ICU patients with drug resistant infections.

Children and infants admitted to the ICU are at a greater risk of death if they acquire a resistant infection

Two studies (both empirical quantitative studies) explored the impact of drug resistant infections on mortality for newborn babies and children admitted to the ICU [90, 92]. The first study, conducted in China, investigated mortality in 160 children admitted to the ICU with pneumonia and found that children with drug resistant pneumonia were over four times more likely to die compared to children with non-resistant infections (18% compared to 4%) [92].⁶² Similarly, a study conducted in Vietnam on 296 newborn babies and children found that those with drug resistant hospital-acquired infections in the ICU had a higher mortality rate than newborn babies with non-resistant infections. In this study, for every additional resistance to a type of antibiotic, the odds of death increased significantly, by 27% [90].⁶³

It is unclear whether adults admitted to the ICU are at risk of death if they acquire a drug resistant infection, although older adults are at greater risk of death

The other six studies primarily focused on adult ICU patients, with two studies exploring mortality for all ICU patients. Five of these were empirical studies (two collected primary data and three conducted secondary analysis of existing patient data and one was a narrative review). One Turkish study exploring the demographic characteristics and clinical outcomes of 29 patients with severe cancers of the blood, bone marrow and lymph nodes with drug resistant infections admitted to the ICU, found that the mortality rate was 82% and that all patients at certain stages of cancer are more at risk (such as newly diagnosed cancer or the presence of several malignancies) died within the first week after testing for the infection [89]. No information was provided on the death rate in patients with non-resistant infections or with no infections and the study is hindered by a small sample size.

One narrative review provided an overview of mortality for all types of patients with drug resistant ventilator-associated pneumonia.⁶⁴ The authors describe studies that show that deaths attributable to drug resistant ventilator-associated pneumonia (in this case, caused specifically by the bacteria *Pseudomonas aeruginosa*) were over 25% of all deaths in this patient population. However, the information in this narrative review should be interpreted with care as comparisons to patients with non-resistant or no infection were not provided [54].

A US study of adults with ventilator-associated pneumonia found that there was no difference in death rate between patients with pneumonia caused by a drug resistant infection (due to bacteria or fungi) compared to a non-resistant infection, however, the study did find that older patients (aged 65 and over) are at greater risk of dying. In the study, 44% of elderly patients died compared to 28% of younger patients.⁶⁵ It is interesting to note that a much higher proportion of older patients' ventilator-assisted pneumonia was caused by a drug resistant pathogen compared to younger patients [95].⁶⁶ Perhaps as a result of these factors, 30-day mortality was significantly higher in older patients.⁶⁷

Two studies found several factors that significantly increased the risk of mortality in ICU patients with drug resistant infections. The first, conducted on 29 patients in a Turkish ICU,

⁶² P= <0.05

⁶³ P= <0.05

⁶⁴ A lung infection in patients on mechanical ventilation.

⁶⁵ This is close to being statistically significant, at p= 0.07.

⁶⁶ 36% vs. 16%; p= 0.01

⁶⁷ p=0.049

associated a higher risk of mortality with having blood diseases, bone marrow transplant, longer length of ICU stay, use of a catheter inserted into a vein and infection with a multi-drug resistant pathogen (rather than resistance to a single drug).⁶⁸ The authors found that the presence of Methicillin-resistant *Staphylococcus aureus* (MRSA) was not linked to an increase in mortality unless elderly patients were infected in which case mortality significantly increased [93].⁶⁹ The second study of 146 patients with pneumonia in a Thai ICU found that the risk of death is higher in ICU patients with septic shock, severe sepsis and the use of antibiotics in the previous 3 days, all of which are likely associated with drug resistance[94].⁷⁰ However, this study reported death rates across their sample of adults (some of whom had drug resistant infections but others with non-resistant infections) and so we are unable to state for certain that the patients who died were those with a drug resistant infection.

Overall, the evidence for the link between drug resistant infections and death in adult ICU patients is unclear and the evidence is fairly weak. For those studies providing a comparator group (i.e. comparing death rates in adults with drug resistant infections to those with non-resistant or no infections), there was no significant difference in mortality between the patient groups. The other studies reviewed here do not provide these comparator groups which creates challenges in understanding if the reported death rates are directly attributable to the drug resistant infection or other factors, and whether the death rate is different to that of other patient groups with non-resistant or no infection.

6.2. Length of stay in hospital

Two studies explored whether patients are more likely to be admitted to the hospital or the ICU if a drug resistant infection develops, and the impacts on length of stay in hospital and the ICU. These are both empirical studies, one collecting primary data and one conducting secondary analysis of existing patient data. Both studies found that patients with drug-resistant infections are more likely to be admitted to hospital (including the ICU) and face longer stays.

Length of ICU stay increases for patients with drug resistant infections

A study analysing the data of 200 adult patients with ventilator-associated pneumonia in the US found that those suffering from an infection with drug resistant bacteria and fungi⁷¹ faced longer stays in the ICU compared with patients with non-resistant infections [95].⁷² Patients with drug resistant bacterial infections stayed in the ICU for a significantly longer time, with an average of 19 days compared to 16 days for those with non-resistant infections.⁷³ Similarly, patients with drug resistant fungal infections required a median stay of 18 days compared to 13.5 days for patients with non-resistant infections.⁷⁴

⁶⁸ Haematologic disease: P=0.18; Bone marrow: P=0.050; length of stay in ICU: P=<0.001; central venous catheter (a catheter placed in a large vein): P=0.006; multi-drug resistance: P= 0.004;

⁶⁹ P= <0.001

⁷⁰ Septic shock: OR=7.68; p<0.01; severe sepsis: OR=2.85; p<0.01; antibiotic use: OR=4.06; p<0.01.

⁷¹ Infection with *Candida* species of fungus.

⁷² Bacterial infection: p=0.02. Fungal infection: p=0.03.

⁷³ P=0.02

⁷⁴ P= 0.03

Increasing antibiotic resistance leads to additional days spent in hospitals for infants

One study of 296 infants admitted to a Vietnamese ICU investigated the impacts on length of hospital stay for ICU infants with drug resistant infections [90]. The study suggests that newborn babies showing resistance to a greater number of antibiotics faced significantly longer hospital stays, with stay increasing by over two days for resistance to every additional antibiotic group [90].⁷⁵

6.3. Risk of AMR

Six studies explored whether patients admitted to the ICU were at greater risk of developing a drug resistant infection, and all studies found this to be the case. These were all quantitative empirical studies, with two collecting primary data and the other four conducting secondary analysis of existing patient data.

Children already in the ICU are at higher risk of developing a drug resistant infection

One study focused on 160 children already admitted to a Chinese paediatric ICU who develop drug resistant pneumonia [92].⁷⁶ This study found that the invasive medical support used within the ICU, including insertion of a tube through the mouth and longer use of mechanical ventilation, was significantly associated with development of drug resistant pneumonia in children.⁷⁷ For intubation, 49% of children requiring this support developed drug resistant pneumonia compared to 22% of patients who did not need intubation. Children who developed drug resistant pneumonia had used mechanical ventilation for an average of 12 days, compared to 8 days for children who did not develop drug resistant pneumonia. In addition, children were at increased risk of developing drug resistant pneumonia when staying in the ICU for longer (17 days average length of stay for children who developed drug resistant pneumonia compared to 14 days for children who did not).⁷⁸ The use of antibiotics in the ICU also influenced the risk of developing drug resistant pneumonia, with children taking a broader range of antibiotics (8 types compared to 6 types) and receiving antibiotics over a longer period (19 days compared to 14 days) being at greater risk of developing drug resistant pneumonia.⁷⁹ Unlike other studies, this paper provides some insight as to why children admitted to the ICU may be at greater risk of developing drug resistant infections. They suggest that, as admission to the ICU is associated with more severe health issues, the patient's immune system is weakened, and the ICU environment results in the presence of drug resistant pathogens on the skin of staff and patients. The use of invasive medical support (intubation and mechanical ventilation) means the upper respiratory tract faces difficulties in removing pathogens, leading to these pathogens moving to the lungs, leading to infection [92].

One study, conducted in South Korea, focused on 59 children admitted to a paediatric ICU with an infection and found that children who had stayed in the ICU in the previous month

⁷⁵ P= 0.05

⁷⁶ *A. baumannii* infection

⁷⁷ Endotracheal intubation: P= <0.01. Mechanical ventilation time: p= 0.001

⁷⁸ P= 0.009

⁷⁹ Number of antibiotics: P=<0.001. Duration of antibiotic use: P=<0.001.

were likely to acquire multi-drug resistant infections [96].⁸⁰ The study did not provide quantitative information on the likelihood or information on the rate of drug-resistant infections in children who were not admitted to the ICU.

Adult patients admitted to the ICU are at a greater risk of developing a drug resistant infection

The other three studies focused either on all ICU patients or only adult patients, in both cases identifying ICU patients at greater risk of developing drug resistant infections. The first study evaluated changes in antibiotic resistance from 1998 to 2009 across 14 Dutch hospitals and identified that patients admitted to the ICU show increased resistance to several antibiotics, resulting in a higher rate of drug resistant infections [97]. The study found that between 1998 and 2009, the prevalence of drug resistance rose from 2% to 8% in the ICUs included in the study.

Two studies found that the use of mechanical ventilation in ICU patients is linked with development of drug resistant ventilator-associated pneumonia, in particular the use of a ventilator for a longer duration (more than 4 days) [93, 94].⁸¹ One study which reviewed the data of 394 patients admitted to the ICU with hospital-acquired infections explored different risk factors faced by some ICU patients that may increase their risk of developing drug resistant infections [93]. These authors found that patients admitted to the ICU with AIDS were at greater risk of developing a drug resistant infection.⁸² The study did not provide quantitative information on the risk or a comparison group to patients with non-resistant or no infections. In addition, this study and one other study (analysis of data from 198 ICU patients undergoing invasive procedures in Saudi Arabia) found that patients spending a longer time in the ICU, and needing invasive procedures, such as a catheter inserted into a vein or needing to be intubated, were more likely to develop a drug resistant infection than patients who did not require this type of support [93, 98].⁸³

The chapters on organ transplants and physical trauma also identified evidence suggesting that patients requiring mechanical ventilation are at a greater risk of developing drug resistant infections. These results are recapped in Box 10.

⁸⁰ Univariate analysis: OR, 6.8; 95% CI, 1.3-35.8. Multivariate analysis: adjusted OR, 6.8; 95% CI, 1.3-35.8, P = 0.023

⁸¹ Werarak et al.: 4 days of ventilator use: OR=4.2; p<0.01; Arvanitis et al: 5 days of ventilator use: p= 0.004; da Silva et al: mechanical ventilation: P= 0.03; longer mechanical ventilation use: P= <0.01.

⁸² AIDS: P= 0.021; diabetes: P= 0.02 (did not remain significant for multivariate analysis); cardiovascular disease: P= <0.01 (did not remain significant for multivariate analysis); gastrointestinal tract disease: P= 0.05 (did not remain significant for multivariate analysis).

⁸³ Da Silva et al: Length of ICU stay: P= <0.01; central venous catheter: P= <0.01. None of these remained statistically significant after multivariate analysis. Al-Gethamy et al.: Central venous catheter: OR=2.9; p=0.001; endotracheal tube: OR=3.4; p=0.001

Box 10: Organ transplant and trauma patients requiring mechanical ventilation

Organ transplant patients who acquire a drug-resistant infection are more likely to require invasive treatment

Two studies investigated the need for mechanical ventilation in adult solid organ transplant patients who acquired a drug resistant infection. Both studies (both conducted in Spain on patients requiring liver, heart or kidney transplant) found that patients who received a liver, heart or kidney transplant and who acquired a bloodstream infection caused by drug resistant bacteria⁸⁴ were twice as likely to require invasive mechanical ventilation compared to transplant patients infected by non-resistant bacteria [53, 56].⁸⁵

Trauma patients with resistant infections are more likely to require mechanical ventilation

One study exploring the characteristics of drug resistant infections in US 2,699 military personnel with trauma found that these patients were at a significantly higher risk of requiring mechanical ventilation while in hospital compared to patients with non-resistant infections. In this study population, only 29% of patients with no or non-resistant infections required mechanical ventilation, compared to 78% of patients with multi-drug resistant infections [99]. Another US study, including 126 burn patients, found that burn patients with multi-drug resistant infections required mechanical ventilation (with an average duration of 21 days) compared to burn patients with non-resistant infections who did not require any mechanical ventilation [100].

⁸⁴ Infection with resistant *Pseudomonas aeruginosa* or ESKAPE bacteria.

⁸⁵ Infection with resistant *Pseudomonas aeruginosa*: p=0.006; ESKAPE: P= 0.001

7. Diabetes

Diabetes mellitus is a chronic condition that causes a person's blood sugar level to become too high. Type I diabetes is when the body's immune system attacks and destroys the cells that produce insulin, while type II diabetes is when the body does not produce enough insulin, or the body's cells do not react to insulin. Diabetes is one of the major causes of morbidity globally. It is estimated that in 2019, the global diabetes prevalence was 463 million, with this projected to rise to 578 million by 2030, and to 700 million by 2045 [101]. In the UK, 3.5 million people have been diagnosed with diabetes, and it is estimated that around 10% of the NHS annual budget is spent on the treatment of diabetes (roughly £173 million a week) [102]. Diabetes is associated with various types of infections – notably skin, soft tissue, urinary tract, respiratory tract and surgical and/or hospital-associated infections. The reason behind this risk of infection is that many diabetic patients are immunocompromised, due to uncontrolled high blood glucose levels [103]. Diabetic patients are also predisposed to fungal infections, which are frequently associated with high glucose levels [104].

This section will describe the impacts of antimicrobial resistance on diabetes patients. Most of the literature on diabetes we reviewed covered type I diabetes, but a few studies specifically focused on type II diabetes. Box 11 provides an overview of the key findings for diabetic patients and Box 12 summarises the available literature on this population.

Box 11: Key findings on diabetes patients

Key findings on impacts:

- **Mortality:** It is unclear whether diabetic patients are at an increased risk of dying if they acquire a drug-resistant infection. For example, one study found that diabetes patients undergoing cardiac surgery are at increased risk of dying due to the development of antimicrobial resistant infections. However, another study found no significant difference in mortality for resistant pneumonia or blood infections between diabetics and non-diabetics
- **Risk of developing resistant tuberculosis (TB):** It is unclear if diabetic patients who acquire a resistant infection have an increased risk of developing drug-resistant TB.
- **Increased risk of AMR:** It is unclear whether diabetic patients may be more likely to develop resistant infections.

Box 12: Summary of the range and nature of studies on diabetes patients

Number of studies: 16

Study types: 13 empirical studies (all quantitative – 8 collecting and analysing primary data, 5 conducting secondary analysis of existing data); 3 reviews (2 systematic reviews and data analysis, 1 narrative review).

Strength of evidence: Moderate-strong. Most of the data is from empirical studies collecting primary data, as well as secondary analysis of data and systematic reviews. Only one of the studies is a narrative review.

Geography: Taiwan, China, Iran, India, Brazil, The Netherlands, Indonesia, Mexico, Pakistan, Indonesia and Peru. One review looked at 15 countries (China, Taiwan, Georgia, Bangladesh, Indonesia, Iran, Thailand, South Korea, Spain, Portugal, Turkey, Mexico, USA, Peru, Egypt). The location was not specified in two studies.

Specific conditions: Diabetes mellitus, sometimes restricted to type II diabetes mellitus.

Type of resistance: Antibacterial and antifungal.

Study populations: 9 studies looked at the impact on adults only, 7 studies looked at the impact on all patients.

Impacts assessed: Mortality, health outcomes, and increased risk of AMR.

7.1. Mortality

Three articles investigated whether diabetes patients with drug-resistant infections have an increased risk of death.

It is unclear whether diabetes patients are at increased risk of dying if they acquire a drug-resistant infection

A narrative review found that diabetes patients undergoing cardiac surgery are at increased risk of dying due to the development of antimicrobial resistant infections [105]. In addition, a study on patients with type II diabetes found that mortality was higher in those with resistant bloodstream infections compared to sensitive infections (10% compared to 7%) [79].⁸⁶ In particular, patients with infections resistant to more than one type of antibiotic were at a greater risk of death than those resistant to only one antibiotic (12% compared to 7%, respectively).⁸⁷

By contrast, an empirical study found no significant difference in mortality for resistant pneumonia or blood infections⁸⁸ between diabetics and non-diabetics. Indeed, in resistant

⁸⁶ P = 0.017 in univariate analysis and P = 0.011 by log-rank test. Various resistant bacteria were identified: *E. coli* (6.1% mortality rate in resistant diabetic patients compared to 3.2% for diabetic patients with a sensitive infection); *Klebsiella* spp. (15.4% vs. 8.3%); *Streptococcus* spp. (7.7% vs. 3.8%); *Pseudomonas* spp. (25% Vs 5.9%); *Acinetobacter* spp. (33.3% Vs 0%).

⁸⁷ P = 0.031

⁸⁸ Caused by carbapenem-resistant *Klebsiella pneumoniae* or ESBL-producing *Klebsiella pneumoniae*.

pneumonia,⁸⁹ diabetics showed lower antimicrobial resistance and different factors were associated with a risk of mortality compared with non-diabetics [106].⁹⁰

7.2. Health outcomes

Ten articles investigated the impacts of diabetes on morbidity. Most articles (seven out of 10) found that diabetes patients may be at **increased risk of developing drug-resistant tuberculosis (TB)**, although the other three studies found no association.

It is unclear whether diabetes patients have an increased risk of developing drug-resistant TB

Seven articles identified a link between having diabetes and developing drug-resistant TB, whilst three found no association.

A meta-analysis concluded that diabetes can significantly increase the odds of developing multi-drug-resistant TB [107]⁹¹. The study found that diabetes patients coinfecting with TB are 97% more likely to develop drug resistant TB than non-diabetic patients. Similarly, an empirical study on the impact of diabetes on resistant TB in Iran found that even after adjusting for other factors, diabetic patients are more likely⁹² to develop drug-resistant TB [108].⁹³ Another empirical study in China found that a higher proportion⁹⁴ of diabetic patients with TB had drug resistant TB compared with non-diabetic patients with TB.⁹⁵ It also identified diabetes as a risk factor for developing drug-resistant TB once infected with TB⁹⁶ [109]. A study conducted in Mexico followed patients aged 15 years and older from the point of their diagnosis with TB that affects the lungs to the end of either the individual's TB treatment or the study [110]. The study found that patients with type II diabetes were more likely to have TB that was resistant to multiple antibiotics than patients without diabetes [110].⁹⁷ The same study found that type II diabetes was associated with a greater risk of adverse clinical outcomes, treatment failure and relapse among TB patients.⁹⁸ An observational study of TB in patients with and without diabetes in Indonesia and Peru found that there was an association between the presence of diabetes and drug resistant TB, particularly resistance to the first-line drug, rifampicin.⁹⁹ The

⁸⁹ Caused by resistant *Klebsiella pneumoniae*.

⁹⁰ Independent risk factors for in-hospital mortality in *Klebsiella pneumoniae* pneumonia among diabetics in this study were male (OR: 5.89, 95% CI: 1.34–25.93, P = 0.019), albumin < 35 g/L (OR: 7.00, 95% CI: 2.02–24.28, P = 0.002), bloodstream infection (BSI) (OR: 21.14, 95% CI: 3.18–140.72, P = 0.002), and invasive ventilation during hospitalisation (OR: 8.00, 95% CI: 2.99–21.42, P < 0.001).

⁹¹ Combined OR 1.83, 95% CI 1.40–2.39

⁹² OR 4.82, 95% CI 1–23.57

⁹³ Resistance to rifampicin may be related to a lower plasma concentration of rifampicin among diabetic patients.

⁹⁴ Adjusted OR 1.30; 95% CI 1.02–1.65

⁹⁵ 22% for patients with diabetes and TB compared to 17% for the TB-only group.

⁹⁶ Totally drug resistant TB refers to strains of TB that are resistant to all first line drugs and the second line TB drugs.

⁹⁷ Hazard ratio = 3.1; 95% CI: 1.7 - 5.8; p < 0.001

⁹⁸ Treatment failure was 24% among the TB-T2DM group, compared with 11% of the subjects with TB-noT2DM

⁹⁹ Link between diabetes and resistant TB: Odds ratio = 1.69; 95% CI = 1.04-2.77. Resistance to rifampicin: Odds ratio = 2.52; 95% CI 1.19-5.34

association was stronger in patients who had not received previous TB treatment [111]. A retrospective study using data collected from over 350 TB patients in Indonesia also found that type II diabetes was significantly associated with the development of drug resistant TB [112].¹⁰⁰ A narrative review found that diabetes has been associated with increased mortality¹⁰¹, recurrence and low treatment success rates among resistant TB patients [103].

By contrast, a study from Taiwan found that diabetes was not associated with multidrug-resistant TB [113].¹⁰² Similarly, a study that assessed whether diabetes had an impact on outcomes associated with drug resistant TB, conducted in Pakistan. This analysis of patient data found that drug resistant TB treatment outcomes were similar regardless of diabetes status, and therefore concluded that there was no association between diabetes and drug resistant TB outcomes in the population studied.¹⁰³ Another study assessed whether diabetes mellitus had an impact on outcomes associated with resistant TB, which was also conducted in Pakistan [114]. This retrospective cross-sectional study of patient data collected between 2010 and 2014 found that drug resistant TB treatment outcomes were similar regardless of diabetes status, and therefore concluded that there was no association between diabetes and resistant TB outcomes in the population studied.¹⁰⁴

7.3. Risk of AMR

Five articles investigated the impacts of diabetes on the increased risk of developing resistant infections other than TB.

It is unclear whether diabetic patients are more likely to develop resistant infections

A narrative review notes that some studies have found that patients with diabetes are at a greater chance¹⁰⁵ of getting a resistant urinary tract infection compared to non-diabetic patients [103].¹⁰⁶ An empirical study of over 160 patients in Brazil found that type I diabetes led to an increased rate of resistance against one type of antibiotic compared to type II diabetic patients (47% vs 6%) [104].¹⁰⁷ In addition, a meta-analysis of studies exploring the relationship between diabetic foot ulcers and antibiotic resistance found that resistant bacteria were found to be the most common reason for diabetic foot ulcers [115].

¹⁰⁰ Patients with T2DM had a 6.8-fold greater risk of developing MDR-TB than those without DM; 95% CI:2.0-23.7, p=0.003

¹⁰¹ A higher mortality rate was observed among diabetic patients in a meta-analysis of 33,000 patients with community-acquired pneumonia.

¹⁰² Adjusted OR 1.88, 95% CI 1.07–3.31

¹⁰³ Risk ratio = 0.90; 95% CI 0.74– 1.05

¹⁰⁴ Risk ratio = 0.90; 95%CI 0.74– 1.05

¹⁰⁵ Urinary tract infections were more common in diabetic patients as compared to that of non-diabetic patients among 89,790 matched pairs of patients with and without type 2 diabetes mellitus.

¹⁰⁶ An association has been found between the presence of co-trimoxazole resistance and diabetes, but no correlation has been reported between *E. coli* resistance against co-trimoxazole or quinolones and diabetes in out-patients.

¹⁰⁷ Caused by the fungus *Candida* being resistant to ketoconazole (47% for type I and 6% for type II). Ketoconazole is one of the antifungals drugs used to treat superficial oral *Candida* infection, which may explain the resistance rate found in the present study

Despite this, an empirical study conducted in India found that diabetic patients were not at increased risk of resistance [116], while an empirical study from the Netherlands found that the frequencies and resistance rates of urinary tract infections did not differ between patients with type II diabetes and those without [117]. The review also found that in ICUs, resistance rates have been reported to be substantially lower in diabetic patients than in non-diabetic individuals [103].¹⁰⁸

¹⁰⁸ Against fosfomycin (42.6% vs 62.6%) aztreonam (53.4% vs 69.5%), tobramycin (42.5% vs 61.0%), meropenem (37.7% vs 59.8%), amikacin (37.8% vs 52.8%) and cefotetan (45.2% vs 63.2%). Only sulfamethoxazole exhibited a low resistance (13.8% vs 25.6%) in non-intensive care unit.

8. HIV

HIV is a virus that attacks the immune system and reduces the body's ability to protect itself against disease and subsequent infection [118]. In 2018, UNAIDS/WHO estimated that there were 37.9 million people with a positive HIV status worldwide [119, 120], with just over 100,000 of these living in the UK [121, 122]. Without appropriate treatment, HIV weakens the immune system and increases the risk of opportunistic infections, increasing the likelihood of requiring and being exposed to antimicrobial drugs [123]. AMR, therefore, presents a serious risk for people living with HIV. Similarly to other patient populations discussed in this report, the likelihood of people living with HIV suffering negative outcomes increases if they acquire a drug-resistant infection [124, 125]. In addition to this, positive HIV status makes people more likely than those without HIV to acquire a drug-resistant infection in the first place [105, 126], as well as more likely to suffer the associated negative outcomes of such infection. Causal pathways for this relationship include HIV-associated immunosuppression [127] and, in the case of TB (the most commonly reported co-infection discussed in this chapter), HIV's ability to accelerate TB disease progression and prevent the absorption of anti-TB drugs¹⁰⁹ [105]. It is due to interactions like these that the relationship between HIV and TB has been described as a 'syndemic' [128], which is when two or more diseases interact in such a way that the burden of each is increased [128]. A near-global meta-analysis estimates that almost a quarter of people living with HIV have comorbid TB [129]¹¹⁰, and a cross-sectional study of people living with comorbid HIV and TB found that 24% of these had some form of drug-resistant TB [130].¹¹¹ Roughly half of those cases of drug-resistant TB are resistant to at least the two most powerful anti-TB drugs[130].¹¹²

The relationship between HIV and AMR (including drug-resistant TB) is therefore bidirectional, and our review identified evidence related to each direction of this relationship (i.e. HIV influencing the risk of developing AMR and the presence of AMR influencing HIV outcomes). The difference between these sets of evidence is subtle but worth distinguishing to avoid confusion over what different study findings represent. This chapter, therefore, presents findings in two main sections, answering each of the following overarching questions in turn:

1. In a sample of people living with HIV, are outcomes for those with drug-resistant infections different to those with no or non-resistant infections? We have grouped

¹⁰⁹ Rifampicin and ethambutol

¹¹⁰ 23.30%; 95% CI 16.69% - 29.91%

¹¹¹ 95% CI 20.9% - 27.0%

¹¹² 12.5% of all patients with comorbid HIV and TB; 95% CI 7.9% - 17.1%

studies looking at the relationship from this angle under the heading of 'HIV as the baseline condition'.

2. In a sample of people with a microbial infection, are outcomes for those with HIV different to those without HIV? We have grouped studies looking at the relationship from this angle under the heading of 'HIV as the risk factor'.

Box 13 presents key findings related to both of the above questions. Box 14 then provides a summary of the range and nature of studies contributing evidence in response to question 1 (HIV as the baseline condition). This evidence is detailed in the subsequent narrative. Box 15 summarises the evidence relating to question 2 (HIV as the risk factor), which is discussed in the latter part of this chapter.

Finally, we also identified evidence that acquiring a drug-resistant sexually transmitted infection (STI) can increase the risk of acquiring HIV. STIs are infections spread through direct sexual contact. The World Health Organisation estimates that over 1 million STIs are acquired each day globally [131]. In England, there were over 447,500 diagnoses of STIs in 2018 which was a 5% increase in the number of diagnoses in the previous year [132]. Almost 13% of these diagnoses in 2018 were for gonorrhoea which is increasing at a faster rate than STIs overall, with cases of gonorrhoea increasing 26% from 2017 to 2018 in England, the largest number of diagnoses since 1978 [132]. This is of particular concern given the increase in resistant gonorrhoea cases, which is causing reduced treatment options for patients, with some resistance emerging for the last-line antibiotic treatment [131, 132]. Untreated gonorrhoea can increase the risk of developing HIV and, in rare cases, can spread to the blood which can be fatal [133]. Box 16 summarises the evidence on the range and nature of studies on the risk of acquiring HIV.

Box 13: Key findings on people living with HIV

HIV AS THE BASELINE CONDITION

- **Mortality:** Drug-resistant TB is a serious mortality risk for people living with HIV. HIV patients who acquire multi-drug resistant TB are more likely to die than those with TB that is resistant to just one type of antibiotic. For example, one study demonstrated that a much greater proportion of the patients with multi-drug resistant TB had died during the year following their TB diagnosis (66% of patients with resistant TB vs. 27% of patients with non-resistant TB).
- **Treatment efficacy:** People with HIV and TB co-infection are less likely to respond successfully to TB treatment if their TB is resistant to antibiotics. The one study exploring this outcome found that a significantly larger proportion of HIV patients with non-resistant susceptible TB were cured of their infection or completed their course of treatment without any signs or symptoms of active TB than achieved the same with resistant TB (63% of HIV patients with non-resistant susceptible TB vs. 22% of those with resistant TB).
- **Length of stay, ICU admission and invasiveness of treatment:** There is insufficient evidence to determine whether HIV patients infected with MRSA endure longer hospital stays, more frequent ICU admission or more invasive treatment than patients with non-resistant infections. One study found that those with HIV and a drug-resistant bacterial infection spend 19 days in hospital compared to 12 for HIV patients with non-resistant infections. In addition, 42% of HIV patients with MRSA were admitted to the ICU compared to 20% of patients with non-resistant infections.

HIV AS THE RISK FACTOR

- **Risk factor for acquiring AMR:** People living with HIV are more likely to develop drug-resistant TB than people without HIV, with one study estimating the risk is 4 times higher. The evidence is unclear regarding whether people living with HIV are more likely to develop other drug-resistant infections than people without HIV.
- **Risk factor for resistant TB mortality:** People living with HIV are more likely to die from resistant TB than people without HIV. There is tentative but non-conclusive evidence that this relationship also holds true for children and adolescents. A prospective cohort study of patients in South Africa, for example, found that patients with HIV were more than twice as likely to die from multi-drug resistant TB than patients without HIV.
- **Risk factor health outcomes relating to resistant TB: The evidence is unclear regarding whether** people living with HIV are more likely to suffer adverse effects from treatment for resistant TB than people without HIV. Further research is required to determine whether this association is significant.
- **Risk factor for resistant TB treatment failure:** Due to **conflicting evidence** across the reviewed studies, the association between HIV status and resistant TB treatment failure is unclear.

RISK OF ACQUIRING HIV

- Resistant gonorrhoea may contribute to a higher risk of contracting and passing on HIV

8.1. HIV as the baseline condition

Box 14: Summary of the range and nature of studies on HIV as the baseline condition

HIV AS THE BASELINE CONDITION

Number of studies: 4 studies

Study types: 3 empirical studies (1 collecting and analysing primary data, and 2 conducting secondary analysis of existing data); 1 systematic review.

Strength of evidence: Moderate. There is only a small total number of studies, but most of the empirical studies reflect on their limitations, and the sample includes one systematic review.

Geography: Iran, USA, Belarus, Latvia, Romania, Russia, Ukraine, and global.

Specific conditions: HIV

Type of resistance: Antibacterial

Study populations: 1 study focuses on all patients and 3 on adults only.

Impacts assessed: Mortality, treatment efficacy, length of hospital stay, ICU admission, and invasiveness of treatment.

8.1.1. Mortality

Four studies explored the link between antibacterial drug resistance in people living with HIV and mortality. These comprised three quantitative empirical studies and a systematic review.

Drug-resistant TB is a serious mortality risk for people with HIV

This finding is supported by three of the included studies. The systematic review concluded that drug-resistant TB can be extremely deadly for people living with HIV and that mortality rates among people with HIV who acquire drug resistant TB are “alarmingly high” [124; p.11].

A cross-sectional study of the pattern of drug-resistant TB in adult patients with HIV and TB co-infection in Iran found that the death rate was significantly higher¹¹³ in patients with multi-drug resistant TB¹¹⁴ than in those whose TB was only resistant to one type of antibiotic [134].¹¹⁵

Similarly, a study comparing the outcomes of people living with HIV receiving treatment for drug resistant TB and non-resistant TB¹¹⁶ in five Eastern European countries¹¹⁷ found a large difference between the two groups’ mortality rates [125]. A much greater proportion of the patients with multi-drug resistant TB had died during the year following their TB diagnosis (66% of patients with resistant TB vs. 27% of patients with non-resistant TB) [125].¹¹⁸ The same study also found that the risk of death increases as TB infection spreads from the lungs to other parts of the body [125].¹¹⁹

The link between mortality and other resistant bacterial infections in HIV patients requires further investigation.

¹¹³Death rate for multi-drug resistant TB patients: 73% (8/11) vs. other patients: 27% (3/11), $p = 0.011$; OR = 7.2, 95% CI 1.6–32.7

¹¹⁴ Resistant to both isoniazid (INH) and rifampicin (RIF) antibiotics

¹¹⁵ $p=0.011$

¹¹⁶ non-resistant to first-line anti-TB drugs

¹¹⁷ Belarus, Latvia, Romania, Russia and Ukraine

¹¹⁸ $P= <0.0001$

¹¹⁹ Disseminated TB vs. localised pulmonary/extra-pulmonary TB; aHR 1.99; $p = 0.022$

Only one of the included studies explored the link between mortality in people living with HIV and a bacterial infection other than TB. A retrospective case-control study of HIV-infected adults admitted to hospital with pneumonia in the USA identified no difference in mortality rates between people with HIV whose pneumonia was resistant and those with non-resistant pneumonia [135].

8.1.2. Effectiveness of treatment

This section is informed by one empirical study, and conclusions are therefore tentative.

People with HIV and TB co-infection are less likely to have successful TB treatment if their TB is resistant

A study comparing the outcomes of people living with HIV receiving treatment for resistant TB and non-resistant TB in five Eastern European countries¹²⁰ found that those with non-resistant TB were much more likely to show TB treatment success [125]. A significantly larger proportion of HIV patients with non-resistant TB were cured of their infection or completed their course of treatment without any signs or symptoms of active TB than achieved the same with resistant TB (63% of HIV patients with non-resistant TB vs. 22% of those with resistant TB) [125].¹²¹

8.1.3. Length of stay in hospital

One study provides all the findings reported in this section, and further research is therefore required before firm conclusions can be reached.

It is unclear whether HIV patients infected with drug-resistant bacterial infection endure longer hospital stays, more frequent ICU admission and more invasive treatment.

A study of HIV-infected adults admitted to hospital with pneumonia in the USA identified some differences between patients with drug-resistant bacterial infection and those with non-resistant infections, some of which were large, but none of which were statistically significant. Patients with drug-resistant bacterial infection had longer hospital stays (19 days compared to 12)¹²² and were more likely to be admitted to the ICU (42% compared to 20%)¹²³ than patients with non-resistant infections [135]. The authors report a non-significant difference in the likelihood of requiring a chest tube¹²⁴ and no difference in the likelihood of requiring intubation [135].¹²⁵

¹²⁰ Belarus, Latvia, Romania, Russia and Ukraine

¹²¹ $P \leq 0.0001$

¹²² $P=0.15$

¹²³ $P=0.15$

¹²⁴ Odds of chest tube 2.7 ($p=0.26$)

¹²⁵ Odds of intubation 1.8 ($p=0.45$)

8.2. HIV as the risk factor

Box 15: Summary of the range and nature of studies on HIV as the risk factor

HIV AS THE RISK FACTOR

Number of studies: 11 studies

Study types: 10 empirical studies (all quantitative, 4 collecting and analysing primary data, and 6 conducting secondary analysis of existing data); 1 narrative review.

Strength of evidence: Moderate – Strong. Reasonable number of quantitative empirical studies, all but one of which reflect on study limitations and many of which took steps to address these where possible.

Geography: South Africa; Brazil, Lithuania, Nigeria, USA, and a study drawing on data from seven countries worldwide (Abkhazia, Armenia, Colombia, Kenya, Kyrgyzstan, Swaziland and Uzbekistan).

Specific conditions: HIV

Type of resistance: Antibacterial and antiviral.

Study populations: 5 studies focus on all patients, 5 on adults and 1 on children.

Impacts assessed: Risk of developing drug-resistant TB or other AMR, risk of drug-resistant TB-related mortality risk of drug-resistant TB-related morbidity, and risk of drug-resistant TB treatment failure.

8.2.1. Risk of AMR

Four empirical studies report that being HIV positive increases the likelihood of developing a drug-resistant infection. Three of these studies focused on the risk of people living with HIV acquiring drug resistant TB.

People living with HIV are more likely to acquire drug-resistant TB than people without HIV

A study of surveillance data from the Californian registry of adult TB cases concluded that being HIV positive conferred an approximately 4-fold increase in the likelihood of acquiring drug resistant TB compared to being HIV negative [136].¹²⁶ Two further studies reported the same relationship, though these did not offer quantitative findings regarding the size or significance of the association. A retrospective review of drug resistant TB treatment¹²⁷ outcomes in people with and without HIV in South Africa reported that HIV infection increases people's susceptibility to resistant TB due to their HIV-associated immunosuppression (although the authors do not provide quantitative data on this increase) [127]. A cross-sectional study of Nigerian patient laboratory records takes this further, reporting that being HIV positive is the greatest risk factor for acquiring TB, including drug resistant TB¹²⁸ when compared to other risk factors, including anaemia, low blood potassium levels, poor thyroid function, diabetes and hearing loss [105]. The authors report that this relationship may exist because HIV accelerates TB disease progression and prevents the absorption of anti-TB drugs [105].

¹²⁶ OR=4.26; p<0.0001

¹²⁷ Adjuvant lung resection

¹²⁸ As well as being the greatest risk factor for acquiring susceptible TB.

The evidence is unclear regarding whether people living with HIV are more likely to develop other (non-TB) drug-resistant infections than people without HIV

We identified one study that explored HIV status as a risk factor for the development of drug resistance in a non-TB infectious disease. A study of the hepatitis B virus (HBV) and its drug-resistant mutations found that co-infection with HIV was significantly associated with the development of resistant HBV [126].¹²⁹ This study was limited by its small sample size and missing data, so conclusions are tentative but indicative of a need for further research.

8.2.2. Mortality

In addition to being a risk factor for acquiring drug resistant TB, positive HIV status appears to be a risk factor for subsequent mortality among patients with resistant TB. The evidence cited in this section comes from eight empirical studies, all of which include some reflection on study limitations and many of which report ways in which efforts have been made to overcome or lessen their impact. Although the majority of the studies have retrospective study designs, conclusions reported in this section can be viewed as strong.

People living with HIV are more likely to die from resistant TB than people without HIV.

A study of Nigerian patient laboratory records reports that, in line with HIV co-infection accelerating TB disease progression, preventing the absorption of anti-TB drugs, and potentially being one of the greatest risk factors for acquiring drug resistant TB, these factors may act together to cause higher mortality rates in drug resistant TB patients with HIV than in those without HIV [105].

A retrospective study of adult resistant TB patients in South Africa identified risk factors for mortality. The analyses found that being HIV positive and on antiretroviral drugs to treat HIV put patients at 3 times higher risk of mortality during the course of drug resistant TB treatment¹³⁰ [137]. The risk was even greater among HIV patients who were not on HIV treatment [137].¹³¹

A comparison of resistant TB treatment outcomes among adult patients with and without HIV in seven countries¹³² found large differences between the mortality rates of HIV positive and negative patients [138]. In cases of multi-drug resistant TB, HIV positive patients were twice as likely to have died than those without HIV [138].¹³³ In poly-resistant TB cases¹³⁴, this difference widened to six times greater [138].¹³⁵ Among those patients who died, the median time to death was shorter in HIV patients [138].¹³⁶ The authors note, however, that these

¹²⁹ P= <0.01.

¹³⁰ IRR=1.4; p<0.001 and aIRR=1.4; p<0.001

¹³¹ IRR=3.2; p<0.001 and aIRR=3.3; p<0.001

¹³² Abkhazia, Armenia, Colombia, Kenya, Kyrgyzstan, Swaziland and Uzbekistan

¹³³ 19.0% in HIV+ vs. 9.4% in HIV-; p<0.01

¹³⁴ Cases of TB that are resistant to two or more anti-TB drugs, but not to both of the most commonly used options – Isoniazid (INH) and Rifampicin (R) – simultaneously (as is the case in multi-drug resistance).

¹³⁵ 19.4% in HIV+ vs. 2.8% in HIV-; p<0.01

¹³⁶ 3.8 months in HIV+ vs. 5.5 months in HIV-; significance not reported.

findings may have been skewed by the high study dropout rate of HIV negative patients, who were twice as likely to be lost to follow-up than those with HIV [138].¹³⁷

Other studies focused on the association between HIV and mortality in patients with multi and extensively drug-resistant TB [139]. A prospective cohort study of patients in South Africa, for example, found that patients with HIV were more than twice as likely to die from multi-drug resistant TB than patients without HIV [140].¹³⁸ Low body weight, which can be associated with positive HIV status and/or antiretroviral HIV treatment, also increased patients' mortality risk [140].¹³⁹

A survival analysis conducted on patient records from 1,809 cases of multidrug-resistant/extensively drug-resistant TB in Lithuania concluded that positive or unknown HIV status at the time of TB diagnosis were less likely to have survived than those with negative HIV status¹⁴⁰ [139]. Overall, the median time to death was 5.5 months among HIV-negative and 3.8 months among HIV-positive patients.

By contrast, however, a prospective cohort study of adults with resistant TB in South Africa found no association between HIV status and mortality, though it did find that patients were more likely to die during TB treatment if they were HIV positive and not on antiretroviral HIV treatment (with 56% of HIV patients not on treatment dying compared to 36% receiving treatment [141]).¹⁴¹ Similarly, a retrospective review of resistant TB treatment¹⁴² outcomes in people with and without HIV in South Africa found that there was no significant relationship between HIV status and mortality in people with resistant TB [127]. The quality of this study, however, suffers from its very small sample size.¹⁴³

It is unclear whether children and adolescents with HIV are more likely to die from resistant TB than those without HIV

We identified tentative but non-conclusive evidence that the association between positive HIV status and increased mortality risk also holds true for children and adolescents. A retrospective study of data from children and adolescents diagnosed with drug resistant TB in South Africa found that a higher proportion of those with HIV died during the course of TB treatment (21% of HIV positive patients vs. 11% of HIV negative) [142].¹⁴⁴ Higher mortality rates were also seen among children and adolescents who were male and/or underweight [142].

¹³⁷ P= <0.001

¹³⁸ 35.2% in HIV+ vs. 16.2% in HIV-; p<0.0001

¹³⁹ P=<0.0001

¹⁴⁰ 5.5 months: IQR 2.0–13.9 among HIV-negative and 3.8 months [IQR 1.8–6.8] among HIV-positive patients.

¹⁴¹ P= 0.03

¹⁴² Adjuvant lung resection

¹⁴³ 28 HIV+ and 21 HIV-

¹⁴⁴ P=0.02

8.2.3. Health outcomes

Only one retrospective review of hospital case records and one narrative review discussed how HIV can impact on resistant TB related health outcomes. The evidence associated with this section is therefore fairly weak.

The evidence is unclear regarding whether people living with HIV are more likely to suffer adverse effects from treatment for resistant TB than people without HIV

A narrative review of the principles associated with treating drug resistant TB in HIV patients in South Africa included a brief discussion of the impact of HIV on resistant TB related morbidity. It reported that people with HIV are more likely to experience adverse effects¹⁴⁵ in response to treatment for resistant TB than people without HIV [143].

A retrospective review of outcomes of treatment for resistant TB¹⁴⁶ in people with and without HIV in South Africa found that there was no significant relationship between HIV status and morbidity in people with resistant TB [127]. It is important to note, however, that this study's sample size was very small¹⁴⁷, and further research into this relationship is therefore merited.

8.2.4. Effectiveness of treatment

Four of the included studies assessed the relationship between HIV status and resistant TB treatment failure. Two of these found that HIV patients were more likely to experience treatment failure [140, 142], one found the opposite [138], and one found no association [127].

It is currently unclear whether HIV status has an impact on treatment outcomes for resistant TB

A prospective cohort study of patients in South Africa found that patients with HIV were about half as likely to demonstrate resistant TB treatment success than patients without HIV [140].¹⁴⁸ Similarly, a retrospective study of data from children and adolescents diagnosed with resistant TB in South Africa found that a lower proportion of those with HIV experienced successful treatment outcomes compared to those without HIV (55% vs 62% respectively) [142].¹⁴⁹

In contrast to the above, a comparison of resistant TB treatment outcomes among adult patients with and without HIV in seven countries¹⁵⁰ found that HIV positive patients with drug resistant TB were 10% more likely to have treatment success than HIV negative patients [138].¹⁵¹ A tendency towards the reverse relationship was identified in the sample of poly-resistant¹⁵² TB patients, but the association did not reach statistical significance [138].¹⁵³ The

¹⁴⁵ Including hypokalaemia, peripheral neuropathy, ototoxicity with aminoglycoside exposure, and hypothyroidism.

¹⁴⁶ Adjuvant lung resection

¹⁴⁷ 28 HIV+ and 21 HIV-

¹⁴⁸ 35.2% in HIV+ vs. 16.2% in HIV-; $p < 0.0001$

¹⁴⁹ 55.0% of HIV+ vs. 61.6% of HIV-; $p = 0.02$

¹⁵⁰ Abkhazia, Armenia, Colombia, Kenya, Kyrgyzstan, Swaziland and Uzbekistan

¹⁵¹ 64.0% in HIV+ vs. 53.2% in HIV-; $p = 0.007$

¹⁵² Cases of TB that are resistant to two or more anti-TB drugs, but not to both of the most commonly used options – Isoniazid (INH) and Rifampicin (R) – simultaneously (as is the case in multi-drug resistance).

¹⁵³ $p = 0.09$

authors note, however, that these findings may have been skewed by the high study dropout rate of HIV negative patients, who were twice as likely to be lost to follow-up than those with HIV[138].¹⁵⁴

Finally, a retrospective review of outcomes of treatment for resistant TB¹⁵⁵ in people with and without HIV in South Africa found that there was no statistically significant relationship between HIV status and treatment failure in people with resistant TB [127]. The quality of this study suffers from its very small sample size.¹⁵⁶

8.3. Risk of acquiring HIV

Box 16: Summary of the range and nature of studies on the risk of acquiring HIV

RISK OF ACQUIRING HIV

Number of studies: 2 studies.

Study types: 2 narrative reviews.

Strength of evidence: Weak. All evidence is from narrative literature reviews, with little information provided about the empirical evidence drawn on to inform review conclusions.

Geography: The reviews do not report country-specific data.

Specific conditions: Gonorrhoea is the focus of both reviews.

Type of resistance: Antibacterial.

Study populations: Specific patients are not included in these articles as they are narrative reviews discussing resistance in STIs more generally.

Impacts assessed: Risk of contracting and transmitting HIV

Two narrative reviews discussed how drug resistant gonorrhoea infection impacts the risk of acquiring and/or transmitting HIV.

We identified insufficient evidence to comment on the relationship between resistant gonorrhoea and the risk of contracting and passing on HIV

Two narrative reviews stated that patients with resistant gonorrhoea are at greater risk of contracting and transmitting HIV [144, 145]. Neither review provided either empirical evidence to support this claim or information about relevant comparison groups, so we do not offer any conclusions regarding a possible relationship between drug-resistant gonorrhoea and HIV acquisition or transmission.

¹⁵⁴ p<0.001

¹⁵⁵ Adjuvant lung resection

¹⁵⁶ 28 HIV+ and 21 HIV-

9. Infant and paediatric patients

A newborn or neonate is a child under 28 days of age. The incidence of severe infections caused by resistant pathogens is rising worldwide, and increasing numbers of newborns with serious bloodstream infections due to resistant bacteria are being reported [146]. In premature infants, the fungus *Candida* is an important cause of late-onset sepsis [147]. The World Health Organisation estimates that 200,000 newborns die annually from infections that do not respond to available treatments and data from large hospitals (where drug resistant is more likely to develop) indicates that approximately 40% of neonatal infections are resistant to treatments [148]. However, very limited data have been published so far on the global impact of infection resistance in childhood.

This section will describe the impacts of drug-resistant infections on newborn patients. The literature we reviewed on newborn patients covered a range of conditions such as sepsis, invasive fungal disease and ICU admissions. Box 17 summarises the identified impacts from resistant infections and Box 18 summarises the available literature on this population.

Box 17: Key findings on newborn patients

Key findings on impacts:

- **Mortality:** It is unclear whether newborn patients with resistant infections are at an increased risk of dying.
- **Health outcomes:** Infants with resistant infections are at a higher risk of developing sepsis although infection with a resistant fungus was not linked to neurodevelopmental impairment. A study analysing patient data from Jordan found that previous long-term exposure to multiple antibiotics was associated with sepsis caused by resistant bacteria. The authors found that exposure to certain types of antibiotics was associated with an over 10-fold increase in the risk of resistant sepsis.
- **Length of stay in hospital:** It is unclear whether newborn patients are more likely to spend longer in hospital if they acquire a resistant infection.

Box 18: Summary of the range and nature of studies on newborn patients

Number of studies: 8 studies.

Study types: 7 empirical studies (4 secondary data, 3 primary data) and 1 review (narrative review).

Strength of evidence: Weak-moderate. Moderate number of studies and most data are from empirical studies, but results are mixed.

Geography: Spain, Bangladesh, Italy, Brazil, USA, Jordan, China. 1 study was global.

Specific conditions: Sepsis, invasive candidiasis (fungal infection) and neonatal ICU admissions.

Type of resistance: Antibacterial and antifungal.

Study populations: Newborns and young children.

Impacts assessed: Mortality, health outcomes and length of stay.

9.1. Mortality

Four articles investigated the impact of neonatal drug-resistant infections on mortality. Three articles found that newborn patients are at **increased risk of dying**, whilst one found no association.

It is unclear whether newborn patients are at increased risk of dying if they acquire a drug-resistant infection

An empirical study conducted in a neonatal intensive care unit (NICU) in Bangladesh found that the mortality rate was significantly higher among resistant sepsis cases when compared with non-drug resistant cases; all patients with multi-drug resistance and 94% of patients with extensive drug resistance died compared to 0-6% of patients with non-resistant infections [149].¹⁵⁷ A study looking at healthcare-associated infections in paediatric and neonatal intensive care units in Italy and Brazil found several factors that were associated with death, which included resistant infections, and that newborns under 28 days old were at a greater risk than older children ages 2-5 [146]. In the study, 25% of infants under 28 days died

¹⁵⁷ P < 0.001

compared to 13% aged 2-5. A retrospective review from Jordan found that sepsis due to drug resistant infections was associated with higher mortality rate compared to non-drug resistant organisms (60% vs 13% respectively).¹⁵⁸ Mortality was also linked to a delay in providing appropriate antimicrobial treatment compared with non-resistant infections [150].

By contrast, an empirical study conducting secondary analysis on antifungal susceptibility and clinical outcomes¹⁵⁹ found that there was no significant difference in the rate of death among infants with a high resistance to any antifungal treatment compared to those with greater sensitivity [147].

9.2. Health outcomes

Four articles investigated the impact of neonatal infections on health outcomes. Three articles found that newborn patients are more likely to face **poorer health outcomes relating to sepsis**, whilst one found **no significant difference when focusing on neurodevelopmental impairment**.

Newborn patients with neonatal infections may be at increased risk of developing sepsis if they acquire a drug-resistant infection

A narrative review found that resistant bacterial infections¹⁶⁰ in children have been associated with negative outcomes, notably secondary complications such as severe sepsis and septic shock [146]. A retrospective review from Jordan found previous long-term exposure to multiple antibiotics was associated with sepsis caused by resistant bacteria [150].¹⁶¹ Similarly, a study looking at 163 cases of early-onset sepsis in a NICU in eastern China found that premature infants with sepsis were at a greater risk of developing resistant sepsis than newborns born at term with sepsis, with resistance to antibiotics ranging from 60-90% in premature infants (depending on the antibiotic) compared to 9-48% in term infants [151].¹⁶²

Infants with drug resistant infections are not more likely to develop neurodevelopmental impairments

In contrast, an empirical study on antifungal susceptibility and clinical outcomes found that there was no significant difference in the rate of neurodevelopmental impairment among infants with resistant and sensitive infections [147].

9.3. Length of stay in hospital

It is unclear whether infants with resistant infections are more likely to spend longer in hospital

¹⁵⁸ (60% vs. 13%, P = 0.002)

¹⁵⁹ A fungal infection caused by the yeast *Candida*. It can cause white patches and soreness of the mouth and tongue, as well as thrush.

¹⁶⁰ Extended-Spectrum B-Lactamase (ESBL) producing Gram-negative bacteria.

¹⁶¹ Sepsis episodes were caused by Gram-negative bacteria (n = 42; 62%), Gram-positive bacteria (n = 21; 31%), or *Candida* species (n = 5; 7%). The most common organisms isolated from blood cultures were: *A. baumannii* (27%) and *Klebsiella pneumoniae* (22%).

¹⁶² Infection with *E. coli*. P=<0.01

A narrative review found that drug resistant bacterial infections¹⁶³ in children have been associated with prolonged length of stay in hospital, although quantitative data on the number of extra days spent in hospital are not provided [146]. By contrast, an empirical study found that there was no significant difference in length of stay between infants with drug resistant and non-resistant infections [147].¹⁶⁴

¹⁶³ Extended-Spectrum B-Lactamase (ESBL) producing Gram-negative bacteria

¹⁶⁴ 114 days (76–268) versus 122 days (69–203) respectively.

10. Immunodeficiency

Immunodeficiency disorders prevent the body from fighting infections and diseases. While there are no data for the total number of people affected by immunodeficiency, there were 39,000 primary immunodeficiency-related hospital admissions in England in 2014-2015 [152]. There are many potential causes of secondary immunodeficiency, with common examples including blood or bone marrow disorders, medicines, and treatment for cancer. Patients with immunodeficiency are particularly vulnerable to drug-resistant microbes and the risks posed by them. Their inability to fight infections leads to increased risk of infection that spreads around the body and greater dependency on antimicrobial treatment [153]. Children with immunocompromising conditions represent a unique group for the acquisition of antimicrobial resistant infections due to their frequent encounters with the health care system, the need for broad-spectrum antimicrobials, and immune dysfunction [154].

This section will describe the impacts of antimicrobial resistance on immunodeficient patients. The literature we reviewed focused on immunosuppressed, immunodeficient and immunocompromised patients. The term immunosuppression includes both beneficial and potential adverse effects of decreasing the function of the immune system¹⁶⁵, while immunodeficiency is generally used to refer to the adverse effect of increased risk of infection. Immunocompromised refers to people who have a weakened immune system, which results in a reduced ability to fight infections and other diseases. Box 19 summarises the identified impacts from resistant infections and Box 20 summarises the available literature on this population.

Box 19: Key findings on immunodeficient patients

Key findings on impacts:

- **Mortality:** It is unclear whether immunodeficient patients are at increased risk of dying if they acquire a drug-resistant infection.
- **Health outcomes:** It is unclear whether immunodeficient patients who acquire a resistant infection have an increased risk of poor health outcomes
- **Risk of AMR:** Immunodeficient patients have an **increased risk of AMR**. One study found that immunodeficient patients were three times more likely to acquire a drug-resistant infection than those without immunodeficiency.

¹⁶⁵ Such as for organ transplantation.

Box 20: Summary of the range and nature of studies on immunodeficient patients

Number of studies: 7

Study types: 3 narrative reviews, 2 case reports, 2 empirical studies (1 primary data collection and 1 secondary analysis)

Strength of evidence: **Weak.** Most data are from narrative reviews and case reports.

Geography: Qatar, Germany, Saudi Arabia, Taiwan. The location was not reported in 3 studies.

Specific conditions: Immunocompromised patients, immunosuppressed patients, hemophagocytic lymphohistiocytosis.

Type of resistance: Antibacterial, antifungal, antiviral, antiparasitic.

Study populations: 2 studies focused on all patients, 3 on adults, 2 on children.

Impacts assessed: Mortality, morbidity, and increased risk of AMR.

10.1. Mortality

Three articles investigated the impacts of immunodeficiency on mortality. Two case studies found that immunocompromised patients with drug-resistant bacteria died, and a narrative review of resistant infections in children with febrile neutropenia found a link between immunocompromised status and death. Therefore, immunodeficient patients may be at **increased risk of death**, but the evidence is weak as it is based on two case reports and a narrative review.

It is unclear if immunodeficient patients are at increased risk of dying if they acquire a drug-resistant infection.

In a case report of an immunocompromised 54-year-old male patient admitted to an orthopaedic department in Germany, the patient acquired a post-operative infection of his hip prosthesis.¹⁶⁶ Over the course of several months, the infection spread further around his body and led to an infected aneurysm,¹⁶⁷ ultimately leading to death [155]. Similarly, in another case report from Qatar, a previously healthy six-year-old boy was diagnosed with hemophagocytic lymphohistiocytosis, a rare immune disorder, after developing a viral infection.¹⁶⁸ This was complicated by both antiviral resistance and sepsis from multiple drug resistant pathogens, including pan drug-resistant superbug¹⁶⁹ bacteria, and resulted in the death of the patient. This case highlights both the risk of acquiring multi-drug-resistant superbugs and the severity of these infections in hemophagocytic lymphohistiocytosis patients [153]. A narrative review of *S. aureus* infections in immunocompromised children found that it has been the most commonly reported cause of infectious death in some studies of paediatric febrile neutropenia [154].

¹⁶⁶ Due to *Mycoplasma hominis* and *Ureaplasma parvum* infection.

¹⁶⁷ An aneurysm is the enlargement of an artery due to weakness in the vessel wall.

¹⁶⁸ Infection with cytomegalovirus.

¹⁶⁹ A superbug is an informal term for a bacterium that has become resistant to antibiotics that usually are used to treat it.

10.2. Health outcomes

Two narrative reviews investigated the impacts of immunodeficiency on morbidity. They found that immunosuppressed patients may have an **increased risk of poor health outcomes**.

It is unclear whether immunodeficient patients who acquire a resistant infection have an increased risk of poor health outcomes

Pregnant women are immunocompromised and therefore more susceptible to acquiring infections. One narrative review noted that there have been reports of abortions in pregnant women who have a parasitic infection due to these atypical strains of the causative parasite [156]. A narrative review of infections in immunocompromised children found that bloodstream infections were the most common healthcare-associated infections in paediatric cancer patients and that bacterial infections were associated with a greater need for catheter removal¹⁷⁰ [154]. However, no quantification of these results was provided, such as how much more common bloodstream infections are compared to other types of infection.

10.3. Risk of AMR

Three articles investigated the impacts of immunodeficiency on AMR and found that immunodeficient patients with an infection are more likely to acquire a drug-resistant infection.

Immunodeficient patients with an infection are more likely to acquire a drug-resistance

An empirical study of 66 adult patients conducted in Saudi Arabia found that immunosuppressed patients were three times more likely to become infected with resistant bacteria than those with a good immune status [98].¹⁷¹ Similarly, a narrative review found that older patients (over 60), female, have diabetes or underlying kidney disease, or live in a long term care facility are more likely to be immunocompromised, and have an increased risk of acquiring a drug-resistant infection [73]. An empirical study from Taiwan of primary drug-resistant TB of the lungs found that patients with underlying diseases were more likely to be immunocompromised and had an increased prevalence of drug-resistant TB (26% compared to 17%)¹⁷² but a similar incidence of drug-related adverse effects compared to an immunocompetent group [157].

¹⁷⁰ A urinary catheter may allow bacteria to enter the body, which can cause an infection in the urethra, bladder or kidneys.

¹⁷¹ Odd ratio=2.9; 95%; Confidence Interval =1 .5-5.6; p=0.002

¹⁷² OR 1.69, 95% CI: 1.04–2.77

11. Liver and kidney disease

Liver cirrhosis is a disease that involves scarring and poor functioning of the liver as a result of long-term damage [158]. In 2017, 1.32 million people worldwide died from cirrhosis [159]. In the UK, over 4,000 people die from cirrhosis every year, and around 700 people require a liver transplant. Patients with cirrhosis require frequent hospitalisation and repeated antibiotic treatment [160]. Overall global prevalence of drug resistant infections in chronic liver disease patients has been estimated at 34% [161]. In Europe, the prevalence of drug resistant infections in cirrhosis patients increased from 29 to 38% over the period 2011–2018 [162]. Chronic kidney disease includes a variety of long-term conditions in which the kidneys are damaged and have a reduced ability to filter waste from blood [163]. Globally, in 2017 1.2 million people died from chronic kidney disease [164]. In the UK, it is estimated to affect around 3 million people, with approximately 3,000 kidney transplants taking place every year, and almost 30,000 people on dialysis [165]. Patients with chronic kidney disease require frequent use of antibiotics to treat and prevent infections associated with dialysis and following a kidney transplant [6]. Therefore, increasing drug resistance represents a serious issue for these two groups of patients, who are more likely to suffer negative health outcomes and death [160].

This section will describe the impacts of AMR on patients with liver cirrhosis and kidney disease. The literature covered advanced cirrhosis; candidates for liver transplant and patients in the post-transplant period; patients with chronic kidney disease, including those with end-stage kidney disease who require dialysis and/or kidney transplantation. Box 21 summarises the literature on this population and Box 22 summarises the identified impacts from resistant infections.

Box 21: Key findings on patients with liver and kidney disease

Key findings

- **Mortality:** Patients with liver cirrhosis and kidney disease are at **risk of death** if they acquire a drug-resistant infection. In one study, 30% of cirrhosis patients with an infection resistant to more than one type of antibiotic died compared to 18% of patients with an infection resistant to fewer types of antibiotics. However, it is unclear how this compares to patients with non-resistant infections.
- **Health outcomes:** Patients with liver disease and kidney disease may be more likely to suffer **negative health outcomes** if they acquire a drug-resistant infection, although this evidence is from lower quality sources. One study found that liver cirrhosis patients who had an infection resistant to more than one type of antibiotic were three times more likely to suffer from a deterioration of kidney function compared to patients with an infection resistant to only one type of antibiotic.
- **Effectiveness of treatment:** It is unclear from the evidence whether patients with liver and kidney disease who acquire a drug-resistant infection are at increased risk of treatment failure (e.g. transplant rejection or dialysis failure). However, there is a lack of information on adequate comparator groups to reach firm conclusions.
- **Hospital admission and length of stay in hospital:** It is unclear whether patients with liver cirrhosis who acquire a drug-resistant infection are **at risk of hospitalisation and face longer hospital stays**. However, one study found that patients with liver cirrhosis who acquire an infection resistant to more than one type of antibiotic face hospital stays of up to a third longer compared to patients with non multi-drug resistant infections.
- **Risk of AMR:** Several risk factors lead to a greater likelihood of developing a resistant infection in liver cirrhosis patients requiring a transplant, such as current or recent contact with the healthcare system, long-term preventive antibiotic treatment or recent use of certain antibiotics and infection by drug resistant bacteria in the last 6 months.

Box 22: Summary of the range and nature of studies on patients with liver cirrhosis

Number of studies: 3

Study types: 1 empirical study (collecting primary data) and 2 narrative reviews (one on liver and one on kidney disease).

Strength of evidence: **Weak.** Only three studies and two are narrative reviews.

Geography: Italy and global.

Specific conditions: Patients with liver cirrhosis, some undergoing liver transplants, and chronic kidney disease.

Type of resistance: Antibacterial.

Study populations: All types of patients.

Impacts assessed: Mortality, health outcomes, effectiveness of treatment, hospital admissions, length of stay in hospital and risk of AMR.

11.1. Mortality

Three articles investigated the impacts on mortality. These comprised one empirical study and two narrative reviews. One empirical study finds that patients with liver cirrhosis who acquire an infection resistant to multiple antibiotics are **more likely to die** than patients with infections resistant to fewer antibiotics. Two articles report that patients with liver cirrhosis and kidney disease who acquire resistant infections may be at increased **risk of death**, but do not provide information on comparator groups to reach firm conclusions.

It is unclear whether patients with liver and kidney disease are at increased risk of dying if they acquire a drug-resistant infection

One narrative review reported that patients with liver cirrhosis (this included advanced cirrhosis, candidates for liver transplant and patients in the post-transplant period) who acquired a drug-resistant infection were at greater risk of dying, both in the pre-transplant and post-transplant stages than patients without these conditions [160]. The review did not quantify the risk and did not report on the risk of death in patients with no infection or with non-resistant infections. The authors highlighted that patients waiting for a liver transplant are at particular risk of complications and death from drug resistant infections as exposure to antimicrobial drugs during the waiting period may influence the risk of acquiring infection after the transplant. In addition, one empirical study of 111 patients with liver cirrhosis found that those who acquired a bacterial infection resistant to more than one type of antibiotic were more likely to die as a result of failure of antibiotic treatment compared to patients with an infection resistant to fewer types of antibiotics [166]. In this study population, 30% of patients with an infection resistant to more than one type of antibiotic died compared to 18% of patients with an infection resistant to fewer types of antibiotics.

A narrative review of the impacts of AMR in kidney-related disease reports that drug-resistant infections increase the risk of mortality caused by infection in patients with kidney disease [6]. The review does not quantify the risk and does not provide information on mortality in patients with non-resistant infections or with no infection.

11.2. Health outcomes

Three articles investigated the impacts on health outcomes. These comprised one empirical study and two narrative reviews. All articles reported that patients with liver cirrhosis and kidney disease who acquire resistant infections are more likely to **suffer negative health outcomes**. However, two narrative reviews do not provide information on comparator groups to reach firm conclusions.

It is unclear whether patients with liver and kidney disease are more likely to suffer negative health outcomes if they acquire a drug-resistant infection

One empirical study of 111 patients with liver cirrhosis found that those who acquired a drug-resistant bacterial infection had a deterioration of liver function [166]. Patients who had an infection resistant to more than one type of antibiotic were more likely to suffer from a deterioration of kidney function compared to patients with an infection resistant to only one type of antibiotic. In this patient population, 23% of patients who had an infection resistant to

more than one type of antibiotic suffered a deterioration of kidney function compared to 7% of patients with an infection resistant to only one type of antibiotic.¹⁷³

A narrative review reported that patients with liver cirrhosis waiting for a liver transplant are particularly affected by drug-resistant infections. If these patients acquire a drug-resistant infection, they are likely to suffer negative health outcomes, including kidney damage, liver failure and septic shock, both in the pre-transplant and the post-transplant stages [160]. However, the review did not quantify the risk and did not provide information on the health outcomes in liver cirrhosis patients without infection or with non-resistant infections.

A narrative review of the impacts of AMR in kidney-related disease reports that drug-resistant infections increase the risk of infection-related morbidity in patients with kidney disease [6]. The review does not quantify the risk and does not provide information on mortality in patients with non-resistant infections or with no infection.

11.3. Effectiveness of treatment

Two narrative reviews investigated the impact on effectiveness of treatment. Both articles report that patients with liver cirrhosis and kidney disease who acquire resistant infections are more likely to demonstrate treatment failure. However, they do not provide information on comparator groups to reach firm conclusions.

It is unclear whether liver and kidney disease patients with drug-resistant infections are more likely to demonstrate treatment failure

A narrative review reported that patients with liver cirrhosis who acquire a drug-resistant infection are at increased risk of treatment failure (i.e. transplant rejection), resulting in negative health outcomes such as kidney and liver damage or failure and septic shock [160]. Patients waiting for a liver transplant are particularly at risk of suffering negative health outcomes. However, the review did not quantify the risk and did not provide information on the effectiveness of treatment in liver cirrhosis patients without infection or with non-resistant infections.

A narrative review of the impacts of antimicrobial resistance in kidney-related disease reports that drug-resistant infections can limit the treatment options available to patients with chronic kidney disease, particularly those with advanced illness requiring dialysis¹⁷⁴ or a kidney transplant [6].

11.4. Length of stay in hospital

Two articles investigated the impact on hospital admission and length of stay in hospital. These comprised an empirical study and a narrative review. Both articles reported that patients with liver cirrhosis who acquire a drug resistant infection are **likely to be admitted to hospital and face longer hospital stays**. However, the evidence from the narrative review is limited by a lack of an adequate comparator group.

¹⁷³ p = 0.02

¹⁷⁴ A procedure used on patients with kidney problems to help remove waste and excess fluid from the blood.

It is unclear whether patients with liver cirrhosis who acquire a drug-resistant infection are at increased risk of hospitalisation and face longer hospital stays

A narrative review reported that patients with liver cirrhosis who acquire a drug-resistant infection are likely to be admitted to hospital [160]. However, the review did not provide information on the impact on hospital admission or length of stay in liver cirrhosis patients without infection or with drug-susceptible infections. Another study of 111 patients (adults and children) with liver cirrhosis found that those who acquired an infection resistant to three or more types of antibiotic had an increased length of hospital stay compared to patients who had an infection resistant to fewer antibiotics (an average of 21 days compared with 14 days, respectively)[166].¹⁷⁵

11.5. Risk of AMR

One narrative review investigated the risk factors associated with the development of drug resistant infections in patients with liver cirrhosis.

Several risk factors lead to a greater likelihood of developing a resistant infection in liver cirrhosis patients requiring a transplant

The authors of one narrative review highlighted the following specific risk factors that were associated with the development of drug-resistant infections in liver transplant patients: current or recent contact with the healthcare system, long-term preventive antibiotic treatment¹⁷⁶ or recent use of certain antibiotics¹⁷⁷ and infection by drug resistant bacteria in the last 6 months [160]. In addition, patients with drug-resistant bacteria present in the body before the transplant were more likely to acquire an infection caused by the same bacteria after the transplant. However, the review did not provide information on the number of deaths in patients without infection or with drug-susceptible infections and does not provide a quantification of this evidence.

¹⁷⁵ 20.6 ± 14 days vs 13.6 ± 11 days; p = 0.003

¹⁷⁶ The use of Norfloxacin as a preventative treatment.

¹⁷⁷ Beta-lactams (in the last 3 months).

12. Physical trauma

For this review, we have defined physical trauma as any serious injury to the body caused by an external force, such as falls, physical violence or road accidents. Worldwide, traumatic injuries such as these are the leading cause of death in people under 45, with roughly 5.8 million people dying from these injuries annually [167]. In England and Wales, around 16,000 patients die after major trauma and many of those who survive are left with severe disability [168]. Infections in these patients are common as physical trauma often leads to open wounds, allowing pathogens to enter the body. Because of this, trauma patients are often given broad-spectrum antibiotics to prevent an infection developing which can contribute to the growth of drug resistant bacteria [169, 170]. These patients may also require ICU admission and invasive medical support, such as mechanical ventilation [170], which as mentioned in Chapter 6, increases the risk of developing a drug resistant infection.

This section will describe the impacts of AMR on patients with physical trauma. The literature covered burn patients, military-related trauma and general (unspecified) trauma. Box 23 summarises the identified impacts from drug resistant infections and Box 24 summarises the available literature on this population.

Box 23: Key findings on patients with physical trauma

Key findings

- **Mortality, health outcomes and length of hospital stay/ICU admissions:** Due to the small number of studies exploring different types of trauma and outcomes, the evidence is mixed for mortality, length of hospital stay/ICU admissions and morbidity.
- **Invasiveness of treatment:** The studies suggest that trauma patients with drug resistant infections are at a **greater risk of requiring mechanical ventilation and are more likely to need this invasive support for a longer period**. For example, one study found that 29% of trauma patients with no infection or non-resistant infections required mechanical ventilation, compared to 78% of trauma patients with drug resistant infections.

Box 24: Overview of the literature on physical trauma

Number of studies: 5

Study types: All are secondary quantitative analysis of patient data

Strength of evidence: **Weak-moderate.** Studies use reliable quantitative analysis of patient data, but only a small number of studies were identified on physical trauma and the differing results across these studies make it difficult to derive conclusions.

Geography: USA, Germany and unspecified (one study).

Specific conditions: Burn patients, military-related physical trauma and unspecified trauma cases admitted to trauma ward.

Type of resistance: Antibacterial.

Study populations: Two studies included any burn patients with infections, two studies focused specifically on adults with trauma injuries (one on any trauma leading to hospital admission and another on trauma from military activity) and the final study included children with burns.

Impacts assessed: Mortality, length of hospital stay/ICU admissions, health outcomes and treatment invasiveness.

12.1. Mortality

Out of the five studies exploring the impact of AMR on physical trauma, four assessed the impact on death rates, with mixed results. These were all empirical studies, conducting secondary analysis of existing patient data.

The evidence for impact on mortality as a result of drug resistant infection in trauma patients is mixed

Two studies did not find that infection with drug resistant bacteria increased the risk of mortality compared to patients with non-resistant infections [171, 172]. These two studies explored the mortality risk in adult patients with any trauma requiring hospital admission (including 10,985 patients) and any burn patients with an infection (with a sample size of 87 patients).

One study analysing the data of 126 US burn patients with drug resistant and non-resistant infections found that the risk of death increased in the presence of a drug resistant infection compared to a non-resistant infection. These authors found that burn patients with drug resistant infections are more likely to develop organ failure in multiple organs and acute kidney injury compared to patients with non-resistant infections (38.3% vs 12.7%, respectively),¹⁷⁸ leaving them at significantly greater risk of death [100].¹⁷⁹

The other study, analysing the mortality data of children admitted to the paediatric burn unit with drug resistant infections, identified that 6% of children in the study died (14 out of 3,359). All of these deaths were attributed to multi-drug resistant bacteria infections, however, no information is provided as to whether this death rate is similar for children with burns and non-resistant infections [173].

¹⁷⁸ The sudden onset (within hours or days) of kidney damage or failure, leading to a build-up of waste products in the bloodstream.

¹⁷⁹ P= <0.0001 for organ failure, OR (95% CI) 85.49 (12.97–563.28); p= 0.001 for acute kidney injury, OR (95% CI) 10.93 (2.74–43.57)

Due to this variation in identified impacts on mortality as a result of trauma patients developing drug resistant infections, further research is needed in this area.

12.2. Health outcomes

Out of the five studies exploring the impact of AMR on physical trauma, two explored the impacts on health outcomes (sepsis and need for long term support). These were both empirical studies, conducting secondary analysis of existing patient data.

Trauma patients with drug resistant infections do not need additional long-term medical support

One study analysed several different health outcomes of 10,985 adult patients admitted to hospital due to trauma who develop infections. The study found that there was no difference in the need for a tracheostomy¹⁸⁰ or long-term rehabilitation for patients with drug resistant compared to non-resistant infections [171].

Burn patients are at greater risk of developing sepsis if they have a drug resistant infection

The other study, analysing the data of 126 US burn patients with infections, found that burn patients with drug resistant infections are at significantly greater risk of developing sepsis compared to patients with non-resistant infections due to the difficulties in treating the bacteria.¹⁸¹ In this study, the number of patients with sepsis almost tripled in drug resistant infections, from 13% to 38% [100].

12.3. Length of stay in hospital

Out of the five studies exploring the impact of AMR on physical trauma, four assessed the impact on length of hospital stay, with mixed results. An additional study explored the impact on ICU admission. These were all empirical studies, conducting secondary analysis of existing patient data.

The evidence for impact on length of hospital stay as a result of physical trauma is mixed, but trauma patients with drug resistant infections may be at higher risk of requiring ICU admission

The same two studies that did not find a difference in mortality between trauma patients with drug resistant and non-resistant infections also did not find any difference in length of hospital stay [171, 172].

The other two studies found that trauma patients with drug resistant infections had longer hospital stays compared to patients with non-resistant infections [99, 100]. The first, exploring the characteristics of drug resistant infections in 2,699 US military personnel with trauma found that patients with drug resistant infections faced significantly longer hospital stays than those with non-resistant infections (a median of 53 days hospitalised compared to 18 days) [99].¹⁸²

¹⁸⁰ The creation of an opening in the neck to insert a tube directly into the windpipe to assist in breathing.

¹⁸¹ P= 0.001

¹⁸² P= < 0.0001

This study also explored ICU admissions and found that patients with drug resistant infections were almost twice as likely to need ICU admission compared to patients with no infection or non-resistant infections (49% compared to 91%). The second study, analysing outcome data of 126 US burn patients with infections, also found that length of hospital stay significantly increased, from 14 days in patients with non-resistant infections to 39 days for patients with drug resistant infections.¹⁸³

Due to this variation in identified impacts on length of hospital stay as a result of trauma patients developing drug resistant infections, further research is needed in this area.

12.4. Invasiveness of treatment

Two studies explored the impact of AMR on treatment invasiveness and duration. These were both secondary analyses of trauma patient data.

Trauma patients with drug resistant infections are more likely to require mechanical ventilation

The first study, exploring the characteristics of drug resistant infections in 2,699 military personnel from the US with trauma found that patients with military-related trauma and drug resistant infections were at a significantly higher risk of requiring mechanical ventilation while in hospital than patients with non-resistant infections.¹⁸⁴ In this study population, only 29% of patients with either no infection or non-resistant infection required mechanical ventilation, compared to 78% of patients with multi-drug resistant infections [99].

The second study, analysing outcome data from 126 burn patients in the US, found that burn patients with drug resistant infections required mechanical ventilation for an average duration of 21 days.¹⁸⁵ By comparison, none of the burn patients with non-resistant infections required mechanical ventilation [100].

¹⁸³ P= < 0.0001

¹⁸⁴ p < 0.0001

¹⁸⁵ p < 0.0001

13. Discussion and conclusions

13.1. Reflections on key findings

This REA highlights how development of a drug resistant infection in patients with non-infectious health conditions can result in a wide variety of other poor outcomes and in some cases can be life-threatening. The evidence demonstrates that for all the health conditions we reviewed¹⁸⁶, at least one study found that patients are at a higher risk of death than patients without infection or with non-resistant infections. In addition, a wide range of poor health outcomes have been associated with health conditions predisposed to the development of drug resistant infections, such as postoperative complications in surgical patients, severe sepsis in infants and development of drug resistant TB in diabetic patients. We have also found evidence that patients with drug resistant infections and other health conditions need additional medical support which is reflected in longer stays in the ICU or hospital (e.g. for liver cirrhosis and surgical patients), the need for more invasive medical support (e.g. organ transplant patients) and less effective treatment options (e.g. STIs and diabetic patients). Below we provide an overview of the key findings for each health condition we reviewed:

- **Surgical patients:** Patients having undergone surgery (in this case, the literature focuses on cancer, eye and orthopaedic related surgery) and who develop drug resistant infections are at risk of death. Surgical patients with drug resistant and face longer hospital stays than those with non-resistant infections.
- **Organ transplant patients:** Organ transplants are a risk factor for the development of drug resistant infections and kidney transplants may be more likely to lead to drug resistant infection compared to other types of transplant. The evidence is unclear as to whether organ transplant patients with drug resistant infections are at a greater risk of death compared to patients with non-resistant infections. However, patients undergoing stem cell transplants who develop a drug resistant infection appear to be at a higher risk of death than those with non-resistant infections. Transplant patients who develop a drug resistant infection are at a greater risk of negative health outcomes (e.g. kidney failure and sepsis). The evidence is mixed as to whether transplant patient with drug resistant infections are at a greater risk of transplant failure, ICU admission or hospital admission compared to patients with non-resistant infections. However, organ transplant patients with cystic fibrosis who acquire a drug-resistant infection are more likely to require longer ICU stays than those with non-resistant infections or no

¹⁸⁶ Except for STIs and autoimmune conditions in which no evidence on mortality was provided.

infection. Organ transplant patients who acquire a drug-resistant infection are more likely to require mechanical ventilation than those with non-resistant infections.

- **Cancer:** Patients with cancer may have a greater risk of developing drug resistant infections than non-cancer patients. Those who do develop drug resistant infections are more likely to develop sepsis. The evidence is mixed as to whether patients with cancer are at greater risk of death if they develop a resistant infection. Cancer patients with drug resistant infections may need to spend longer periods in hospital than those with non-resistant infections, although these studies did not provide comparative data for patients with a non-resistant infection.
- **ICU patients:** Admission to the ICU is associated with development of drug resistant infections. Children in the ICU who develop drug resistant infections are at a greater risk of death compared to those with non-resistant infections. The evidence for mortality in adult patients is less clear, although the studies indicate that elderly patients may be more at risk of death if they develop a drug resistant infection compared to a non-resistant one. Patients who develop drug resistant infections require longer stays in hospital. These results are particularly relevant given the COVID-19 pandemic which is still ongoing at the time of writing and had led to an increase in ICU admissions and use of invasive medical support, such as mechanical ventilation.
- **Diabetes:** The evidence is unclear as to whether patients with diabetes have a greater risk of developing drug resistant infections than non-diabetic patients, are at a greater risk of death or show a higher risk of developing drug resistant TB.
- **HIV:** People living with HIV are more likely develop drug resistant TB than those without HIV, and for those co-infected with HIV and drug resistant TB, they are at a greater risk of death and are less likely to successfully treat their drug resistant TB. HIV patients infected with drug resistant bacteria may need to spend longer in hospital, ICU admission or more invasive medical treatment. The link between the impact of treatment for drug resistant TB is unclear and further research is needed. The strength of the evidence for the impact of resistance on STIs is low; however, the limited evidence does indicate that resistance leads to reduced treatment options for patients and increases the risk of contracting and transmitting HIV.
- **Infants and children:** It is unclear whether infants who develop drug resistant infections are at an increased risk of death or require longer lengths in hospital than patients with non-resistant infections. However, they do appear to have a higher risk of developing sepsis than those with non-resistant infections.
- **Immunodeficient patients:** Patients with deficiencies in their immune systems may be at a greater risk of developing a drug resistant infection than patients with fully functioning immune systems. Those patients who develop resistance are at a greater risk of death and poor health outcomes (in pregnant women) than those with non-resistant infections, although the evidence base for this condition is fairly weak.
- **Liver and kidney disease:** Patients with diseases of the liver and kidney may be at a greater risk of death and poor health outcomes (e.g. poor liver and kidney function or sepsis), treatment failure (e.g. transplant rejection), require hospitalisation or longer

stays in hospital if they acquire a drug resistant infection compared to patients with a non-resistant infection. However, the evidence for these outcomes is fairly weak as most are based on narrative review.

- **Physical trauma:** Clear conclusions on the impact of drug resistant infections on mortality, length of hospital stay, ICU admissions and health outcomes could not be made due to the differing results from the studies. However, the evidence does suggest that trauma patients with drug resistant infections are more likely to need mechanical ventilation and require this support for longer periods than those with non-resistant infections.

A summary of the strength of the evidence across each of these conditions is provided in Table 4.

As none of the literature we identified in our original search provided information on how to model the future impact of AMR on non-infectious health conditions, we conducted an additional small search to explore this topic. The detailed findings of this are outlined in Chapter 2.

13.2. Areas for future research

Box 25: Summary of key areas for future research

Summary of key areas for future research:

- Good quality evidence on the impacts of AMR on a wider range of conditions, e.g. childbirth; abortions; asthma; stroke; heart disease; dermatological conditions; rheumatological conditions; Common Variable Immune Deficiency; autoimmune conditions; immunosuppressed patients; liver cirrhosis and dental health
- Better evidence on the effectiveness and invasiveness of treatments where drug resistant infections are present
- Collection of data on prevalence of AMR in relation to different conditions
- Evidence on impact of wider types of AMR beyond bacterial infections
- Better quality modelling studies to understand the likely future trends and implications, drawing on higher quality prevalence and impact data as outlined above
- Ongoing synthesis and review of the evidence to inform future research directions

Our Rapid Evidence Assessment highlights several gaps in the evidence which could benefit from additional research to better understand and plan for the impacts of AMR on non-infectious health conditions. However, we note that these gaps in evidence should not serve as a barrier to action now. It is already well understood that the risks posed by AMR are significant. Although understanding these better and in context will be important to help us address them in specific settings and situations, this research should be in parallel with action to address and reduce AMR at both a policy and practice level.

There are some health conditions which we included in the literature search, but for which no studies were identified. These include childbirth; abortions; asthma; stroke; heart disease; dermatological conditions; rheumatological conditions; Common Variable Immune Deficiency; and dental health.

In addition, there are some health conditions for which fewer than 5 studies were identified, including autoimmune conditions, immunosuppressed patients and liver cirrhosis. Given the risk posed to patients with autoimmune conditions and immunosuppression from infections, particularly drug resistant ones, it is important that further research is conducted to understand the potential impacts of AMR on these groups of patients.

On the other hand, we identified a larger number of studies for some conditions, but the strength of evidence was still poor. For example, treatment efficacy in transplant patients, mortality in diabetic and trauma patients, risk of AMR in diabetic patients and hospital/ICU stay in neonates and trauma patients. These highlight additional areas which may benefit from further research. The strength of the evidence across conditions is summarised in Table 4. Each combination of health condition and impact is awarded a strength of evidence rating based on a scale of strong (dark green) to weak (red). The below classification describes the volume and type of evidence that we identified for combinations awarded each rating.

- **Strong.** For each combination of health condition and impact for which we rated the identified evidence as 'strong' (e.g. HIV and mortality), we identified ten or more studies including a systematic review and meta-analysis.
- **Moderate-strong.** For each combination of health condition and impact for which we rated the identified evidence as 'moderate-strong' (e.g. diabetes and risk of AMR), we identified either eight or more studies, or five or more studies including a systematic review and meta-analysis.
- **Moderate.** For each combination of health condition and impact for which we rated the identified evidence as 'moderate' (e.g. organ transplant and effectiveness of treatment), we identified five to seven studies, usually including five to six empirical studies. There were two cases when we applied the 'moderate' rating to a condition and impact combination represented by just four empirical studies, but for each of these we also identified either two or three narrative reviews.
- **Weak-moderate.** For each combination of health condition and impact for which we rated the identified evidence as 'weak-moderate' (e.g. newborns and health outcomes), we identified four to five studies. In most cases these included three to four empirical studies, but in one case (surgery and effectiveness of treatment) this comprised one empirical study, three narrative reviews and one case report.
- **Weak.** For each combination of health condition and impact for which we rated the identified evidence as 'weak' (e.g. cancer and length of stay in hospital), we identified three or fewer studies, including no more than two empirical studies.

Any impacts with a classification of weak or moderate evidence requires further research. Perhaps even more important is to fill the gaps where we did not find any evidence for an impact on a certain condition, such as invasiveness of treatment for most health conditions. While it is important to note the limitation of this study in terms of the timeframe placed on reviewed literature (published since 2010) and the search protocol used, both of which may have meant some relevant studies were not included, it does suggest that little research has been conducted in these areas recently and suggests that further investment may be of value. Reviewing Table 3, we observe that most studies across conditions focus on mortality, and to a slightly lesser extent, health outcomes – though the range and nature of health outcomes

analysed varies by condition. Much fewer studies look at the impact of AMR on effectiveness and invasiveness of treatment. This is a clear gap and an important one. If treatments for other conditions are rendered less effective than this, combined with the increased risk associated with treatments due to the risk of AMR, could have a significant impact on the extent to which existing interventions can be effectively employed. Secondly, we note across all areas there is very limited data on the prevalence of AMR in relation to different health conditions, at a UK or international level. Understanding the potential implication of AMR only gives us a partial picture. To truly understand the implications for healthcare we also need to understand the prevalence and trends in prevalence of AMR in relation to these different health conditions. This is an important gap in the existing evidence.

Table 4: Overall strength of evidence across conditions and impacts

	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
HIV	Strong	Weak	Moderate	Weak	Weak	Weak-moderate
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		

In addition, for the conditions where we identified a larger number of studies, these were sometimes restricted to a small subset of the type of condition, e.g. for surgery, the literature only covered three types of surgical procedures (relating to cancer, eye and orthopaedics). It may be that other types of surgery (such as that considered to be 'dirty', i.e. exposed to faecal matter from the bowels or pus) lead to different impacts for patients.

The majority of the literature focuses on bacterial infections and the impacts of antibiotic resistance. It is important to improve the understanding of other types of microbes and the impacts of drug resistance, including viruses (particularly other than HIV), fungi and parasites. This need is also reflected in the AMR modelling studies we identified, in which most studies focus on modelling the future impacts of a small group of disease (e.g. TB, HIV, influenza). Additional modelling studies are needed to better understand the potential future impacts of other important pathogens, including fungi, parasites and non-influenza viruses.

A number of reviewed papers highlight the importance of researching the impacts of AMR on non-infectious health conditions across multiple centres and countries to obtain data that is more generalisable to an entire disease population, rather than a subset of patients within one hospital, for example. Linked to this, we note a fairly limited number of systematic reviews of the evidence – only 4 systematic reviews (2 with meta-analyses) were identified in our search.

Also within scope of this review was the modelling of the future impact of AMR on non-infectious health conditions. However, we did not identify any studies directly addressing this issue at the level of individual conditions or patient groups. Because of this, we conducted a small additional search to better understand the models and datasets used for AMR. The reviewed literature suggests several areas of improvement for modelling studies, such as the need for better data (e.g. on antimicrobial consumption and prevalence of AMR among non-infectious health conditions and healthcare areas which are not well recorded) and model validation and improved incorporation of the wider context in which AMR occurs - for example, the uncertainties around incidence of infections, the fact that AMR is often not assessed in a timely manner and the behavioural changes needed to combat resistance. Because of the poor amount and quality of data on AMR (including for non-infectious health conditions and healthcare areas), the current models for the future impact on AMR may not be sufficiently useful for informing policy and practice.

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Annex A. Methods

This annex provides a more detailed overview of the methodological approach to this Rapid Evidence Assessment and its accompanying limitations.

A.1. Overview of methodology

As outlined in section 1.1, this study was based on the following two research questions:

1. What impact is AMR currently having on non-infectious health conditions, e.g. cancer or diabetes, or areas of health services, e.g. ICU (where AMR could be a complicating factor impacting on the ability to treat the condition and health outcomes)?
2. What impact, demonstrated by modelling studies, could AMR have on modern medicine in the future for non-infectious health conditions or areas of health services?

To address these research questions, the study team conducted a Rapid Evidence Assessment (REA). An REA involves a structured and rigorous search of evidence on a particular topic in a short timeframe. They are useful in situations where evidence is uncertain and provide an overview of the 'breadth, depth and comprehensiveness' of evidence on a topic [9, 10]. This approach is suitable to answer these two research questions for these reasons, i.e. the evidence-based for the impact of AMR on non-infectious diseases and health conditions is unclear.

This REA followed the standard steps for the type of literature search¹⁸⁷:

1. Define research questions and develop robust search protocol.
2. Define inclusion and exclusion criteria.
3. Conduct literature search.
4. Screening.
5. Extraction and analysis.

Each of these steps will be discussed in turn.

¹⁸⁷ REAs can include quality appraisals of the included studies. This was not undertaken for this study as no other reviews of evidence on the topic of AMR in non-infectious health conditions had been identified. Therefore, the study aimed to gain an understanding of the extent and type of evidence available on this topic, rather than the quality. However, a high-level assessment of the quality of the literature is provided in each chapter.

A.2. Define research questions and develop robust search protocol

There are several different ways of finding sources for a literature review. REAs usually include a protocol-driven approach where literature database(s) are searched using structured and pre-defined search teams. These search terms are defined based on the research questions and are combined using Boolean logic operators (e.g. 'AND', 'OR') and other special search string characters to maximise the number of relevant studies that are returned.

Based on these research questions, a search protocol was designed with Wellcome and RAND Knowledge Services librarians¹⁸⁸ (Table 5). The health terms were developed to be as broad as possible, to identify any non-infectious health condition and a specific set of health service areas that may be impacted by resistant infections. To ensure this broad approach we included a range of categories of non-infectious (e.g. oncology, cardiology, injury) and specific areas of health service (e.g. emergency medicine).

Table 5: Search protocol (these terms were tailored to each of the three databases)

Search term group	Search terms
AMR terms: This set of search terms limits the search hits to those relating to AMR	Antimicrobial resistance OR AMR OR antibiotic resistance OR antiviral resistance OR antiparasitic resistance OR antifungal OR drug resistance OR drug resistant OR superbug*
Health terms: This set of search terms seeks to identify sources that consider some form of link between AMR and the pre-defined non-infectious health conditions and areas of health services.	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

A.2.1. Identifying additional literature on AMR modelling

After screening and extracting the literature from this search, it became clear that we had identified little to no evidence on the future impact of AMR on the health conditions and areas of healthcare of interest (particularly in the form of modelling searches). Therefore, we ran a series of targeted searches to obtain a set of relevant articles focussing on peer-reviewed

¹⁸⁸ The RAND Knowledge Services is an extensive, up-to-date resource providing access to over a hundred on-line journal and literature databases.

journal articles and conference publications that covered this topic. The indicative search strings used to capture the most relevant articles are listed in Table 8.

Table 6: Indicatives search strings to identify evidence on AMR modelling

#	Indicative search string(s)
1	(antimicrobial OR anti-microbial) AND (resistance) AND (modelling OR modeling)
2	(antibiotic OR anti-biotic) AND (resistance) AND (modelling OR modeling)
3	(AMR) AND (modelling OR modeling)
4	(ABR) AND (modelling OR modeling)

A.3. Define inclusion and exclusion criteria

To support the screening and extraction of relevant studies, it is important to develop a clear set of inclusion and exclusion criteria to ensure a standardised approach to study selection. The criteria used for this REA are provided in Table 7. Note that while the study primarily focused on non-infectious diseases, on the request of Wellcome, resistance of STIs was also an inclusion criterion due to the recent increase seen in extensively drug resistant STIs, particularly gonorrhoea [174].

Table 7: Inclusion and exclusion criteria

Criteria	Inclusion criteria	Exclusion criteria
Publication date	Published 2010-2020	Published before 2010
Location	All countries	N/A
Language	English	Non-English
Study type	Peer-reviewed journal publications presenting empirical evidence, review papers, grey literature with clear authorship, book chapter, theses, conference proceedings.	Documents without clear organisational authorship, theoretical work, letters, editorials, comments or opinion pieces, book reviews.
Diseases	Any non-infectious health conditions or type of health service, including (but not limited to) cancer, cardiovascular disease, stroke, surgery, trauma, pregnancy and birth, neonatal and child health conditions, immunocompromising conditions, cystic fibrosis, respiratory conditions, diabetes, obesity, TB, HIV/AIDS, STIs, UTIs, conditions of the liver, eyes, skin, kidneys, circulation, musculoskeletal system, digestive system, and dentistry. Also include: Direct resistance in STIs	Any infectious diseases/pathogens (except STI and HIV). In particular, we are focusing on secondary conditions affected by AMR rather than conditions where the primary pathogen itself becomes drug resistant. Direct resistance to STIs does not include HIV
Study participants	Humans	Animals and plants

For the additional search for AMR modelling studies, while grey literature was not explicitly excluded, the searches emphasised peer-reviewed journal articles and conference publications to ensure alignment with the REA approach outlined in the previous section. Similarly, although literature from 2014 onwards was prioritised, articles before 2014 were considered if relevant in the context of the discussion. Any literature discussing changes to the business models of healthcare systems, insurance, and pharmaceutical industries, and potential changes to payment models of healthcare in high-income countries were excluded to ensure the focus on the findings aligned with the overall objectives of the study.

A.4. Conduct literature search

Using the search terms outlined in Table 5, along with the inclusion/exclusion criteria outlined in Table 7, three academic databases were searched for relevant literature: PubMed, Web of Science and Embase. These were selected as they include studies relating to biomedical science, pharmacology, life sciences and health sciences. The approach to searching each database followed the same structure and terms, however, each was tailored slightly to meet the search requirements of the database it was being used for.

The database searches were run on the 3 April 2020 and returned 24,422 articles. After duplicates were removed, this left 11,309 articles for screening.

For the additional search for AMR modelling studies conducted after this, we conducted targeted searches of Google and Google Scholar. The results from these searches were combined with 'snowballing' where necessary. To enable a quick high-level overview of the available evidence, 28 relevant articles/reports were identified through the searches. Additional 6 articles were identified through snowballing.

A.5. Screening

Screening involves assessing the title and abstract of all studies identified through the literature search against the inclusion and exclusion criteria. For this REA, the reference management software, EndNote, was used for this purpose. Only sources that meet the inclusion criteria progress to the next stage (extraction); those that do not meet the criteria are excluded from the study. The screening acts as an initial sift to ensure that only relevant sources are read in full, which is particularly important for the output of the protocol-driven literature search which typically returns a high number of sources that are not relevant to the research question.

To ensure reliability and consistency of the screening process across the research team, a pilot of 50 articles (selected in a pseudorandomised way) were screened by all team members. This ensured that a standardised approach to screening was taken across the research team and any uncertainties were discussed and ways forward decided upon (in consultation with the project leader).

The remaining 11,259 articles were divided among the research team to screen. In total, 198 were identified as relevant and taken forward to the extraction stage.

A.6. Extraction and analysis

After selecting the relevant articles based on title and abstract during the screening phase, the research team proceeded to extract the relevant data from these studies. To ensure a consistent approach to extraction as was applied in screening, the same researchers undertook the extraction, however, each extracted different articles to the ones they had screened to provide an extra check that the article was relevant to the study. Each team member worked independently during this stage of the study; however, any uncertainties or questions were discussed among the team and project leader. If a full-text was not available (not available freely and a high-cost to buy), any relevant data were extracted based on information in the abstract (three articles).

The extraction was conducted in Excel, and a template was designed in consultation with Wellcome. Where possible, drop-down lists were created based on the keywords in the title/abstract of included studies to aid in analysis. The extraction template is provided in Table 8. The 198 articles identified at the screening stage were divided equally among the research team.

Table 8: Extraction template

Component	Information extracted
Coder	Initials of researcher extracting data
Include/exclude	Whether the study should be included/excluded based on full-text
Citation number	Unique number assigned to each reference
Reference	Study reference
Summary	Abstract
Publication type	Dropdown list: journal article; report; book chapter; conference proceeding; thesis; other
Study type	Dropdown list: empirical study; review/systematic review/meta-analysis; case report; other
Methodology type	Dropdown list: quantitative - primary data collection; quantitative - secondary data; qualitative; mixed methods; case report; narrative review; systematic review; systematic review and meta-analysis; scoping review; other
Methodology	Brief outline of methodology used (as described by study authors)
Geographical location	Country the study was conducted in
General disease or health condition	Dropdown list: autoimmune disease; cancer; diabetes; HIV; kidney disease; liver disease; mental health; neonatal infection; organ transplant; physical trauma; stem cell transplant; STI; surgery; TB; immunosuppression; ICU; other
Specific disease or health condition	Specific disease of focus, e.g. lung cancer, renal transplant, type II diabetes.
Type of resistance	Dropdown list: antibacterial; antifungal; antiviral; antibacterial/antiviral; antiparasitic; other
Specific resistant pathogen	Name of resistant pathogen
Drug pathogen is resistant to	Name of drug the pathogen is resistant to
Study group (general)	Dropdown list: neonates; children; adults; elderly; pregnant women; military; all patients
Study group (specific)	Specific study group of focus, e.g. lung cancer patients aged 60+, premature neonates with HIV
Type of current impact on modern medicine	Dropdown list: mortality; morbidity (general); morbidity (specific outcome mentioned); hospital admissions; length of stay; treatment duration; treatment efficacy; invasiveness of treatment; ICU admission; increased risk of AMR; other
Description of current impact on modern medicine	Further detail of the current impact of AMR on the health conditions specified in the inclusion criteria. Specific outcome measures reported where possible.
Quantitative data on impact	Quantitative data related to the impact, e.g. significant information.

Component	Information extracted
Populations at higher risk	Groups currently more vulnerable to the impacts of AMR and reasons if available.
Potential future impact on modern medicine	Description of future impacts on the health conditions specified in the inclusion criteria that could occur in future, and reasons for change.
Future research needs/gaps in knowledge	Description of remaining gaps in knowledge for the impact of AMR on the health conditions specified in the inclusion criteria.
Strengths and limitations	Descriptions of the strengths and limitations of the study.
Other reviewer comments	Any other relevant information in the document that does not fit into one of the previous categories

As the full-text of articles provides further detail than the abstract, some articles were found to not meet the inclusion criteria. Therefore, they were excluded at the start of the extraction stage and no information was recorded for these. A total of 97 articles were identified as not relevant at this stage and excluded, leaving 101 that were fully extracted.

For the additional search conducted on AMR modelling studies, the 34 articles/reports identified included a 2014 studies on AMR conducted by KPMG [10] and RAND Europe [11] as part of Wellcome's AMR review [2] highlighting the potential healthcare and economic crisis implications of AMR, and two studies by the European Centre for Disease Prevention and Control (ECDC) published in 2009 [12] and 2014 [13] as part of their AMR surveillance strategy. These reports were primarily used to understand the context and relevance of modelling for AMR. The peer-reviewed journal articles/conference publications were examined in more detail to identify specific evidence related to the following key aspects:

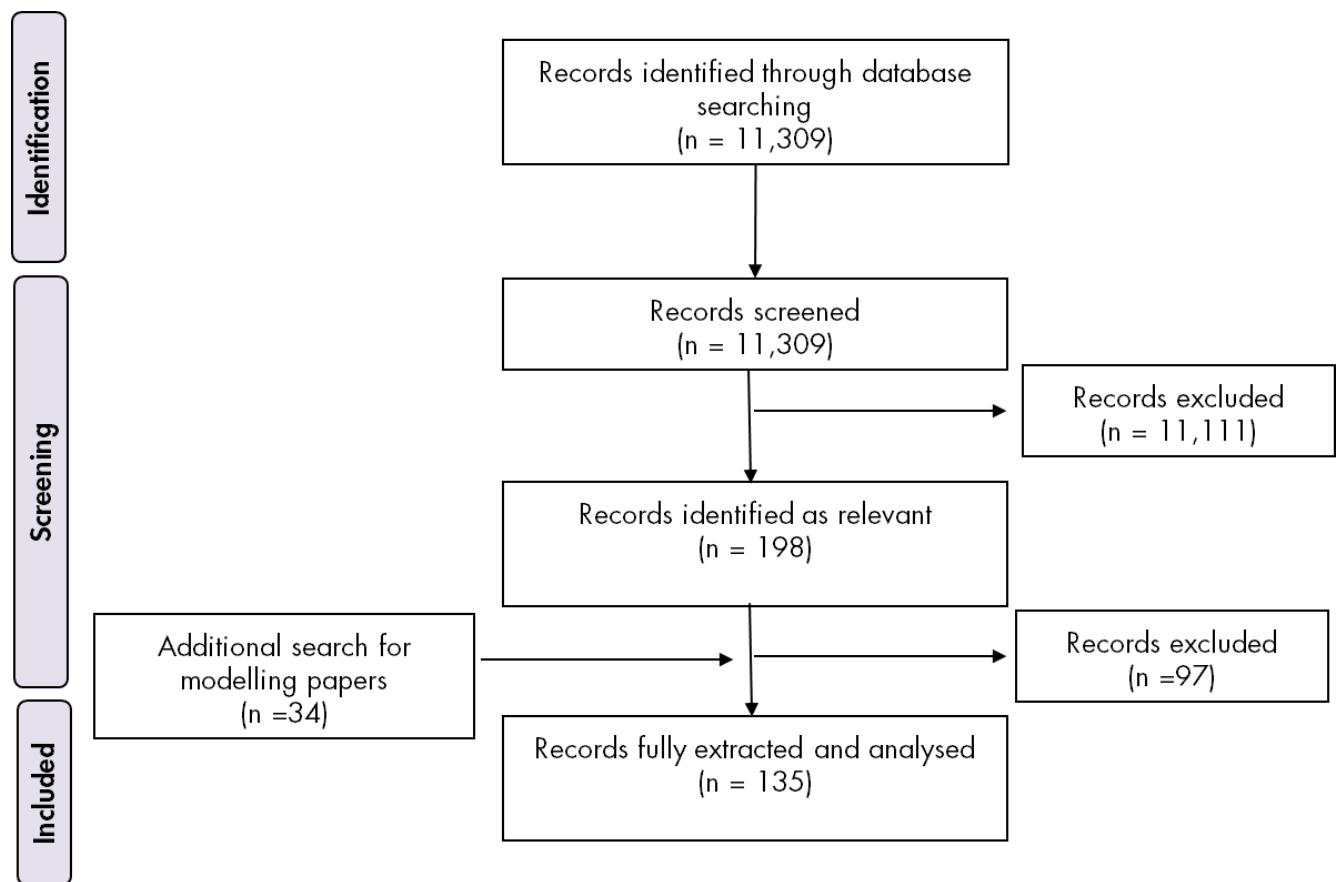
- Bacterial pathogens / diseases / secondary conditions covered in the study
- Antibiotics covered in the study
- Description of the modelling approaches used
- Description of the data sources used
- AMR-related estimates reported
- Known limitations to the models and data sources used, and any estimates produced
- Implications for future research

The information extracted formed the basis of the high-level overview of evidence presented in Chapter 2.

Overall, across the initial literature search and additional AMR modelling study search, 135 studies were reviewed.

The PRISMA diagram below outlines the number of articles excluded at each stage.

Figure 2: Preferred reporting items for systematic reviews (PRISMA) diagram



Adapted from: Adapted from Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G., The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*, 6(7), e1000097. <https://doi.org/10.1371/journal.pmed.1000097>.

Analysis was conducted in Excel, with each member of the research team analysing a different disease/health condition, splitting the analysis by the different types of impacts. Table 9 provides a breakdown of the number of studies identified for each disease/health area covered in this report. The table also outlines the number of studies focusing on different types of resistance (antibacterial, antiviral, antifungal and antiparasitic).

Table 9: Number of studies covering the diseases/health areas of interest and the number of papers focusing on the different types of resistance¹⁸⁹

General disease/condition	No. Papers	Antibacteria l	Antivira l	Antifunga l	Antiparasiti c
Organ transplant	22	18	4		
Diabetes	15	14		1	
HIV	15	15	1		
ICU	11	10		1	
Surgery	11	11			
Cancer	10	9		1	
Infant and paediatric infection	8	7		1	
Immunodeficiency	7	6	1	1	1
Physical trauma	5	5			
Liver and kidney disease	3	3			
<hr/>					
Total	107				

There were some health conditions/areas of health services included in the literature search protocol that we did not identify any literature for. These were: childbirth; abortions; asthma; stroke; heart disease; dermatological conditions; rheumatology conditions; Common Variable Immune Deficiency; dental health.

¹⁸⁹ The total number of papers more than the number of papers extracted as some covered multiple disease conditions. The number of papers covering the different types of resistance does not always equal the total number of papers as some studies researched more than one type of resistance.